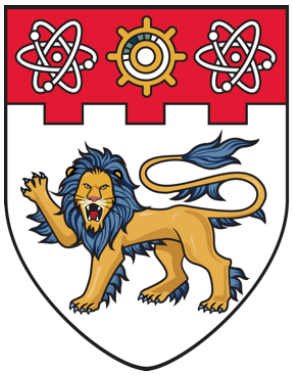

NANYANG TECHNOLOGICAL UNIVERSITY
SINGAPORE

CARBENE-CATALYZED ENANTIOSELECTIVE CARBON-HETEROATOM BOND (C-N, C-P, C-S) CONSTRUCTION

MAITI RAKESH

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2021

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

2021

Statement of Originality

I hereby certify that the work embodied in this thesis is the result of original research done by me except where otherwise stated in this thesis. The thesis work has not been submitted for a degree or professional qualification to any other university or institution. I declare that this thesis is written by myself and is free of plagiarism and of sufficient grammatical clarity to be examined. I confirm that the investigations were conducted in accord with the ethics policies and integrity standards of Nanyang Technological University and that the research data are presented honestly and without prejudice.

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Rakesh Maiti
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Dec 16, 2020
Date

Robin Chi
Professor Yonggui Robin Chi

Authorship Attribution Statement

This thesis contains material from 1 paper(s) published in the following peer-reviewed journal(s) / from papers accepted at conferences in which I am listed as an author.

Chapter 2 is published as Rakesh Maiti, Jun Xu, Jia-Lei Yan, Bivas Mondal, Xing Yang, Huifang Chai, Lin Hao, Zhichao Jin, and Yonggui Robin Chi, "Carbene-Catalyzed Selective Addition of Isothioureas to Enals for Access to Sulphur-Containing 5,6-Dihyropyrimidin-4-ones" *Org. Chem. Front.* Accepted (https://doi.org/10.1039/D0QO01380C)

The contributions of the co-authors are as follows:

- Prof. Chi conceptualized the project and revised the manuscript draft.
- I conducted the experiments and prepared the manuscript.
- Jun Xu checked the reproducibility of the reaction.
- Jia-Lei Yan, Bivas Mondal, Xing Yang, Prof. Huifang Chai, Lin Hao, Zhichao Jin, contributed to the discussion and manuscript revision.
- All authors contributed to discussions and manuscript preparation.

16/12/2020
Date

Rakesh Maiti
Rakesh Maiti

Abstract

Over the past decades, N-Heterocyclic carbene (NHC) has emerged as one of the crucial synthetic tools for asymmetric transformations of readily available materials into complex moieties. Particularly, a great deal of success has been achieved on the front of enantioselective carbon-carbon bond formation. However, in sharp contrast, NHC-mediated asymmetric carbon-heteroatom bond (C-X) construction was seldomly explored. In this thesis, I have disclosed three new NHC-catalyzed strategies to access asymmetric C-N, C-P, and C-S bonds.

In chapter 1, I have discussed briefly about the different activation modes, enabled by NHC catalysts and their applications in formation of complex structures. I have also demonstrated a few examples of carbon-heteroatom bond formation through NHC-catalysis.

In chapter 2, carbene-catalyzed selective addition of isothioureas to enals has been discussed for access to sulphur-bearing 5,6-dihydropyrimidin-4-ones (DHPMs). DHPM scaffolds were afforded in excellent yields and enantioselectivites (up to 90% yield and 96:4 e.r.). Moreover, the product from our catalytic cycle has also been converted to useful optically enriched dihyrouracil, dihydropyrimidine moieties.

In chapter 3, asymmetric construction of carbon-phosphorous (C-P) bond has been achieved via NHC-catalysis. The carbon-centered chiral tertiary phosphines were obtained in moderate to high yield (up to 86%) and excellent optical purity (up to 99:1 e.r.). Later, the transformation of the products to bidentate bis-phosphine and bifunctional phosphine has also been shown.

In chapter 4, an introduction of sulphur atom to the β-position of the less explored alkyne acyl azolium intermediate has been demonstrated. Through NHC-mediated asymmetric C-S bond formation strategy, challenging atroposelective axially chiral sulfone-containing styrene derivative has been obtained. Our catalytic cycle enabled to deliver the sulfone-containing axially chiral styrenes in excellent outcomes (up to 99% yield, >99:1 e.r. E/Z >99:1).

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Table of Contents

Publications

1. **Maiti, R.**; Xu, J.; Yan, J.-L.; Mondal, B.; Yang, X.; Chai, H.; Hao, L.; Jin, Z; and Chi, Y. R.; "Carbene-Catalyzed Selective Addition of Isothioureas to Enals for Access to Sulphur-Containing 5,6-Dihyropyrimidin-4-ones" *Org. Chem. Front.* **2021**, *8*, 743.

2. Wu, X.; Zhou, L.; **Maiti, R.**; Mou, C.; Pan, L.; and Chi, Y. R.; "Sulfinate and Carbene Co-catalyzed Rauhut-Currier Reaction for Enantioselective Access to Azepino[1,2-a]indole" *Angew. Chem. Int. Ed.* **2019**, *58*, 477.

