NANYANG TECHNOLOGICAL UNIVERSITY

Asymmetric Reactions of Unsaturated Esters and Desymmetrizations of P-Stereogenic Phosphinates via Carbene Catalysis and Oxidative Carbene Catalysis

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Asymmetric Reactions of Unsaturated Esters and Desymmetrizations of P-Stereogenic Phosphinates via Carbene Catalysis and Oxidative Carbene Catalysis

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ABSTRACT

This thesis focuses on esters activation and desymmetrization for enantioselective reactions enabled by *N*-heterocyclic carbenes (NHCs) organocatalysts. It contains four parts:

Chapter 1 gives brief introductions to the history and development of NHC catalysis classified by common active intermediates within this field. Representative examples and furture challenges are summarized and reviewed as well in this part.

Chapter 2 describes a formal LUMO activation of α, β-unsaturated esters enabled by NHC catalyst for highly enantioselective lactam formation. Sterically bulky β, β-disubstituted esters can also be used in this strategy, which delivers the optically enriched product containing a quarternary carbon center.

Chapter 3 is about NHC-catalyzed cascade reaction for synthesis of functionalized pyrrolo[3,2-*c*]quinolones. The products from Michael-Mannich-Lactamization cascade reaction are obtained in good yield and enantioselectivity with three consecutive stereogenic centers.

Chapter 4 introduces a rapid approach to P-stereogenic phosphinates via NHC-catalyzed desymmetrization of bisphenols. Due to the high efficiency of the reaction, the enantiomerically enriched P-stereogenic phosphinates can be prepared in large scale under low catalyst loading. The chiral phosphinates are also demonstrated as a good catalyst in the reductive aldol reaction.

PUBLICATIONS

1. Access to P-Stereogenic Phosphinates via NHC-Catalyzed Desymmetrization of Bisphenols.

   Zhijian Huang, Xuan Huang, Baosheng Li, Chengli Mou, Baoan Song, Yonggui Robin Chi, *J. Am. Chem. Soc.* **2016**,*138*, 7524.

2. NHC organocatalytic formal LUMO activation of α,β-unsaturated esters for reaction with enamides.

   Jiajia Cheng, **Zhijian Huang**, Yonggui Robin Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592.

3. N-Heterocyclic Carbene-Catalyzed [3+4] Cycloaddition and Kinetic Resolution of Azomethine Imines.

   Ming Wang, **Zhijian Huang**, Jianfeng Xu, and Yonggui Robin Chi, *J. Am. Chem. Soc.* **2014**, *136*, 1214.

4. Carbene-Catalyzed Radical Reactions for Highly Enantioselective β-Hydroxylation of Enals.

   Yuexia Zhang, Yu Du, **Zhijian Huang**, Jianfeng Xu, Xingxing Wu, Yuhuang Wang, Ming Wang, Song Yang, Richard D. Webster, and Yonggui Robin Chi, *J. Am. Chem. Soc.* **2015**, *137*, 2416.

5. Enantioselective Synthesis of Cyclic β-Amino Acid via Amine-Catalyzed Addition of Unsaturated Imine γ-Carbon to Enal.

   Zhijian Huang, Shitian Zhuo, Zhichao Jin, Chengli Mou, Yonggui Robin Chi (to be submitted)

ABBREVIATIONS

Ac	acetyl
AIBN	2,2'−azo *bis*isobutyronitrile
Am	amyl (*n*−pentyl)
Boc	*tert*−butyloxycarbonyl
BQ	benzoquinone
Bu	butyl
Bn	benzyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
DABCO	1,4−diazabicyclo[2.2.2]octane
DBU	1,8−diazabicyclo[5.4.0]undec−7−ene
DCM	dichloromethane
DDQ	2,3−dichloro−5,6−dicyano−1,4−benzoquinone
DIBAL	diisobutylaluminum hydride
DMA	*N*,*N*−dimethylacetamide
DMAP	4−dimethylaminopyridine
DME	1,2−dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Equiv	equivalent
ESI	electrospray ionization
GC	gas chromatography
HRMS	high−resolution mass spectrometry

HPLC	high performance liquid chromatography
HWE	Horner−Wadsworth−Emmons
IBX	*o*−iodoxybenzoic acid
IPA	isopropyl alcohol
^{i}Pr	isopropyl
KIE	kinetic isotope effect
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
m−CPBA	*meta*−chloroperbenzoic acid
Mes	mesityl
MOM	methoxymethyl
Ms	mesyl (methanesulfonyl)
NBS	*N*−bromosuccinimide
NMO	*N*−methylmorpholine oxide
OAc	acetoxy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Piv	pivaloyl
p−TsOH	*p*−toluenesulfonic acid
SET	single electron transfer
TBAB	tetra−*n*−butylammonium bromide
TLC	thin layer chromatography
TMS	trimethylsilyl

α	alpha
β	beta
γ	gamma
μ	micro
π	pi
η	eta
ω	omega
σ	sigma

Chapter 1

Introduction

1.1 Introduction on Asymmetric Organocatalysis

Organocatalysis now is widely accepted as one of the three main pillars of enantioselective synthesis (the other two are enzymatic catalysis and organometallic catalysis). The use of small molecules to facilitate enantioselective transformation can be traced back to one century ago. In 1912, Bredig and Fiske[1a] reported a cinchonidine catalyzed asymmetric reaction between hydrocyanic acid and benzaldehyde. However, only few transformations that used small molecules as catalyst had been documented over past century. Before the word "organanocatalysis" was coined, there were some excellent work reported in 1990's, such as Corey's guanidine for Strecker reaction;[1b-c] fructose-derived ketone for asymmetric epoxidation by Shi;[1d-f] Fu's chiral DMAPs for desymmetrization[1g] and Miller's peptide catalysts for kinetic resolution reactions,[1h] *etc*. It was not until the early 21th century, the field of organocatalysis was reborn and received a thriving development when Barbas, List and Macmillan published their seminal work simultaneously (enamine and iminium chemistry). [2] Since then, the number of publications on the topic of "Organocatalysis" gained an explosion of growth, from 4 manuscripts in 2000 to 1509 manuscripts in 2015 (**Fig 1.1**).

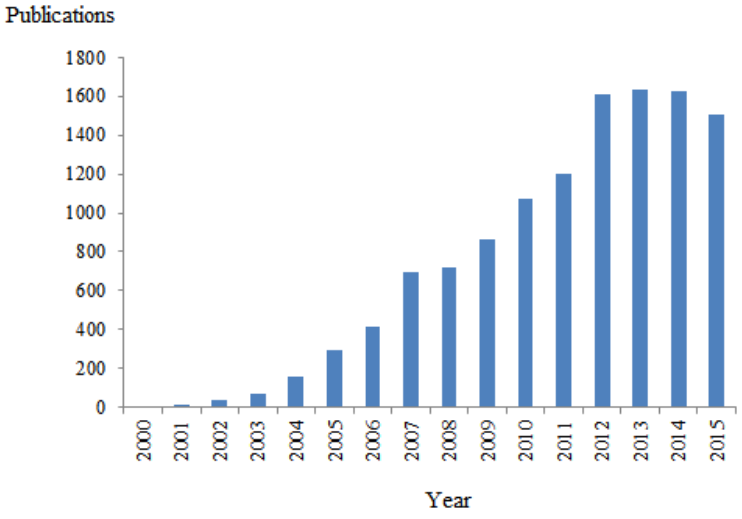


Fig 1.1 The number of publications on the topic of organocatalysis. The data were obtained by searching the keyword "organocatalysis" in SciFinder.

There are several advantages that make organocatalysis rapidly growing in the fields of asymmetry catalysis: (a) mild reaction conditions. Organocatalysts are usually not sensitive to air and moisture, that makes the operation of the reaction more simple; (b) inexpensive and easy to prepare. Optical pure starting materials can be obtained abundantly from natural sources, such as amino acids, plant-extracted alkaloids; (c) lower toxic or even nontoxic to human and environment friendly.

Based on the interaction between the catalysts and substrates, two types of organocatalysts can be categorized, namely non-covalent catalysts and covalent catalysts. [3] The typical catalysts are summarized in **Fig 1.2**.

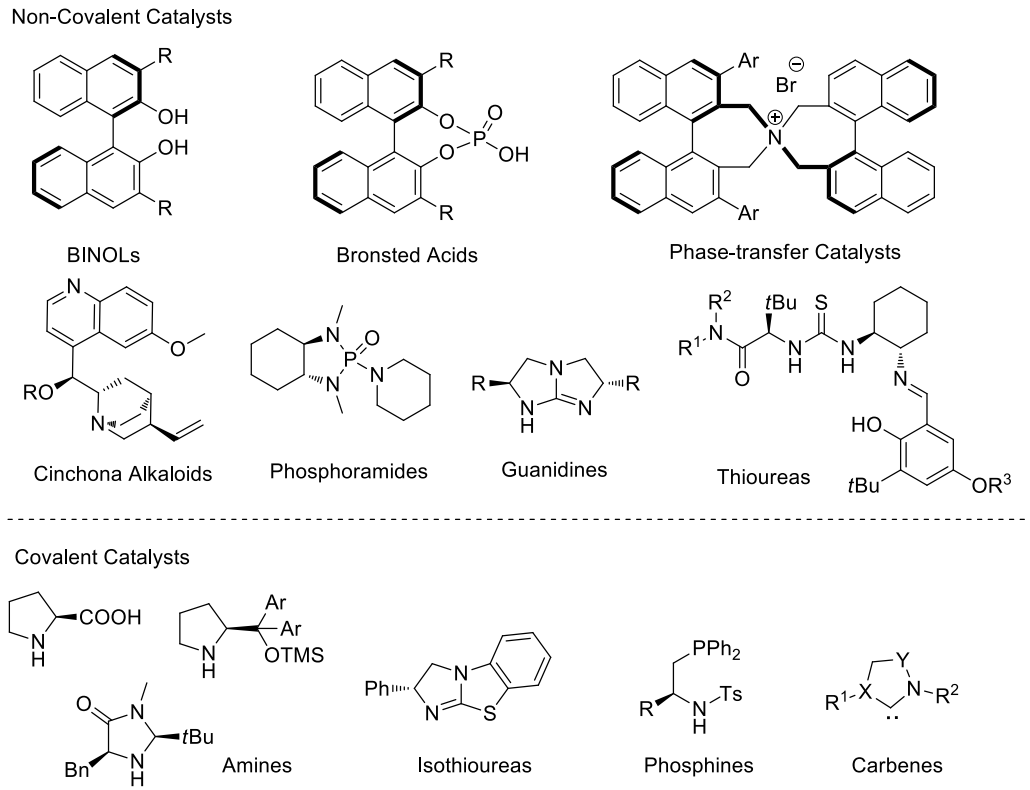
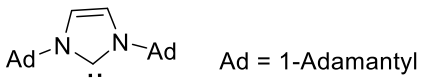


Fig 1.2 Typical organocatalysts

1.2 Introduction on N-heterocyclic Carbenes

N-heterocyclic carbenes are neutral compounds with a six-electron valence shell carbon atom.[4] The incomplete octet structure of carbene species is traditionally considered as the main reason of inherently unstable property. The isolation and characterization of a free carbene was challenged until the pioneer work was reported by Arduengo in 1991 (**Fig 1.3**).[5] Since then, novel NHCs have been synthesized and extensively investigated.



Arduengo, 1991

Fig 1.3 First example of stable N-heterocyclic carbene

1.2.1 Properties of N-Heterocyclic Carbenes

An NHC is usually described as a cyclic compound that contains at least one nitrogen atom and divalent carbene carbon atom. A typical example imidazol-2-ylidene is selected to demonstrate the general structure and properties of an NHC in **Fig 1.4**. In the ground state of an NHC, the central carbene carbon atom is probably described as sp^2 hybridization, with the lone pair electrons occupied the sp^2 orbital and unoccupied *p* orbital. This carbene center can be stabilized by the σ-electron-withdrawing and π-electron-donating effect by the adjacent nitrogen atom. A bulky substituent attached to the nitrogen can help to prevent the dimerization of the carbene species. Moreover, different R groups such as mesityl or pentafluorophenyl greatly influenced the electron property of carbene center.

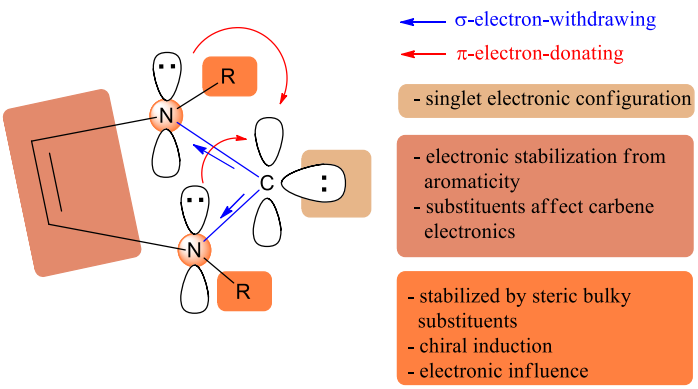


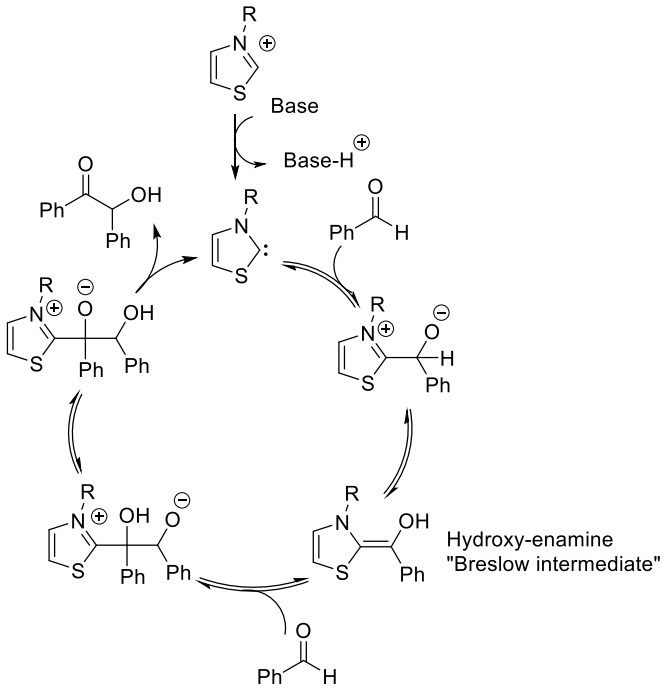
Fig 1.4 Structure and general properties of imidazol-2-ylidene

1.2.2 Applications of N-heterocyclic carbenes

The original applications of NHCs mainly involve the coordination to transition metals. The metal-NHC complexes were first synthesized by Öfele and Wanzlick in 1968, respectively.[6] These results were 23 years earlier than that stable carbene was isolated. Imidazolylidenes and imidazolinylidenes are broadly applied for the coordination to transition metals,[7] and the distinguished example would be the Grubbs' second generation olefin metathesis catalyst.[8] On the other hand, due to the strong σ-donating effect from the carbene center, the NHCs can also be served as a powerful nucleophilic organocatalysts in copious types of chemical reactions. In this part, applications of NHCs as organocatalyst will be given and discussed.[9]

Dated back to the early 1940s when Ugai and co-workers used thiazolium salts as catalysts in benzoin reaction, the NHCs were found to be capable for umpolung of organic molecules.[10] The formation of hydroxyl-enamine which now widely accepted as Breslow[11] intermediate was the key step of this process (**Scheme 1.1**). However, the application of NHCs as organocatalysts was documented sporadically until the last decade did NHCs get prosperous rise within the field of organocatalysis.

In N-heterocyclic carbene catalysis, a covalent bond between the carbene and the substrate is formed, activating the interaction between the substrate and other reagent in the reaction. Generally, NHC and substrate could generate different active intermediates: (a) acyl anions; (b) homoenolates; (c) saturated acyl azoliums; (d) unsaturated acyl azoliums (**Fig 1.5**).



Scheme 1.1 Mechanism of benzoin reaction

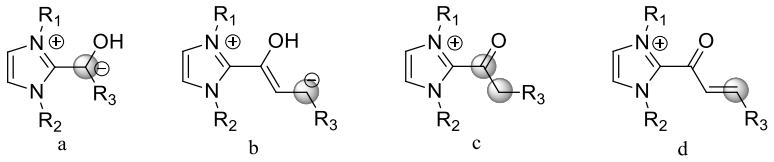


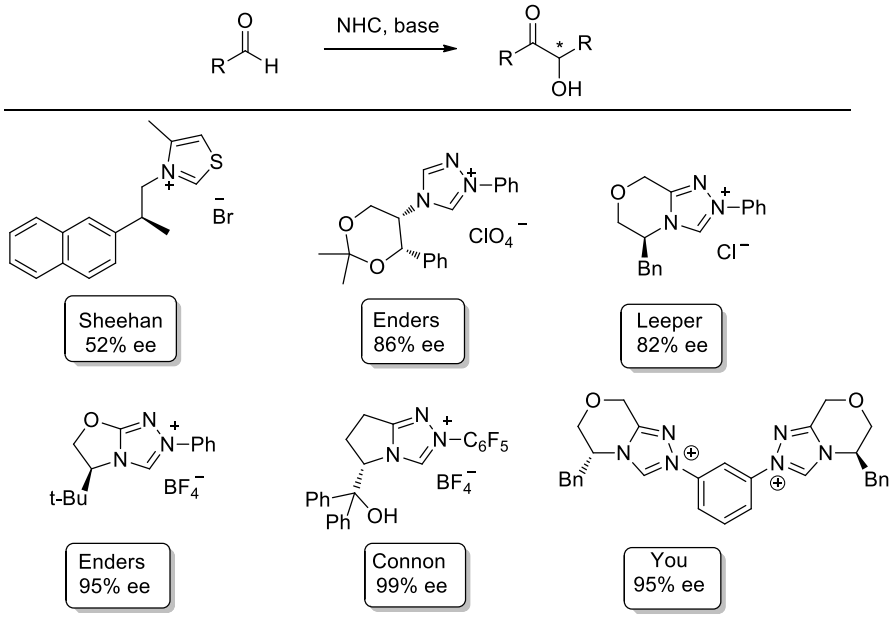
Fig 1.5 General NHC-bound intermediates

1.3 Reactions involving Acyl Anions

Aldehydes are good electrophiles in many organic reactions. After nucleophilic attacked by the NHC and proton shift process, the NHC-bound aldehyde would convert into a nucleophile, which so-called acyl anion equivalent. This equivalent

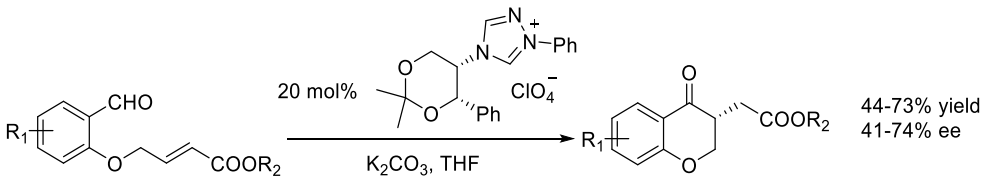
can further react with aldehyde (benzoin reaction) or Micheal acceptor (Stetter reaction).

The first asymmetric benzoin reaction was reported by Sheehan and coworkers[12] in 1966, but only little enantioselectivity could be achieved. Many new NHC were developed for this reaction and up to 99% ee could be obtained (**Scheme 1.2**).[13]

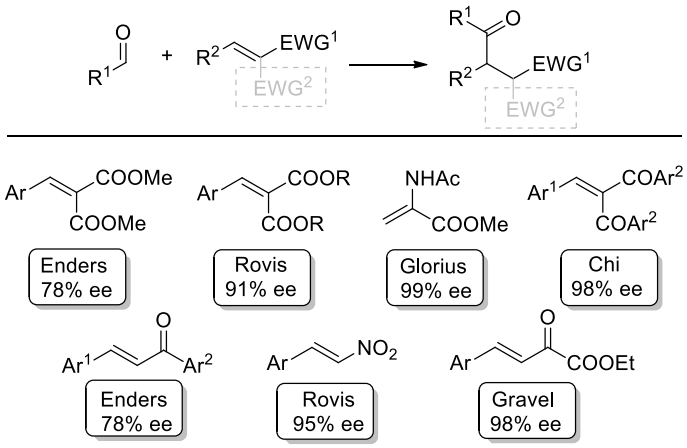


Scheme 1.2 Milestones in NHC catalyzed benzoin reaction

Since the benzoin reaction is reversible, it gives this acyl anion a way to react with another electrophile. In 1976, Stetter reported this intermediate reacted with Michael acceptors, giving 1,4-dicarbonyl compounds.[14] In additioin, different types of Michael acceptors such as α, β-unsaturated ketones, esters, nitriles, nitros, are in the scope of this reaction. In 1996, Enders et al. reported the first asymmetric intramolecular Stetter reaction by utilizing a triazolium salt as a precatalyst and obtained moderate yield and enantioselectivity (**Scheme 1.3**).[15, 16] More challenging intermolecular Stetter reaction in good enantionselective version could be overcome successfully by several research groups.[17] The results are summarized in **Scheme 1.4**.



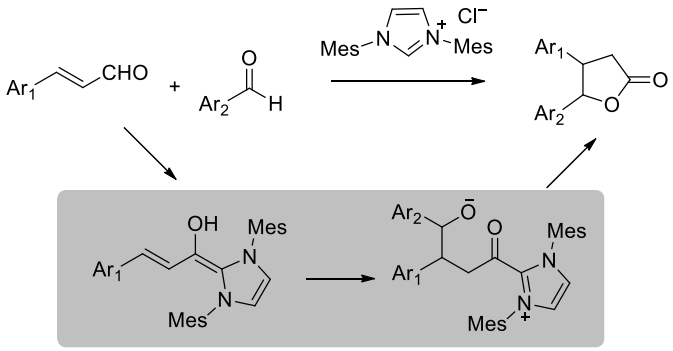
Scheme 1.3 Ender's first intramolecular Stetter reaction



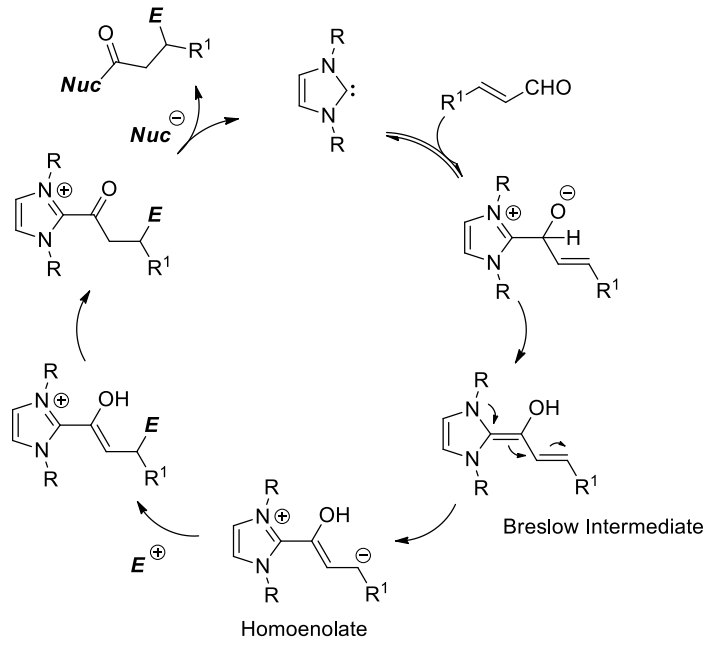
Scheme 1.4 Examples of asymmetric Stetter reaction

1.4 Reactions involving Homoenolates

As described above, the NHC catalysts can effectively convert the aldehyde electrophilic carbon to a nucleophilic center. Most importantly, this inherent property can further deduce to α, β-unsaturated aldehydes, which commonly refer to homoenolate reaction. The mechanism of this type of reaction is illustrated in **Scheme 1.5**. This concept of the formation of homoenolate equivalents was first proposed by Bode and Glorius in 2004 independently.[18] They used enals and aldehydes to obtain γ-butyrolactones in moderate to good yields (**Scheme 1.6**). It is worthy to note that bisarylimidazolium salt as NHC precatatlysts were required in order to suppress the benzoin reaction and Stettter reaction through the shielding effect by the catalysts.

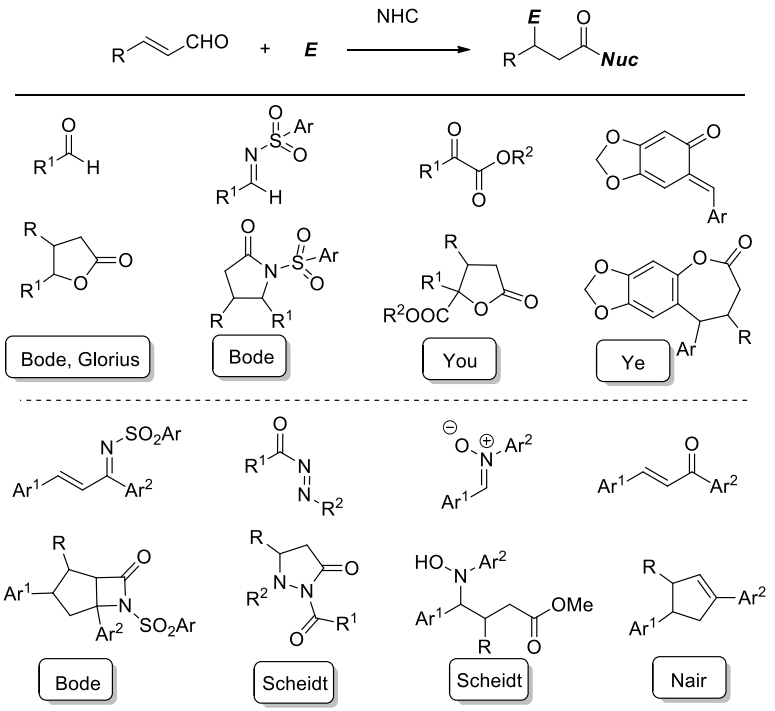


Scheme 1.6 Homoenolate pioneering work reported by Bode and Glorius



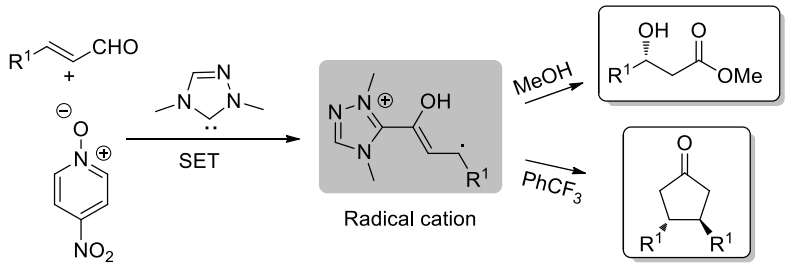
Scheme 1.5 Homoenolate activation enabled by NHC catalyst.

After the fundamental and influential examples of homoenolate reactions were established, many kinds of electrophiles were selected for complement of this field (**Scheme 1.7**). These electrophiles included aldehydes, imines, ketones, enones, azomethines, hydrozones, *etc*. [19]



Scheme 1.7 Electrophiles in homoenolate activation reaction

All these reactions catalyzed by NHC through homoenolate activation are presumably undergone a two-electron pathway. In 2014, Rovis and coworkers reported that homoenolate equivalents could be removed one electron to form radical intermediates with the treatment of electron-deficient nitroarenes as oxidants. β-hydroxyl ester and cyclopentanone products (**Scheme 1.8**) are both accessible with alternative solvents.[20]



Scheme 1.8 Radical reactions in NHC catalysis

1.5 Reactions involving Saturated Acyl Azoliums

NHC-bound saturated acyl azoliums are excellent precursors of enolate chemistry for asymmetry transformations. These active intermediates can be generated from

enals, α-halo aldehydes, ketenes, esters, and simple aliphatic aldehydes under oxidative condition (**Fig. 1.6**).[21]

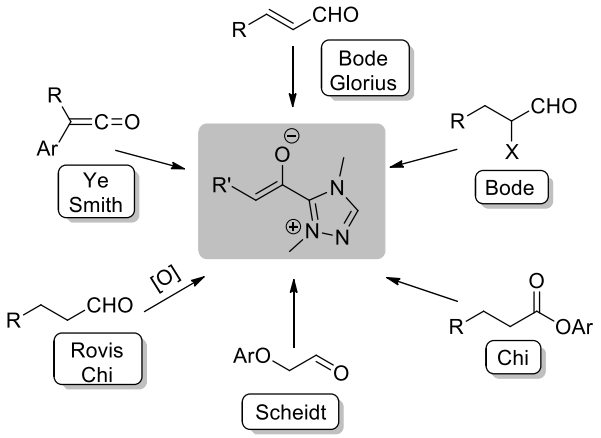
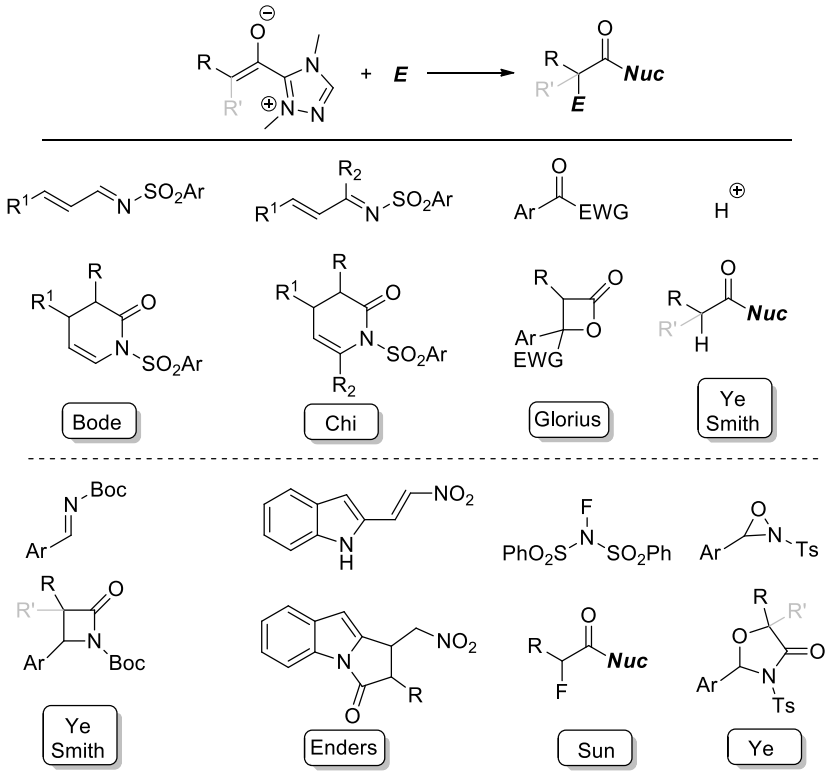


Fig 1.6 Enolate precursors in NHC catalysis

In 2006, Bode and coworkers first reported the [4+2] aza-Diels-Alder reaction between enals and N-protected α, β-unsaturated imines via NHC-bound enolate intermediates in high chemo- and enantioselective manner.[21a] Since then, a lot of research groups devoted many efforts to this area (**Scheme 1.9**). Remarkably, Chi and coworkers disclosed the "backward" pathway of the enolate chemistry, which starting from the stable carboxylic esters.[21c] Moreover, the same group also realized the direct β-carbon activation as a nucleophile from esters enabled by NHC catalysis.[22]



Scheme 1.9 Electrophiles in enolate activation reaction

1.6 Reactions involving Unsaturated Acyl Azoliums

Unsaturated acyl azoliums are one the most investigated intermediates in carbene catalysis. This is a formal LUMO activation process by the inductive effect of electron-withdrawing NHC moiety, which is unlike the umpolung chemistry (benzoin, Stetter, homoenolate reactions). The active intermediates can be produced from ynals,[23] in situ mixed anhydrides,[24] acyl fluorides,[25] or enals and simple aliphatic aldehydes under oxidative conditions (**Fig 1.7**).[26]

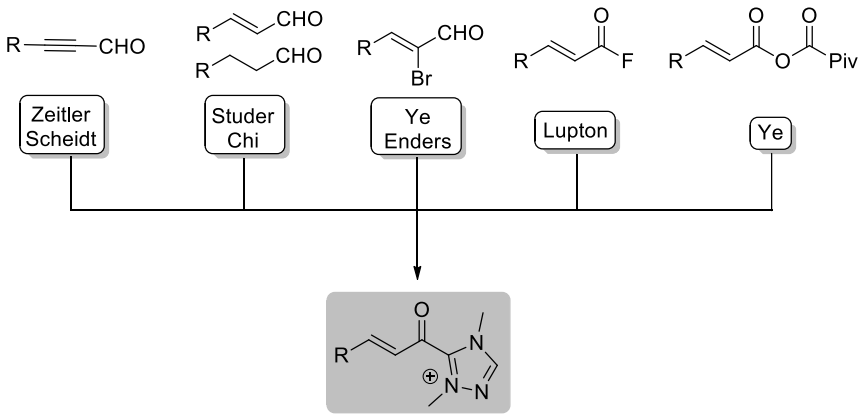
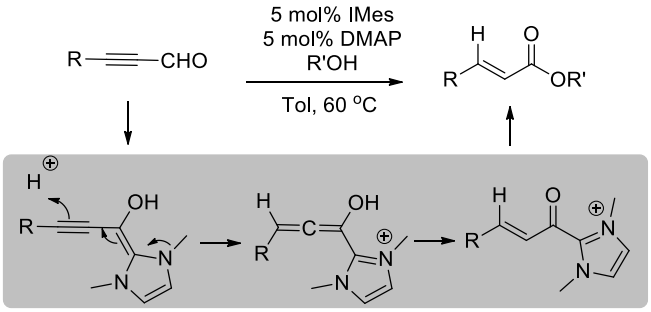


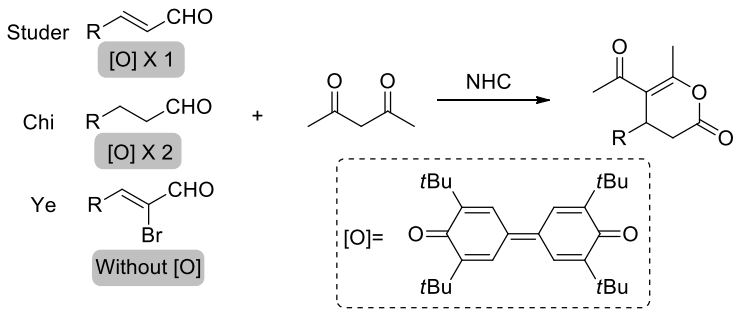
Fig 1.7 Unsaturated acyl azolium precursors in NHC catalysis

The first example of esterification reaction using the ynals as substrates was reported by Zeitler's group in 2006 (**Scheme 1.10**).[23a] This process involved an internal redox reaction to give unsaturated acyl azolium, followed by interception of an alcohol to form the desired ester.