3. Wu, X.; Hao, L.; Zhang, Y.; **Maiti**, **R.;** Reddi, R. N.; Yang, S.; Song, B.; and Chi, Y. R.; "Construction of Fused Pyrrolidines and β-Lactones by Carbene-Catalyzed C−N, C−C, and C−O Bond Formations" *Angew. Chem. Int. Ed*. **2017**, *56*, 4201.

4. **Maiti**, **R.;** Chi, Y. R.; "Carbene-Catalyzed Asymmetric Hydrophosphination of Bromoenals" Manuscript submitted.

5. Yan,[†] J.-L.; **Maiti**,[†] **R.;** ([†]equal contribution) and Chi, Y. R.; "Carbene-Catalyzed Atroposelective Access to Axially Chiral Sulfone-containing Styrenes" Manuscript in preparation.

Abbreviations

Ac	Acetyl
Ar	aryl
Boc	*tert*−butyloxycarbonyl
Bn	benzyl
Bu	butyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DKR	dynamic kinetic resolution
dr	diastereomeric ratio
e.r.	enantiomeric ratio
Equiv	equivalent
ESI	electrospray ionization
HRMS	High resolution mass spectrometry
HPLC	High-performance liquid chromatography
^{i}Pr	isopropyl
Mes	mesityl
NHC	*N*-heterocyclic carbene
TBS	tert-butyldimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
α	alpha

β	beta
γ	gamma
δ	delta
π	pi
σ	sigma
ω	Omega

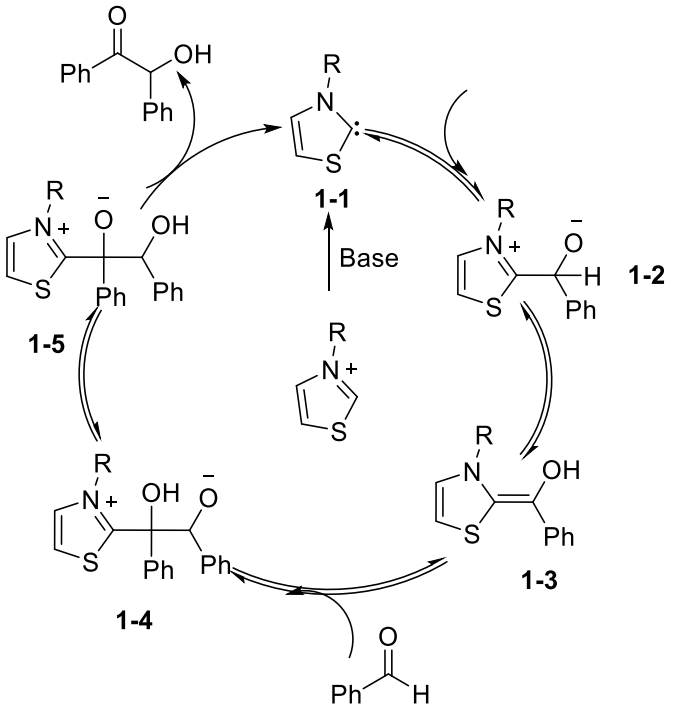
Chapter 1

Introduction

1.1 Introduction of N-Heterocyclic carbene (NHC) catalysis

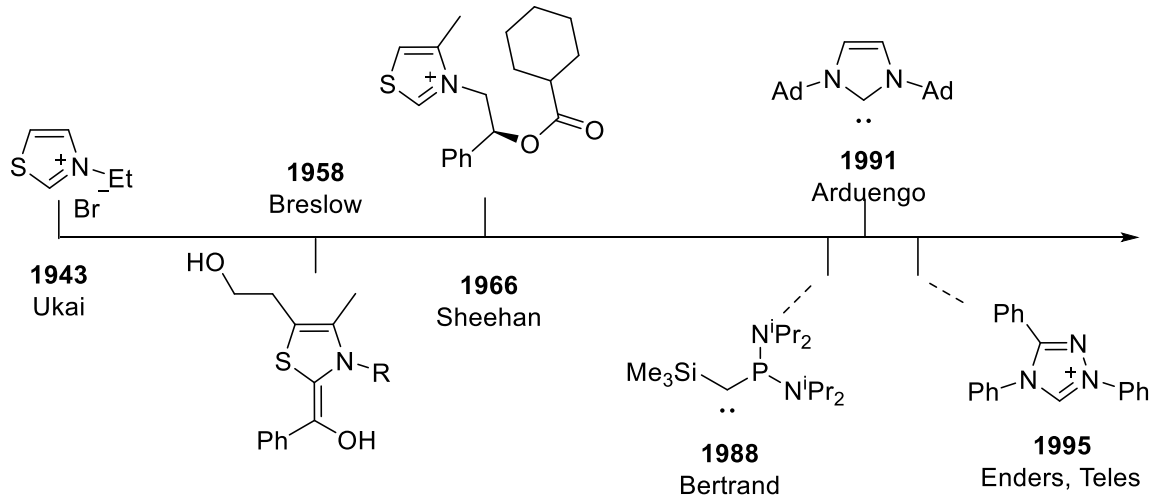
Since the early 2000s, N-heterocyclic carbenes (NHCs) as organocatalyst have experienced explosive and rapid development and emerged as a powerful tool to furnish complex molecules alongside other organocatalysts like proline, urea, thiourea etc.[1-4] Although, the utilization of the NHC-carbenes as a ligand in metal catalysis has been started and investigated thoroughly long before due to its strong electron-donating feature. The efficiency of carbenes in transition metal catalysis can easily be understandable by simply one gold standard example, Grubbs' second-generation metathesis catalyst.[5] The distinct electronic effect and steric property of carbene set up a special place in transition metal catalysis and open a new era of synthetic chemistry.