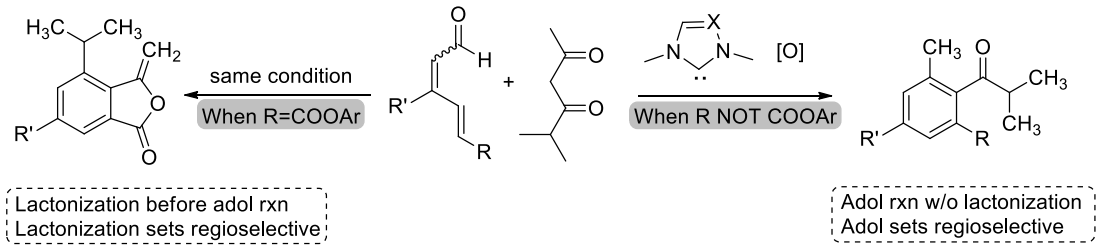
Scheme 1.10 Esterification reactions by Zeitler

In 2010, Studer and co-workers reported that enals reacted with 1,3 dicarbonyl compound could provide dihydropyranones in excellent yield under the oxidative NHC catalysis.[27] Quinone oxidant was found to be superior for this reaction. Recently, Chi's group disclosed that saturated aldehydes could also undergo such reaction by doubly oxidizing the NHC-aldehyde adduct into α,β-unsaturated acyl azolium intermediates.[26d] When enal was bearing good leaving group such as bromo in α-position, no external oxidant was required to form the same active species (**Scheme 1.11**).[28]



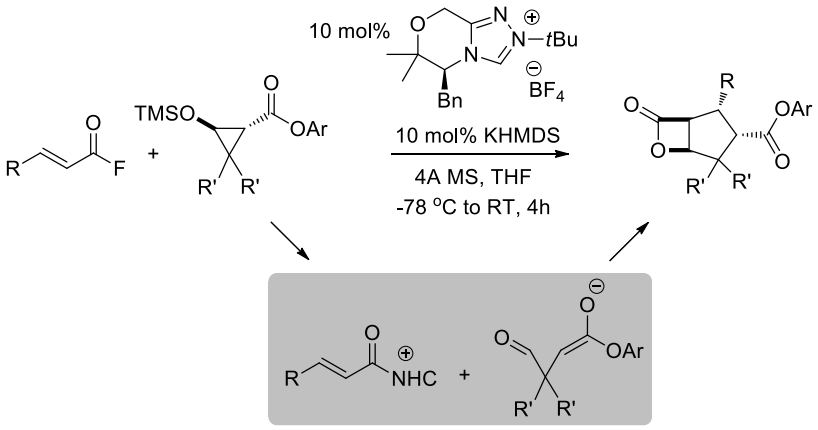
Scheme 1.11 Dihydropyranone synthesis in NHC catalysis

Recently, Chi and coworkers demonstrated that δ-carbon of the unsaturated aldehyde could also be activated by the NHC to form the multisubstituted arenes with highly chemo- and regioselective manner.[29] The simple change of the substrate significantly affected the reaction process and led to divergent outcomes (**Scheme 1.12**).

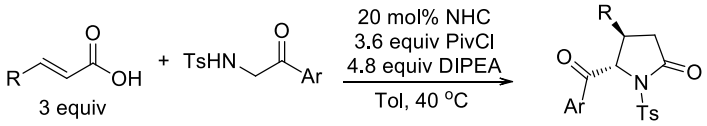


Scheme 1.12 δ-carbon activation by Chi's group

Besides the above activation modes, acyl fluorides and and mixed anhydrides can be served as substrates for diastereo- and enantioselective annulations. In 2013, Lupton and coworkers reported the asymmetric Ireland-Coates-Clasisen rearrangement catalyzed by *N*-*tert*-butyl triazolylidene NHC with α, β-unsaturated acid fluorides and donor-acceptor cyclopropane (**Scheme 1.13**).[25] The mechanism of this reaction involved the addition of NHC to acyl fluoride and the formation of bifunctional enolate from desilylation. These two active species combined and formed the hemiacetal, followed by Ireland-Coates-Claisen rearrangement, aldol reaction and lactonization to afford the desired product. In 2014, Ye's group established carboxylic acid activation by mixing PivCl to yield anhydrides *in situ*. By adopting this strategy, a collection of pyrrolidinones and dihydropyridinones could be obtained in good yield and excellent enantioselectivity (**Scheme 1.14**).[30]



Scheme 1.13 Acyl fluorides activation by Lupton's group



Scheme 1.14 Acids activation by Ye's group

1.7 Summary and Research Designs

The exploration and development of NHCs is unquestionable one of the greatest successes in organocatalysis. Many research groups make tremendous contributions into this field for discovery of new activation modes. α, β-unsaturated compounds are useful building blocks in chemical science, and α, β-unsaturated acyl azoliums are well studied in NHC catalysis. As described above, there are many ways to generate such active species. However, each method has its own limits and drawbacks, which restricts practical applications more or less. For example, relatively expensive organic oxidants are required when α, β-unsaturated aldehydes are used as substrates; disubstitutions at the α- and β-carbons are not possible for ynals; acyl fluorides are not easy to prepared and stored and when using in situ mixed anhydrides (usually 2~3

equivalents of acids, PivCl and bases) as substrates, the reactions produced a lot of chemical waste.

On the other hand, carboxylic acid derivatives such as esters are readily available and easy to handle. Nevertheless, the catalytic generations of unsaturated acyl azoliums for chemo- and enantioselective reactions from esters still remain challenging. Therefore I aim at expanding the substrate scope in NHC catalysis, mainly focusing on the ester activations in this thesis.

1.8 References

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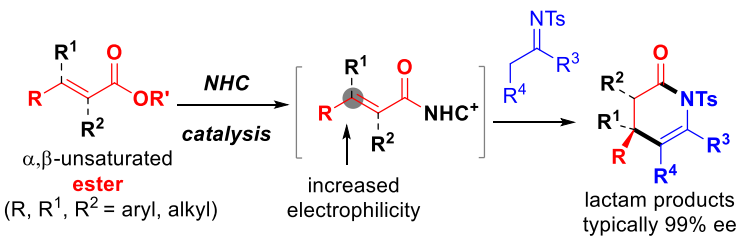
Chapter 2

NHC Organocatalytic Formal LUMO Activation of α, β-Unsaturated Esters for Reaction with Enamides



2.1 Introduction

2.1.1 Activation of α, β-Unsaturated Carbonyl Compounds

α, β-unsaturated carbonyl derivatives are useful building blocks for catalytic asymmetric reactions in chemical science.[1,2] The activation of this type of substrates includes the coordination to Lewis acids or interactions with hydrogen bonding donors (**Fig 2.1**). As a result of these activations, the energy of the lowest unoccupied molecular orbital (LUMO) decreases, made it easier attacked by a nucleophile reagent. Representative examples include Evan's metal-bisoxazoline complexes,[3] Feng's metal-*N,N'*-dioxides,[4] Shibasaki's bifunctional Lewis acid/base catalysts,[5] and quinine type of hydrogen bonding donor catalysts (**Fig 2.2**).[6]

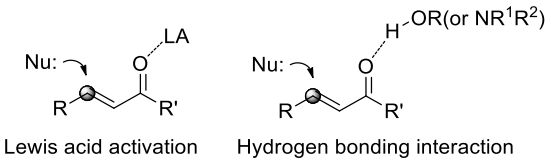


Fig 2.1 Activations of α, β-unsaturated carbonyl derivatives by Lewis acids or hydrogen bonding donor

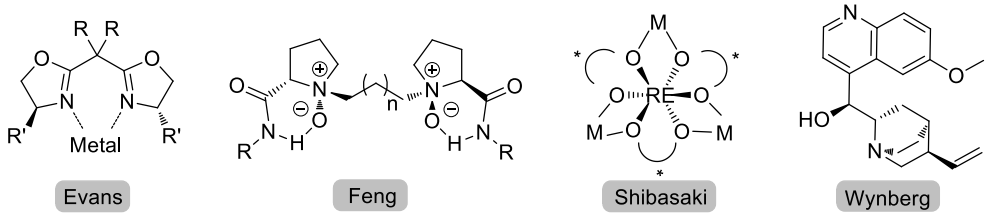
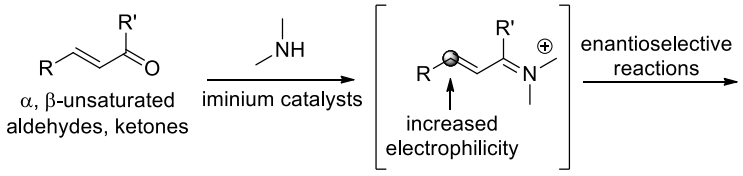


Fig 2.2 Examples of catalyst

Moreover, α, β-unsaturated aldehydes and ketones can also be activated by iminium organocatalysts, which pioneered by MacMillan and coworkers in the past decade (**Scheme 2.1**).[7] On the other hand, the lower active ester substrates are excluded from the scope of enamine/iminium catalysis for enantioselective reactions. I hope that the equally

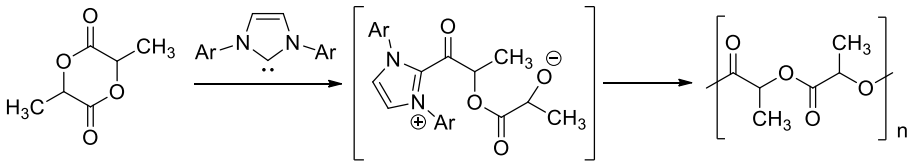
useful ester substrates can further undergo transformations enabled by NHCs, which makes significant contributions in the field of organocatalysis.



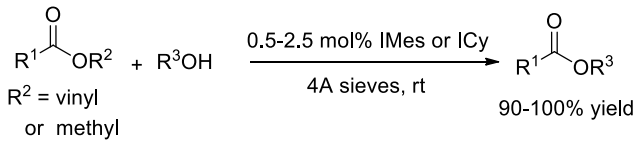
Scheme 2.1 Iminium catalysts pioneered by MacMillan

2.1.2 Ester Activations Enabled by NHCs

The initial findings of ester activation enabled by NHC were first reported by Hedrick for ring-opening polymerization of lactides and lactones (**Scheme 2.2**).[8] Simultaneously, Nolan disclosed the transesterification reaction between vinyl acetate and benzyl alcohol (**Scheme 2.3**).[9] More challenging methyl esters for this transformation were also successful when using molecular sieves to absorb the liberated methanol with higher nucleophilic N-alkyl NHCs. The mechanism for this reaction was involved the nucleophilic addition of NHC to the esters to provide acyl azoliums. On the other hand, Studer believed that alcohol activation occurred in the subsequent selective O-acylation step.[10] DFT calculations revealed that strong hydrogen bond formation between the NHC and the alcohol could increase the the nucleophilicity of the alcohol.[11]

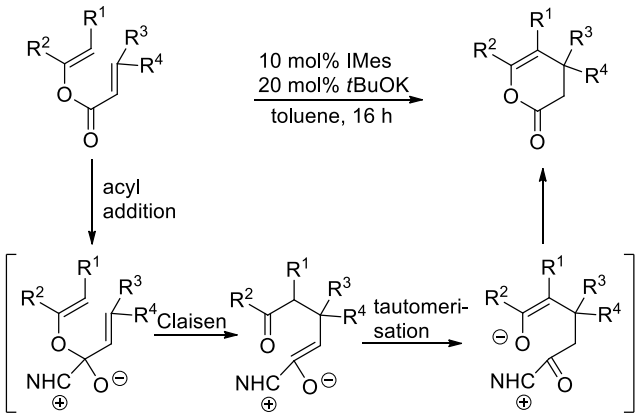


Scheme 2.2 Hedrick's ring-opening polymerization mediated by NHC



Scheme 2.3 Nolan's NHC catalyzed transesterification

In 2009, Lupton and coworkers reported NHC-catalyzed isomerization of enol esters to dihydropyranones.[12] Crossover studies and other relevant evidences implicated the mechanism involved the formation of hemiacetal followed by Claisen rearrangement.

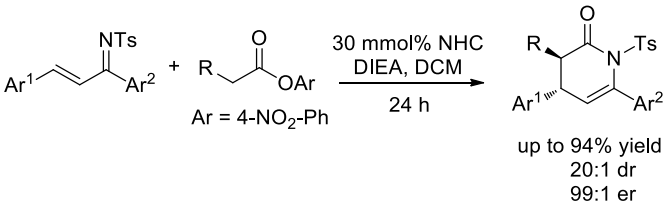


Scheme2.3 Dihydropyranone synthesis via Claisen rearrangement

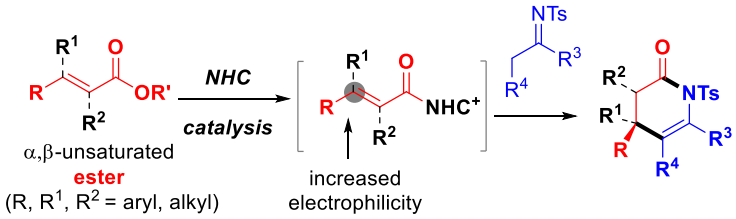
2.1.3 Proposal

As described in the previous chapter, the NHC-bound α, β-unsaturated acyl azolium could be generated from enals, α-bromo enals, ynals, and acid fluorides. Although these methods have reached great achievement in asymmetric NHC catalysis, the drawbacks of each method could not be ignored. For example, relatively expensive organic oxidants are required when α, β-unsaturated aldehydes are used as substrates; disubstitutions at the α- and β-carbons are not possible when ynals are used as substrates; Acyl fluorides are highly reactive and difficult to be prepared and stored. Carboxylic esters are easily sythesized and stable under the aerobic and moist condition. However, the catalytic formation of acyl azolium from esters is far more challenging. Recently, Chi's group

realized ester activation in a variant of (4+2) annulation between NHC-bound enolate and chalcone-derived tosyl imine (**Scheme 2.4**).[13] In this chapter, a new strategy of LUMO activation of α, β-unsaturated esters to react with enamides was disclosed. (**Scheme 2.5**).



Scheme 2.4 HOMO activation of esters enabled by NHC



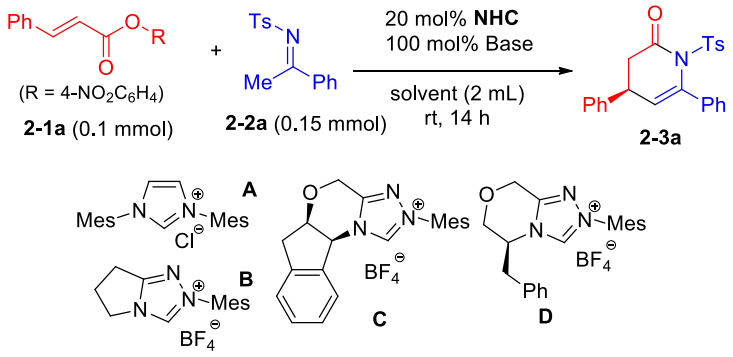
Scheme 2.5 LUMO activation of esters enabled by NHC

2.2 Results and Discussions

First of all, ester **2-1a** and acetonphenone-derived imine **2-2a** were chosen as the model substrates and the investigation began with the screening of different NHC catalysts. There was no backgroup reaction occurred in the absent of NHC catalyst (**Table 2.1**, entry 1). Imidazolium type of NHC catalyst **A** was not effective for the ester activation, while triazolium type of catalyst **B** showed superior reactivity on the reaction with 76% isolated yield (entry 3). Aminoindanol- or phenylalanine-derived catalysts could give similar result with good yield and excellent enantioselectivity (entry 4-5). Then the effects of solvents (entries 6-8) and bases (entries 9-12) were evaluated. However, no better result was observed, compared to the use of combination of THF and DBU. The tolerance

of different catalysts, solvents and bases suggested that the catalytic system may be further developed for diverse substrates.

Table 2.1 Condition Optimization



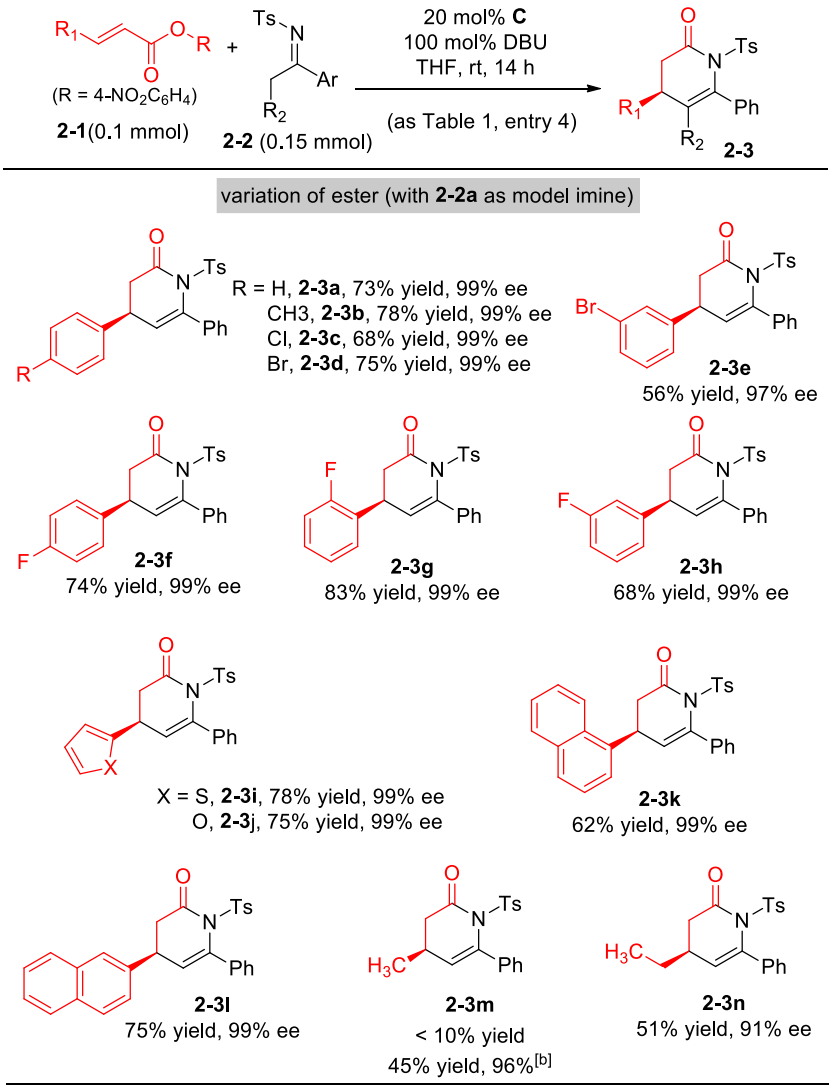
entry	NHC	base, solvent	yield (%)[a]	ee [b]
1	-	DBU, THF	-	-
2	**A**	DBU, THF	-	-
3	**B**	DBU, THF	76	-
4	**C**	DBU, THF	73	99
5	**D**	DBU, THF	69	95
6	**C**	DBU, CH_2Cl_2	47	97
7	**C**	DBU, toluene	35	97
8	**C**	DBU, CH_3CN	56	96
9	**C**	DIEA, THF	10	97
10	**C**	DMAP, THF	17	98
11	**C**	Cs_2CO_3, THF	30	97
12	**C**	*t*-BuOK, THF	36	96

[a] Isolated yield based on **1a** after SiO_2 column chromatography. [b] Enantiomeric excess of **2-3a** was determined *via* chiral phase HPLC analysis; absolute configuration of the major enantiomer was assigned based on X-ray structure of **2-3c**.

With an optimized condition (**Table 2.1**, entry 4) on hand, the scope of this annulation reaction was examined to illustrate the enerality of the approach. Firstly, the β-mono substituted unsaturated ester and the imine **2-2a** were evaluated as the model nucleophile (**Table 2.2**). A wide range of β-mono substituted unsaturated esters with both electron-donating and electron-withdrawing phenyl substituents were tolerated (**2-3b** to **3h**). Bearing other heterocycles such as furan, thiophene and naphthyl instead of phenyl group

on β-position, the reaction could also complete with little influence on the reaction outcomes (**2-3i to 3l**). Replacing the β-aryl group of the ester with alkyl substituent (**2-3m** and **2-3n**), a slight decrease in the yields was observed. It was worth to note that NHC pre-catalyst **D** performed better than **C** in the formation of **2-3m**.

Table 2.2 Substrate Scope with Variation of Ester[a]

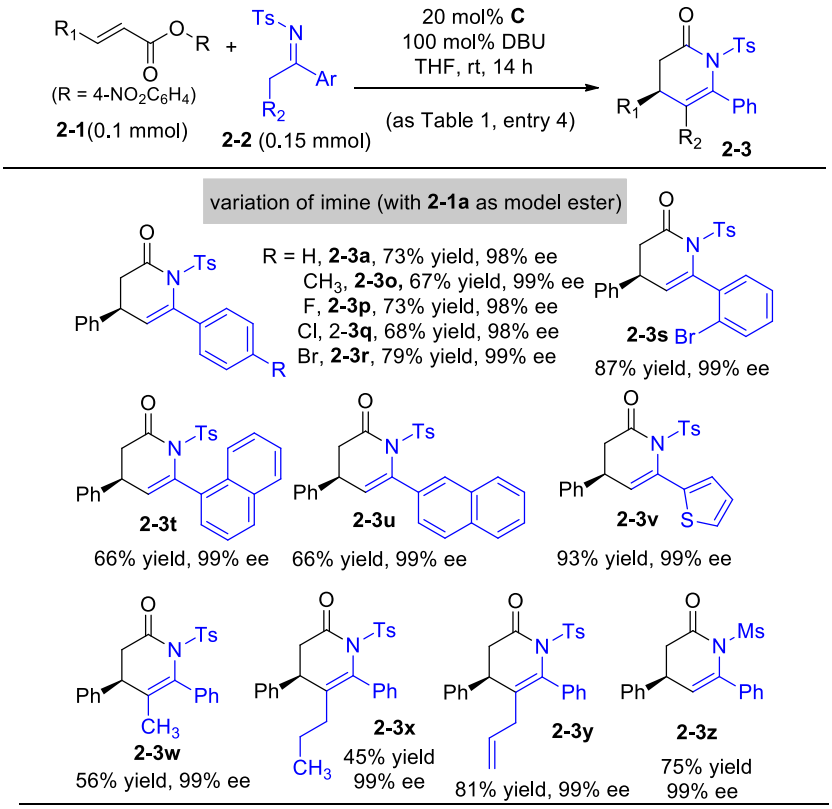


[a] Unless otherwise noted, all the reactions were carried out at room temperature using **2-1** (0.10 mmol), **2-2a** (0.15 mmol), 20 mol% of catalyst **C**, 100 mol % of DBU, 1.0 mL of THF at room termperature for 14h. [b] 20 mol% catalyst **D** was used.

The scope of the imines was also explored, using the α, β-unsaturated esters 2-**1a** as the model electrophile (**Table 2.3**). As outlined below, the yields and enantioselectivities had

little effect by all of the (hetero)aryl imines. If the methyl group of imine **2-2a** was changed into other alkyl substituent [ethyl (**2-3w**), *n*-butyl (**2-3x**) or homoallyl (**2-3y**)], the desired products could be obtained in moderate yield with excellent enantiomeric excess. The sulfonyl groups such as tosyl and methylsulfonyl substituent (**2-3z**) could be altered, while the Boc-group was inefficient in this reaction. The acetone or methyl isopropyl ketone-derived *N*-Ts imines remained unsuccessful due to the hydrolysis of the substrates.

Table 2.3 Substrate scope with variation of imine[a]

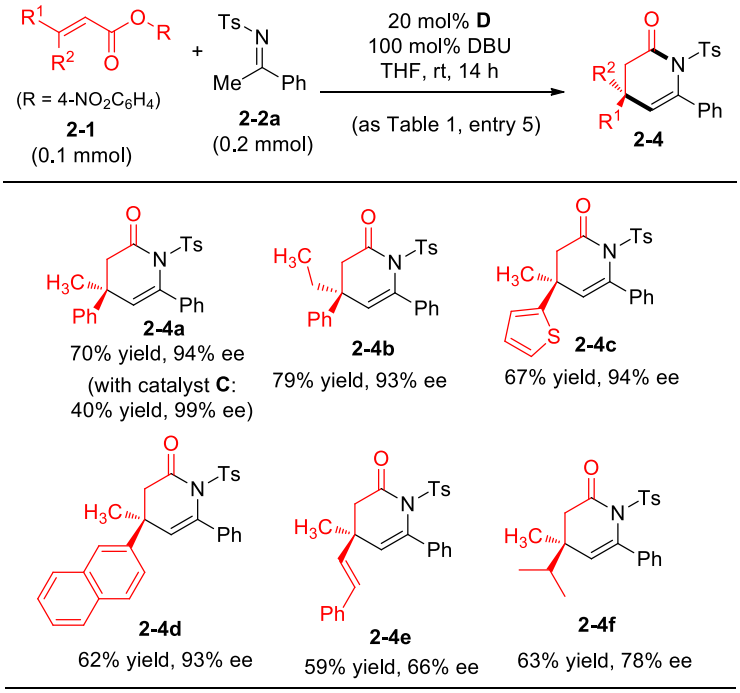


[a] All the reactions were carried out at room temperature using **2-1a** (0.10 mmol), **2-2** (0.15 mmol), 20 mol% of catalyst **C**, 100 mol % of DBU, 1.0 mL of THF at room temperature for 14h.

Next the unsaturated β, β'-disubstituted esters **2-1** were examined (**Table 2.4**). Interestingly, the use of trizolium catalyst **D** led to a better yield with a slightly decrease of enantioselectivity (70% yield, 94% ee) in the formation of **2-4a**, compared to the use of

catalyst **C** (40% yield 99% ee). So I expanded the scope of unsaturated β, β'-disubstituted esters with trizolium salt D as a precatalyst.

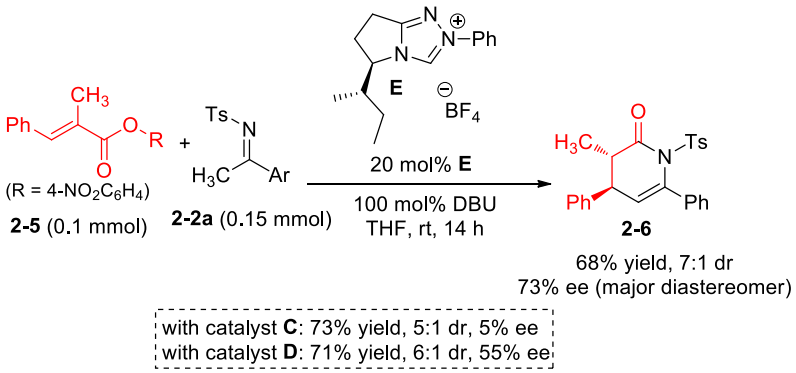
Table 2.4 Substrate scope with β, β'-disubstituted esters[a]



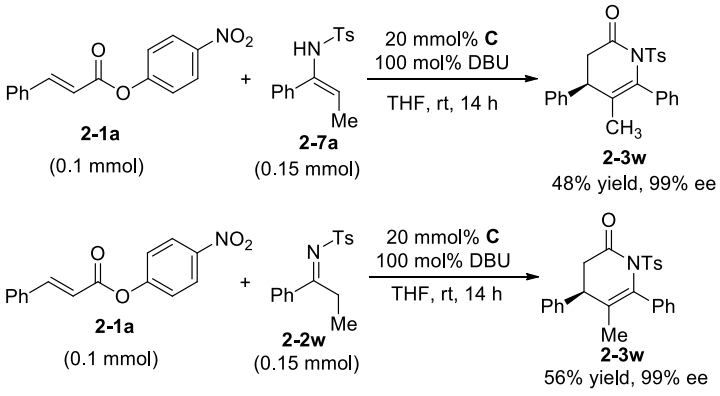
[a] All the reactions were carried out at room temperature using **2-1** (0.10 mmol), **2-2a** (0.20 mmol), 20 mol% of catalyst **D**, 100 mol % of DBU, 1.0 mL of THF at room temperature for 14h.

Next, I wanted to verify whether α, β-disubstituted unsaturated ester **2-5** could also undergo successfully under the standard condition. Unfortunately, using catalyst **C** in this reaction only gave poor enantiomeric excess (5%). Some improvement could be obtained by utilizing catalyst **D** with 71% yield, 6:1 dr, and 55% ee. After extensively screening of chiral NHC screening, it is demonstrated that catalyst **E** was the most effective in this α, β-disubstituted unsaturated ester activation with 68% yield, 7:1 dr, and 73% ee (**Scheme 2.6**). Notably, the type of catalyst **E** was ineffective in the reaction with β-mono substituted ester.