The first utilization of neutral two-electron-donor stable carbenes as organocatalyst was rightly judged by Ugai and co-workers[4] in 1943 when they successfully mimicked the benzoin reaction employing thiazolium carbene salts as organocatalyst instead of cyanide. Based on



Scheme 1.1 Breslow's mechanism of the Benzoin condensation catalyzed by NHC

previous work, the umpolung property of the carbonyl carbon of benzaldehyde under carbene catalysis has been explained remarkably by Breslow fifteen years later (Scheme 1.1).[6] According to Breslow's proposal, the actual catalytic species, free carbene **1-1** is generated from thiazolium salt after deprotonation by the base. Then, benzaldehyde is attacked by NHC to form a zwitter ion **1-2** by free carbene **1-1**. Afterwards, zwitterion **1-2** undergoes a proton transfer process to provide the key Breslow intermediate **1-3.** After that, the critical Breslow intermediate **1-3** reacts with another benzaldehyde to furnish the intermediate **1-4** which eventually undergoes a proton transfer process and provides intermediate **1-5**. Finally, Benzoin product is obtained from intermediate **1-5** after releasing the free carbene to complete the catalytic cycle. This most widely accepted reaction mechanism (Scheme 1.1) has established the backbone of NHC organocatalysis and helps others to explore more activation mode within this field. However, isolation of the free carbene has been successfully acheived after 30 years later by Bertrand when he prepared of phosphinosilyl-based carbene in 1988 (Scheme 1.2).[7]



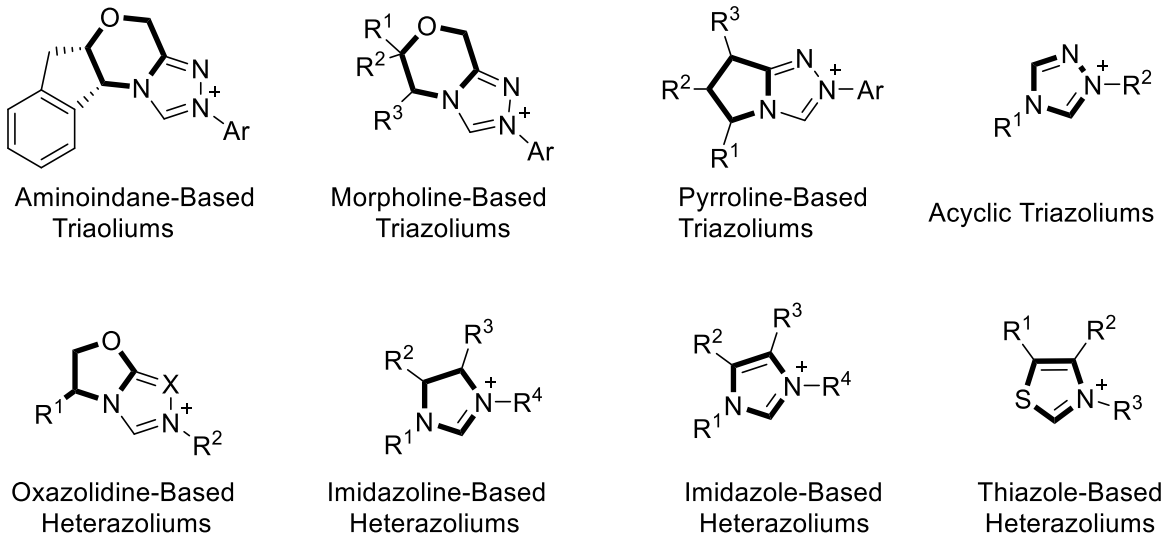
Scheme 1.2 Development of N-heterocyclic carbene (NHC) organocatalysts

In 1991, the first stable crystalline N-heterocyclic carbene (NHC) was synthesized successfully by Arduengo. He employed the concept of steric hindrance (a bulky adamantyl group as the N-protecting group) to prevent the dimerization of the active free carbene (Scheme 1.2).[8] These

pioneering studies led to establishing the pillar of the modern carbene organocatalytic field. To date, the synthetic community has employed NHC numerous times to form carbon-carbon or carbon-heteroatom bonds, especially in the asymmetric fashion.

1.1.1 Classification of NHC catalysts

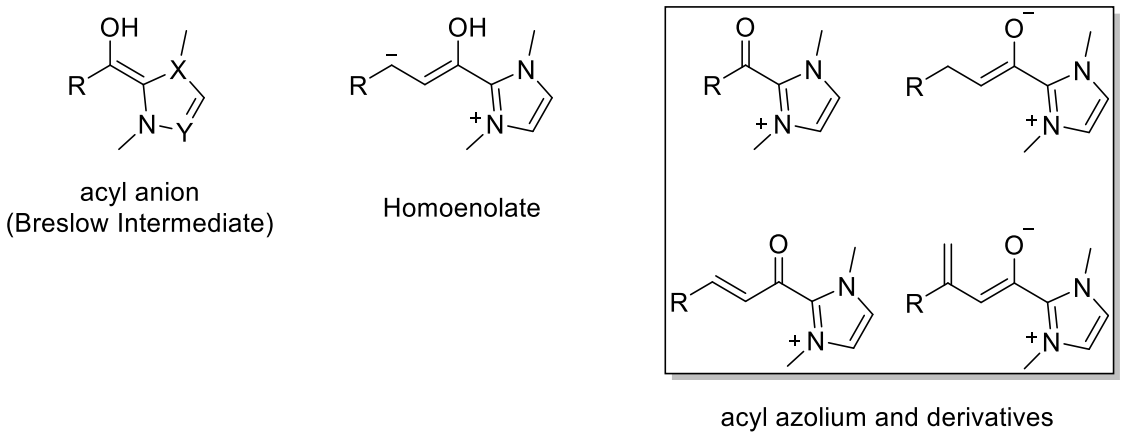
Although, at the beginning of the NHC catalysis, thiazolylidene carbenes were frequently used in the reaction, as for example, Benzoin condensation, and Stetter reaction. But the recent asymmetric carbene catalytic field is dominated by triazoliums salts. These chiral triazolium salts as carbene precursors were introduced in 1995 by groups of Enders and Teles independently.[9] Since then, several groups have successfully attached different types of chiral variants to triazolium core and applied in enantioselective transformations.[10-11] Generally, most NHC precursors in synthetic chemistry can be simply classified into 8 groups (Scheme 1.3) according to their chemical structure.[4] They are listed as follows - (1) aminoindane-based triazoliums, (2) morpholin-based triazaoliums (3) pyrroline-based triazoliums, (4) acyclic triazoliums, (5) oxazolidine-based heterazoliums, (6) imidazoline-based heterazoliums, (7) imidazole-based heterazoliums, (8) thiazole-based heterzoliums. Imidazolylidene and imidazolinylidene carbenes.



Scheme 1.3 General types of NHCs

1.2 NHC-catalyzed different activation modes of reaction

Mostly carbonyl compounds such as aldehydes, carboxylic acid and their derivatives are activated by NHC organocatalysis.[12-16] Till now, NHC organocatalysis has achieved amazing success in terms of functionalization of different sites of the carbonyl compounds like α, β, γ or remote carbon atoms, as well as the carbonyl carbon atom. In this chapter, we will discuss the three main aspects in NHC catalysis focusing on the types of generated intermediates. These three aspects are as follows (a) catalysis involving umpolung acyl-anion, (b) homoenolate catalysis, (c) reactions involving acyl azolium intermediates (Scheme 1.4).



Scheme 1.4 Different types of NHC catalyzed activation mode

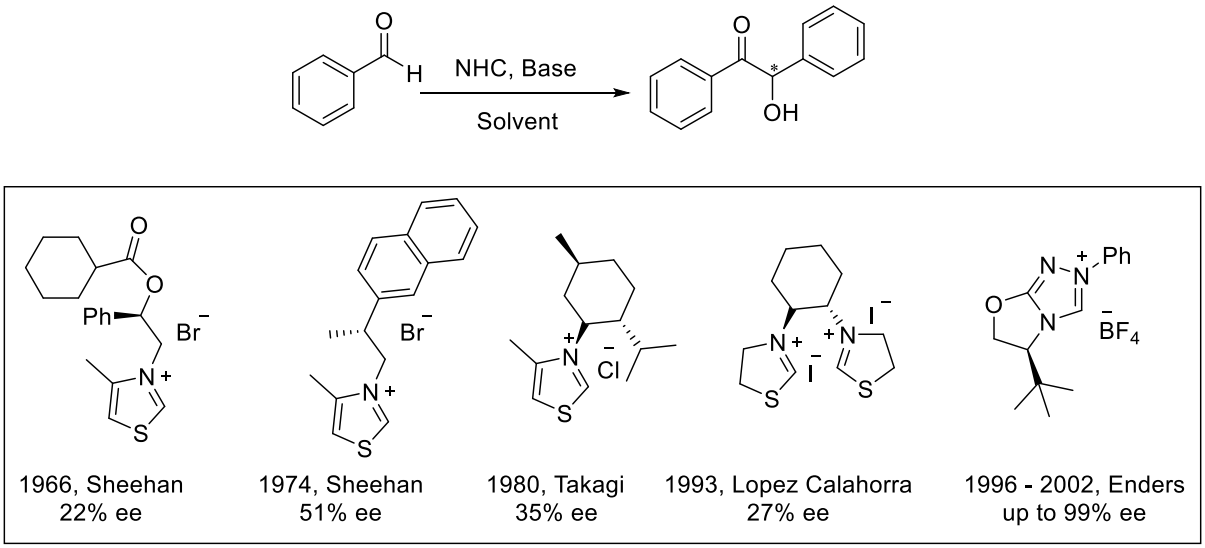
1.2.1 NHC catalysis involving umpolung acyl anion intermediate