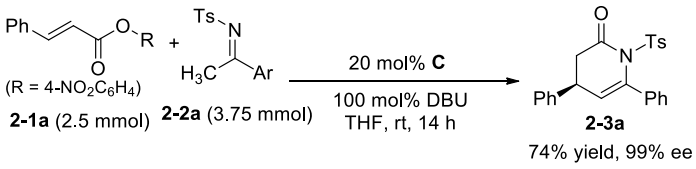
The imine/enamine isomerization was a facile process under the catalytic conditions. For example, the catalytic reaction using pre-formed enamine substrate (**2-7a**) or the corresponding imine precursor (**2-2w**) gave essentially the same results (**Scheme 2.7**). The method for the preparation of δ-lactams was amenable for gram-scale synthesis. Under the optimal condition, the product could be obtain in 74% yield and 99% ee (**Scheme 2.8**)



Scheme 2.6 Catalytic reaction with α, β-disubstituted unsaturated ester

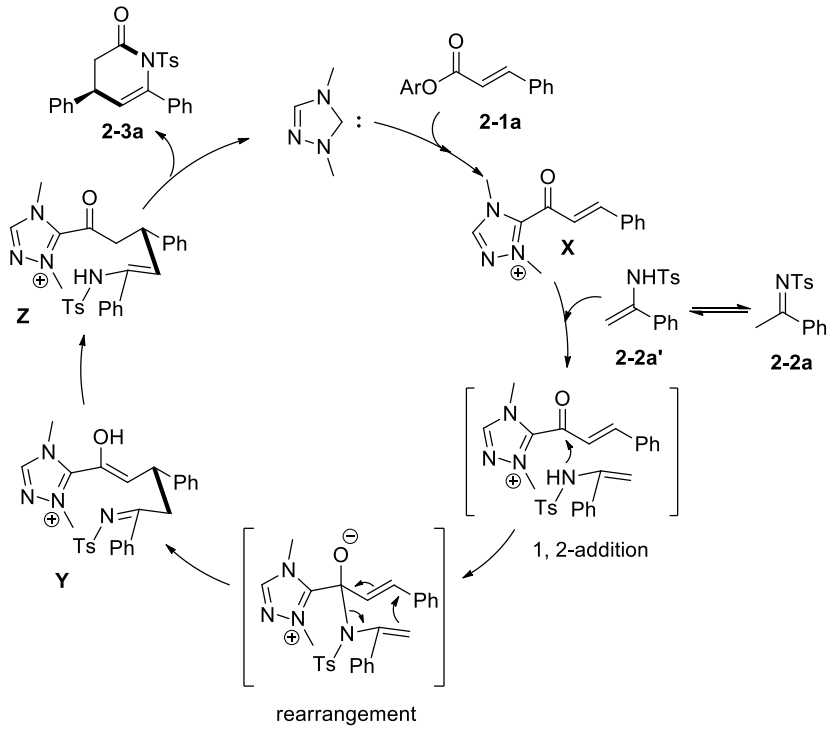


Scheme 2.7 Control reaction with enamine



Scheme 2.8 Gram-scale of catalytic reaction

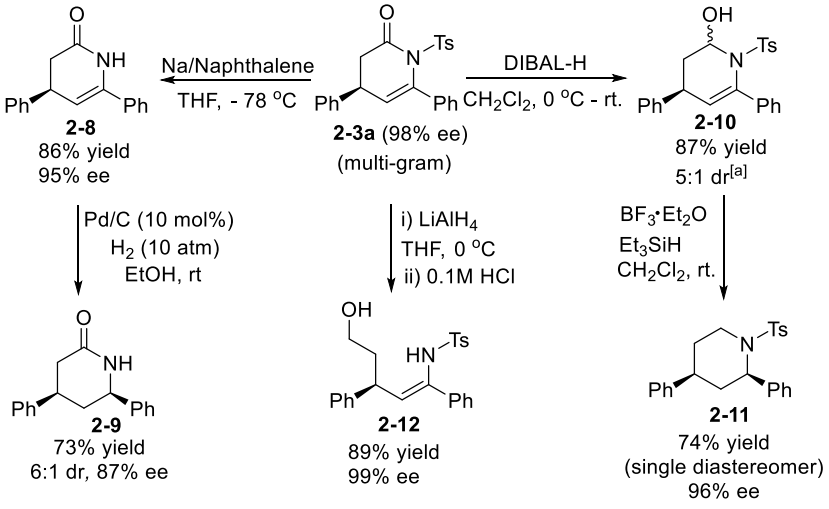
A proposed reaction pathway was summarized in **Scheme 2.9**. NHC nucleophilic attacked the α, β-unsaturated ester **2-1a** to give the key acyl azolium intermediate **X**. The imine substrate **2-2a** could isomerize to enamide **2-2a'** to behave as a nucleophile in the presence of a base. 1, 2-addition of enamide **2a'** to intermediate **X**, followed by a Claisen-type rearrangement, affords intermediate **Y,** which was proposed by Bode[14] as well. Finally, tautomerization and lactam formation gives the product **2-3a** and NHC regenerates.



Scheme 2.9 Proposed mechanism

The δ-lactams and their derivatives are basic building blocks in organic synthesis. Plenty of numbers of bioactive molecules and prescribed pharmaceuticals contain this moiety, such as local anaesthetic ropivacaine,[15] HIV protease inhibitor palinavir,[16] thrombin inhibitor argatroban,[17] antitumour antibiotic tetrazomine, [18] and paroxetine [19]. Derivatization of the optical pure compound (**2-3a**) can be implemented by using simple strategies (**Scheme 2.10**). Fox examples, the tosyl group of compound **3a** can be removed

under the conditions of Na/naphthalene, giving the product **8** with high yield and enantioselectivity. Further hydrogenation of compound **2-8** affords disubstituted δ-lactam **2-9** using Pd/C and H_2 . Reduction of **2-3a** could give cyclic *N,O*-acetal **2-10** and disubstituted piperidine **2-11**. Under the conditions of $LiAlH_4$, the lactam (**2-3a**) can be converted to amino alcohol **2-12** in 89% yield and 99% ee (**Scheme 10**).



Scheme 2.10 Synthetic transformations

2.3 Summary.

In summary, a new methodology for the LUMO activation of α, β-unsaturated esters catalyzed by N-heterocyclic carbene organocatalysts has been developed. This strategy is suitable for a broad range of substrates. The sterically bulky β, β'-disubstituented esters which ultimately forming a quaternary stereogenic center, can undergo smoothly as well with the developed method. I hope this efficient and flexible route for rapid construction of δ-lactams will play a greater role in organic synthesis.

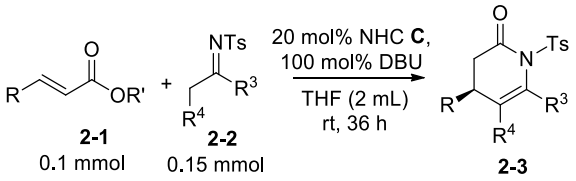
2.4 Experimental Section

2.4.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were

used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets) , tt (triplet of triplets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

2.4.2 General Procedure for the Catalytic Reactions

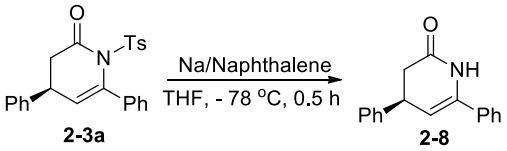


To a dry Schlenk tube equipped with a magnetic stir bar, was added ester **2-1** (0.1 mmol), imine **2-2** (0.15 mmol), triazolium salt **C** (0.02 mmol), and DBU (0.1 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled

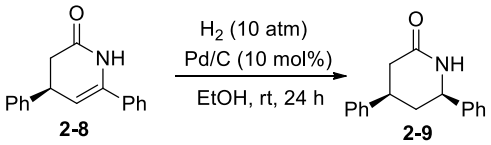
THF (2 mL) was added and the reaction mixture was then stirred at room temperature till ester was completely consumed (monitored by TLC). The mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel (15:1 hexanes/EtOAc) to afford the desired product **2-3**.

Note: Racemic samples for chiral phase HPLC analysis were prepared using **B** as the NHC pre-catalyst. Absolute configuration of the product was assigned based on x-ray structure of 2-**3c.**

2.4.3 Synthetic Transformations of Product 2-3a

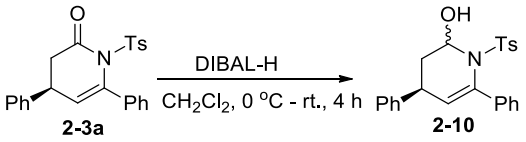


To a stirred solution of **2-3a** (80.7 mg, 0.2 mmol) in THF (5.0 mL) at -78 ^{o}C, under N_2, was added freshly prepared sodium (46.0 mg, 2.0 mmol) and Naphthalene (256.1 mg, 2.0 mmol) in dry THF (15 mL) solution. The reaction mixture was stirred for 30 minutes at -78 ℃ and then quenched with brine. The solution was allowed to reach room temperature and the solution was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via SiO_2 flash chromatography (*n*-Hexane/AcOEt 5:1) to afford **2-8** (43.0 mg, 86%) as a white solid in 95% ee.

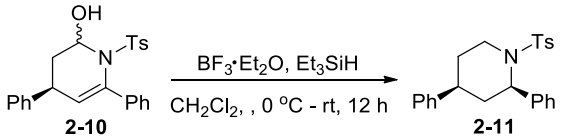


To a stirred solution of **2-8** (43.0 mg, 0.17 mmol) in AR grade ethanol (4 ml) was added Pd/C (10 mol%), H_2 (10 atm). After stirring for 24 h, the solvent was removed in vacuo and the product re-dissolved in ethyl acetate. Then, the solvent was filtered through

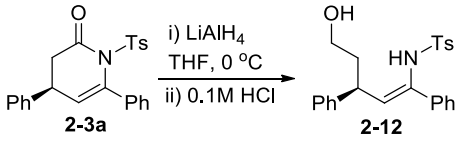
a plug of celite, evaporated, and purified by column chromatography to afford **2-9** (31.4 mg, 73%) as a inseparable *cis* (major) and *trans* (minor) mixture in 87% ee (major isomer) and 6:1 dr.



To a stirred solution of **2-3a** (20.0 mg, 0.05 mmol) in DCM (1.0 mL) at 0 °C, under N_2, was dropwise added DIBAL-H (1.0 M in THF, 2.0 ml, 0.2 mmol). The mixture was raised to room temperature and stirred for 4 h. Then the reaction was quenched with brine and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via SiO_2 flash chromatography (*n*-Hexane/AcOEt 10:1) to afford **2-10** (17.5 mg, 87%) as a white solid in 5:1 dr.

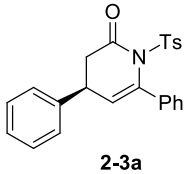


To a stirred solution of **2-10** (20.3 mg, 0.05 mmol) in DCM (2.0 mL) at 0 °C, under N_2, was added $BF_3 \cdot Et_2O$ (21 μL, 0.0165 mmol) and Et_3SiH (17.4 mg, 0.15 mmol). The mixture was raised to room temperature and stirred for 12 h. Then the reaction was quenched with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via SiO_2 flash chromatography (*n*-Hexane/AcOEt 20:1) to afford **2-11** (14.5 mg, 74%) as a while solid and single diastereoisomer in 96% ee.



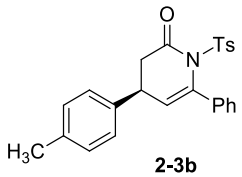
To a stirred solution of 2-**3a** (20.0 mg, 0.05 mmol) in THF (1.0 mL) at 0 ^{o}C, under N_2 atmosphere, was dropwise added $LiAlH_4$ (6.0 mg, 0.15 mmol) in dry THF (1 mL). The reaction was stirred at 0 ^{o}C for 1 h. Then the solution was quenched with an 0.1 M HCl solution. The aqueous phase was extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified via SiO_2 flash chromatography (*n*-Hexane/AcOEt 5:1) to afford **2-12** (18.0 mg, 89%) as a colorless oil.

2.4.4 Characterization of Products.



2-3a

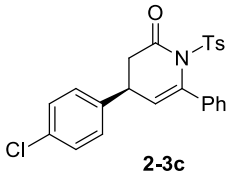
(*S*)-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3a): Colorless solid, yield: 29.5 mg (73%); $[\alpha]_D^{20}$ = -5.1 °(*c* 3.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 8.4 Hz, 2 H), 7.45-7.17 (m, 12 H), 5.98 (d, *J* = 4.4 Hz, 1 H), 3.92-3.82 (m, 1 H), 2.82 (d, *J* = 8.4 Hz, 2 H), 2.43 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 144.9, 141.0, 140.4, 137.2, 136.4, 129.12, 129.09, 129.0, 128.37, 128.35, 127.4, 127.1, 126.0, 123.2, 42.8, 37.1, 21.7; HRMS (ESI) calcd for $C_{24}H_{22}NO_3S$ $(M+H)^+$: 404.1320 Found: 404.1317; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 30.7 min, $t_{r\ min}$ = 24.3 min.



2-3b

(*S*)-6-phenyl-4-(p-tolyl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3b): Colorless solid, yield: 32.4 mg (78%); $[\alpha]_D^{20}$ = -1.1 °(*c* 3.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77

(d, *J* = 8.3 Hz, 2 H), 7.40 (dd, *J* = 6.6, 2.9 Hz, 2 H), 7.37-7.31 (m, 3 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 7.15-7.04 (m, 4 H), 5.97 (d, *J* = 4.4 Hz, 1 H), 3.82 (ddd, *J* = 9.1, 6.9, 4.5 Hz, 1 H), 2.84-2.74 (m, 2 H), 2.43 (s, 3 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 144.9, 140.8, 137.4, 137.2, 137.0, 136.4, 129.6, 129.1, 129.0, 128.3, 126.9, 125.9, 123.5, 42.9, 36.7, 21.7, 21.0; HRMS (ESI) calcd for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1475 Found: 418.1477; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 27.9min, $t_{r\ min}$ = 25.1 min.

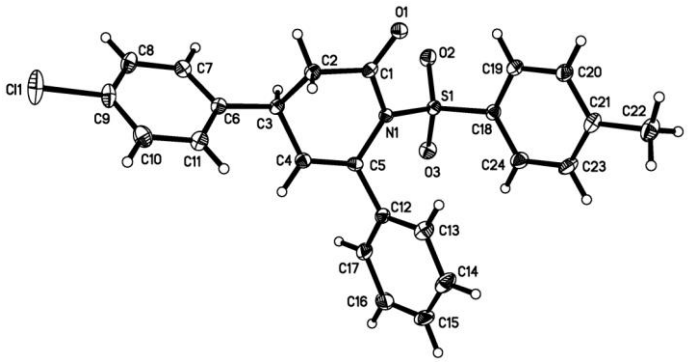


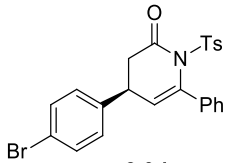
2-3c

(*S*)-4-(4-chlorophenyl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3c): Colorless solid, yield: 29.6 mg (68%); $[\alpha]_D^{20}$ = -13.2 ° (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2 H), 7.43-7.32 (m, 5 H), 7.29-7.19 (m, 4 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 5.96 (d, *J* = 4.8 Hz, 1 H), 3.87-3.78 (m, 1 H), 2.87-2.74 (m, 2 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 145.0, 141.4, 138.8, 137.1, 136.1, 133.2, 129.13, 129.07, 129.0, 128.5, 128.40, 128.38, 125.9, 122.1, 42.4, 36.2, 21.7; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SCl$ $(M+H)^+$: 438.0931 Found: 438.0934; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 36.0 min, $t_{r\ min}$ t_r(*S*) = 31.9 min.

Crystal Data and Structure Refinement for Enantiopure 2-3c

Relative configurations of the product **2-3** were assigned based on the crystal X-ray structures of **2-3c**. CCDC 932918 (**2-3c**, obtained as colorless needles *via* evaporization of a Hexane/EtOAc solution) contains the supplementary X-ray crystallographic data.

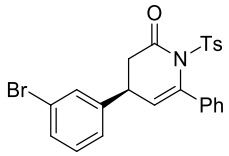




2-3d

(*S*)-4-(4-bromophenyl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3d):

Colorless solid, yield: 36.3 mg (75%); $[\alpha]_D^{20}$ = -13.0 ° (*c* 3.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.4 Hz, 2 H), 7.44-7.33 (m, 7 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 5.96 (d, *J* = 4.9 Hz, 1 H), 3.85-3.75 (m, 1 H), 2.85-2.76 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 145.1, 141.5, 139.4, 137.1, 136.1, 132.0, 129.14, 129.05, 128.8, 128.5, 128.4, 125.9, 122.0, 121.2, 42.3, 36.3, 21.7; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SBr$ $(M+H)^+$: 482.0426 Found: 482.0424; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 39.2 min, $t_{r\ min}$ = 36.7 min.

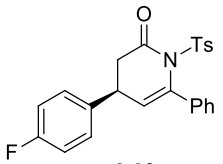


2-3e

(*S*)-4-(3-bromophenyl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3e):

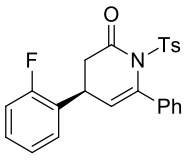
Colorless solid, yield: 27.1 mg (56%); $[\alpha]_D^{20}$ = -6.1 °(*c* 3.7, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2 H), 7.44-7.39 (m, 3 H), 7.38-7.34 (m, 4 H), 7.26-7.14 (m, 4 H), 5.94 (d, *J* = 4.6 Hz, 1 H), 3.83 (ddd, *J* = 8.6, 6.6, 4.8 Hz, 1 H), 2.85-2.75 (m, 2 H),

2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 145.1, 142.7, 141.5, 137.0, 136.2, 130.6, 130.2, 129.14, 129.11, 128.6, 128.4, 126.0, 125.8, 123.1, 121.8, 42.5, 36.7, 21.7; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SBr$ $(M+H)^+$: 482.0426 Found: 482.0427; 97% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 30.4 min, $t_{r\ min}$ = 24.7 min.



2-3f

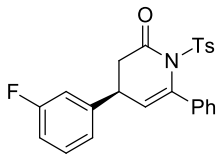
(*S*)-4-(4-fluorophenyl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3f): Oil, yield: 31.0 mg (74%); $[\alpha]_D^{20}$ = 3.8 °(*c* 3.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2 H), 7.42-7.32 (m, 5 H), 7.23 (d, *J* = 8.1 Hz, 2 H), 7.20-7.13 (m, 2 H), 6.99 (t, *J* = 8.6 Hz, 2 H), 5.95 (d, *J* = 4.7 Hz, 1 H), 3.89-3.78 (m, 1 H), 2.85-2.72 (m, 2 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 161.9 (d, *J* = 244 Hz), 145.0, 141.2, 137.1, 136.3, 136.1 (d, *J* = 3 Hz), 129.12, 129.05, 128.6 (d, *J* = 8 Hz), 128.5, 128.4, 126.0, 122.7, 115.8 (d, *J* = 21 Hz), 42.8, 36.3, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.0; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SF$ $(M+H)^+$: 422.1226 Found: 422.1226; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 36.8 min, $t_{r\ min}$ = 29.9 min.



2-3g

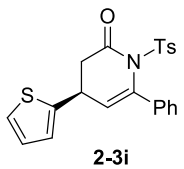
(*S*)-4-(2-fluorophenyl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3g): Colorless oil, yield: 35.1 mg (83%); $[\alpha]_D^{20}$ = -9.9 °(*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.41-7.32 (m, 5 H), 7.29-7.17 (m, 4 H), 7.11-7.01 (m, 2 H), 5.98-5.91 (d, *J* = 4.8 Hz, 1 H), 4.11 (dt, *J* = 9.9, 5.1 Hz, 1 H), 2.95-2.77 (m, 2 H),

2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 160.1 (d, *J* = 245 Hz), 145.0, 141.3, 137.1, 136.3, 129.2, 129.1, 129.0, 128.4, 128.3, 128.0 (d, *J* = 4 Hz), 126.9 (d, *J* = 14 Hz), 126.0, 124.5 (d, *J* = 4 Hz), 121.5, 115.8 (d, *J* = 22 Hz), 41.1, 31.0, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.9; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SF$ $(M+H)^+$: 422.1226 Found: 422.1223; 99% ee as determined by HPLC (AD-H, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.7ml/min), $t_{r\ maj}$ = 37.1 min, $t_{r\ min}$ = 56.5 min.



2-3h

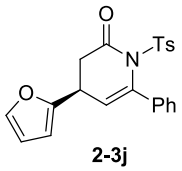
(*S*)-4-(3-fluorophenyl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3h): Colorless oil, yield: 29.0 mg (68%); $[\alpha]_D^{20}$ = -0.8 °(*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.4 Hz, 2 H), 7.38-7.27 (m, 5 H), 7.25-7.18 (m, 3 H), 7.04-6.85 (m, 3 H), 5.95 (d, *J* = 4.6 Hz, 1 H), 3.96-3.80 (m, 1 H), 2.88-2.74 (m, 2 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 163.0 (d, *J* = 245 Hz), 145.1, 142.9 (d, *J* = 7 Hz), 141.4, 137.0, 136.2, 130.5 (d, *J* = 9 Hz), 129.2, 129.1, 128.5, 128.4, 126.0, 122.8 (d, *J* = 3 Hz), 120.0, 114.20, 114.19 (d, *J* = 42 Hz), 42.5, 36.7, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.8; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SF$ $(M+H)^+$: 422.1226 Found: 422.1230; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 32.4 min, $t_{r\ min}$ = 24.5min.



2-3i

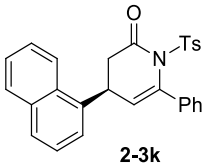
(*S*)-6-phenyl-4-(thiophen-2-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3i): Colorless solid, yield: 32.1 mg (78%); $[\alpha]_D^{20}$ = 4.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.70 (d, *J* = 8.4 Hz, 2 H), 7.44-7.39 (m, 2 H), 7.38-7.32 (m, 3 H), 7.23-7.18 (m, 3 H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1 H), 6.88-6.84 (m, 1 H), 6.02 (d, *J* = 5.0 Hz, 1 H), 4.13-4.05 (m, 1 H), 2.89 (qd, *J* = 16.5, 7.1 Hz, 2 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 144.9, 143.6, 141.2, 137.0, 136.2, 129.09, 129.05, 128.5, 128.4, 127.1, 126.0, 124.43, 124.36, 121.9, 43.0, 32.5, 21.6; HRMS (ESI) calcd for $C_{22}H_{20}NO_3S_2$ $(M+H)^+$: 410.0885 Found: 410.0882; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 104.9 min, $t_{r\ min}$ = 101.2 min.



2-3j

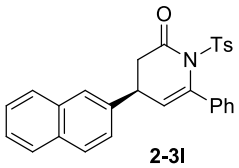
(*S*)-4-(furan-2-yl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3j): Colorless oil, yield: 29.5 mg (75%); $[\alpha]_D^{20}$ = -10.6 °(*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2 H), 7.45-7.29 (m, 6 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 6.28 (s, 1 H), 6.09 (d, *J* = 3.1 Hz, 1 H), 5.96 (d, *J* = 5.0 Hz, 1 H), 3.95-3.84 (m, 1 H), 2.85 (d, *J* = 7.4 Hz, 2 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 152.8, 145.0, 142.2, 141.4, 137.1, 136.3, 129.2, 129.1, 128.5, 128.3, 126.0, 119.3, 110.4, 105.9, 39.9, 31.1, 21.7; HRMS (ESI) calcd for $C_{22}H_{20}NO_4S$ $(M+H)^+$: 394.1113 Found: 394.1111; 99% ee as determined by HPLC (IA, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.7ml/min), $t_{r\ maj}$ = 27.2 min, $t_{r\ min}$ = 35.5 min.



2-3k

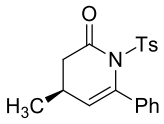
(*S*)-4-(naphthalen-1-yl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3k): Colorless solid, yield: 28.0 mg (62%); $[\alpha]_D^{20}$ = -30.3 °(*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.3 Hz, 1 H), 7.90 (d, *J* = 7.8 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 2

H), 7.78 (d, *J* = 8.1 Hz, 1 H), 7.62-7.51 (m, 2 H), 7.43-7.26 (m, 9 H), 6.03 (d, *J* = 4.6 Hz, 1 H), 4.59 (m, 1 H), 3.02 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 145.1, 141.0, 137.1, 136.4, 135.3, 134.1, 130.9, 129.22, 129.15, 128.4, 128.3, 128.1, 126.6, 126.0, 125.9, 125.4, 123.6, 123.3, 122.8, 41.5, 33.1, 21.7; HRMS (ESI) calcd for $C_{28}H_{24}NO_3S$ $(M+H)^+$: 454.1477 Found: 454.1473; 99% ee as determined by HPLC (IA, 98:2 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 103.0 min, $t_{r\ min}$ = 98.4 min.



2-3l

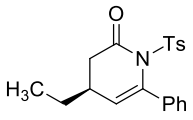
(*S*)-4-(naphthalen-2-yl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3l): Colorless solid, yield: 34.0 mg (75%); $[\alpha]_D^{20}$ = -3.4 °(*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.77 (m, 2 H), 7.76-7.70 (m, 1 H), 7.66 (d, *J* = 8.3 Hz, 2 H), 7.61 (s, 1 H), 7.54-7.42 (m, 4 H), 7.41-7.29 (m, 4 H), 7.01 (d, *J* = 8.2 Hz, 2 H), 6.13 (d, *J* = 5.0 Hz, 1 H), 4.04-3.96 (m, 1 H), 3.03-2.85 (m, 2 H), 2.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 144.8, 141.3, 137.7, 137.3, 136.1, 133.4, 132.5, 129.1, 128.9, 128.8, 128.4, 127.8, 127.6, 126.4, 126.0, 125.9, 125.4, 125.3, 122.5, 42.1, 36.7, 21.6; HRMS (ESI) calcd for $C_{28}H_{24}NO_3S$ $(M+H)^+$: 454.1477 Found: 454.1472; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH 0.7ml/min), $t_{r\ maj}$ = 41.5 min, $t_{r\ min}$ = 30.6 min.



2-3m

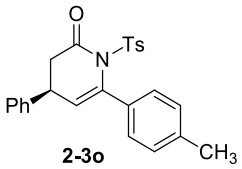
(*S*)-4-methyl-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3m): Colorless oil, yield: 13.6 mg (40%); $[\alpha]_D^{20}$ = 5.2 °(*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2 H), 7.40-7.32 (m, 5 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 5.71 (d, *J* = 4.0 Hz, 1 H), 2.73-2.61 (m, 1 H), 2.56 (dd, *J* = 16.2, 4.3 Hz, 1 H), 2.43 (s, 3 H), 2.32 (dd, *J* = 16.3, 10.9

Hz, 1 H), 1.11 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 144.9, 140.2, 137.5, 136.6, 129.11, 129.07, 128.3, 128.1, 125.8, 125.1, 43.0, 26.3, 21.7, 18.8; HRMS (ESI) calcd for $C_{19}H_{20}NO_3S$ $(M+H)^+$: 342.1164 Found: 342.1166; 96% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.5 ml/min), $t_{r\ maj}$ = 27.8 min, $t_{r\ min}$ = 25.5 min.



2-3n

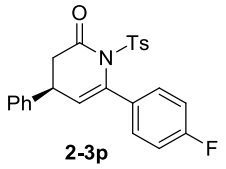
(*S*)-4-ethyl-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3n): Colorless oil, yield: 18.0 mg (51%); $[\alpha]_D^{20}$ = -1.1 °(*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2 H), 7.39-7.30 (m, 5 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 5.75 (d, *J* = 4.2 Hz, 1 H), 2.59 (dd, *J* = 15.8, 4.0 Hz, 1 H), 2.51-2.40 (m, 4 H), 2.34 (dd, *J* = 15.8, 10.6 Hz, 1 H), 1.52-1.37 (m, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 144.9, 140.5, 137.6, 136.5, 129.12, 129.06, 128.3, 128.1, 125.8, 123.8, 41.0, 33.0, 26.3, 21.7, 11.3; HRMS (ESI) calcd for $C_{20}H_{22}NO_3S$ $(M+H)^+$: 356.1320 Found: 356.1317; 91% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.5 ml/min), $t_{r\ maj}$ = 25.3 min, $t_{r\ min}$ = 23.3 min.



2-3o

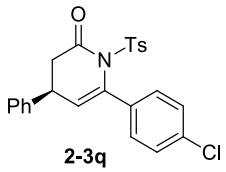
(*S*)-4-phenyl-6-(p-tolyl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3o): Colorless solid, yield: 28.0 mg (67%); $[\alpha]_D^{20}$ = -1.4 °(*c* 2.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2 H), 7.36-7.13 (m, 11 H), 5.95 (d, *J* = 4.4 Hz, 1 H), 3.90-3.80 (m, 1 H), 2.86-2.73 (m, 2 H), 2.43 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 144.9, 141.0, 140.5, 138.3, 136.5, 134.4, 129.14, 129.07, 129.0, 127.3, 127.1, 125.8, 122.4, 42.9, 37.1, 21.7, 21.3; HRMS (ESI) calcd for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1477

Found: 418.1475; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 48.8 min, $t_{r\ min}$ = 37.5 min.



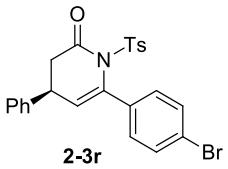
2-3p

(*S*)-6-(4-fluorophenyl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (3p): Colorless oil, yield: 37.0 mg (88%); $[\alpha]_D^{20}$ = -1.0 °(*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2 H), 7.41-7.18 (m, 9 H), 7.08-6.99 (m, 2 H), 5.94 (d, *J* = 4.4 Hz, 1 H), 3.88-3.82 (m, 1 H), 2.90-2.76 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 162.7 (d, *J* = 247 Hz), 145.1, 140.2 (d, *J* = 26 Hz), 136.3, 133.3, 129.2, 129.05, 129.02, 127.8 (d, *J* = 8 Hz), 127.4, 127.0, 123.0, 115.5, 115.3, 42.8, 37.1, 21.7 ; ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.0; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SF$ $(M+H)^+$: 422.1226 Found: 422.1228; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 39.4 min, $t_{r\ min}$ = 27.1 min.



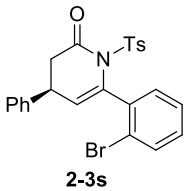
2-3q

(*S*)-6-(4-chlorophenyl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3q): Colorless solid, yield: 30.0 mg (68%); $[\alpha]_D^{20}$ = -7.0 °(*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2 H), 7.41-7.28 (m, 6 H), 7.41-7.24 (m, 3 H), 7.23-7.15 (m, 2 H), 5.97 (d, *J* = 4.4 Hz, 1 H), 3.87-3.82 (m, 1 H), 2.87-2.78 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 145.2, 140.2, 140.0, 136.2, 135.8, 134.2, 129.2, 129.1, 129.0, 128.6, 127.4, 127.2, 127.0, 123.5, 42.6, 37.1, 21.7; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SCl$ $(M+H)^+$: 438.0931 Found: 438.0934; 98% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 57.8 min, $t_{r\ min}$ = 33.5 min.



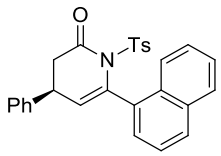
2-3r

(*S*)-6-(4-bromophenyl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3r): Colorless solid, yield: 38.3 mg (79%); $[\alpha]_D^{20}$ = -8.0 °(*c* 3.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.48 (d, *J* = 8.5 Hz, 2 H), 7.34-7.23 (m, 7 H), 7.19 (d, *J* = 6.8 Hz, 2 H), 5.98 (d, *J* = 4.4 Hz, 1 H), 3.88-3.78 (m, 1 H), 2.81 (d, *J* = 8.6 Hz, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 171.4, 145.2, 140.2, 140.1, 136.3, 136.2, 131.5, 129.2, 129.1, 129.0, 127.5, 127.4, 127.0, 123.5, 122.3, 42.6, 37.1, 21.7; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SBr$ $(M+H)^+$: 482.0426 Found: 482.0427; 99% ee as determined by HPLC (OD, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 33.0 min, $t_{r\ min}$ = 26.6 min.



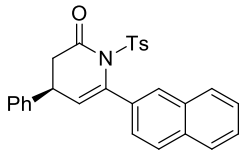
2-3s

(*S*)-6-(2-bromophenyl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3s): Colorless solid, yield: 42.0 mg (87%); $[\alpha]_D^{20}$ = -28.3 °(*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.46 (m, 3 H), 7.43-7.30 (m, 4 H), 7.30-7.20 (m, 4 H), 7.15 (d, *J* = 8.2 Hz, 2 H), 5.86 (d, *J* = 3.9 Hz, 1 H), 4.08-3.97 (m, 1 H), 3.00-2.86 (m, 2 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.2, 144.8, 140.3, 138.8, 136.4, 135.7, 132.6, 132.2, 129.9, 129.0, 128.9, 128.7, 127.4, 127.3, 127.2, 123.2, 77.2, 43.2, 37.2, 21.7; HRMS (ESI) calcd for $C_{24}H_{21}NO_3SBr$ $(M+H)^+$: 482.0426 Found: 482.0427; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 33.4min, $t_{r\ min}$ = 24.6 min.



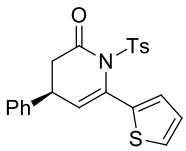
2-3t

(*S*)-6-(naphthalen-1-yl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3t): Colorless solid, yield: 30.0 mg (66%); $[\alpha]_D^{20}$ = 11.7 °(*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88-7.79 (m, 2 H), 7.65-6.87 (m, 14 H), 6.04 (d, J = 4.2 Hz, 1 H), 4.16-4.07 (m, 1 H), 3.11-2.89 (m, 2 H), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 144.4, 140.4, 138.6, 135.5, 133.3, 131.1, 129.0, 128.9, 128.7, 128.5, 128.3, 127.4, 127.2, 126.4, 125.7, 125.0, 43.6, 37.5, 21.5; HRMS (ESI) calcd for $C_{22}H_{20}NO_4S$ $(M+H)^+$: 454.1477 Found: 454.1481; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 24.7 min, $t_{r\ min}$ = 23.0 min.



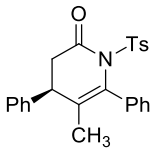
2-3u

(*S*)-6-(naphthalen-2-yl)-4-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3u): Colorless solid, yield: 30.0 mg (66%); $[\alpha]_D^{20}$ = 10.6 °(*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2 H), 7.81-7.73 (m, 3 H), 7.72-7.70 (m, 1 H), 7.54 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.51-7.45 (m, 2 H), 7.38-7.25 (m, 2 H), 7.24-7.17 (m, 5 H), 6.10 (d, *J* = 4.4 Hz, 1 H), 3.97-3.92 (m, 1 H), 2.91-2.85 (m, 2 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 145.0, 141.0, 140.4, 136.5, 134.5, 133.2, 132.9, 129.2, 129.1, 129.0, 128.2, 128.1, 127.8, 127.4, 127.1, 126.5, 126.3, 124.8, 124.1, 123.8, 43.0, 37.3, 21.7; HRMS (ESI) calcd for $C_{28}H_{24}NO_3S$ $(M+H)^+$: 454.1477 Found: 454.1477; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 39.4 min, $t_{r\ min}$ = 29.9 min.



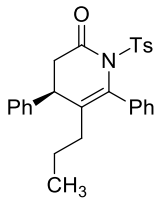
2-3v

(*S*)-4-phenyl-6-(thiophen-2-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3v): Colorless solid, yield: 37.9 mg (93%); $[\alpha]_D^{20}$ = 1.0 °(*c* 3.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2 H), 7.36-7.17 (m, 8 H), 7.09 (dd, *J* = 3.6, 0.9 Hz, 1 H), 6.99 (dd, *J* = 5.0, 3.7 Hz, 1 H), 6.09 (d, *J* = 4.4 Hz, 1 H), 3.88-3.78 (m, 1 H), 2.89-2.74 (m, 2 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 145.0, 140.1, 139.1, 136.5, 134.6, 129.2, 129.1, 129.0, 127.4, 127.1, 125.5, 124.9, 123.4, 42.8, 37.2, 21.7; HRMS (ESI) calcd for $C_{22}H_{20}NO_3S_2$ $(M+H)^+$: 410.0885 Found: 410.0885; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\,maj}$ = 46.3 min, $t_{r\,min}$ = 37.0 min.



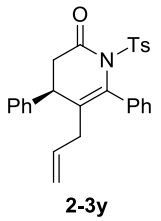
2-3w

(*R*)-5-methyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3w): Colorless solid, yield: 23.2 mg (56%); $[\alpha]_D^{20}$ = -13.6 °(*c* 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 10 H), 7.25-7.21 (m, 2 H), 7.05 (d, *J* = 8.1 Hz, 2 H), 3.67 (t, *J* = 5.1 Hz, 1 H), 3.06-2.93 (m, 2 H), 2.35 (s, 3 H), 1.81 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 144.2, 138.4, 136.5, 135.1, 134.0, 129.9, 129.0, 128.74, 128.72, 127.8, 127.7, 127.5, 127.4, 42.7, 41.2, 21.6, 18.8; HRMS (ESI) calcd for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1477 Found: 418.1479; 99% ee as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\,maj}$ = 44.0 min, $t_{r\,min}$ = 40.2 min.



2-3x

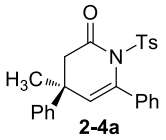
(*R*)-4,6-diphenyl-5-propyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3x): Colorless oil, yield: 20 mg (45%); $[\alpha]_D^{20}$ = -11.1 °(*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.17 (m, 12 H), 7.02 (d, *J* = 8.2 Hz, 2 H), 3.67 (t, *J* = 4.3 Hz, 1 H), 3.08-2.90 (m, 2 H), 2.34 (s, 3 H), 2.25-2.17 (m, 1 H), 2.14-2.07 (m, 1 H), 1.46-1.23 (m, 2 H), 0.72 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 144.1, 138.6, 136.5, 135.0, 134.8, 131.2, 130.0, 128.9, 128.68, 128.65, 127.8, 127.7, 127.6, 127.3, 42.4, 40.6, 34.4, 21.6, 21.5, 14.1; HRMS (ESI) calcd for $C_{27}H_{28}NO_3S$ $(M+H)^+$: 446.1790 Found: 446.1786; 99% ee as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH 0.5ml/min), $t_{r\,maj}$ = 39.5 min, $t_{r\,min}$ = 35.3 min.



2-3y

(*R*)-5-allyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-3y): Colorless solid, yield: 36.0 mg (81%); $[\alpha]_D^{20}$ = -49.2 °(*c* 1.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.14 (m, 12 H), 7.03 (d, *J* = 8.2 Hz, 2 H), 5.59-5.49 (m, 1 H), 5.02-4.88 (m, 2 H), 3.72 (t, *J* = 4.6 Hz, 1 H), 3.09-3.04 (m, 1 H), 3.03-2.91 (m, 2 H), 2.82-2.76 (m, 1 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 144.2, 138.4, 136.4, 135.6, 134.5, 134.2, 130.0, 129.0, 128.9, 128.73, 128.65, 128.0, 127.8, 127.6, 127.3, 117.3, 42.1, 39.8, 36.4, 21.6; HRMS (ESI) calcd for $C_{27}H_{26}NO_3S$ $(M+H)^+$: 444.1633 Found: 444.1632; 99% ee as

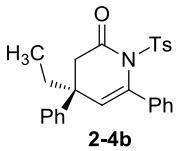
determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 21.3 min, $t_{r\ min}$ = 25.4 min.



2-4a

(*S*)-4-methyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-4a): with catalyst **C**: Colorless solid, yield: 17.0 mg (40%); $[\alpha]_D^{20}$ = 22.6 °(*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.50 (m, 2 H), 7.44-7.32 (m, 5 H), 7.30-7.20 (m, 5 H), 6.98 (d, *J* = 8.1 Hz, 2 H), 6.03 (d, *J* = 0.7 Hz, 1 H), 3.05 (dd, *J* = 16.3, 0.9 Hz, 1 H), 2.72 (d, *J* = 16.3 Hz, 1 H), 2.34 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 145.4, 144.2, 140.2, 137.6, 135.6, 129.0, 128.9, 128.8, 128.41, 128.35, 127.5, 126.9, 125.8, 125.6, 47.0, 38.7, 30.3, 21.6; HRMS (ESI) calcd for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1477 Found: 418.1473; 99% ee as determined by HPLC (IA, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.7ml/min), $t_{r\ maj}$ = 24.9 min, $t_{r\ min}$ = 35.5 min.

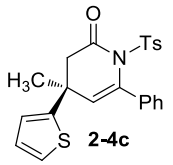
With catalyst **D**: Colorless solid, yield: 29.8 mg (70%); 94% ee as determined by HPLC (IA, 90:5:5 hexanes/*i*-PrOH/MeOH, 0.7ml/min), $t_{r\ maj}$ = 24.7 min, $t_{r\ min}$ = 35.4 min.



2-4b

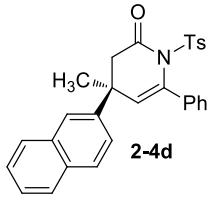
(*S*)-4-ethyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-4b): Colorless solid, yield: 22.0 mg (51%); $[\alpha]_D^{20}$ = 20.5 °(*c* 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.0 Hz, 2 H), 7.45-7.33 (m, 3 H), 7.29 (d, *J* = 8.3 Hz, 2 H), 7.27-7.16 (m, 5 H), 6.94 (d, *J* = 8.1 Hz, 2 H), 6.05 (s, 1 H), 3.02 (d, *J* = 16.3 Hz, 1 H), 2.71 (d, *J* = 16.2 Hz, 1 H), 2.32 (s, 3 H), 1.72-1.57 (m, 2 H), 0.69 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 144.0, 143.3, 140.5, 137.8, 135.6, 128.8, 128.70, 128.65, 128.4, 128.3,

126.8, 126.5, 126.1, 125.8, 44.7, 42.5, 35.5, 21.5, 8.4; HRMS (ESI) calcd for $C_{26}H_{26}NO_3S$ $(M+H)^+$: 432.1633 Found: 432.1628; 93% ee as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 39.9 min, $t_{r\ min}$ = 33.2 min.



2-4c

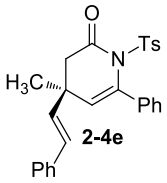
(*S*)-4-methyl-6-phenyl-4-(thiophen-2-yl)-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-4c): Colorless solid, yield: 30.0 mg (71%); $[\alpha]_D^{20}$ = 14.3 °(*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.44 (m, 4 H), 7.44-7.31 (m, 3 H), 7.18 (d, *J* = 5.0 Hz, 1 H), 7.11 (d, *J* = 8.2 Hz, 2 H), 6.88-6.82 (m, 1 H), 6.82-6.76 (m, 1 H), 5.94 (s, 1 H), 2.98 (d, *J* = 16.4 Hz, 1 H), 2.77 (d, *J* = 16.3 Hz, 1 H), 2.38 (s, 3 H), 1.51 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 150.1, 144.5, 140.6, 137.4, 135.8, 129.2, 128.8, 128.5, 128.4, 127.0, 126.2, 126.0, 124.1, 123.2, 48.7, 37.1, 30.4, 21.6; HRMS (ESI) calcd for $C_{23}H_{22}NO_3S_2$ $(M+H)^+$: 424.1041 Found: 424.1038; 94% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 30.0 min, $t_{r\ min}$ = 36.5 min.



2-4d

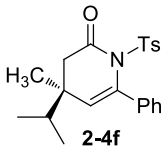
(*S*)-4-methyl-4-(naphthalen-2-yl)-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-4d): Colorless solid, yield: 29.0 mg (62%); $[\alpha]_D^{20}$ = 43.0 °(*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 1 H), 7.77 (d, *J* = 8.6 Hz, 1 H), 7.64 (d, *J* = 7.9 Hz, 2 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.54-7.33 (m, 7 H), 7.09 (d, *J* = 8.0 Hz, 2 H), 6.27 (d, *J* = 8.1 Hz, 2 H), 6.16 (s, 1 H), 3.19 (d, *J* = 16.3 Hz, 1 H), 2.79 (d, *J* = 16.3 Hz, 1 H), 1.99 (s, 3 H), 1.45 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.0, 143.0, 140.6, 137.8,

135.0, 133.4, 132.4, 128.7, 128.5, 128.4, 128.08, 128.06, 127.4, 127.2, 126.3, 126.0, 125.6, 124.6, 123.5, 46.3, 38.9, 30.9, 21.3; HRMS (ESI) calcd for $C_{29}H_{26}NO_3S$ $(M+H)^+$: 468.1633 Found: 468.1626; 93% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 34.9 min, $t_{r\ min}$ = 22.6 min.



2-4e

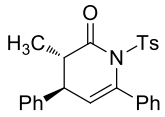
(*R*,*E*)-4-methyl-6-phenyl-4-styryl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-4e): Colorless oil, yield: 26.0 mg (59%); $[\alpha]_D^{20}$ = -47.0 °(*c* 3.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2 H), 7.50 (d, *J* = 6.9 Hz, 2 H), 7.44-7.17 (m, 8 H), 6.84 (d, *J* = 8.1 Hz, 2 H), 6.37 (d, *J* = 16.1 Hz, 1 H), 6.05 (d, *J* = 16.1 Hz, 1 H), 5.71 (s, 1 H), 2.73-2.54 (m, 2 H), 2.21 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 144.6, 140.4, 137.8, 136.5, 135.8, 132.9, 129.6, 128.9, 128.7, 128.5, 128.4, 128.3, 127.6, 126.5, 125.8, 125.3, 46.8, 37.0, 27.2, 21.5; HRMS (ESI) calcd for $C_{22}H_{20}NO_4S$ $(M+H)^+$: 444.1633 Found: 444.1629; 66% ee as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 30.4 min, $t_{r\ min}$ = 22.0 min.



2-4f

(*S*)-4-isopropyl-4-methyl-6-phenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-4f): Oil, yield: 24.0 mg (63%); $[\alpha]_D^{20}$ = 0.7 °(*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2 H), 7.37-7.30 (m, 5 H), 7.30-7.23 (m, 2 H), 5.64 (s, 1 H), 2.54 (d, *J* = 16.1 Hz, 1 H), 2.43 (s, 3 H), 2.34 (d, *J* = 16.1 Hz, 1 H), 1.67-1.58 (m, 1 H), 0.98 (s, 3 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 145.0, 138.8, 138.0, 135.9, 129.6, 128.9, 128.4, 128.2, 128.0, 125.9, 45.4, 37.4, 34.4, 21.7,

19.8, 17.9, 16.7; HRMS (ESI) calcd for $C_{22}H_{26}NO_3S$ $(M+H)^+$: 384.1633 Found: 384.1633; 77% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 24.8 min, $t_{r\ min}$ = 21.7 min.

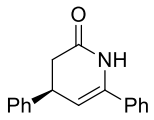


2-6

(3*S*,4*R*)-3-methyl-4,6-diphenyl-1-tosyl-3,4-dihydropyridin-2(1H)-one (2-6): With catalyst **E**: Colorless solid, dr = 7:1, yield: 24.0 mg (58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.77 (m, 2 H), 7.40-7.23 (m, 10 H), 7.19-7.15 (m, 2 H), 5.91 (d, *J* = 3.8 Hz, 1 H), 3.45 (dd, *J* = 12.0, 3.7 Hz, 1 H), 2.83-2.64 (m, 1 H), 2.45 (s, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 144.9, 140.6, 139.6, 137.2, 136.6, 129.1, 128.9, 128.4, 128.3, 127.8, 127.4, 125.9, 124.4, 46.4, 44.6, 21.7, 13.6; HRMS (ESI) calcd for $C_{25}H_{24}NO_3S$ $(M+H)^+$: 418.1477 Found: 418.1476; 73% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 16.8 min, $t_{r\ min}$ = 15.9 min.

With catalyst **C**: dr = 5:1, yield: 25.0 mg (61%); -5% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 17.5 min, $t_{r\ min}$ = 18.5 min.

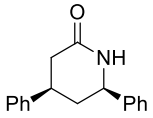
With catalyst **D**: dr = 6:1, yield: 25.0 mg (61%); 55% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 18.4 min, $t_{r\ min}$ = 17.5 min.



2-8

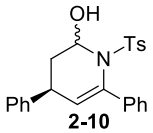
(*S*)-4,6-diphenyl-3,4-dihydropyridin-2(1H)-one (**2-8**): White solid, yield: 43.0 mg (86%); $[\alpha]_D^{20}$ = -25.3 °(*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.27 (m, 10 H), 5.55 (dd, *J* = 3.9, 1.3 Hz, 1 H), 4.01-3.90 (m, 1 H), 2.88 (dd, *J* = 16.2, 6.9 Hz, 1 H), 2.72 (dd, *J* = 16.2, 10.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 143.0, 137.0, 134.8,

129.1, 129.0, 128.9, 127.13, 127.05, 125.0, 106.8, 38.9, 38.7; HRMS (ESI) calcd for $C_{17}H_{16}NO(M+H)^+$: 250.1232 Found: 250.1232; 95% ee as determined by HPLC (IC, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 35.5 min, $t_{r\ min}$ = 51.2 min.



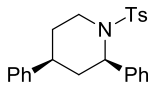
2-9

(4*R*, 6*R*)-4,6-diphenylpiperidin-2-one (**2-9**): White solid, 6:1 dr, yield: 31.4 mg (73%); $[\alpha]_D^{20}$ = 6.3 °(*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 7 H), 7.26-7.20 (m, 3 H), 6.05 (s, 1H), 4.65 (dd, *J* = 11.4, 4.2 Hz, 1 H), 3.23 (tdd, *J* = 12.6, 4.8, 2.6 Hz, 1 H), 2.77 (ddd, *J* = 17.5, 4.9, 2.2 Hz, 1 H), 2.55 (dd, *J* = 17.5, 12.7 Hz, 1 H), 2.32-2.25 (m, 1 H), 1.90-1.83 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 143.1, 142.0, 129.0, 128.8, 128.2, 126.9, 126.4, 126.0, 58.1, 40.1, 39.1, 38.9; HRMS (ESI) calcd for $C_{17}H_{18}NO$ $(M+H)^+$: 252.1388 Found: 252.1389; 87% ee as determined by HPLC (ID, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 52.5 min, $t_{r\ min}$ = 91.6 min.



2-10

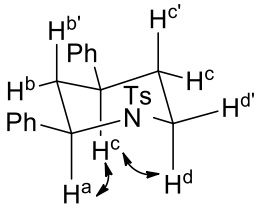
(4*S*)-4,6-diphenyl-1-tosyl-1,2,3,4-tetrahydropyridin-2-ol (**2-10**): White solid, 5:1 dr, yield: 17.5 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2 H), 7.47-7.41 (m, 2 H), 7.33-7.30 (m, 5 H), 7.21-7.17 (m, 3 H), 6.82-6.76 (m, 2 H), 5.97-5.92 (m, 1 H), 5.46 (d, *J* = 3.2 Hz, 1 H), 3.74-3.65 (m, 1 H), 3.16 (s, 1 H), 2.44 (s, 3 H), 2.11-2.05 (m, 1 H), 1.27-1.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 143.1, 139.6, 135.7, 135.1, 129.7, 128.5, 127.9, 127.8, 127.7, 127.5, 127.2, 126.7, 122.4, 79.3, 36.4, 34.5, 21.6; HRMS (ESI) calcd for $C_{24}H_{24}NO_3S$ $(M+H)^+$: 406.1477 Found: 406.1476.

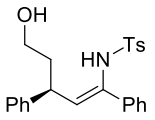


2-11

(2*R*,4*S*)-2,4-diphenyl-1-tosylpiperidine (**2-11**): White solid, yield: 14.5 mg (74%); $[\alpha]_D^{20}$ = 179.2 °(*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.28-7.16 (m, 10 H), 7.11 (d, *J* = 7.1 Hz, 2 H), 4.17 (dd, *J* = 11.0, 4.6 Hz, 1 H), 4.07 (dt, *J* = 12.8, 5.2 Hz, 1 H), 3.17 (ddd, *J* = 13.2, 9.0, 4.4 Hz, 1 H), 2.56 (tt, *J* = 11.8, 4.4 Hz, 1 H), 2.42 (s, 3 H), 2.15-1.79 (m, 4 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 143.1, 141.6, 135.7, 129.2, 128.6, 128.0, 127.8, 127.4, 127.3, 126.6, 126.5, 62.2, 46.2, 41.9, 40.5, 31.9, 21.5; HRMS (ESI) calcd for $C_{24}H_{26}NO_2S$ $(M+H)^+$: 392.1684 Found: 392.1686; 96% ee as determined by HPLC (OD-H, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\,maj}$ = 21.8 min, $t_{r\,min}$ = 20.5 min.

The absolute configuration of the product **2-11** is assigned by its NOESY spectrum. The cross peak of H^a [4.17 (dd, *J* = 11.0, 4.6 Hz, 1 H)] and H^c [2.56 (tt, *J* = 11.8, 4.4 Hz, 1 H)], H^d [3.17 (ddd, *J* = 13.2, 9.0, 4.4 Hz, 1 H)] and H^c [2.56 (tt, *J* = 11.8, 4.4 Hz, 1 H)] indicates that H^a, H^c and H^d of **2-11** is on the same side (*cis*). The inactive chiral center of **2-3a** do not changed in the chemical transformation, so the absolute configuration of **2-11** is assigned as (2*R*,4*S*). This could be further confirmed by the coupling constants. The coupling constant observed for $J_{Ha\text{-}Hb'}$, $J_{Hc\text{-}Hc'}$, $J_{Hc\text{-}Hb'}$ and $J_{Hd\text{-}Hc'}$ were all greater than 10.0 Hz, which showed that H^a, H^c, H^d are all axial protons.





2-12

(*S*,*Z*)-*N*-(5-hydroxy-1,3-diphenylpent-1-en-1-yl)-4-methylbenzenesulfonamide (**2-12**): oil, yield: 18.0 mg (89%); $[\alpha]_D^{20}$ = -5.0 °(*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, CDCl3) δ 8.21 (br, 1H), 7.62-7.56 (m, 2 H), 7.49-7.45 (m, 2 H), 7.30-7.14 (m, 8 H), 6.77 (dd, *J* = 7.6, 1.6 Hz, 2 H), 5.46 (d, *J* = 10.3 Hz, 1 H), 3.92-3.74 (m, 1 H), 3.63-3.47 (m, 2 H), 2.37 (s, 3 H), 2.13-1.92 (m, 1 H), 1.74-1.62 (m, 2 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 143.3, 137.8, 137.0, 136.2, 129.5, 128.4, 128.3, 127.9, 127.5, 127.2, 127.1, 126.42, 126.40, 59.9, 39.1, 37.7, 21.5; HRMS (ESI) calcd for $C_{24}H_{26}NO_3S$ $(M+H)^+$: 408.1633 Found: 408.1629; 99% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\,maj}$ = 28.2 min, $t_{r\,min}$ = 26.3 min.

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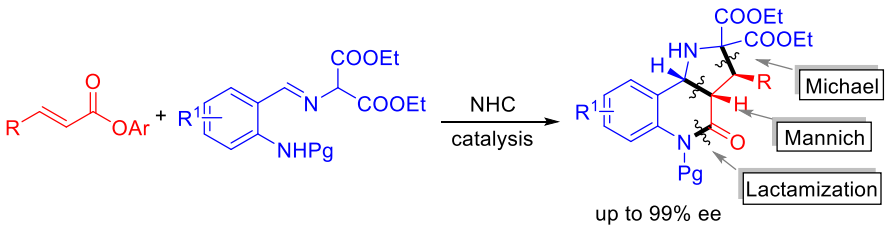
Chapter 3

NHC Catalyzed Cascade Reaction for Synthesis of Functionalized Pyrrolo[3,2-c]quinolines



3.1 Introduction

3.1.1 Synthesis of Pyrroloquinolines Scaffolds

The pyrroloquinolines moiety, a unique ring system, is found in several natural products with good bioactivities. For example, the martineline and martinellic acid (**Fig 3.1**), first isolated from tropical plant *Martinella iquitosensis* (Bignoniaceae), exhibited strong potency in antagonism of bradykinin receptor and other related activities such as antibiotic, cytotoxic as well as lytic activity.[1] Due to its fascinating Pyrrolo[3,2-*c*]quinolines structure unit and attractive bioactivity, the synthesis of this type of molecules has received considerable attention and many elegant approaches have been developed, involved intramolecular [3+2] azomethine ylide-alkene cycloaddition,[2] silicon-tether ring-closing metathesis and allylic amination,[3] tandem Mukaiyama-Mannich reaction/aminal cyclization,[4] radical addition cyclization elimination reaction,[5] and diphenylprolinol triethylsilyl ether catalyzed tandem Michael-aldol reaction.[6]

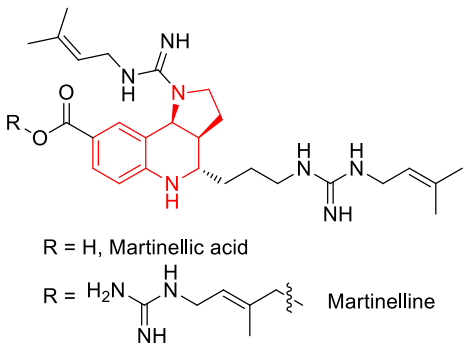
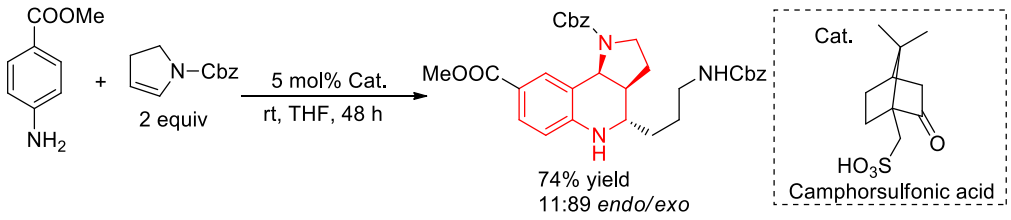


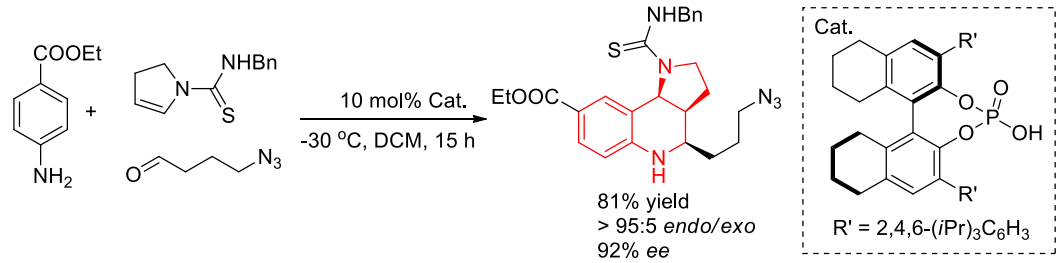
Fig 3.1 Chemical structure of martinellic acid and martinelline

The total synthesis of racemic martinelline and martinellic acid were realized by Batey and coworkers in 2002, with the pyrroloquinoline core synthesized *via* a hetero Diels-Alder multicomponent coupling reaction (**Scheme 3.1**).[7] The camphorsulfonic acid could catalyzed this reaction to give the corresponding *exo* product in 74% yield, while the Lewis acid such as $Dy(OTf)_3$ promoted the reaction with undesired *endo* product.



Scheme 3.1 Camphorsulfonic acid catalyzed multicomponent coupling reaction

In 2012, Masson and Zhu reported chiral phosphoric acid-catalyzed enantioselective Povarov reaction with three components for the construction of Pyrrolo[3,2-*c*]quinolines (**Scheme 3.2**).[8] In this multicomponent reaction, enethioureas was selected as dienophile, and a wide range of aldehydes and anilines with different electronic properties were well tolerated.

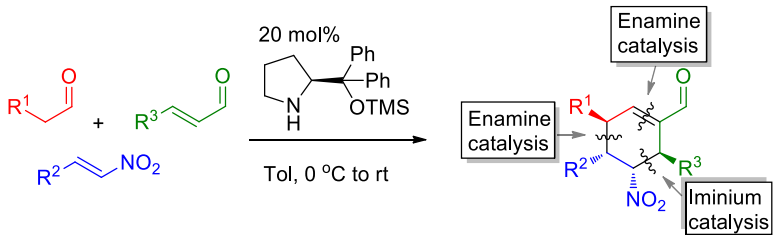


Scheme 3.2 Povarov reaction reported by Masson and Zhu

3.1.2 Cascade Reaction Enabled by Organic Catalysts

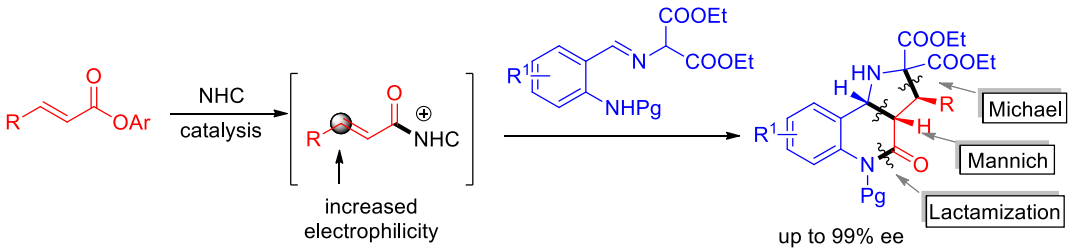
Rapid and efficient synthetic methods of complex molecules with various chiral centers are highly desirable no matter in the academic or industrial laboratories.[9] Notably, the development of catalytic asymmetric cascade reaction provoked increasing attention in recent years, due to its excellent atom economy, and reduction of chemical waste generated from the process as well as requirement of manipulation time. In a cascade reaction, the isolation of intermediates is not needed, especially beneficial when some intermediates are unstable.[10] In 2006, Enders and coworkers reported an unprecedented triple cascade organocatalytic reaction (**Scheme 3.3**), which controlled four stereocenters

in one pot.[11] The reaction delivered a tetra-substituted cyclohexene carbaldehyde with high diastereo- and complete enantiomeric manner from simple starting materials.



Scheme 3.3 Enders' three components cascade reaction

In recent years, the cascade reaction promoted by N-heterocyclic carbenes (NHC) has emerged as one of the most attractive topics in organcatalysis chemistry.[10f] Many of the NHC-catalyzed cascade reactions were triggered by active homoenolate (or enolate)[12] or α, β-unsaturated acyl azolium intermediates.[13] Reactions initiated by the interaction between umpolung carbonyls and electrophiles to form complex molecules were also documented.[14] Our group is interested in the construction of multicyclic complex molecules in facile and readily access from simple aldehydes, esters and anhydrides.[12g, 12i, 13e, 15] In this chapter, a new method for highly enantioselective synthesis of Pyrrolo[3,2-c]quinolines via NHC-catalyzed cascade sequence was introduced (**Scheme 3.4**).



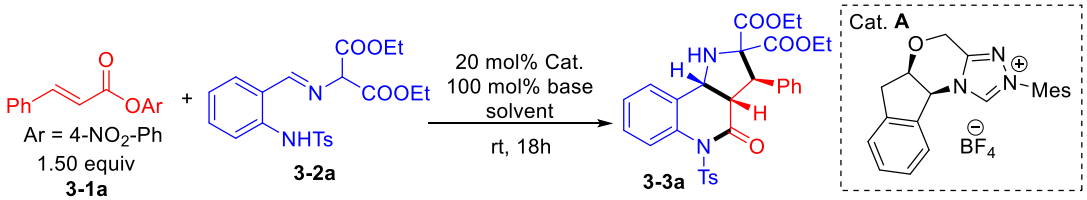
Scheme 3.4 NHC-catalyzed cascade reaction

3.2 Results and Discussions

First of all, ester **3-1a** and aldimine **3-2a** were selected as the model substrate and the investigation began with the screening of different bases with aminoindanol-derived NHC

catalyst **A** as precatalyst. Product **3-3a** was obtained with unsatisfied yield and enantioselectivity (entries 1 and 2). Inspired by the pioneered work reported by Bode[16] that the formation of amide could be achieved by NHC and hydroxamic acid cocatalysis, I used HOBt as additive for further screening. Fortunately, with the help of HOBt, the yield and enantioselectivity were dramatically increased in an acceptable level (entries 3 and 4). Strong base such DBU gave the best e.e. value and weak base such DIEA could not deliver the desired product (entries 5 and 6). Different solvents were also screened. The result showed that THF remains the best choice (entries 7-10). When using two equivlants of DBU, the yield could be increased to 80% with little enantiomeric excess erosion (98% ee, entry 12). When raising the concentration of the reaction mixture, both d.r. and e.e. dropped (entries 13).