Benzoin reaction catalyzed by NHC is the earliest studied reaction in this field. According to Breslow, the electrophilic character of the aldehyde acyl carbon is converted to nucleophilic by the carbene catalyst. This inversion of reactivity is commonly known as the "umpolung" effect.[16-17] This concept of umpolung is widely used to develop NHC chemistry, particularly for Benzoin and Stetter reactions

1.2.1.1 NHC-catalyzed Benzoin condensation

One of the powerful methods to construct a carbon-carbon bond is Benzoin reaction. The first example of benzoin condensation reaction catalysed by cyanide was reported by Wohler and Liebig in 1832. Later, same benzoin product has been obtained by Ukai who used the

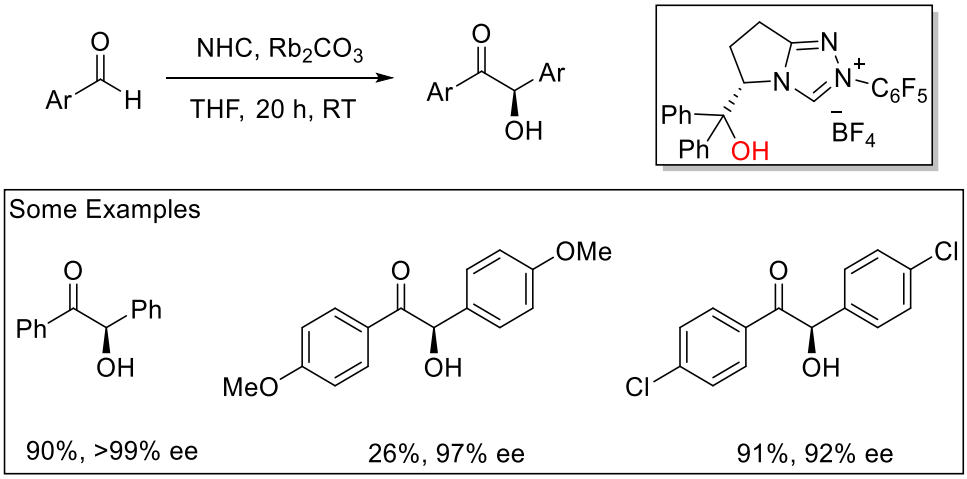
thiazolium salt as a catalyst. Inspiring from the previous work, Sheehan and Hunneman tried to achieve the asymmetric version of the reaction using a chiral thiazolium carbene catalyst.[18] However, only moderate ee (~22% ee) has been obtained at the end. Since then, many groups have focused to develop more efficient catalytic systems to improve the enantioselectivity (Scheme 1.5). In 2002, a breakthrough in the asymmetric benzoin reaction with excellent enantioselectivity has been reported by Enders using chiral morpholine-based triazolium salt as pre-catalyst. Employment of this newly designed carbene catalyst can give the desired product readily with 99% ee value.[19]



Scheme 1.5 Evolution of various Chiral NHCs for asymmetric Benzoin reaction

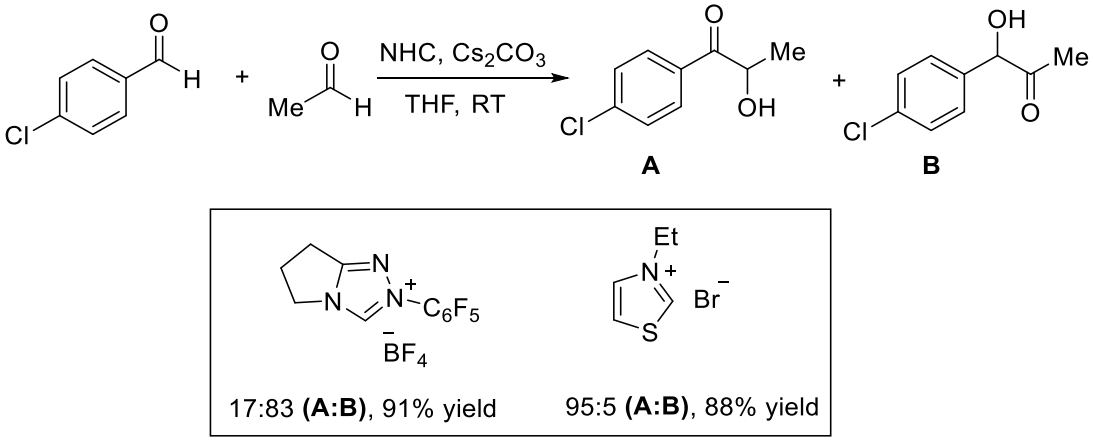
Recently, a new catalyst with a potential H-bonding group (OH), developed by Connon and Zeitler has provided the product in more efficient manner (90% yield, >99% ee).[20] The impact of the hydroxyl group in the selectivity of the benzoin reaction is quite remarkable. Till to date, this catalytic system to furnish benzoin product remains to be the best among other systems (Scheme 1.6). The cross-benzoin reactions between two different aldehydes to construct a new carbon-carbon bond have also been published. For example, Yang examined

the cross-benzoin condensation between aromatic aldehyde and alkyl aldehyde using thiazolium and triazolium catalyst separately (Scheme 1.7).[21-22]