Table 3.1 Condition Optimization[a]



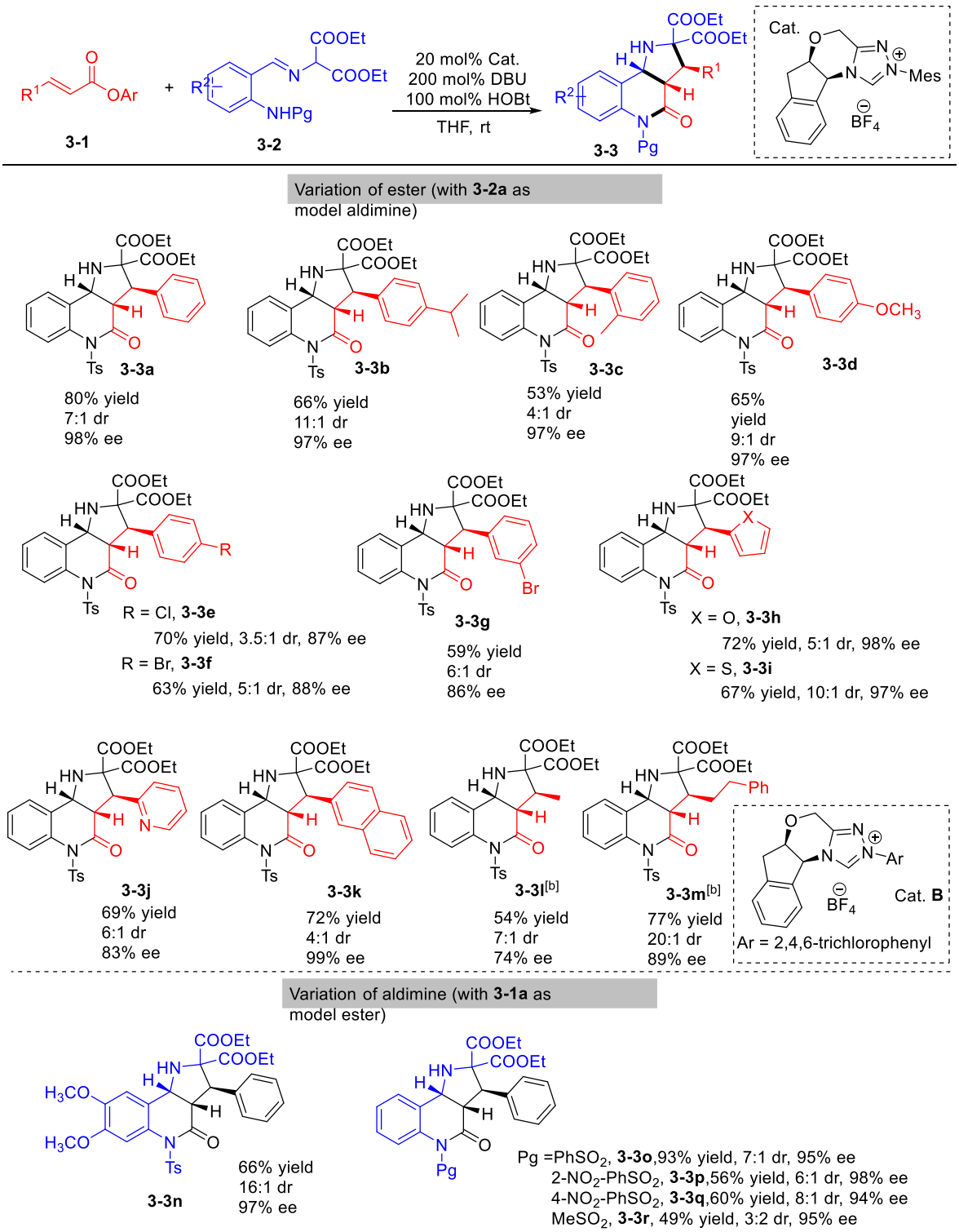
Entry	Base	Solvent	Additive[b]	Yield[c]	d.r.[d]	e.e.[e]
1	Cs_2CO_3	THF	-	32	10:1	24
2	K_2CO_3	THF	-	14	N.D.	39
3	Cs_2CO_3	THF	HOBt	69	7:1	94
4	K_2CO_3	THF	HOBt	74	8:1	91
5	DBU	THF	HOBt	49	7:1	99
6	DIEA	THF	HOBt	No reaction	N.D.	N.D.
7	DBU	DCM	HOBt	trace	N.D.	N.D.
8	DBU	Toluene	HOBt	38	10:1	75
9	DBU	CH_3COOEt	HOBt	20	N.D.	94
10	DBU	CH_3CN	HOBt	10	N.D.	N.D.
11	DBU	Dioxane	HOBt	24	N.D.	99
12	DBU[f]	THF	HOBt	84(80)	7:1	98
13	DBU[f]	THF[g]	HOBt	82	5:1	91

[a] Reaction condition: 1.5 equiv of **3-1a** (0.075 mmol), 1 equiv of **3-2a** (0.05 mmol), 20 mol% of NHC, 1

equiv of base and 2 mL of solvent at rt (24 °C) for 18 h. [b] 1 equiv of additive was used. [c] Yield was determined by ^{1}H NMR using trimethoxylbenzene as internal standard, and yield in parenthesis was isolated yield after column chromography. [d] Diastereomeric ratio was determined by ^{1}H NMR of the unpurified reaction mixture [e] Enantiomeric ratio was determined *via* chiral HPLC. [f] 2.0 equiv of DBU (0.1 mmol) was used. [g] 1 mL of THF was used. N.D. = Not Determined.

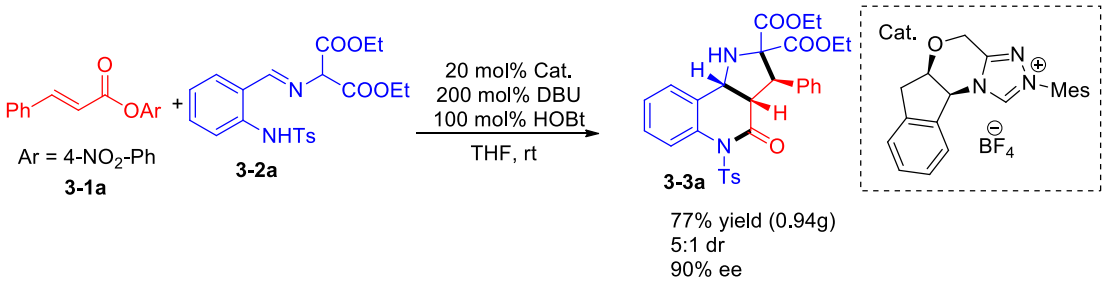
Having the optimized reaction condition in hand, the reaction scope with different esters as well as variant aldimines was examined (**Table 3.2**). Aldimine (**3-2a**) was first selected as the model nucleophile to check the generality of the reaction with a variety of unsaturated esters. To our delight, both electron-donating (product **3-3b** to **3-3d**) and electron-withdrawing (product **3-3e** to **3-3g**) substituents at different position of the β-phenyl group were well tolerated. Changing the phenyl group with a heteroaryl such as furanyl (**3-3h**), thiophenyl (**3-3i**) or naphthyl (**3-3k**) unit did not affect the reaction outcomes. β-pyridinyl unsaturated ester could also delivere the corresponding product (**3-3j**), albeit with some enantiomeric ratio loss. When β-aryl group of the ester was replaced with an alkyl unit, the yield and ee were decreased significantly. Therefore, the screening of the catalysts for this reaction was conducted. Finally, aminoindanol-derived catalyst with a trichlorophenyl substituent (**B**) performed better, compared with the standard condition (**3-3l** and **3-3m**). Methoxyl group could be installed at the phenyl ring of aldimine (**3-3n**). Switching other different sulfonyl protecting groups gave similar results except methylsulfonyl group. Relative low yield and diastereomeric ratio were observed (**3-3r**).

Table 3.2 Reaction scope[a]

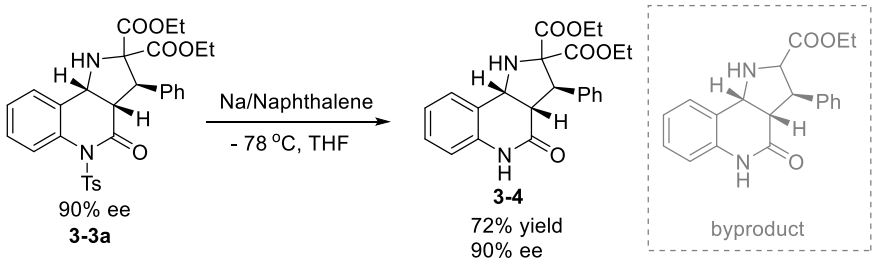


[a] Reaction conditions unless otherwise specified: ester **3-1**(0.15 mmol), aldimine **3-2** (0.1 mmol), catalyst (0.02 mmol), DBU (0.2 mmol), HOBt (0.1 mmol) in 4 mL THF at rt; Yield was isolated yield after SiO_2 column chromatography; Diastereomeric ratio was determined by 1H NMR of crude reaction mixture; Enantiomeric ratio was determined by chiral phrase HPLC. [b] 20 mol% catalyst **B** was used.

The catalytic asymmetric reaction could be easily scaled up into gram-scale without affecting the chemical yield (**Scheme 3.5**). However, the diastereomeric and enantiomeric ratio were decreased (5:1 dr, 90% ee). The optically enriched pyrroloquinoline (**3-3a**) obtained in this study could be readily deprotected with Na/Naphthalene reduction condition (**Scheme 3.6**). Good yield was achieved with no enantiomeric ratio lost and trace amount of decarboxylate byproduct was observed.

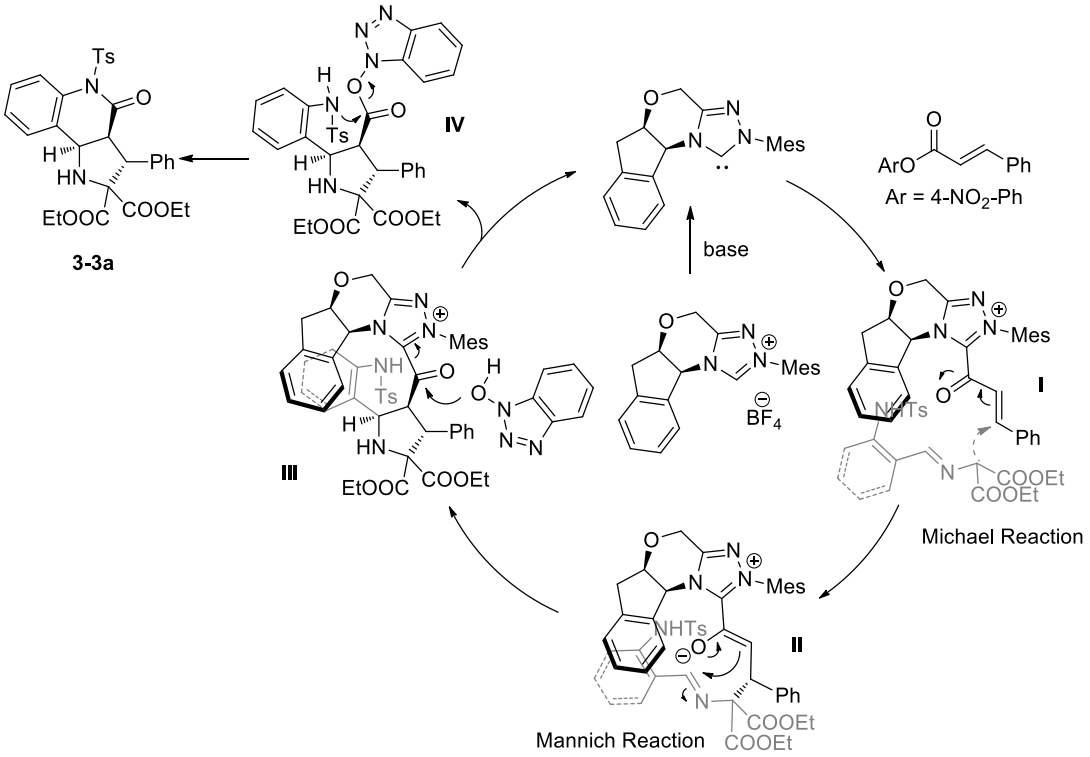


Scheme 3.5 Gram-scale reaction



Scheme 3.6 Deprotection of product **3-3a**

A plausible catalytic pathway for this cascade reaction was proposed in **Scheme 3.7**. A free NHC catalyst first reacted with ester to form a NHC-bound α, β-unsaturated acyl azolium intermediate **I**. Under basic condition, Michael addition of aromatic aldimine from *re*-face afforded enolate intermediate **II**, which subsequently *re*-face attacked to the imine unit to give intermediate **III**. Finally, with the help of hydroxybenzotriazole, lactamization was completed and NHC catalyst regenerated.



Scheme 3.7 Proposed mechanism

3.3 Summary.

In summary, an NHC-catalyzed Michael-Mannich-lactamization cascade reaction from carboxylate esters and protected *o*-amino aromatic aldimines with good yield and excellent enantioselectivity has been described. Three consecutive stereogenic centers are constructed by using this strategy in one single step. The potential use of this method for the synthesis of Martinella-type analogues and relative bioactive test are ongoing in collaborated lab. During the preparation of the manuscript, a similar work was published by Hui's group, and they used α-bromoenal as α,β-unsaturated acyl azolium precursors.[17]

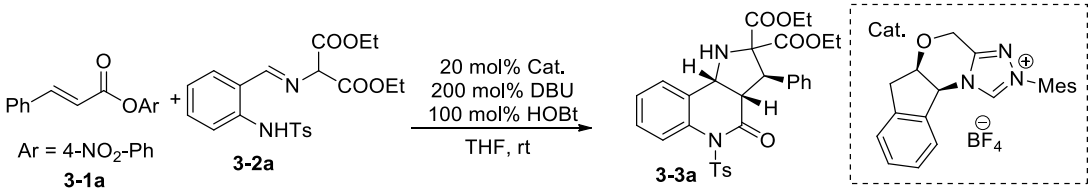
3.4 Experimental Section

3.4.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were

used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker (300 or 400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.r.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

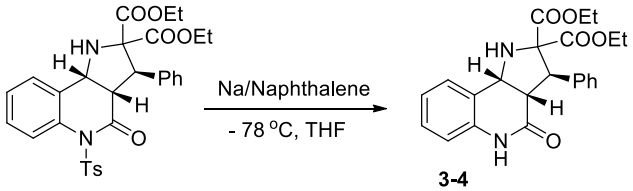
3.4.2 General Procedure for the Asymmetric Synthesis of Functionalized Pyrrolo[3,2-*c*]quinolines



To a 10 mL Schlenk tube equipped with a magnetic stirring bar was added ester **3-1a** (0.15 mmol), aldimine **3-2a** (0.1 mmol), NHC precursor (0.02 mmol), and HOBt (0.1

mmol). The tube was closed with a septum, evacuated and refilled with nitrogen (3 cycles). Flesh distilled THF (4 mL) was added to the reaction mixture at room temperature followed by adding DBU (0.1 mmol) via microsyringe. Upon the reaction completed (monitored by TLC), the solvent was evaporated and subjected to SiO_2 column chromatography using hexane/EtOAc as eluent to yield the corresponding product as white solid.

3.4.3 Deprotection of Product 3-3a



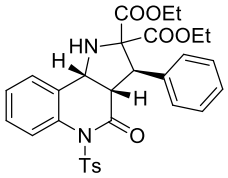
3-3a **3-4**

72% yield
98% ee

To a 20 mL Schlenk tube equipped with a magnetic stirring bar was added naphthalene (0.5 mmol). The tube was closed with a septum, evacuated and refilled with nitrogen (3 cycles). Flesh distilled THF (5 mL) was injected. After the naphthalene solid was dissolved, metal sodium (0.5 mmol, removed the metal oxide from the surface) was added to the solution at room temperature for one hour. When the solution became dark blue, the Na/Naphthalene reagent was completed.

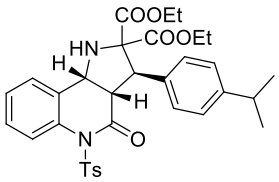
To a stirred of 3-3a (0.1 mmol) in THF (4 mL) at -78 ^{o}C under inert atmosphere was added freshly prepared Na/Naphthalene reagent dropwise. When the color of the reaction solution did not fade away, the mixture was stirred for another 10 minutes and then quenched with brine, followed by extracted with EtOAc (5 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified via SiO_2 column chromatography using hexane/EtOAc as eluent to yield the corresponding product as white solid.

3.4.4 Characterization of Products.



3-3a

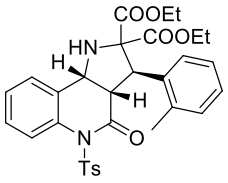
(3R,3aS,9bR)-diethyl 4-oxo-3-phenyl-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3a); White solid, 45 mg (80% yield); $[\alpha]^{D}_{20}$ = -64.5 °(*c* = 1.0, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.68 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.39 (td, *J* = 7.6, 1.2 Hz, 1H), 7.32 – 7.25 (m, 3H), 7.24 – 7.14 (m, 5H), 4.85 (t, *J* = 4.8 Hz, 1H), 4.36 (d, *J* = 9.2 Hz, 1H), 4.20 – 4.04 (m, 2H), 3.72 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.60 (d, *J* = 4.4 Hz, 1H), 3.39 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.26 (dq, *J* = 10.4, 7.2 Hz, 1H), 2.43 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.4, 169.3, 144.8, 136.4, 134.0, 129.4, 128.7, 128.3, 128.2, 127.6, 127.5, 126.1, 123.2, 62.1, 61.8, 57.8, 53.5, 52.1, 21.6, 13.9, 13.1; IR (*v* cm^{-1})3335, 3030, 2982, 2928, 1730, 1599, 1497, 1456, 1366, 1292, 1269, 1207, 1169, 1113, 1088, 1036; HRMS (ESI) calcd for $C_{30}H_{31}N_2O_7S$ $(M+H)^+$: 563.1846 Found: 563.1846; 98% ee as determined by HPLC (OD, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 28.9 min, $t_{r\ min}$ = 37.0 min.



3-3b

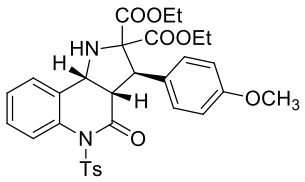
(3R,3aS,9bR)-diethyl 3-(4-isopropylphenyl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3b); White solid, 40mg (66% yield); $[\alpha]^{D}_{20}$ = -45.4 °(*c* = 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.43 – 7.35 (m, 1H), 7.32 – 7.22 (m, 3H), 7.17 – 7.10 (m, 4H), 7.10 – 7.03 (m, 2H), 4.83 (d, *J* = 6.0 Hz, 1H), 4.32 (d, *J* = 9.6

Hz, 1H), 4.17 – 4.01 (m, 2H), 3.69 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.60 (brs, 1H), 3.38 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.26 (dq, *J* = 10.4, 7.2 Hz, 1H), 2.90 – 2.75 (m, 1H), 2.44 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.16 (d, *J* = 6.8 Hz, 6H), 0.63 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.44, 169.38, 148.3, 144.8, 136.5, 13.0, 133.6, 129.4, 128.8, 128.7, 128.3, 128.2, 127.7, 126.3, 126.1, 123.4, 62.1, 61.8, 57.7, 53.5, 51.80, 33.7, 23.9, 21.7, 13.9, 13.1; HRMS (ESI) calcd for $C_{33}H_{37}N_2O_7S$ $(M+H)^+$: 605.2316 Found: 605.2313; IR (ν cm^{-1})3333, 3026, 2960, 2930, 1730, 1599, 1456, 1366, 1298, 1269, 1206, 1169, 1113, 1088, 1138; 97% ee as determined by HPLC (OD, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 28.3 min, $t_{r\ min}$ = 43.3 min.



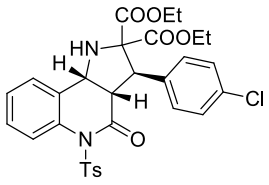
3-3c

(3R,3aS,9bR)-diethyl 4-oxo-3-(o-tolyl)-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3c); White solid, 30 mg (53% yield); $[\alpha]^{D}_{20}$ = 3.8 °(*c* = 4.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.76 – 7.71 (m, 1H), 7.53 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.39 (td, *J* = 8.0, 1.6 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.12 – 6.99 (m, 4H), 5.03 (d, *J* = 4.8 Hz, 1H), 4.93 (d, *J* = 5.6 Hz, 1H), 4.17 – 3.94 (m, 2H), 3.72 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.45 (brs, 1H), 3.26 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.15 (t, *J* = 5.2 Hz, 1H), 2.43 (s, 3H), 2.39 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 170.3, 168.5, 144.5, 138.5, 137.7, 136.5, 134.9, 130.3, 129.2, 129.0, 128.7, 128.6, 127.2, 126.4, 126.0, 125.9, 125.8, 122.8, 61.8, 61.7, 59.1, 55.7, 47.8, 21.6, 20.3, 13.8, 13.1; IR (ν cm^{-1})3340, 3024, 2982, 2938, 1732, 1715, 1597, 1493, 1464, 1366, 1267, 1215, 1167, 1105, 1088,1045; HRMS (ESI) calcd for $C_{31}H_{33}N_2O_7S$ $(M+H)^+$: 577.2003 Found: 577.2001; 99% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 15.7 min, $t_{r\ min}$ = 18.6 min.



3-3d

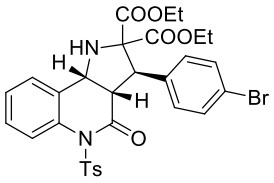
(3R,3aS,9bR)-diethyl 3-(4-methoxyphenyl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3d); White solid, 39 mg (65% yield); $[\alpha]^{D}_{20}$ = -47.6 °(*c* = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.43 – 7.34 (m, 1H), 7.33 – 7.21 (m, 3H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 4.82 (d, *J* = 6.0 Hz, 1H), 4.28 (d, *J* = 10.0 Hz, 1H), 4.16 – 4.05 (m, 2H), 3.82 – 3.74 (m, 1H), 3.73 (s, 3H), 3.42 – 3.26 (m, 2H), 2.43 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.5, 169.3, 159.0, 144.8, 136.4, 133.9, 129.8, 129.4, 128.7, 128.3, 128.11, 128.07, 127.7, 126.1, 123.2, 113.6, 62.1, 61.8, 57.5, 55.2, 53.6, 51.4, 21.6, 13.9, 13.2; HRMS (ESI) calcd for $C_{31}H_{33}N_2O_8S$ $(M+H)^+$: 593.1952 Found: 593.1956; IR (*v* cm^{-1})3332, 3019, 2980, 2959, 2928, 1728, 1611, 1514, 1458, 1368, 1294, 1250, 1213, 1171, 1113, 1088,1036; 97% ee as determined by HPLC (OD, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 47.7 min, $t_{r\ min}$ = 71.8 min



3-3e

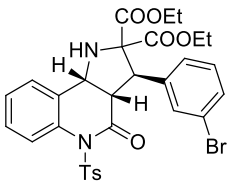
(3R,3aS,9bR)-diethyl 3-(4-chlorophenyl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3e); White solid, 42 mg (70% yield); $[\alpha]^{D}_{20}$ = -49.8 °(*c* = 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.34 – 7.12 (m, 7H), 4.83 (d, *J* = 5.6 Hz, 1H), 4.28 (d, *J* = 10.0 Hz, 1H), 4.20 – 4.01 (m, 2H), 3.78 (dq, *J* = 10.4, 7.2 Hz, 1H), 3.62 (brs, 1H), 3.47 – 3.28 (m, 1H), 2.44 (s, 3H), 1.22 (t, *J* = 7.2 Hz,

3H), 0.73 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.3, 169.1, 145.0, 136.4, 134.7, 133.8, 133.6, 130.2, 129.5, 128.8, 128.4, 128.3, 128.1, 127.5, 126.2, 123.2, 62.4, 62.0, 57.5, 53.4, 51.4, 21.7, 13.9, 13.2; HRMS (ESI) calcd for $C_{30}H_{30}ClN_2O_7S$ $(M+H)^+$: 597.1457 Found: 597.1449; 87% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 18.5 min, $t_{r\ min}$ = 25.3 min.



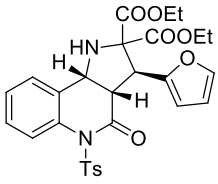
3-3f

(3R,3aS,9bR)-diethyl 3-(4-bromophenyl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3f); White solid, 40 mg (63% yield); $[\alpha]^{D}_{20}$ = -49.8 °(*c* = 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.33 – 7.23 (m, 3H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.83 (t, *J* = 5.6 Hz, 1H), 4.26 (d, *J* = 10.0 Hz, 1H), 4.12 (qd, *J* = 6.8, 2.0 Hz, 2H), 3.77 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.62 (d, *J* = 5.2 Hz, 1H), 3.44 – 3.32 (m, 2H), 2.44 (s, 3H), 1.22 (t, *J* = 6.8 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.3, 169.0, 145.0, 136.3, 135.2, 133.8, 131.3, 130.5, 129.4, 128.8, 128.4, 128.0, 127.5, 126.2, 123.2, 121.7, 62.4, 62.0, 57.5, 53.3, 51.4, 21.7, 13.9, 13.2; IR (ν cm^{-1}) 3333, 3069, 3026, 2980, 2924, 1728, 1608, 1489, 1366, 1298, 1171, 1113, 1088, 1036; HRMS (ESI) calcd for $C_{30}H_{30}BrN_2O_7S$ $(M+H)^+$: 641.0952 Found: 641.0953; 88% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 17.9 min, $t_{r\ min}$ = 24.5 min.



3-3g

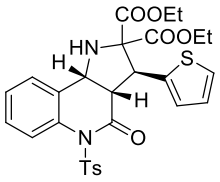
(3R,3aS,9bR)-diethyl 3-(3-bromophenyl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3g); White solid, 38 mg (59% yield); $[\alpha]^{D}_{20}$ = -49.8 °(*c* = 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.22 (m, 6H), 7.21 – 7.06 (m, 2H), 4.84 (t, *J* = 5.2 Hz, 1H), 4.30 (d, *J* = 9.2 Hz, 1H), 4.19 – 4.05 (m, 2H), 3.78 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.60 (d, *J* = 4.8 Hz, 1H), 3.45 – 3.27 (m, 2H), 2.44 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ169.9, 169.10, 169.08, 144.9, 138.8, 136.4, 133.9, 132.2, 130.8, 129.8, 129.5, 128.8, 128.5, 128.2, 127.3, 127.2, 126.2, 123.3, 122.3, 62.4, 62.0, 57.7, 53.4, 51.7, 21.7, 13.9, 13.2; IR (*v* cm^{-1}) 3339, 3022, 2982, 2961, 2926, 1728, 1597, 1568, 1368, 1300, 1271, 1213, 1171, 1113, 1088,1036; HRMS (ESI) calcd for $C_{30}H_{30}BrN_2O_7S$ $(M+H)^+$: 641.0952 Found: 641.0950; 86% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\,maj}$ = 21.4 min, $t_{r\,min}$ = 27.2 min.



3-3h

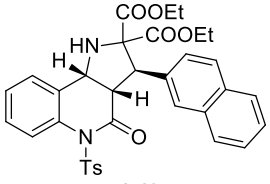
(3S,3aS,9bR)-diethyl 3-(furan-2-yl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3h); White solid, 38 mg (72% yield); $[\alpha]^{D}_{20}$ = -12.2 °(*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.75 – 7.66 (m, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.42 – 7.35 (m, 1H), 7.32 – 7.21 (m, 4H), 6.28 – 6.23 (m, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 4.79 (d, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 7.2 Hz, 1H), 4.13 – 4.02 (m, 2H), 4.01 – 3.92 (m, 1H), 3.66 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.55 (brs, 1H), 3.23 (t, *J* = 6.0 Hz, 1H), 2.43 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.2, 168.4, 150.7, 144.7, 142.1, 136.4, 134.4, 129.3, 128.9, 128.7, 128.5, 126.7, 126.1, 123.1, 110.6, 109.0, 75.0, 62.6,

61.9, 57.8, 52.7, 46.0, 21.7, 13.9, 13.6; HRMS (ESI) calcd for $C_{28}H_{29}N_2O_8S$ $(M+H)^+$: 533.1639 Found: 533.1641; 98% ee as determined by HPLC (ODH, 95:5 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 30.2 min, $t_{r\ min}$ = 34.0 min.



3-3i

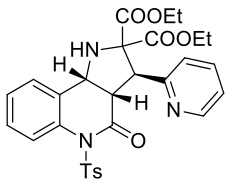
(3S,3aS,9bR)-diethyl 4-oxo-3-(thiophen-2-yl)-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3i); White solid, 38 mg (67% yield); $[\alpha]^{D}_{20}$ = -27.0 °(*c* = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.39 (td, *J* = 8.8, 1.2 Hz, 1H), 7.34 – 7.21 (m, 3H), 7.16 – 7.11 (m, 1H), 6.93 (d, *J* = 3.2 Hz, 1H), 6.90 – 6.84 (m, 1H), 4.81 (brs, 1H), 4.63 (d, *J* = 9.2 Hz, 1H), 4.20 – 4.04 (m, 2H), 3.84 (dq, *J* = 10.4, 7.2 Hz, 1H), 3.62 (brs, 1H), 3.51 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.31 (dd, *J* = 8.8, 6.0 Hz, 1H), 2.44 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.1, 168.7, 144.9, 139.1, 136.4, 134.0, 129.5, 128.9, 128.5, 128.3, 127.4, 126.8, 126.7, 126.2, 124.9, 123.4, 62.5, 62.0, 57.6, 55.1, 47.5, 21.7, 14.0, 13.4; IR (*v* cm^{-1}) 3337, 3071, 3026, 2982, 2938, 2905, 1732, 1715,1599, 1485, 1450, 1368, 1300, 1206, 1171, 1113, 1088,1036; HRMS (ESI) calcd for $C_{28}H_{29}N_2O_7S_2$ $(M+H)^+$: 569.1411 Found: 569.1412; 97% ee as determined by HPLC (ODH, 95:5 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 44.9 min, $t_{r\ min}$ = 53.7 min



3-3k

(3R,3aS,9bR)-diethyl 3-(naphthalen-2-yl)-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3k); White solid, 45 mg (72%

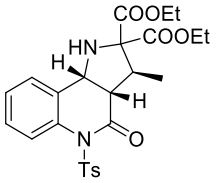
yield); $[\alpha]^{D}_{20}$ = -64.4 °(*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.76 – 7.67 (m, 5H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.36 (m, 3H), 7.34 – 7.23 (m, 4H), 4.93 (d, *J* = 6.0 Hz, 1H), 4.53 (d, *J* = 9.6 Hz, 1H), 4.17 – 4.08 (m, 2H), 3.70 (brs, 1H), 3.60 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.54 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.08 (dq, *J* = 10.8, 7.2 Hz, 1H), 2.41 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.37 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.32, 169.30, 144.8, 136.4, 134.0, 133.8, 133.0, 132.7, 129.4, 128.7, 128.3, 128.2, 127.91, 127.87, 127.7, 127.5, 127.3, 126.4, 126.1, 126.0, 125.9, 123.1, 62.0, 61.8, 57.8, 53.7, 52.3, 21.6, 13.9, 12.8; HRMS (ESI) calcd for $C_{34}H_{33}N_2O_7S$ $(M+H)^+$: 631.2003 Found: 631.2000; 99% ee as determined by HPLC (ODH, 95:5 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ = 55.0 min, $t_{r\ min}$ = 84.1min



3-3j

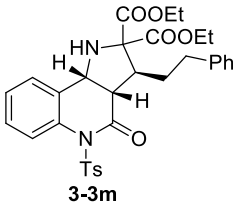
(3S,3aS,9bR)-diethyl 4-oxo-3-(pyridin-2-yl)-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3j); White solid, 39 mg (69% yield); $[\alpha]^{D}_{20}$ = -17.7 °(*c* = 2.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.42 – 7.35 (m, 1H), 7.26 (dd, *J* = 15.2, 8.7 Hz, 5H), 7.14 – 7.08 (m, 1H), 4.96 (d, *J* = 5.6 Hz, 1H), 4.62 (d, *J* = 6.0 Hz, 1H), 4.16 – 4.00 (m, 2H), 3.86 – 3.76 (m, 1H), 3.57 (brs, 1H), 3.52 (t, *J* = 6.0 Hz, 1H), 3.39 (dq, *J* = 10.4, 7.2 Hz, 1H), 2.44 (s, 3H), 1.19 (t, *J* = 6.8 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 169.6, 168.7, 158.1, 149.2, 144.6, 136.5, 136.3, 134.7, 129.3, 129.0, 128.8, 128.4, 126.8, 125.9, 125.3, 122.9, 122.3, 76.3, 61.9, 61.8, 58.2, 54.1, 53.8, 21.7, 13.9, 13.3; IR (ν cm^{-1}) 3333, 3069, 3013, 2984, 2938, 1732, 1713, 1591, 1493, 1441, 1362, 1269, 1234,1202, 1169, 1115, 1089, 1038; HRMS

(ESI) calcd for $C_{29}H_{30}N_3O_7S$ $(M+H)^+$: 564.1799Found: 564.1805; 83% ee as determined by HPLC (ASH, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 64.3 min, $t_{r\ min}$ = 77.4 min



3-3l

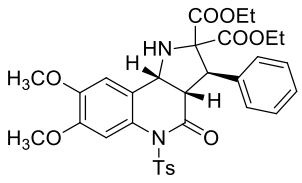
(3S,3aS,9bR)-diethyl 3-methyl-4-oxo-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3l); White solid, 27 mg (54% yield); $[\alpha]^{D}_{20}$ = -9.9 °(*c* = 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.61 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.35 – 7.29 (m, 3H), 7.20 (td, *J* = 7.6, 0.8 Hz, 1H), 4.59 (d, *J* = 6.4 Hz, 1H), 4.30 – 4.16 (m, 2H), 4.10 (d, *J* = 7.2 Hz, 2H), 2.99 – 2.87 (m, 1H), 2.69 (dd, *J* = 10.4, 6.4 Hz, 1H), 2.44 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 169.8, 169.7, 145.0, 136.5, 133.3, 129.5, 128.7, 128.4, 128.0, 127.9, 126.0, 122.7, 74.7, 62.4, 61.7, 56.1, 55.2, 41.4, 21.6, 14.9, 14.0, 13.9; IR (ν cm^{-1}) 3345, 3069, 3026, 2982, 2928, 1732, 1715,1599, 1485, 1456, 1368, 1260, 1236, 1211, 1171, 1088, 1034, 1018; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_7S$ $(M+H)^+$: 501.1690 Found: 501.1690; 74% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 35.6 min, $t_{r\ min}$ = 42.9 min.