Scheme 1.6 Connon and Zeitler's enantioselective benzoin reactions

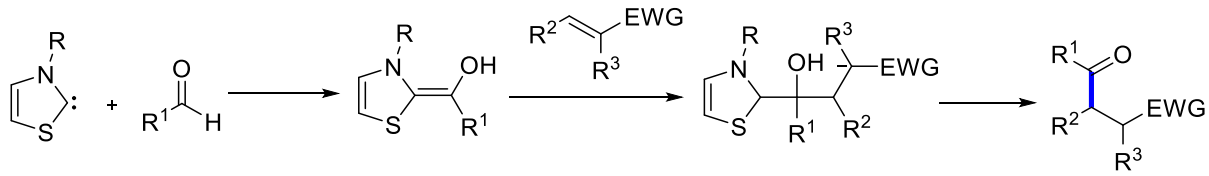
An interesting phenomenon was noticed during this investigation. Under the thiazolium carbene condition, free carbene preferred to attach with the aromatic aldehyde to construct the Breslow intermediate, then the Breslow intermediate attacks the alkyl aldehyde; while the triazolium catalyst first tried to form the Breslow intermediate with the alkyl aldehyde, followed by coupling with the aromatic aldehyde to obtain the other benzoin product.



Scheme 1.7 Yang's cross-benzoin condensation.

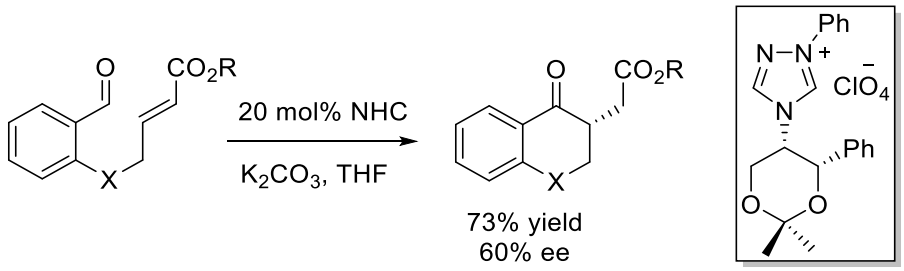
1.2.1.2 NHC-catalyzed Stetter reactions

The NHC-catalyzed Stetter reaction is another example of the utilization of umpolung acyl-anion catalysis. In this type of reaction, a carbon-carbon bond is formed between aldehydes and electron-deficient Michael acceptor catalyzed by carbene (Scheme 1.8). In 1973, Stetter first demonstrated the intermolecular 1,4-coupling of acetaldehydes to the unsaturated enone with the thiazolium catalyst.[23] Since then, the addition of umpolung acyl-anion to Michael acceptor has been named as Stetter reaction.[24-30] From the mechanistic viewpoint, initiation of the Stetter reaction was governed by the Breslow intermediate, generated from the reaction of free carbene and aldehyde. Next, a 1,4-addition happens when the umpolung acyl anion attacks the enone and the desired product forms.

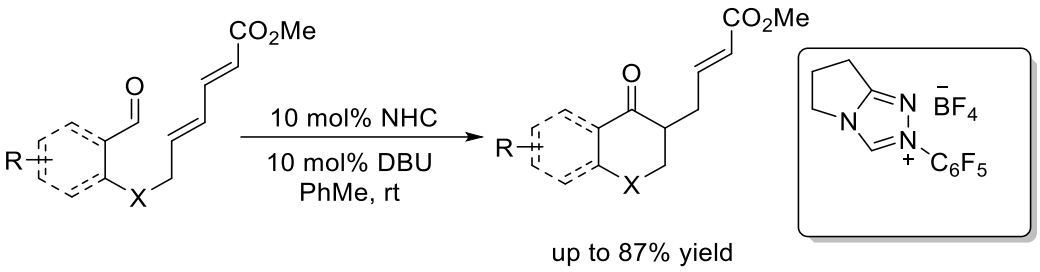


Scheme 1.8 General Stetter reaction mechanism

In 1996, Enders has first achieved an asymmetric intramolecular Stetter reaction (Scheme 1.9) using chiral acyclic triazolium salt.[9] A triazolium carbene catalyzed cyclization process provides the product with 73% yield and 60% ee. Since then, a great effort has been imposed to achieve both intramolecular and intermolecular version of asymmetric Stetter reaction.



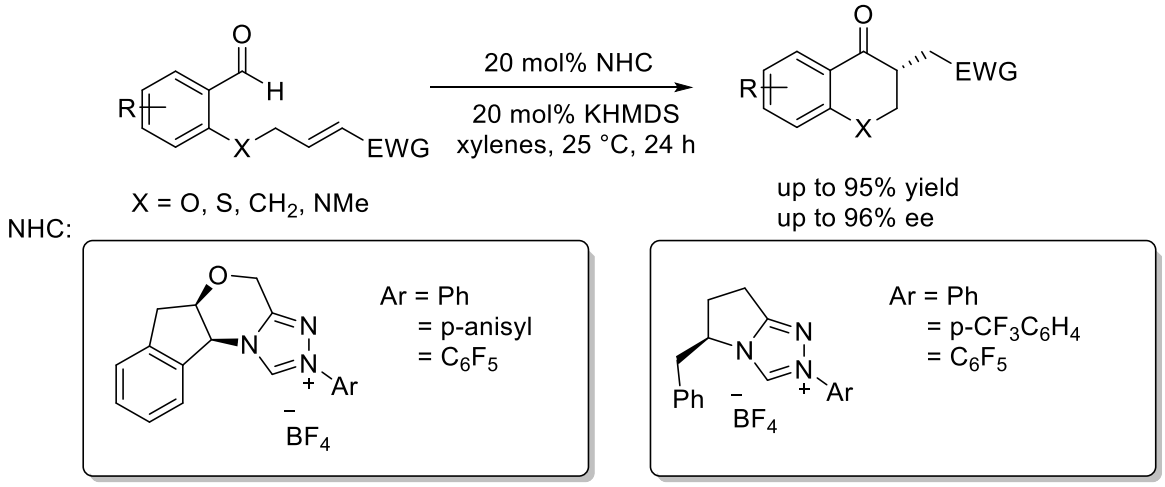
Scheme 1.9 Enders' intramolecular asymmetric Stetter Reaction



Scheme 1.10 McErlean's extended Stetter reaction

Later, based on Enders' work, Law and McErlean[31] enabled to expand the substrate scope from 1,4-addition to 1,6-Michael acceptor (Scheme 1.10).

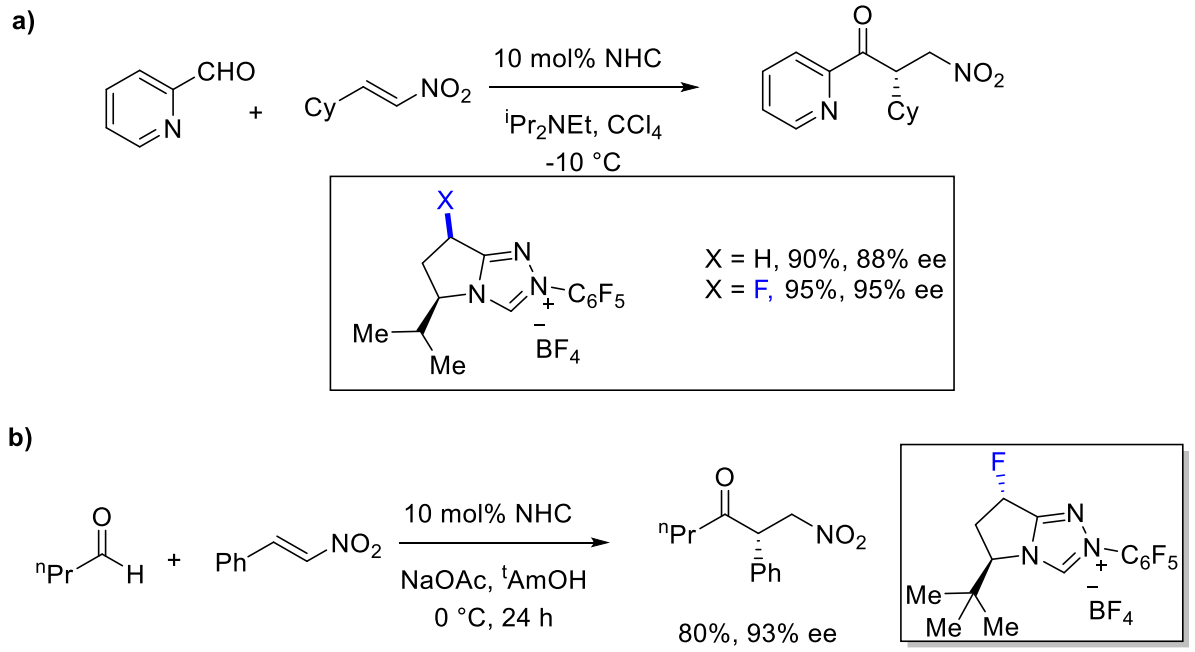
Extensive work on enantioselective intramolecular Stetter reaction was also studied by Rovis *et al.* Both aminoindane-based triazoliums and pyrroline-based triazoliums NHC precatalyst were used in this type of Stetter reaction and they worked very well, providing the corresponding product with high yield and enantioselectivity (Scheme 1.11).[11, 32-33]



Scheme 1.11 Rovis's asymmetric intramolecular Stetter reaction

Later, Rovis and his co-worker have also contributed significantly to develop intermolecular Stetter reaction successfully. For example, a new fluorinated triazolium catalyst was discovered by Rovis and co-workers to perform the Stetter reaction of aryl aldehydes with nitroalkenes.[28] In comparison with the non-fluorinated carbene catalyst, the fluorinated one

gave much better reactivity and selectivity (95% yield, 95% ee vs 90% yield, 88% ee) (Scheme 1.12a).