3-3m

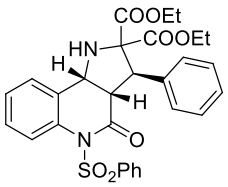
(3S,3aS,9bR)-diethyl 4-oxo-3-phenethyl-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3m); White solid, 45 mg (77% yield); $[\alpha]^{D}_{20}$ = -5.9 °(*c* = 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.70 – 7.65 (m, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.35 (td, *J* = 7.6, 1.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23 – 7.17 (m, 3H), 7.14 – 7.09 (m, 1H), 7.09 – 7.02 (m, 2H), 4.58 (d, *J* = 6.0 Hz, 1H),

4.30 – 4.21 (m, 1H), 4.20 – 4.12 (m, 1H), 4.12 – 4.02 (m, 2H), 3.13 – 3.04 (m, 1H), 2.80 (dd, *J* = 7.6, 6.0 Hz, 1H), 2.71 – 2.54 (m, 2H), 2.43 (s, 3H), 1.88 – 1.77 (m, 1H), 1.77 – 1.65 (m, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 170.7, 169.3, 144.8, 141.3, 136.4, 134.0, 129.3, 128.7, 128.4, 128.23, 128.16, 127.4, 126.0, 125.8, 122.9, 74.7, 62.3, 61.6, 56.7, 53.0, 46.6, 33.9, 31.5, 21.6, 14.0, 13.9; IR (*v* cm^{-1}) 3347, 3063, 3026, 2982, 2928, 1732, 1599, 1495, 1456, 1366, 1258, 1217, 1169, 1113, 1088, 1045; HRMS (ESI) calcd for $C_{32}H_{35}N_2O_7S$ $(M+H)^+$: 591.2159 Found: 591.2161; 89% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 26.9 min, $t_{r\ min}$ = 43.4 min.



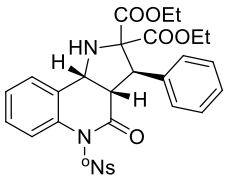
3-3n

(3R,3aS,9bR)-diethyl 7,8-dimethoxy-4-oxo-3-phenyl-5-tosyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3n); White solid, 41 mg (66% yield); $[\alpha]^{D}_{20}$ = -60.5 °(*c* = 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.32 – 7.24 (m, 3H), 7.24 – 7.15 (m, 5H), 7.12 (s, 1H), 4.73 (d, *J* = 6.4 Hz, 1H), 4.36 – 4.29 (m, 1H), 4.17 (dq, *J* = 10.4, 6.8 Hz, 1H), 4.09 – 3.99 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.79 – 3.60 (m, 2H), 3.35 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.25 (dq, *J* = 10.8, 7.2 Hz, 1H), 2.43 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 169.5, 169.4, 148.2, 147.3, 144.8, 136.3, 136.1, 129.4, 128.8, 128.6, 128.2, 127.6, 127.0, 119.8, 110.4, 108.0, 62.2, 61.8, 57.5, 56.2, 56.1, 53.8, 52.0, 21.6, 13.9, 13.1; IR (*v* cm^{-1}) 3331, 3026, 2982, 2963, 2938, 1732, 1715,1614, 1514, 1454, 1360, 1285, 1236, 1171, 1123, 1089,1038; HRMS (ESI) calcd for $C_{32}H_{34}N_2O_9S$ $(M+H)^+$: 623.2058 Found: 623.2050; 97% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 58.5 min, $t_{r\ min}$ = 50.8 min.



3-3o

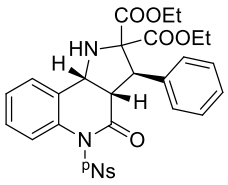
(3R,3aS,9bR)-diethyl 4-oxo-3-phenyl-5-(phenylsulfonyl)-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3o); White solid, 51 mg (93% yield); $[\alpha]^{D}_{20}$ = -38.2 °(*c* = 3.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.98 (m, 2H), 7.72 – 7.66 (m, 1H), 7.66 – 7.54 (m, 2H), 7.57 – 7.47 (m, 2H), 7.40 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.32 – 7.13 (m, 6H), 4.87 (t, *J* = 5.2 Hz, 1H), 4.39 (d, *J* = 8.8 Hz, 1H), 4.16 – 4.06 (m, 2H), 3.72 (dq, *J* = 10.4, 7.2 Hz, 1H), 3.58 (d, *J* = 4.4 Hz, 1H), 3.39 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.26 (dq, *J* = 10.4, 7.2 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 169.5, 169.2, 139.4, 136.6, 134.0, 133.7, 128.8, 128.73, 128.68, 128.4, 128.3, 128.2, 127.6, 127.4, 126.2, 123.2, 62.1, 61.9, 57.9, 53.5, 52.1, 13.9, 13.2; IR (*v* cm^{-1}) 3337, 3065, 3032, 2984, 2938, 1732, 1715, 1603, 1497, 1450, 1368, 1269, 1233, 1173, 1126, 1086, 1036; HRMS (ESI) calcd for $C_{29}H_{29}N_2O_7S$ $(M+H)^+$: 549.1690 Found: 549.1688; 95% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\,maj}$ = 20.6min, $t_{r\,min}$ = 22.9 min.



3-3p

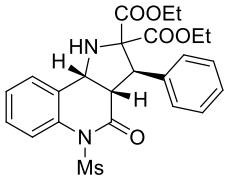
(3R,3aS,9bR)-diethyl 5-((2-nitrophenyl)sulfonyl)-4-oxo-3-phenyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3p); White solid, 34 mg (56% yield); $[\alpha]^{D}_{20}$ = -116.9 °(*c* = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 – 8.38 (m, 1H), 7.87 – 7.70 (m, 4H), 7.63 – 7.56 (m, 1H), 7.41 – 7.34 (m, 1H), 7.30 (td, *J* = 7.2, 0.8 Hz, 1H), 7.25 – 7.12 (m, 5H), 5.09 (d, *J* = 4.8 Hz, 1H), 4.29 (d, *J* = 12.0 Hz, 1H), 4.17 – 4.07 (m, 2H), 3.85 (brs, 1H), 3.74 (dq, *J* = 10.4, 7.2 Hz, 1H), 3.52 (dd, *J*

= 12.4, 6.8 Hz, 1H), 3.26 (dq, *J* = 10.8, 7.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 169.8, 168.6, 135.6, 135.2, 134.7, 133.4, 132.4, 132.2, 128.8, 128.5, 128.3, 128.1, 128.0, 127.8, 126.7, 124.8, 123.1, 77.20, 77.16, 62.3, 62.0, 57.5, 53.4, 52.1, 14.0, 13.2; HRMS (ESI) calcd for $C_{29}H_{27}N_3O_{10}S$ $(M+H)^+$: 610.1490 Found: 610.1497; 98% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 44.7 min, $t_{r\ min}$ = 53.2 min.



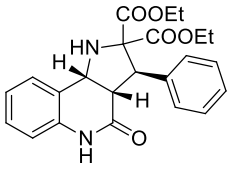
3-3q

(3R,3aS,9bR)-diethyl 5-((4-nitrophenyl)sulfonyl)-4-oxo-3-phenyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3q); White solid, 36 mg (60% yield); $[\alpha]^{D}_{20}$ = -10.7 °(*c* = 2.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.25 (m, 2H), 8.22 – 8.15 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.59 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.45 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.26 – 7.15 (m, 5H), 4.94 (d, *J* = 5.2 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.16 – 3.98 (m, 2H), 3.71 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.43 (brs, 1H), 3.34 – 3.19 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 0.67 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 170.3, 168.6, 150.5, 144.6, 137.6, 134.0, 130.2, 129.2, 128.9, 128.6, 128.4, 127.7, 126.6, 126.4, 123.8, 123.1, 76.8, 62.0, 61.8, 58.7, 53.2, 52.1, 13.9, 13.2; ;IR (ν cm^{-1})3341, 3107, 3067, 3032, 2984, 2938, 1732, 1715, 1607, 1537, 1497, 1456, 1368, 1350, 1271, 1207, 1172, 1109, 1086,1043; HRMS (ESI) calcd for $C_{29}H_{27}N_3O_{10}S$ $(M+H)^+$: 610.1490 Found: 610.1497; 94% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 25.2 min, $t_{r\ min}$ = 31.6 min.



3-3r

(3R,3aS,9bR)-diethyl 5-(methylsulfonyl)-4-oxo-3-phenyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-3r); White solid, 24 mg (49% yield); $[\alpha]^{D}_{20}$ = -34.7 °(*c* = 2.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.21 (m, 7H), 4.97 (t, *J* = 5.2 Hz, 1H), 4.74 (d, *J* = 7.6 Hz, 1H), 4.23 – 4.07 (m, 2H), 3.77 (dq, *J* = 10.4, 6.8 Hz, 1H), 3.57 (d, *J* = 4.4 Hz, 1H), 3.50 (t, *J* = 6.8 Hz, 1H), 3.45 (s, 3H), 3.33 (dq, *J* = 10.4, 7.2 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 170.3, 169.5, 137.3, 133.7, 128.8, 128.58, 128.55, 128.4, 127.8, 127.0, 126.1, 122.6, 76.96, 62.1, 62.0, 58.4, 53.7, 52.6, 43.5, 13.9, 13.2; IR (*v* cm^{-1}) 3333, 3019, 2982, 2959, 2928, 1730,1714, 1611, 1456, 1360, 1269, 1227, 1207, 1169; HRMS (ESI) calcd for $C_{24}H_{27}N_2O_7S$ $(M+H)^+$: 487.1533 Found: 487.1530; 95% ee as determined by HPLC (IB, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 32.4 min, $t_{r\ min}$ = 36.5 min.



3-4

(3R,3aS,9bR)-diethyl 4-oxo-3-phenyl-3,3a,4,5-tetrahydro-1H-pyrrolo[3,2-c]quinoline-2,2(9bH)-dicarboxylate (3-4); White solid, 29 mg (72% yield); $[\alpha]^{D}_{20}$ = -8.4 °(*c* = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (brs, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.33 – 7.15 (m, 4H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 5.02 (q, *J* = 2.8 Hz, 1H), 4.87 (d, *J* = 6.8 Hz, 1H), 4.23 – 4.11 (m, 1H), 4.10 – 4.01 (m, 1H), 3.77 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.51 (brs, 1H), 3.42 – 3.30 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H), 0.73 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.1, 169.7, 138.5, 135.8, 129.1, 128.8, 128.7, 128.3, 127.4, 123.2, 122.2, 115.6, 76.74, 61.91, 61.86, 58.8, 53.1, 50.6, 13.8, 13.2; IR (*v* cm^{-1}) 3325, 3211, 3063, 3032, 2984, 2934, 1732, 1688,1599, 1494, 1445, 1368, 1277, 1206, 1127, 1113, 1043; HRMS (ESI) calcd for

$C_{23}H_{24}N_2O_5$ $(M+H)^+$: 409.1758 Found: 409.1758; 90% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 15.4 min, $t_{r\ min}$ = 29.6 min.

3.5 References

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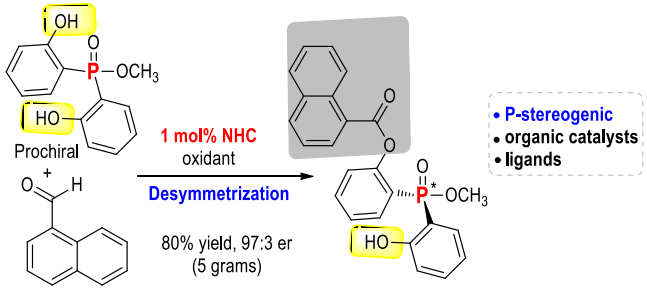
Chapter 4

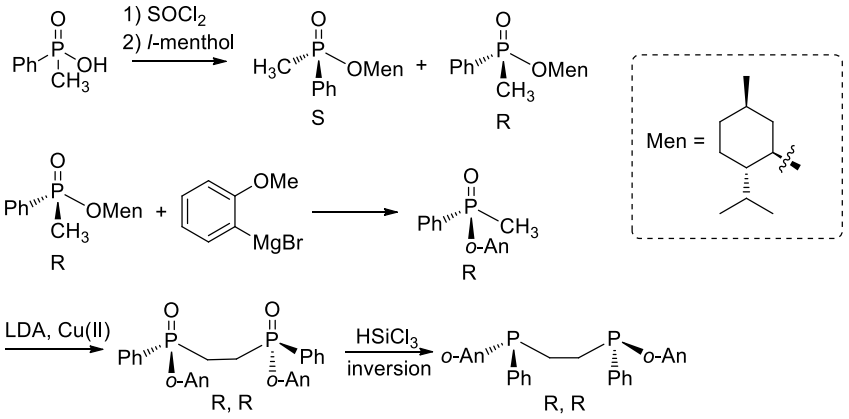
Access to P-Stereogenic Phosphinates via NHC-Catalyzed Desymmetrization of Bisphenols



4.1 Introduction

4.1.1 Conventional Methods for the Synthesis of P-stereogenic Compounds

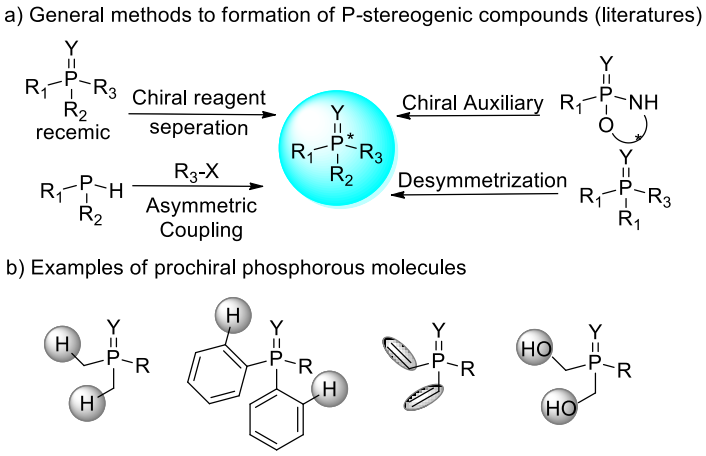
P-stereogenic phosphorous compounds possess proven utility in numerous asymmetric processes as ligands[1] or as organocatalysts[2]. However, efficient and ready access to these enantiomerically pure forms still remains a challenge. The most remarkable P-chiral phosphine DiPAMP was successfully synthesized in 1970s by Knowles (**Scheme 4.1**).[3] Menthol was introduced to form easily-separable diastereomers in Knowles' method. Since then, it arouses researchers' expectations about its values of this kind of ligands in catalysis, especially in asymmetric hydrogenation.



Scheme 4.1 Synthetic route of DiPAMP

Conventional approaches[4] (**Chart 4.1**) to optical phosphorous compounds include resolution of diastereomeric mixtures[5], transition-metal-catalyzed asymmetric cross couplings[6], desymmetrization of prochiral phosphorous molecules[7], and chiral-auxiliary inductions[8]. Particularly, the desymmetrization of prochiral phosphorous molecules include deprotonation of dimethyl phosphine borane adducts or phosphine sulfides[7a-c], C-H activation of diphenyl phosphinamides[7d-g], olefin metathesis of divinyl phosphinates[7h], and lipase catalyzed monoacetylation of diol or diacetate phosphine-borane percursors[7i-k].

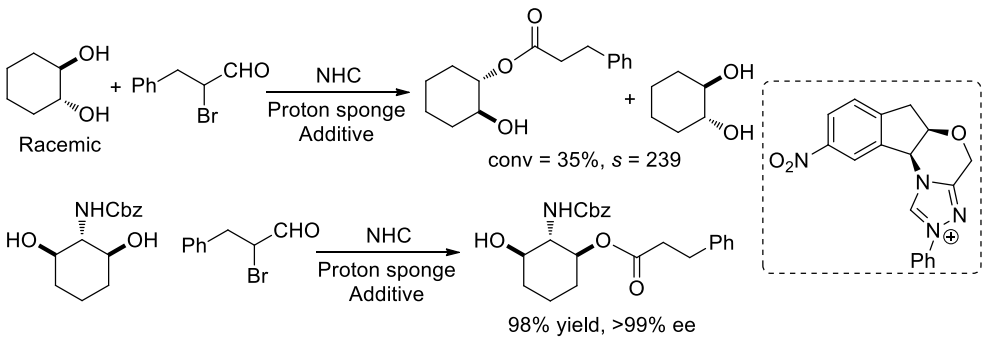
Chart 4.1 Gerneral approaches for synthesis of P-stereogenic compounds



Unfortunately, the synthetic routes are usually tedious, especially if the resolution approach is utilized, as it requires multiple recrystallizations or chromatography and lead to low overall yield. Compared to the construction of chiral carbon center, the establishment of P-stereogenic chiral center is much less investigated. Therefore, the efficient and accessible methods for approaching this kind of molecules are highly desired.

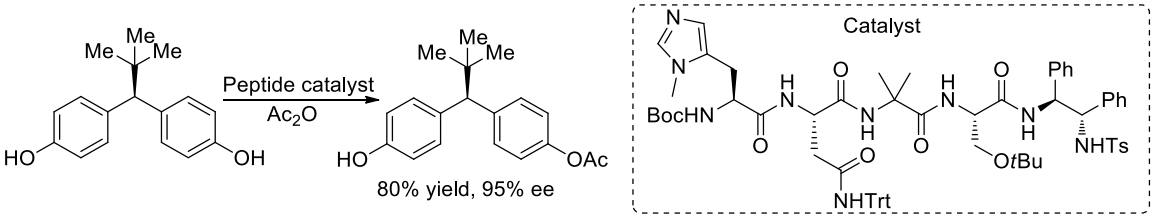
4.1.2 Desymmetrization Reaction Catalyzed by Organic Catalysts

As described in previous chapters, N-heterocyclic carbenes (NHCs) organocatalysts have shown great power in rapidly assembling functional molecules. NHCs react with functionalized aldehydes (α, β-unsaturated or α-halo aldehydes) through internal redox reactions, or simple aldehydes with external oxidant, to generated active acyl azolium species. These chiral intermediates are usually engaged for enantioselective C-C bond formation or acylation of alcohols.[9] In 2013, Takasu, Yamada and coworkers reported kinetic resolution of diols and amino alcohols in high selectivity under NHC catalysis (**Scheme 4.2**).[9f] This methodology could also be employed for desymmetrization of meso-diol with excellent efficiency.



Scheme 4.2 Resolution and desymmetrization of diols by Takasu and Yamada

It is worthy to note that asymmetric desymmetrization of diols has received remarkable success in the past decades, with the help of organocatalysts such as chiral DMAP, diamines, histidine-based peptides, isothioureas, etc.[10] However, desymmetrization of relative bisphenols is much more challenging, due to the differential difficulties of enantiotopic sites that are remote from prochiral centers.[11] Miller and co-workers reported an unprecedented desymmetrization of bisphenols methane derivative using peptide-based catalyst (**Scheme 4.3**).[11c-e]

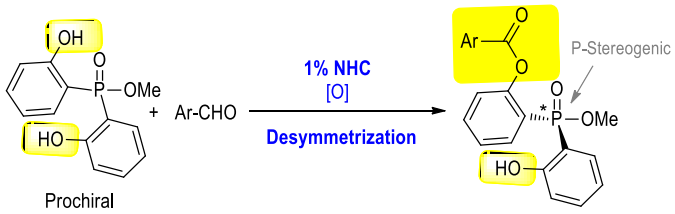


Scheme 4.3 Miller's desymmetrization of bis(phenol)

4.1.3 Proposal.

I assumed that desymmetric acylation reaction of prochiral bisphenol phosphinate could take place under oxidative NHC catalysis. The enantioselectivity could be induced by the NHC-bound chiral acyl azolium, which was for differentiating of enantiotopic site of two reactive hydroxyl groups (**Scheme 4.4**). Furthermore, the chiral phosphinate product

obtained from this method might be transformed into useful molecules such as organic catalysts.

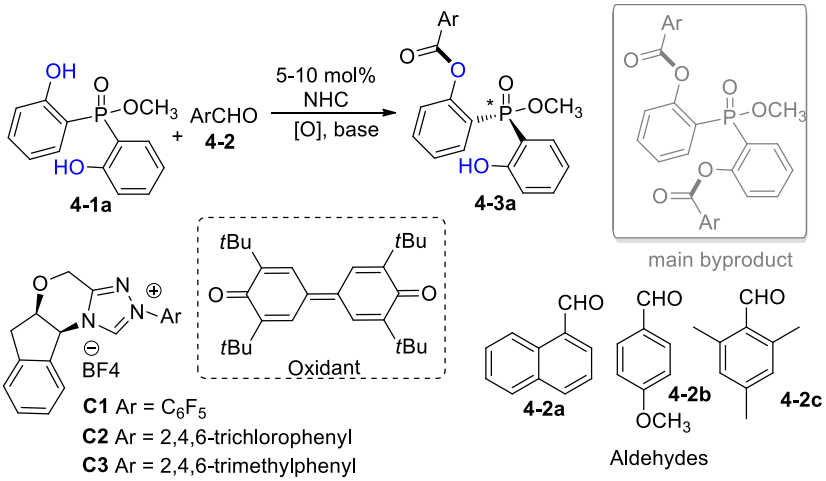


Scheme 4.4 Desymmetrization of prochiral phosphinate by NHC catalysis

4.2 Results and Discussions

The reaction that using bis(2-hydroxylphenyl) phosphinate (**4-1a**) as the model prochiral substrate was tested, and aryl aldehydes such as 1-naphthaldehyde (**4-2a**), p-methoxyl benzaldehyde (**4-2b**) and mesitaldehyde (**4-2c**) were chosen as the desymmetrizing agents. The results of the condition optimization are summarized in **Table 4.1**. To our delight, the reaction went smoothly with aminoindanol derived NHC catalysts **C1**. Sterically hindered 1-nathpthaldehyde (**4-2a**) led to a better result, compared to other two aldehydes (entry 1 *vs* entry 2 and 3). Screening of catalysts showed that the use of NHCs bearing an electron-withdrawing substituent like pentafluorophenyl or 2,4,6-trichlorophenyl could give similar yields and enantioselectivities (entry 4). Upon switching to an electron-donating mesityl group on the catalyst, the product could only be obtained in 55% yield and 60% ee along with much longer reaction time required (entry 5). It appears that NHCs with an electron-donating N-aryl substituent is not suitable for this esterification reaction. Further lowering of the catalyst loading to 5 mol% and temperature to -40^{o}C, the desired product was formed in excellent yield and enantioselectivity (entry 6). Screening of common solvents (DCM, Tol, and CH_3CN) and bases (Cs_2CO_3, K_2CO_3, and NaOAc) showed no better result than the combination of TEA and THF.

Table 4.1 Conditional Optimization[a]



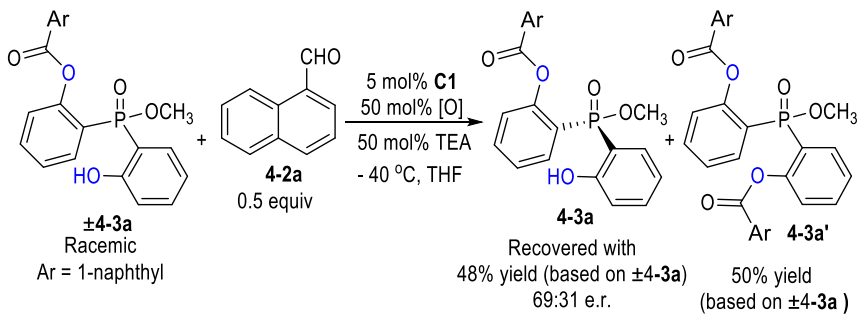
Entry[a]	NHC, Aldehyde	Condition	Yield (%)[b]	e.r.[c]
		entries 1-7, 10 mol% NHC, Et_3N, THF		
1	**C1, 4-2a**	rt, < 5 min	90	87:13
2	**C1, 4-2b**	rt, < 5 min	65	87:13
3	**C1, 4-2c**	rt, < 5 min	63	89:11
4	**C2, 4-2a**	rt, 5 min	87	88:12
5	**C3, 4-2a**	rt, 18 h	55	80:20
6	**C1, 4-2a**	-15 °C, 2h	96	93:7
7	**C1, 4-2a**	-40 °C, 2h	87	97:3
		entries 8-14, 5 mol% NHC, -40 °C, 24 h		
8	**C1, 4-2a**	Et_3N, THF	88	97:3
9	**C1, 4-2a**	Cs_2CO_3, THF	47	87:13
10	**C1, 4-2a**	K_2CO_3, THF	65	92:8
11	**C1, 4-2a**	NaOAc, THF	70	95:5
12	**C1, 4-2a**	Et_3N, DCM	69	93:7
13	**C1, 4-2a**	Et_3N, Tol	94	94:6
14	**C1, 4-2a**	Et_3N, CH_3CN	56	90:10

[a] Reactions conditions: phosphinate **4-1a** (0.1 mmol), aldehyde **4-2** (0.1 mmol), NHC (5-10 mol%), base (0.1 mmol) and oxidant (0.1 mmol) in 1 mL solvent. [b] Isolated yields after SiO_2 column chromatography. [c] Enantiomeric ratio determined *via* chiral phase HPLC analysis.

With the established optimal conditions in hand (entry 8, **Table 4.1**), we moved on to examine the substrate scope of the methodology. Electron-donating substituents such as methyl (**4-3b**) or methoxyl (**4-3c**) groups on the phenyl ring were well tolerated with excellent yield and good enantiomeric ratio. However, when an electron-withdrawing group such as a halogen atom on the phosphinate was installed (**4-3d**, **4-3e**, and **4-3f**), the

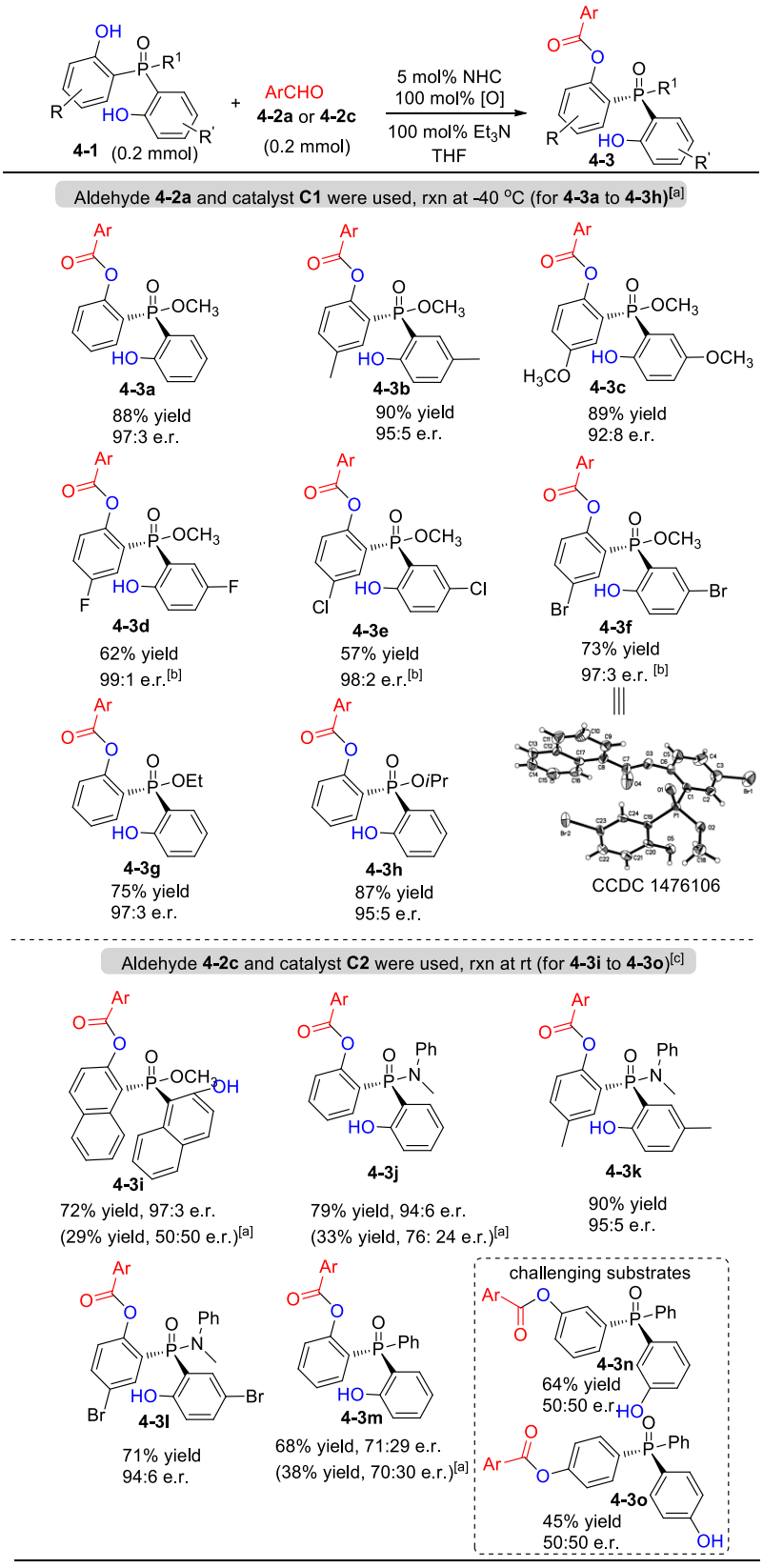
yield decreased to about 30% level, owing to the formation of the double-esterification byproduct. To address this issue, the aldehyde and TEA were slowly added by syringe pump, although some formation of the byproduct (~10% yield) was inevitable. A sterically crowded substrate (**4-3g**) could not give satisfactory results under the standard condition (29% yield, 50:50 e.r.), so a relative small aldehyde was considered be favorable for this substrate. Fortunately, it is found that mesitaldehyde (**4-2c**) instead of 1-naphthaldehyde (**4-2a**) proceeded well under the catalyst of **C2** with 72% yield and 97:3 e.r. Changing the methyl phosphinate to ethyl or isopropyl phosphinate (4-3h and **4-3i**) also led to encouraging results. Notably, bulkier phosphinamides (**4-3j**, **4-3k** and **4-3l**) were desymmetrized in good yield and enatiomeric ratio under the same condition of **4-3g**. Triaryl phosphorous oxide (**4-3m**) was also examined, and moderate yield and e.r. were obtained. Meta- and para- hydroxylphenyl phosphorous oxides (**4-3n** and **4-3o**) were extremely challenging under the reaction condition.

I suspected whether kinetic resolution occurred during the reaction process. Racemic **4-3a** was chosen as resolution substrate for control experiment. Moderate enantioselective **4-3a** was obtained in 48% recovered yield (**Scheme 4.5**). This result revealed that the kinetic resolution process had a positive effect on the enantioselectivity of the reaction. On the basis of above speculation, a good explanation could be made that the reactions with higher enantioselectivity sacrificed some reaction yield (**Table 4.2**, compared **4-3c** with **4-3d**, **4-3g** with **4-3h**).



Scheme 4.5 Kinetic resolution is not a main contributor for the observed enantioselectivity

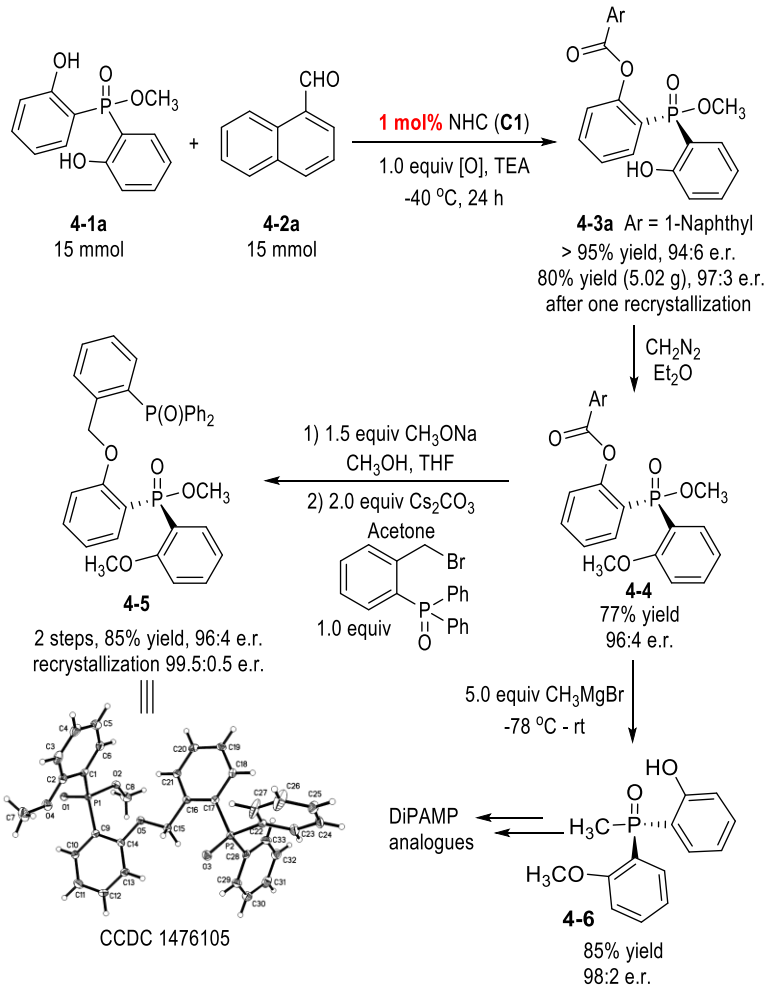
Table 4.2 Reaction Scope



[a] Reaction condition as in **Table 1**, entry 8 unless otherwise noted. [b] Slow addition of aldehyde (**4-2a**) and Et_3N in 1 mL THF to the reaction mixture *via* syringe pump; Absolutely configuration of the major

enantiomer was assigned on the basis of X-ray structure of **4-3f**. [c] Aldehyde **4-2c** and catalyst **C2** were used, and reactions were carried out at room temperature.

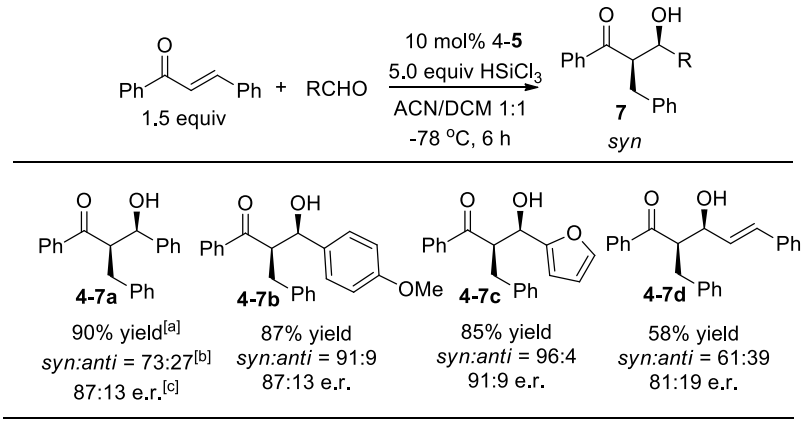
The strategy that desymmetrized bis(2-hydroxylphenyl) phosphinate to generate optical pure phosphorous compound is highly efficient, and can be scaled up to five grams (80% yield, 97:3 e.r., one single recystalization) by further cutting down the catalyst loading to 1 mol% (**Scheme 4.6**). The product (**4-3a**) has the advantage of possessing a free hydroxyl and –OMe group, which provides two paths for steady functionalization. First, the free –OH group was protected to methyl ether (**4-4**) by utilizing diazomethane in 77% yield combined with tiny enantioselectivity erosion (96:4 e.r.). Hydrolysis of the ester to introduce a second phosphorous oxide gave a bidentate Lewis base (**4-5**), while direct neucleophilic attack by MeMgBr gave **4-6** in excellent yield and e.r.



Scheme 4.6 Synthetic transformations of Product **4-3a**

The newly synthesized P-stereogenic bidentate Lewis base **4-5** can be directly used as a catalyst in the asymmetric tandem reaction.[12] The preliminary result indicated that **4-5** could promote the conjugate reduction of chalcone with trichlorosilane to form a trichlorosilyl enolate intermediate, which further underwent an aldol reaction with an aldehyde to deliver a *syn* product **4-7** (**Chart 4.2**). The inspiring result revealed that the novel P-stereogenic Lewis base as organocatalyst in asymmetric reaction has great potential for future syntheses.

Chart 4.2 Application of P-stereogenic phosphinate (**4-5**) as catalyst



[a] Isolated yield combined with diastereomers; [b] Determined by chiral phase HPLC analysis; [c] Enantiomeric ratio of major diastereomers.

4.4 Summary.

In summary, an efficient and facile procedure for the asymmetric desymmetrization of P-stereogenic molecules by oxidative NHC catalysis was developed. These optically rich phosphinates can be prepared in gram-scale with relatively low catalyst loading (1 mol%), owing to the high efficiency of the ester formation. The chiral phosphinates can be further transformed to other useful molecules such as organic catalyst, which are demonstrated to

be efficient for the asymmetric reductive adol reaction. Desymmetrizaton of more challenging compounds are currently ongoing.

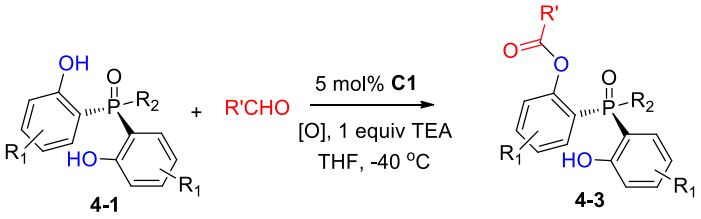
4.5 Experimental Section

4.5.1 General Information.

Commercially available materials purchased from Alfa Aesar or Sigma-Aldrich were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker (400 MHz) spectrometer. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00) or chloroform (δ = 7.26, singlet). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), dd (doublet of doublets) , tt (triplet of triplets); m (multiplets), and etc. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker (400 MHz) (100 MHz) spectrometer. High resolution mass spectral analysis (HRMS) was performed on Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). The determination of *e.e.* was performed via chiral HPLC analysis using Shimadzu LC-20AD HPLC workstation. X-ray crystallography analysis was performed on Bruker X8 APEX X-ray diffractionmeter. Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Jasco P-1030 polarimeter and are reported as follows: $[\alpha]^{rt}_D$ (*c* in g per 100 mL solvent). Analytical thin-layer chromatography (TLC) was carried out on Merck 60 F254 pre-coated silica gel plate (0.2 mm thickness). Visualization was performed using a UV lamp.

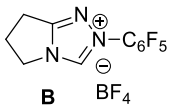
4.5.2 General Procedures for the Catalytic Reactions

Procedure for the Preparation of 4-3a to 3c, 4-3g, 4-3h

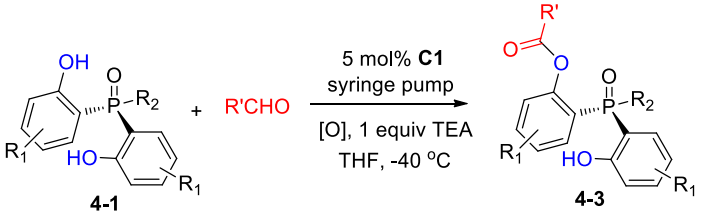


To a dry Schlenk tube equipped with a magnetic stir bar, was added phosphinate (0.2 mmol), aldehyde (0.2 mmol), triazolium salt **C1** (0.01 mmol), quinone oxidant (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (2 mL) was added and the reaction mixture was then stirred at -40 °C for 5 minutes, followed by triethylamine (0.2 mmol). The reaction was kept in this temperature for 24 hours. Upon the reaction completed, the mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel to afford the desired products.

Note: Racemic samples for chiral phase HPLC analysis were prepared using **B** as the NHC pre-catalyst. Absolute configuration of the product was assigned based on x-ray structure of **4-3f** and **4-5.**



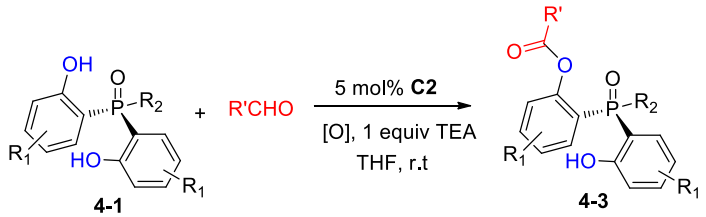
Procedure for the Preparation of 4-3d to 3f



To a dry Schlenk tube equipped with a magnetic stir bar, was added phosphinate (0.2 mmol), triazolium salt **C1** (0.01 mmol), quinone oxidant (0.2 mmol). The tube was closed

with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (2 mL) was added and the reaction mixture was then stirred at -40 ^{o}C for 5 minutes. Aldehyde (0.2 mmol) and triethylamine (0.2 mmol) were mixed in 1 mL THF and slowly added to the reaction mixture via syringe pump (0.1 mL /h). The reaction was kept in this temperature for another 12 hours. Upon the reaction completed, the mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel to afford the desired product **4-3d, 4-3e,** and **4-3f**.

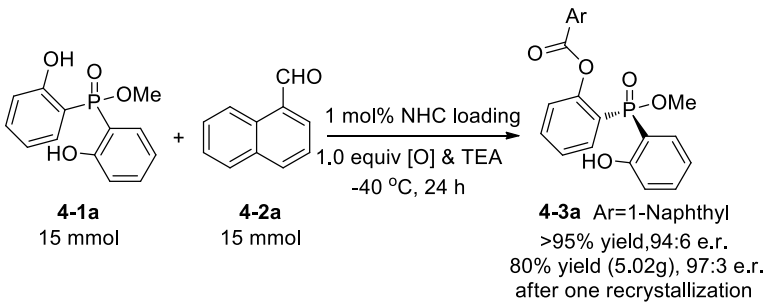
Procedure for the Preparation of 4-3i to 3o



To a dry Schlenk tube equipped with a magnetic stir bar, was added phosphorus substrate (0.2 mmol), mesitaldehyde (0.2 mmol), triazolium salt **C2** (0.01 mmol), triethylamine (0.2 mmol), quinone oxidant (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (2 mL) was added and the reaction mixture was then stirred at room temperature for 24 hours. Upon the reaction completed, the mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* column chromatography on silica gel to afford the desired product.

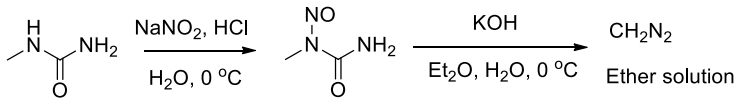
4.5.3 Synthetic Transformation

Gram-scale Reaction of 4-3a



To a dry 250 ml three-neck RBF equipped with a magnetic stir bar, was added phosphinate (15 mmol), triazolium salt **C1** (0.15 mmol), quinone oxidant (15 mmol). The flask was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (130 mL) was added and the reaction mixture was then stirred at -40 °C for 5 minutes. Aldehyde (15 mmol) and triethylamine (15 mmol) were mixed in 20 mL THF and slowly added to the reaction mixture via syringe pump (1 mL /h). The reaction was kept in this temperature for another 12 hours. Upon the reaction completed, the mixture was concentrated under reduced pressure. The resulting crude residue was purified *via* short pad of silica gel. Washed with 200 mL hexane/EA (20:1), discarded (oxidant portion), another 200 mL hexane/EA (1:1), concentrated under vacuum to give crude **4-3a** (>95% yield, 94:6 e.r.). After single recrystallization, **4-3a** was obtained 5.02 g (80% yield, 97:3 e.r.).

Preparation of CH_2N_2

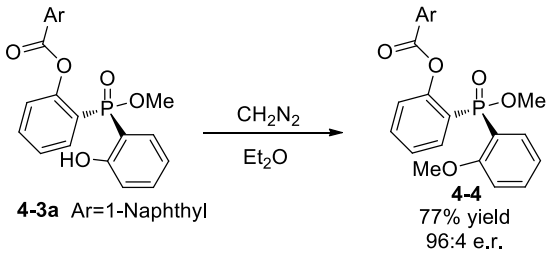


N-methylurea (14.8 g, 200 mmol) was dissolved in H_2O (120 mL). $NaNO_2$ (15.2 g, 220 mmol) was added and the mixture cooled to 0 ℃ in an ice bath. Conc. aq. HCl (26.7 mL, 0.26 mol) was added dropwise over a period of 1 h. The mixture was left to stir for 30 min at 0 ℃. The precipitate was filtered off, washed with H_2O (*ca*. 20 mL), dried under

vacuum. *N*-Methyl-*N*-nitrosourea was obtained as a light beige powder (16.4 g, 159 mmol, 79%) and was found to be sufficiently pure for further reactions. It was stored at –28 ℃.

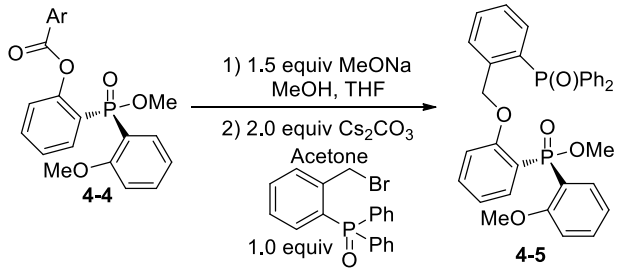
A 100 mL Erlenmeyer flask containing a stir bar was filled with 30 mL of Et_2O and 3.0 g of N-methyl-N-nitrosourea. The flask was then placed in an ice bath, and 12 mL of 50% KOH (aq) solution was added slowly. After stirring for 10 minutes, the neon-yellow ether layer was separated, and directly used in the next step.

Preparation of 4-4



To a 100 ml RBF equipped with a magnetic stir bar, was added **4-3a** (5 mmol) and fresh prepared CH_2N_2 solution above (30 mL). The reaction was stirred for 2 hours opened to air in room temperature. After the reaction completed, the mixture was concentrated and purified via column chromatography on silica gel to afford **4-4.**

Preparation of 4-5

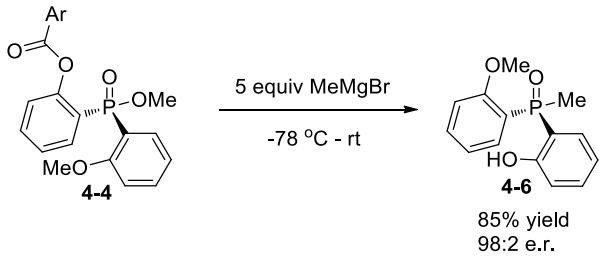


To a 50 ml RBF equipped with a magnetic stir bar, was added **4-4** (1 mmol)**,** MeONa (1.5 mmol), THF (10 mL), and MeOH (2 mL). The reaction was stirred overnight in room temperature. Quenched the reaction with 30 mL sat. NH_4Cl, and extracted with EA

(20mL*3). Combined the organic layer and dried with $MgSO_4$. The organic solvent was concentrated under vacuum to give crude methanolysis product.

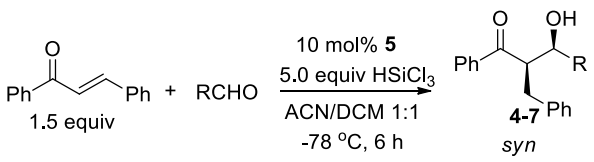
(2-(bromomethyl)phenyl)diphenylphosphine oxide (1 mmol), Cs_2CO_3 (2 mmol) and acetone (20 mL) were added to the above mixture. The flask was placed in 60 ^oC oil bath with water-jacketed condenser and stirred for 6 hours. After the reaction completed, the mixture was filtered. Then the filtrate was evaporated and the crude mixture was purified via column chromatography on silica gel to afford **4-5**.

Preparation of 4-6



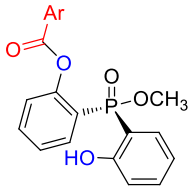
To a dry Schlenk tube equipped with a magnetic stir bar, was added phosphinate **4-4** (0.2 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Freshly distilled THF (2 mL) was added and the reaction mixture was then stirred at dry-ice-acetone bath for 5 minutes, followed by MeMgBr solution (1 mmol) dropwise. The reaction was allowed to warm up to room temperature. Upon the reaction completed, the mixture was quenched with sat. NH_4Cl (10 mL), extracted by EA (10 mL*3), dried with $MgSO_4$. The organic solvent was concentrated under reduced pressure, and the resulting crude residue was purified *via* column chromatography on silica gel to afford the desired product **4-6**.

Preparation of 4-7



To a dry Schlenk tube equipped with a magnetic stir bar, was added chalcone (0.15 mmol), aldehyde (0.1 mmol) and **4-5** (0.01 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen. Dried acetonitrile and dichloromethane (1 mL, 1:1) was added and the reaction mixture was cooling down to -78 ^{o}C. Then, trichlorosilane (0.5 mmol) was added. Upon the reaction was completed, saturated aqueous $NaHCO_3$ (5 mL) was required to quench the reaction. The mixture was extracted with dichloromethane. Combined the organic layer and dried with Na_2SO_4. Evaporated the solvent and the crude product was purified by chromatography.

4.5.4 Characterization of Product

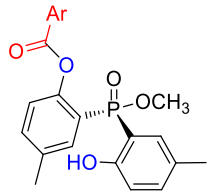


Ar = 1-naphthyl

4-3a

(R)-2-((2-hydroxyphenyl)(methoxy)phosphoryl)phenyl 1-naphthoate (3a). White solid, yield: 74 mg (88%); $[\alpha]_D^{20}$ = -89.9 °(c 4.9, $CHCl_3$); mp 125 – 128 ^{o}C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.61 (s, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 8.45 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.98 (ddd, *J* = 13.2, 7.6, 1.6 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.72 – 7.63 (m, 1H), 7.61 – 7.51 (m, 3H), 7.41 (tdd, *J* = 8.0, 2.8, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.0, 5.6 Hz, 1H), 7.17 – 7.00 (m, 2H), 6.77 – 6.64 (m, 1H), 6.53 – 6.44 (m, 1H), 3.66 (d, *J* = 11.6 Hz, 3H)； **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.4, 163.0 (d, *J* = 5.4 Hz), 152.9 (d, *J* = 3.5 Hz), 134.9 (d, *J* = 2.2 Hz), 134.7, 134.2 (d, *J* = 2.0 Hz), 133.7, 133.3 (d, *J* = 6.1 Hz), 132.1, 131.8, 131.4 (d, *J* = 9.8 Hz), 128.6, 128.1, 126.2, 125.9 (d, *J* = 12.1 Hz), 125.7, 124.5, 124.40, 124.36 (d, *J* = 12.1 Hz), 123.5 (d, *J* = 146.5 Hz), 119.3 (d, *J* = 13.4 Hz), 117.7 (d, *J* = 9.5 Hz), 109.8 (d, *J* = 133.6 Hz), 51.7 (d, *J* = 5.8 Hz)； **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 38.3； **IR (*ν* cm^{-1})** 3065, 3051, 2949, 2847, 2716, 1732, 1595, 1508,

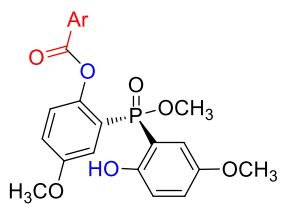
1445, 1240, 1184, 1111, 1030, 978, 804, 781, 756; **HRMS (ESI)** calcd for $C_{24}H_{20}O_5P$ $(M+H)^+$: 419.1048 Found: 419.1049; 98:2 e.r. as determined by HPLC (ADH, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 18.2 min, $t_{r\ min}$ = 24.3 min.



Ar = 1-naphthyl

4-3b

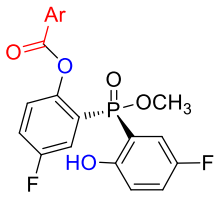
(R)-2-((2-hydroxy-5-methylphenyl)(methoxy)phosphoryl)-4-methylphenyl 1-naphthoate (4-3b). White solid, yield: 80 mg (90%); $[\alpha]_D^{20}$ = -70.0 °(c 6.7, $CHCl_3$); mp 95 – 100 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.44 (d, *J* = 1.2 Hz, 1H), 8.90 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 13.2 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.46 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.22 (dd, *J* = 8.5, 6.1 Hz, 1H), 6.91 (d, *J* = 15.2 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.41 – 6.34 (m, 1H), 3.64 (d, *J* = 11.6 Hz, 3H), 2.44 (s, 3H), 2.02 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.6, 160.7 (d, *J* = 5.3 Hz), 150.3 (d, *J* = 3.5 Hz), 135.8, 135.74, 135.72, 134.8 (d, *J* = 2.2 Hz), 134.5, 133.6, 133.5 (d, *J* = 6.0 Hz), 131.9, 131.7, 130.7 (d, *J* = 9.9 Hz), 128.5, 128.3 (d, *J* = 13.4 Hz), 127.9, 126.2, 125.6, 124.4, 124.3, 124.0 (d, *J* = 8.8 Hz), 123.1 (d, *J* = 144.1 Hz), 117.4 (d, *J* = 10.2 Hz), 109.5 (d, *J* = 132.8 Hz), 51.5 (d, *J* = 5.8 Hz), 20.8, 20.1; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 38.5; **IR (*v* cm^{-1})** 3086, 3051, 2947, 2847, 2735, 1738, 1593, 1485, 1408, 1292, 1238, 1201, 1184, 1030, 980, 899; **HRMS (ESI)** calcd for $C_{26}H_{24}O_5P$ $(M+H)^+$: 447.1361 Found: 447.1358; 95:5 e.r. as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 30.0 min, $t_{r\ min}$ = 26.8 min.



Ar = 1-naphthyl

4-3c

(R)-2-((2-hydroxy-5-methoxyphenyl)(methoxy)phosphoryl)-4-methoxyphenyl 1-naphthoate (4-3c). White solid, yield: 85 mg (89%); $[\alpha]_D^{20}$ = -63.0 °(c 5.9, $CHCl_3$); mp 130 – 133 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.17 (s, 1H), 8.90 (d, *J* = 8.8 Hz, 1H), 8.43 (d, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.62 – 7.51 (m, 3H), 7.48 (dd, *J* = 14.0, 2.8 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.19 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.70 – 6.58 (m, 2H), 6.43 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.87 (s, 3H), 3.66 (d, *J* = 11.6 Hz, 3H), 3.55 (s, 3H)； **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.0, 157.1, 157.0 (d, *J* = 9.4 Hz), 152.2 (d, *J* = 16.4 Hz), 145.9 (d, *J* = 3.0 Hz), 134.6, 133.7, 131.9, 131.7, 128.6, 128.0, 126.2, 125.6, 125.4 (d, *J* = 10.0 Hz), 124.4, 124.0 (d, *J* = 145.4 Hz), 122.3 (d, *J* = 3.0 Hz), 119.9 (d, *J* = 2.4 Hz), 118.8 (d, *J* = 11.6 Hz), 117.7 (d, *J* = 7.1 Hz), 114.1 (d, *J* = 11.1 Hz), 109.5 (d, *J* = 133.9 Hz), 55.9, 55.7, 51.8 (d, *J* = 5.8 Hz) ; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 37.6. **IR (*ν* cm^{-1})** 3092, 2951, 1728, 1504, 1485, 1267, 1184, 1117, 1030, 982; **HRMS (ESI)** calcd for $C_{26}H_{24}O_7P$ $(M+H)^+$: 479.1260 Found: 479.1261; 91:9 e.r. as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 77.5 min, $t_{r\ min}$ = 63.8 min.

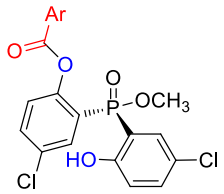


Ar = 1-naphthyl

4-3d

(R)-4-fluoro-2-((5-fluoro-2-hydroxyphenyl)(methoxy)phosphoryl)phenyl 1-naphthoate (4-3d). White solid, yield: 56 mg (62%); $[\alpha]_D^{20}$ = -95.5 °(c 2.8, $CHCl_3$); mp 190 – 193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 8.41 (d, *J* = 7.2 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.71 (ddd, *J* = 13.2, 8.0, 2.8 Hz, 1H), 7.64 – 7.50 (m, 3H), 7.43 – 7.29 (m, 2H), 6.84 – 6.74 (m, 2H), 6.44 – 6.35 (m, 1H), 3.69 (d, *J* = 11.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 159.7 (dd, *J* = 248.7, 16.9 Hz), 159.2 (dd, *J* = 4.9, 1.4 Hz), 155.4 (dd, *J* = 241.0, 18.7 Hz), 148.69,

148.69 (d, *J* = 6.0 Hz), 135.0, 133.7, 132.1, 131.7, 128.7, 128.3, 126.4, 126.3 (d, *J* = 8.0 Hz), 125.5, 124.8 (dd *J* = 145.6, 6.4 Hz), 124.4, 123.8, 122.7 (dd, *J* = 23.3, 2.3 Hz), 121.5 (dd, *J* = 23.5, 2.3 Hz), 119.8 (dd, *J* = 25.1, 6.2 Hz), 119.3 (dd, *J* = 11.5, 7.1 Hz), 116.2 (dd, *J* = 23.3, 10.7 Hz), 109.7 (dd, *J* = 135.0, 5.5 Hz), 52.1 (d, *J* = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 34.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -114.7, -123.6; IR (*v* cm^{-1}) 2951, 2872, 1738, 1732, 1476, 1418, 1246, 1175, 1105, 1063, 1078, 974; HRMS (ESI) calcd for $C_{24}H_{18}O_5PF_2$ $(M+H)^+$: 455.0860 Found: 455.0857; 99:1 e.r. as determined by HPLC (ADH, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 22.4 min, $t_{r\ min}$ = 19.4 min.

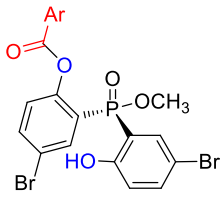


Ar = 1-naphthyl

4-3e

(R)-4-chloro-2-((5-chloro-2-hydroxyphenyl)(methoxy)phosphoryl)phenyl 1-naphthoate (4-3e). White solid, yield: 56 mg (57%); $[\alpha]_D^{20}$ = -70.4 °(c 1.4, $CHCl_3$); mp 184 – 186 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.47 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 8.40 (dd, *J* = 7.2, 0.8 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.00 (dd, *J* = 12.8, 2.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.66 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.56 (t, *J* = 8.0 Hz, 2H), 7.31 (dd, *J* = 8.8, 6.4 Hz, 1H), 7.08 (dd, *J* = 15.2, 2.8 Hz, 1H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.34 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.70 (d, *J* = 11.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.1, 161.5 (d, *J* = 5.1 Hz), 151.3 (d, *J* = 4.0 Hz), 135.15, 135.13, 134.5 (d, *J* = 2.0 Hz), 133.7, 133.0 (d, *J* = 6.1 Hz), 132.1, 131.9 (d, *J* = 16.2 Hz), 131.8, 130.1 (d, *J* = 11.1 Hz), 128.7, 128.3, 126.4, 126.0 (d, *J* = 9.1 Hz), 125.5, 124.9 (d, *J* = 146.5 Hz), 124.5, 124.4 (d, *J* = 18.2 Hz), 123.7, 119.4 (d, *J* = 11.1 Hz), 111.0 (d, *J* = 133.3 Hz), 52.1 (d, *J* = 6.1 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 34.4; **IR (*v* cm^{-1})** 3092, 2947, 1736, 1508, 1472, 1404, 1288, 1236, 1204, 1182, 1101, 1028, 974; **HRMS (ESI)**

calcd for $C_{24}H_{18}O_5PCl_2$ $(M+H)^+$: 487.0269 Found: 487.0261; 98:2 e.r. as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 15.9 min, $t_{r\ min}$ = 12.6 min.



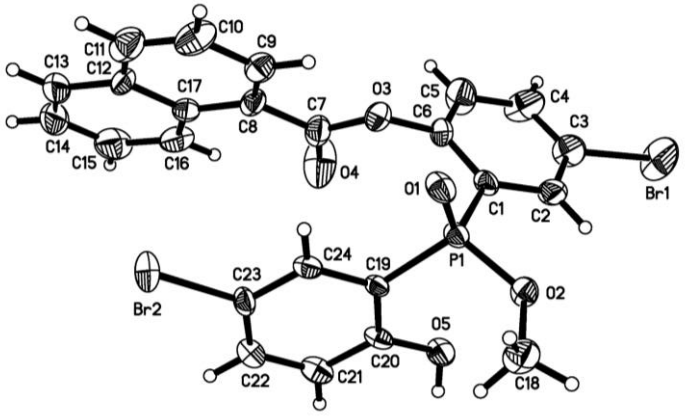
Ar = 1-naphthyl

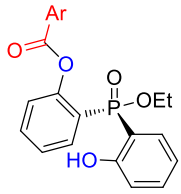
4-3f

(R)-4-bromo-2-((5-bromo-2-hydroxyphenyl)(methoxy)phosphoryl)phenyl 1-naphthoate (4-3f). White solid, yield: 56 mg (57%); $[\alpha]_D^{20}$ = -34.3 °(c 4.0, $CHCl_3$); mp 204 – 207 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.50 (s, 1H), 8.84 (d, *J* = 8.8 Hz, 1H), 8.40 (dd, *J* = 7.2, 0.8 Hz, 1H), 8.20 – 8.08 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.81 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.59 – 7.52 (m, 2H), 7.26 – 7.20 (m, 2H), 7.09 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.27 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.69 (d, *J* = 11.6 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.0, 161.9 (d, *J* = 5.2 Hz), 151.8 (d, *J* = 3.6 Hz), 137.9 (d, *J* = 2.1 Hz), 135.8 (d, *J* = 6.1 Hz), 135.1, 133.7, 133.0 (d, *J* = 10.7 Hz), 132.1, 131.7, 128.7, 128.3, 126.4, 126.3 (d, *J* = 8.9 Hz), 125.5, 125.2 (d, *J* = 144.1 Hz), 124.5, 123.6, 119.8 (d, *J* = 10.4 Hz), 119.4 (d, *J* = 15.2 Hz), 111.6 (d, *J* = 132.5 Hz), 111.3 (d, *J* = 17.0 Hz), 52.1 (d, *J* = 5.8 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 34.0; **IR (*ν* cm^{-1})** 3053, 2851, 1738, 1657, 1464, 1402, 1288, 1236, 1204, 1182, 1107, 1091, 1028, 974; **HRMS (ESI)** calcd for $C_{24}H_{18}O_5PBr_2$ $(M+H)^+$: 574.9259 Found: 574.9267; 95:5 e.r. as determined by HPLC (IB, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 16.4 min, $t_{r\ min}$ = 13.2 min.

Crystal Data and Structure Refinement for Enantiopure 4-3f

Relative configurations of the product **4-3** were assigned based on the crystal X-ray structures of **4-3f**. CCDC 1476106 (**4-3f**, obtained as colorless needles *via* evaporization of a hexane/EtOAc solution) contains the supplementary X-ray crystallographic data.



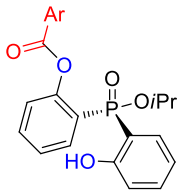


Ar = 1-naphthyl

4-3g

(R)-2-(ethoxy(2-hydroxyphenyl)phosphoryl)phenyl 1-naphthoate (4-3g). White solid, yield: 65 mg (75%); $[\alpha]_D^{20}$ = -70.8 °(c 3.1, $CHCl_3$); mp 177 – 182 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.68 (s, 1H), 8.91 (d, *J* = 8.8 Hz, 1H), 8.46 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.99 (ddd, *J* = 12.8, 7.6, 1.6 Hz, 1H), 7.94 – 7.85 (m, 1H), 7.71 – 7.62 (m, 1H), 7.61 – 7.51 (m, 3H), 7.41 (tdd, *J* = 7.6, 2.4, 0.8 Hz, 1H), 7.35 (ddd, *J* = 8.4, 5.6, 0.8 Hz, 1H), 7.17 – 7.08 (m, 2H), 6.76 – 6.64 (m, 1H), 6.54 – 6.44 (m, 1H), 4.25 – 4.05 (m, 1H), 4.00 – 3.82 (m, 1H), 1.19 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.4, 162.8 (d, *J* = 5.4 Hz), 152.8 (d, *J* = 3.5 Hz), 134.8, 134.7 (d, *J* = 2.2 Hz), 134.1 (d, *J* = 2.0 Hz), 133.7, 133.3 (d, *J* = 6.0 Hz), 132.2, 131.8, 131.4 (d, *J* = 9.8 Hz), 128.6, 128.0, 126.2, 125.8 (d, *J* = 12.2 Hz), 125.7, 124.4, 124.3 (d, *J* = 8.2 Hz), 124.2, 123.9 (d, *J* = 145.0 Hz), 119.3 (d, *J* = 13.3 Hz), 117.7 (d, *J* = 9.5 Hz), 110.62 (d, *J* = 133.3 Hz), 61.68

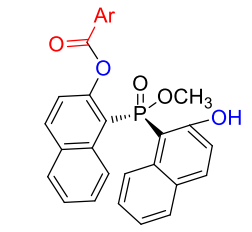
(d, *J* = 5.7 Hz), 16.1 (d, *J* = 6.7 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 36.4; **IR (*ν* cm^{-1})** 3231, 1734, 1653, 1610, 1445, 1303, 1242, 1202, 1186, 1113, 1015, 947; **HRMS (ESI)** calcd for $C_{25}H_{22}O_5P$ $(M+H)^+$: 433.1205 Found: 433.1201; 97:3 e.r. as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 17.4 min, $t_{r\ min}$ = 23.1 min.



Ar = 1-naphthyl

4-3h

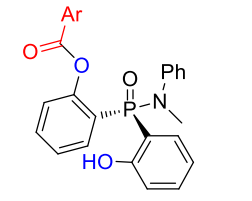
(R)-2-((2-hydroxyphenyl)(isopropoxy)phosphoryl)phenyl 1-naphthoate (3h). White solid, yield: 78 mg (87%); $[\alpha]_D^{20}$ = -72.5 ° (c 8.2, $CHCl_3$); mp 116 – 122 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.80 (s, 1H), 8.92 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.01 (ddd, *J* = 12.4, 7.6, 1.6 Hz, 1H), 7.92 – 7.85 (m, 1H), 7.64 (td, *J* = 7.2, 0.4 Hz, 1H), 7.60 – 7.48 (m, 3H), 7.40 (td, *J* = 7.6, 2.8 Hz, 1H), 7.32 (ddd, *J* = 8.1, 5.6, 0.7 Hz, 1H), 7.17 – 7.05 (m, 2H), 6.69 (tdd, *J* = 7.6, 2.8, 0.8 Hz, 1H), 6.51 – 6.40 (m, 1H), 4.70 – 4.53 (m, 1H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.3, 162.6 (d, *J* = 5.4 Hz), 152.8 (d, *J* = 3.7 Hz), 134.8, 134.5 (d, *J* = 1.9 Hz), 133.9 (d, *J* = 1.8 Hz), 133.7, 133.2 (d, *J* = 5.6 Hz), 132.3, 131.8, 131.5 (d, *J* = 10.0 Hz), 128.5, 128.0, 126.1, 125.7, 125.6, 124.4, 124.3 (d, *J* = 145.6Hz), 124.2 (d, *J* = 8.1 Hz), 124.1, 119.1 (d, *J* = 13.4 Hz), 117.6 (d, *J* = 9.5 Hz), 111.4 (d, *J* = 130.0 Hz), 71.3 (d, *J* = 5.8 Hz), 24.3 (d, *J* = 3.0 Hz), 23.5 (d, *J* = 5.4 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 34.8; **IR (*ν* cm^{-1})** 3069, 2980, 2933, 1736, 1595, 1474, 1445, 1304, 1240, 1184, 1111, 978; **HRMS (ESI)** calcd for $C_{26}H_{24}O_5P$ $(M+H)^+$: 447.1361 Found: 447.1360; 96:4 e.r. as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 14.6 min, $t_{r\ min}$ = 19.0 min.



Ar = 2,4,6-trimethylphenyl

4-3i

(R)-1-((2-hydroxynaphthalen-1-yl)(methoxy)phosphoryl)naphthalen-2-yl 2,4,6-trimethylbenzoate (4-3i). White solid, yield: 74 mg (72%); $[\alpha]_D^{20}$ = 25.3 °(c 1.7, $CHCl_3$); mp 213 – 219 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.21 (s, 1H), 8.73 (d, *J* = 14.8 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 5.6 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 16.4 Hz, 1H), 7.64 – 7.49 (m, 3H), 7.44 – 7.35 (m, 1H), 7.23 – 7.14 (m, 2H), 7.04 (d, *J* = 5.6 Hz, 1H), 6.95 (s, 2H), 3.80 (d, *J* = 11.6 Hz, 3H), 2.41 (s, 3H), 2.29 (s, 6H)； **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.8, 157.4 (d, *J* = 6.4 Hz), 147.1 (d, *J* = 4.1 Hz), 140.7, 137.4 (d, *J* = 2.0 Hz), 137.3, 136.6 (d, *J* = 6.4 Hz), 135.9 (d, *J* = 1.8 Hz), 134.3 (d, *J* = 8.8 Hz), 130.2 (d, *J* = 13.5 Hz), 129.2, 129.0, 128.5 (d, *J* = 2.7 Hz), 128.4, 127.5, 127.1 (d, *J* = 14.3 Hz), 126.7, 126.2, 123.4, 121.9 (d, *J* = 144.0 Hz), 120.2 (d, *J* = 7.8 Hz), 114.3 (d, *J* = 134.2 Hz), 111.6 (d, *J* = 9.3 Hz), 52.0 (d, *J* = 5.9 Hz). 21.3, 20.5; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 36.5; **IR (*ν* cm^{-1})** 3001, 2943, 2849, 1734, 1636, 1595, 1456, 1441, 1375, 1231, 1163, 1040, 918; **HRMS (ESI)** calcd for $C_{31}H_{27}O_5PNa$ $(M+Na)^+$: 533.1494 Found: 533.1492; 97:3 e.r. as determined by HPLC (IB, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 51.5 min, $t_{r\ min}$ = 17.0 min.

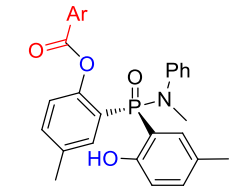


Ar = 2,4,6-trimethylphenyl

4-3j

(S)-2-((2-hydroxyphenyl)(methyl(phenyl)amino)phosphoryl)phenyl 2,4,6-trimethylbenzoate (4-3j). White solid, yield: 77 mg (87%); $[\alpha]_D^{20}$ = -7.7 °(c 6.0, $CHCl_3$);

mp 164 – 168 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 11.20 (s, 1H), 8.03 (ddd, *J* = 13.6, 7.6, 1.2 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.43 (dd, *J* = 8.0, 4.8 Hz, 1H), 7.33 (td, *J* = 7.6, 1.6 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.14 (dd, *J* = 14.0, 7.6 Hz, 1H), 7.10 – 7.01 (m, 4H), 7.01 – 6.93 (m, 3H), 6.78 (dd, *J* = 8.4, 5.6 Hz, 1H), 6.49 (td, *J* = 7.6, 2.8 Hz, 1H), 3.07 (d, *J* = 10.0 Hz, 3H), 2.39 (s, 6H), 2.36 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.8, 163.5 (d, *J* = 5.5 Hz), 151.8, 144.5 (d, *J* = 2.7 Hz), 140.9, 137.4, 135.5 (d, *J* = 7.7 Hz), 134.3 (d, *J* = 2.2 Hz), 133.8 (d, *J* = 2.1 Hz), 132.3 (d, *J* = 8.2 Hz), 129.2, 128.9, 128.3, 125.7 (d, *J* = 12.3 Hz), 125.5 (d, *J* = 4.7 Hz), 125.2, 122.9 (d, *J* = 128.1 Hz), 122.7 (d, *J* = 7.5 Hz), 118.6 (d, *J* = 12.8 Hz), 117.9 (d, *J* = 9.6 Hz), 110.7 (d, *J* = 133.6 Hz), 38.6 (d, *J* = 5.2 Hz), 21.2, 20.7; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 33.2; **IR (*ν* cm^{-1})** 3061, 2972, 2934, 1744, 1611, 1578, 1493, 1454, 1252, 1194, 1161, 1126, 1084, 1049, 1024, 891; **HRMS (ESI)** calcd for $C_{29}H_{29}NO_4P$ $(M+H)^+$: 486.1834 Found: 486.1837; 94:6 e.r. as determined by HPLC (ID, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 55.4 min, $t_{r\ min}$ = 34.0 min.

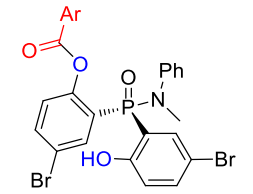


Ar = 2,4,6-trimethylphenyl

4-3k

(S)-2-((2-hydroxy-4-methylphenyl)(methyl(phenyl)amino)phosphoryl)-4-methylphenyl 2,4,6-trimethylbenzoate (4-3k). White solid, yield: 93 mg (87%); $[\alpha]_D^{20}$ = -18.4 °(c 4.5, $CHCl_3$); mp 187 – 190 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.99 (s, 1H), 7.88 (dd, *J* = 14.0, 2.0 Hz, 1H), 7.39 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.10 – 6.92 (m, 9H), 6.69 (dd, *J* = 8.4, 5.6 Hz, 1H), 3.04 (d, *J* = 10.4 Hz, 3H), 2.39 (s, 9H), 2.35 (s, 3H), 1.88 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.3, 161.3 (d, *J* = 5.1 Hz), 149.4, 144.7 (d, *J* = 2.6 Hz), 140.9, 137.5 (s), 136.0 (d, *J* = 7.6 Hz), 135.7 (d, *J* = 12.1 Hz), 135.2 (d, *J* = 2.4 Hz), 134.4 (d, *J* = 2.4 Hz), 132.0 (d, *J* = 8.5 Hz), 129.3, 128.8, 128.4 , 127.6 (d, *J* = 13.0 Hz), 125.3 (d, *J* = 4.9 Hz), 125.0, 122.6 (d, *J* = 8.1 Hz), 122.54 (d, *J* = 127.4 Hz),

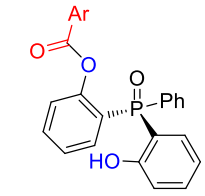
117.7 (d, *J* = 10.1 Hz), 110.5 (d, *J* = 133.0 Hz), 38.6 (d, *J* = 5.1 Hz), 21.22, 20.83, 20.71, 20.0; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 33.4; **IR (*ν* cm^{-1})** 3057, 2965, 2922, 1742, 1611, 1595, 1485, 1254, 1240, 1196, 1161, 1144, 1047, 1028, 895; **HRMS (ESI)** calcd for $C_{31}H_{33}NO_4P$ $(M+H)^+$: 514.2147 Found: 514.2144; 96:4 e.r. as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 15.5 min, $t_{r\ min}$ = 12.7 min.



Ar = 2,4,6-trimethylphenyl

4-3l

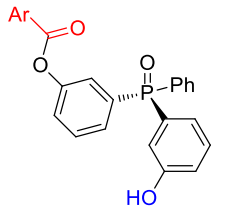
(S)-4-bromo-2-((4-bromo-2-hydroxyphenyl)(methyl(phenyl)amino)phosphoryl)phenyl 2,4,6-trimethylbenzoate (4-3l). White solid, yield: 93 mg (87%); $[\alpha]_D^{20}$ = 2.7 °(c 3.3, $CHCl_3$); mp 197 – 200 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 11.18 (s, 1H), 8.17 (dd, *J* = 13.6, 2.4 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.32 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.14 – 6.99 (m, 5H), 6.98 (s, 2H), 6.64 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.07 (d, *J* = 10.8 Hz, 3H), 2.42 (s, 6H), 2.36 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.7, 162.7 (d, *J* = 5.2 Hz), 150.7, 143.8 (d, *J* = 2.2 Hz), 141.3, 138.1 (d, *J* = 8.3 Hz), 137.6, 137.4 (d, *J* = 2.1 Hz), 137.0 (d, *J* = 2.1 Hz), 133.9 (d, *J* = 9.2 Hz), 129.6, 129.2, 127.5, 126.3, 126.2, 126.15, 124.9 (d, *J* = 8.2 Hz), 124.8 (d, *J* = 127.1 Hz), 120.2 (d, *J* = 10.4 Hz), 119.2 (d, *J* = 15.6 Hz), 112.2 (d, *J* = 132.7 Hz), 110.5 (d, *J* = 16.4 Hz), 38.89 (d, *J* = 4.9 Hz), 21.3, 20.9; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 30.2; **IR (*ν* cm^{-1})** 3088, 2999, 2938, 1751, 1611, 1491, 1460, 1400, 1375, 1238, 1198, 1161, 1088, 1024, 893; **HRMS (ESI)** calcd for $C_{29}H_{27}NO_4PBr_2$ $(M+H)^+$: 642.0044 Found: 642.0055; 94:6 e.r. as determined by HPLC (ADH, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 16.1 min, $t_{r\ min}$ = 14.1 min.



Ar = 2,4,6-trimethylphenyl

4-3m

(S)-2-((2-hydroxyphenyl)(phenyl)phosphoryl)phenyl 2,4,6-trimethylbenzoate (4-3m). White solid, yield: 71 mg (78%); $[\alpha]_D^{20}$ = -0.4 ° (c 6.0, $CHCl_3$); mp 175 – 179 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.97 (s, 1H), 7.71 – 7.58 (m, 4H), 7.58 – 7.52 (m, 1H), 7.52 – 7.45 (m, 1H), 7.41 – 7.27 (m, 4H), 6.91 (ddd, *J* = 13.6, 7.6, 1.6 Hz, 1H), 6.83 – 6.79 (m, 1H), 6.79 (s, 2H), 6.62 (tdd, *J* = 7.6, 2.4, 0.8 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 6H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.2, 163.8 (d, *J* = 3.1 Hz), 152.6 (d, *J* = 2.1 Hz), 140.6, 137.5, 134.4 (d, *J* = 8.3 Hz), 134.1 (d, *J* = 2.1 Hz), 132.3 (d, *J* = 2.8 Hz), 131.8 (d, *J* = 10.3 Hz), 131.4 (d, *J* = 107.8 Hz), 131.2 (d, *J* = 10.6 Hz), 128.9, 128.6 (d, *J* = 12.8 Hz), 127.5, 125.4 (d, *J* = 11.7 Hz), 123.7 (d, *J* = 102.7 Hz), 122.8 (d, *J* = 6.4 Hz), 118.7 (d, *J* = 12.8 Hz), 118.4 (d, *J* = 7.8 Hz), 110.8 (d, *J* = 107.4 Hz), 21.2, 20.5; **^{31}P NMR (162 MHz, $CDCl_3$):** δ 36.6; IR (ν cm^{-1}) 3034, 2922, 2857, 1741, 1611, 1576, 1443, 1379, 1300, 1238, 1198, 1161, 1107, 1049, 1024; HRMS (ESI) calcd for $C_{28}H_{26}O_4P$ $(M+H)^+$: 457.1569 Found: 457.1569; 71:29 e.r. as determined by HPLC (ADH, 85:15 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 20.2 min, $t_{r\ min}$ = 15.2 min.

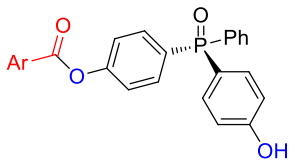


Ar = 2,4,6-trimethylphenyl

4-3n

3-((3-hydroxyphenyl)(phenyl)phosphoryl)phenyl 2,4,6-trimethylbenzoate (4-3n). White solid, yield: 58 mg (64%); mp 190 – 192 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.34 (s, 1H), 8.07 (d, *J* = 14.0 Hz, 1H), 7.66 (dd, *J* = 12.4, 7.2 Hz, 2H), 7.57 – 7.40 (m, 7H), 7.27 – 7.20 (m, 1H), 7.08 – 7.02 (m, 1H), 6.89 (s, 2H), 6.74 (dd, *J* = 12.0, 7.6 Hz, 1H),

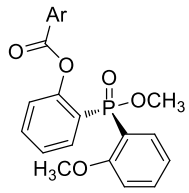
2.38 (s, 6H), 2.30 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 168.0, 158.6 (d, *J* = 14.6 Hz), 150.8 (d, *J* = 16.0 Hz), 140.2, 135.8, 134.0 (d, *J* = 103.8 Hz), 132.3 (d, *J* = 2.7 Hz), 132.1, 132.0, 131.8 (d, *J* = 38.2 Hz), 130.8 (d, *J* = 38.4 Hz), 129.9 (d, *J* = 13.8 Hz), 129.6 (d, *J* = 7.8 Hz), 129.5 (d, *J* = 1.7 Hz), 129.4, 125.5 (d, *J* = 2.4 Hz), 125.2 (d, J = 10.9 Hz), 122.4 (d, *J* = 12.2 Hz), 120.4 (d, *J* = 2.7 Hz), 119.3 (d, *J* = 8.7 Hz), 21.2, 20.1; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 30.7 **IR (*ν* cm^{-1})** 3063, 2924, 2858, 1746, 1611, 1580, 1439, 1416, 1269, 1242, 1200, 1163, 1117, 1049, 997; δ 30.7; HRMS (ESI) calcd for $C_{28}H_{26}O_4P$ $(M+H)^+$: 457.1572 Found: 457.1569.



Ar = 2,4,6-trimethylphenyl

4-3o

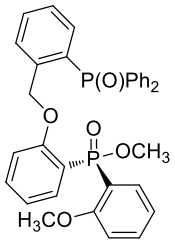
4-((4-hydroxyphenyl)(phenyl)phosphoryl)phenyl 2,4,6-trimethylbenzoate (4-3o). White solid, yield: 41 mg (45%); mp 107 – 116 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 10.42 (*br*s, 1H), 7.77 – 7.63 (m, 4H), 7.57 – 7.50 (m, 1H), 7.49 – 7.30 (m, 6H), 6.97 (dd, *J* = 8.8, 2.4 Hz, 2H), 6.92 (s, 2H), 2.42 (s, 6H), 2.31 (s, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 167.8, 161.9 (d, *J* = 2.8 Hz), 153.7 (d, *J* = 3.1 Hz), 140.4, 135.9, 133.9 (d, *J* = 11.8 Hz), 133.8 (d, *J* = 11.2 Hz), 132.1, 132.0, 131.99 (d, *J* = 106.1 Hz), 129.9 (d, *J* = 107.0 Hz), 129.3, 128.8, 128.6 (d, *J* = 12.3 Hz), 121.9 (d, *J* = 13.0 Hz), 119.8 (d, *J* = 114.1 Hz), 116.4 (d, *J* = 13.6 Hz), 21.2, 20.1; **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 31.2; **IR (*ν* cm^{-1})** 3061, 2926, 2860, 1746, 1600, 1582, 1504, 1435, 1287, 1244, 1202, 1163, 1120, 1047, 910; **HRMS (ESI)** calcd for $C_{28}H_{26}O_4P$ $(M+H)^+$: 457.1567 Found: 457.1569.



Ar = 1-naphthyl

4-4

(R)-2-(methoxy(2-methoxyphenyl)phosphoryl)phenyl 1-naphthoate (4-4). White solid, yield: 1.67 g (77%); $[\alpha]_D^{20}$ = 35.1 °(c 2.2, $CHCl_3$); mp 117 – 123 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.92 (d, *J* = 8.8 Hz, 1H), 8.20 (dd, *J* = 13.2, 7.6 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.47 (m, 4H), 7.47 – 7.39 (m, 2H), 7.27 – 7.16 (m, 2H), 6.80 – 6.69 (m, 1H), 6.51 (td, *J* = 7.6, 2.0 Hz, 1H), 3.69 (d, *J* = 11.2 Hz, 3H), 3.56 (d, *J* = 2.4 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 164.4, 161.0 (d, *J* = 4.7 Hz), 151.9 (d, *J* = 3.4 Hz), 134.7 (d, *J* = 6.2 Hz), 134.3, 133.9 (d, *J* = 1.6 Hz), 133.8 (d, *J* = 5.8 Hz), 133.6, 133.0 (d, *J* = 2.0 Hz), 132.0, 131.7, 128.4, 127.9, 126.1, 125.6, 125.5 (d, *J* = 12.0 Hz), 125.0 (d, *J* = 137.4 Hz), 124.3, 124.2, 123.4 (d, *J* = 7.8 Hz), 120.0 (d, *J* = 12.6 Hz), 118.8 (d, *J* = 143.9 Hz), 111.2 (d, *J* = 8.1 Hz), 55.5, 51.2 (d, *J* = 5.7 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 26.7; **IR (*ν* cm^{-1})** 3067, 3011, 2945, 1732, 1593, 1576, 1508, 1479, 1435, 1277, 1240, 1184, 1113, 1026, 980; **HRMS (ESI)** calcd for $C_{25}H_{22}O_5P$ $(M+H)^+$: 433.1205 Found: 433.1211; 97:3 e.r. as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 21.6 min, $t_{r\ min}$ = 19.4 min.



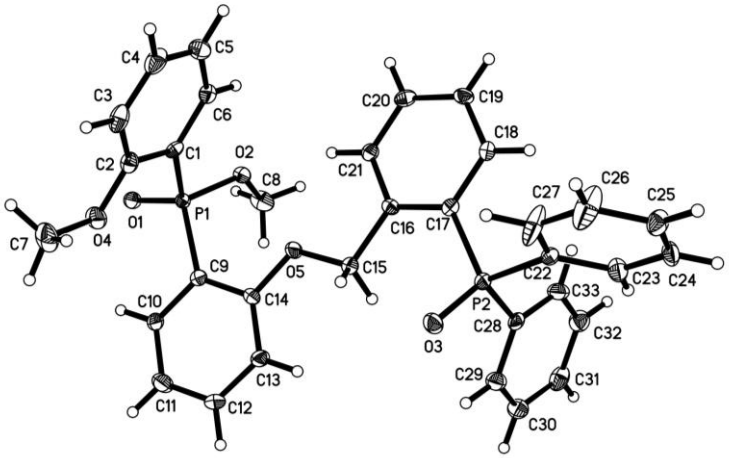
4-5

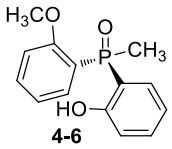
(R)-methyl (2-((2-(diphenylphosphoryl)benzyl)oxy)phenyl)(2-methoxyphenyl)phosphinate (4-5). White solid, yield: 481 mg (85%); $[\alpha]_D^{20}$ = 40.3 °(c 1.2, $CHCl_3$); mp 183 – 185 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.01 – 7.88 (m, 2H), 7.68

– 7.57 (m, 4H), 7.58 – 7.50 (m, 2H), 7.50 – 7.34 (m, 7H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.22 – 7.13 (m, 1H), 7.04 – 6.91 (m, 3H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.60 (t, *J* = 7.2 Hz, 1H), 5.30 (dd, *J* = 18.4, 15.2 Hz, 2H), 3.73 (dd, *J* = 11.2, 2.0 Hz, 3H), 3.54 (d, *J* = 2.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 160.8 (d, *J* = 4.4 Hz), 159.1 (d, *J* = 4.1 Hz), 141.8 (d, *J* = 7.1 Hz), 134.5 (d, *J* = 6.4 Hz), 134.4 (d, *J* = 6.3 Hz), 133.506 (d, *J* = 5.1 Hz), 133.505 (d, *J* = 1.2 Hz), 132.4, 132.0 (d, *J* = 2.4 Hz), 131.9 (d, *J* = 118.2 Hz), 131.86 (d, *J* = 5.1 Hz), 131.86, 131.7, 131.6, 128.5 (d, *J* = 3.3 Hz), 128.43 (d, *J* = 100.2 Hz), 128.36 (d, *J* = 3.3 Hz), 127.5 (d, *J* = 9.7 Hz), 126.3 (d, *J* = 12.6 Hz), 120.1 (d, *J* = 10.0 Hz), 120.0 (d, *J* = 10.1Hz) 119.7 (d, *J* = 140.2 Hz), 119.3 (d, *J* = 139.9 Hz) 111.9 (d, *J* = 7.8 Hz), 111.1 (d, *J* = 7.9 Hz), 67.1 (d, *J* = 4.8 Hz), 55.41, 50.9 (d, *J* = 5.7 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 31.4, 28.9; **IR (*ν* cm^{-1})** 3059, 2974, 2841, 1591, 1479, 1437, 1279, 1248, 1223, 1182, 1028; **HRMS (ESI)** calcd for $C_{33}H_{31}O_5P_2$ $(M+H)^+$: 569.1647 Found: 569.1650; 96:4 e.r. as determined by HPLC (ODH, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\,maj}$ = 15.5 min, $t_{r\,min}$ = 22.2 min.

Crystal Data and Structure Refinement for Enantiopure 4-5

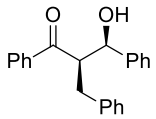
The absolute configurations of the product **4-5** were assigned based on the crystal X-ray structures. CCDC 1476105 (**4-5**, obtained as colorless needles *via* evaporization of a hexane/EtOAc solution) contains the supplementary X-ray crystallographic data.





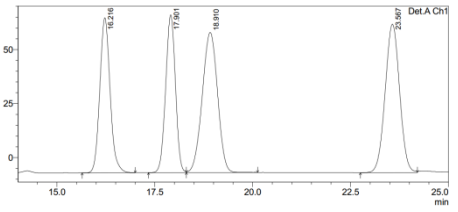
4-6

(S)-(2-hydroxyphenyl)(2-methoxyphenyl)(methyl)phosphine oxide (4-6). White solid, yield: 44 mg (85%); $[\alpha]_D^{20}$ = -140.7 °(c 2.4, $CHCl_3$); mp 221 – 224 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δ 11.27 (s, 1H), 7.77 (ddd, *J* = 14.0, 7.6, 2.0 Hz, 1H), 7.54 – 7.46 (m, 1H), 7.38 – 7.25 (m, 2H), 7.06 (tdd, *J* = 7.6, 2.0, 0.8 Hz, 1H), 6.96 – 6.87 (m, 2H), 6.84 (td, *J* = 8.0, 1.2 Hz, 1H), 3.88 (s, 3H), 2.15 (d, *J* = 14.0 Hz, 3H); **^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.1 (d, *J* = 2.8 Hz), 160.1 (d, *J* = 4.0 Hz), 134.3 (d, *J* = 2.1 Hz), 133.8 (d, *J* = 2.2 Hz), 133.7 (d, *J* = 7.1 Hz), 130.3 (d, *J* = 10.9 Hz), 121.1 (d, *J* = 99.8 Hz), 121.0 (d, *J* = 11.6 Hz), 118.8 (d, *J* = 12.6 Hz), 118.1 (d, *J* = 7.4 Hz), 113.6 (d, *J* = 103.4 Hz), 111.1 (d, *J* = 6.7 Hz), 55.4, 17.5 (d, *J* = 74.8 Hz); **^{31}P NMR (162 MHz, $CDCl_3$)**: δ 41.5; **IR (*ν* cm^{-1})** 3067, 2940, 2841, 1635, 1591, 1477, 1445, 1379, 1296, 1248, 1140, 1123, 1020, 891; **HRMS (ESI)** calcd for $C_{14}H_{16}O_3P$ $(M+H)^+$: 263.0837 Found: 263.0844; 98:2 e.r. as determined by HPLC (ID, 80:20 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ = 35.0 min, $t_{r\ min}$ = 33.6 min.



4-7a

(2R,3R)-2-benzyl-3-hydroxy-1,3-diphenylpropan-1-one (4-7a). 90% yield. The NMR data is in accord with literature[12b]. 73:27 d.r. and 87:13 e.r. as determined by HPLC (IC, 90:10 hexanes/*i*-PrOH, 0.5ml/min), $t_{r\ maj}$ (syn) = 17.9 min, $t_{r\ min}$ (syn)= 16.3 min. $t_{r\ maj}$ (anti) = 18.8 min, $t_{r\ min}$ (anti)= 23.4 min.



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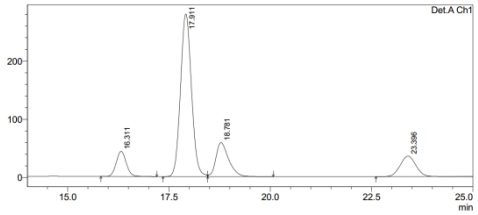
2	17.901	1270901	73027	20.786	26.230
3	18.910	1763897	64883	28.849	23.305
4	23.567	1760003	68686	28.785	24.671
Total		6114343	278409	100.000	100.000



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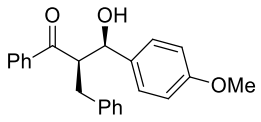
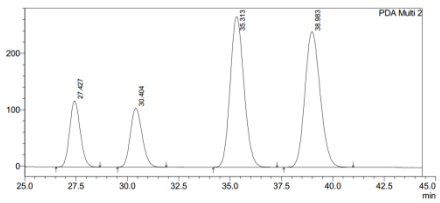
3	18.781	1278820	58402	15.536	14.044
4	23.396	946414	35341	11.498	8.498
Total		8231134	415855	100.000	100.000



4-7b

(2R,3R)-2-benzyl-3-hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (4-7b). 87% yield. The NMR data is in accord with literature[12b]. 91:9 d.r. and 87:13 e.r. as determined by HPLC (ADH, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ (syn) = 30.1 min, $t_{r\ min}$ (syn)= 27.1 min. $t_{r\ maj}$ (anti) = 35.0 min, $t_{r\ min}$ (anti)= 38.7 min.



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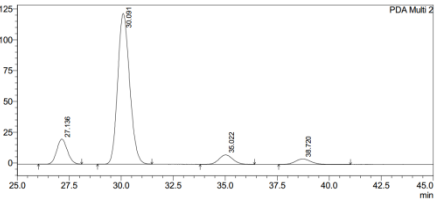
3	35.313	12536341	267738	37.424	36.624
4	38.983	12533264	241070	37.415	32.976
Total		33497884	731055	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	27.136	721623	20327	11.644	13.156
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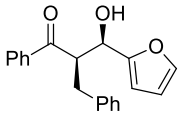
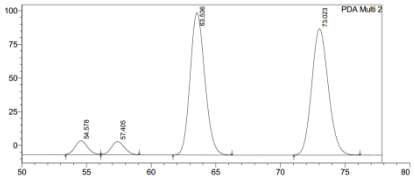
3	35.022	350969	7617	5.663	4.930
4	38.720	228890	4418	3.693	2.860
Total		6197634	154505	100.000	100.000



4-7c

(2R,3R)-2-benzyl-3-(furan-2-yl)-3-hydroxy-1-phenylpropan-1-one (4-7c). 85% yield. The NMR data is in accord with literature[12b]. 96:4 d.r. and 91:9 e.r. as determined by HPLC (ADH, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ (syn) = 65.7 min, $t_{r\ min}$ (syn)= 75.2 min. $t_{r\ maj}$ (anti) = 59.4 min, $t_{r\ min}$ (anti)= 56.5 min.



PDA Ch2 220nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
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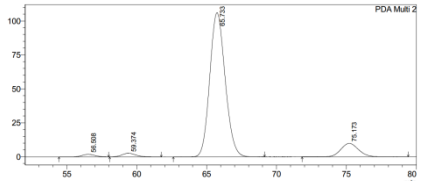
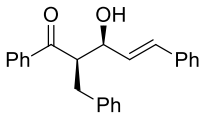
4	73.023	8413269	93743	46.247	42.717
Total		18192198	219449	100.000	100.000

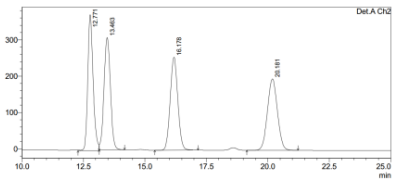


Peak#	Ret. Time	Area	Height	Area %	Height %
1	56.508	118422	1911	1.270	1.582
2	59.374	185625	2706	1.991	2.240
3	65.733	8137679	106251	87.283	87.934
4	75.173	881625	9962	9.456	8.245
Total		9323351	120831	100.000	100.000

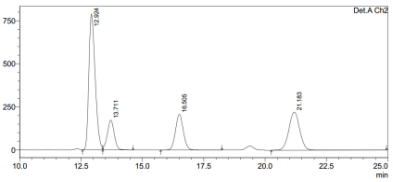


4-7d

(2R,3S,E)-2-benzyl-3-hydroxy-1,5-diphenylpent-4-en-1-one (7d). 58% yield. The NMR data is in accord with literature[12b]. 61:39 d.r. and 81:19 e.r. as determined by HPLC (IC, 90:10 hexanes/*i*-PrOH, 0.7ml/min), $t_{r\ maj}$ (syn) = 12.9 min, $t_{r\ min}$ (syn)= 13.7 min. $t_{r\ maj}$ (anti) = 21.2 min, $t_{r\ min}$ (anti)= 16.5 min.



Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.771	5610185	373951	25.196	32.942
2	13.463	5597636	308888	25.139	27.210
3	16.178	5515543	255886	24.771	22.541
4	20.181	5543043	196466	24.894	17.307
Total		22266407	1135191	100.000	100.000



Peak#	Ret. Time	Area	Height	Area %	Height %
1	12.924	14218290	790413	49.009	56.808
2	13.711	3368245	172983	11.610	12.433
3	16.505	4619999	207548	15.925	14.917
4	21.183	6804996	220431	23.456	15.843
Total		29011531	1391375	100.000	100.000

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