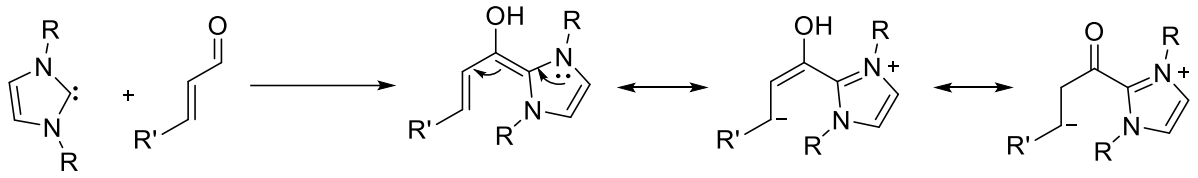


Scheme 1.12 Rovis's asymmetric intermolecular Stetter Reaction

In 2012, Rovis and his coworkers also demonstrated the Stetter reaction between nitroalkenes and alkyl aldehydes using a similar fluorinated NHC catalyst.[34] Again, in this case, the fluorinated carbene was proven to be a better choice (Scheme 1.12b).

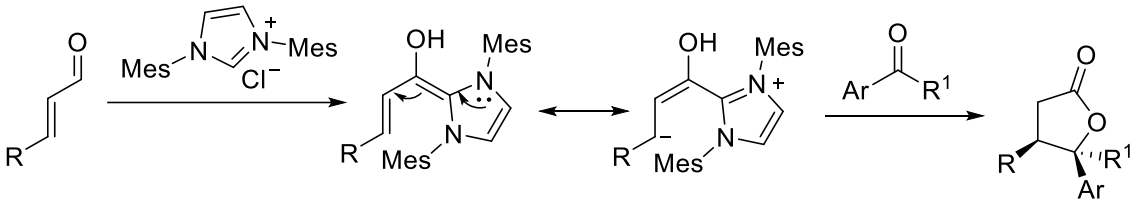
1.2.2 NHC-catalyzed homoenolate intermediate involving reactions

When free carbene adds to the α,β-unsaturated aldehyde, an 'umpolung' process of β-carbon (inversion of the electrophilic character of β-carbon) has been observed. The presence of extended conjugation in the system facilitates to transfer of the electron-pair of acyl anion to *β*-positioned carbon and it leads to build a significant nucleophilic character at *β*-carbon (Scheme 1.13). This newly formed unique nucleophilic intermediate, 'umpolung' activation mode, is called homoenolate.



Scheme 1.13 Mechanism of homoenolate activation.

The discovery of NHC-catalyzed homoenolate intermediate was first reported by Bode and Glorius independently in 2004.[35-37] Bode reported the annulations between a variety of enals and aryl aldehydes to synthesize γ-lactone products (41-87% yield with moderate diastereoselectivity, Scheme 1.14a). Meanwhile, Glorius used enal to generate homoenolate, and then the homoenolate intermediate reacts with activated trifluoromethyl ketones or aldehydes. He also got a similar γ-lactones with 32-70% yield and moderate diastereoselectivity (Scheme 1.14b).



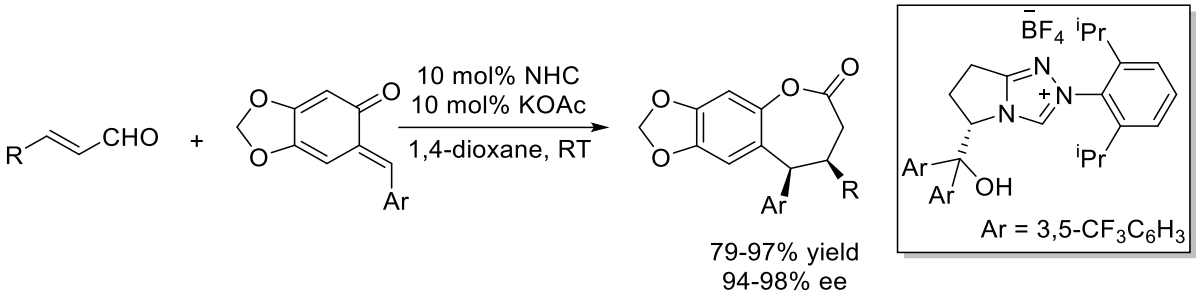
a) Bode's Condition	b) Glorius's Condition
R^1 = H	R^1 = H or CF_3
8 mol% NHC	5 mol% NHC
7 mol% DBU,	10 mol% ^{t}BuOK
THF/ ^{t}BuOH(10:1)	THF
RT, 15 h	RT, 16 h
41-87% yield, d.r. 3:1-5:1	32-70% yield, d.r. 2:1-4:1

Scheme 1.14 (a) Bode's [3+2] annulation of enal with aldehydes; (b) Glorius' annulation of enal with aldehydes or activated ketones.

After these two pioneering reports, this activation mode has been employed substantially to extend the substrates scope using other electrophiles like ketones, isatins, imines, 1,4-

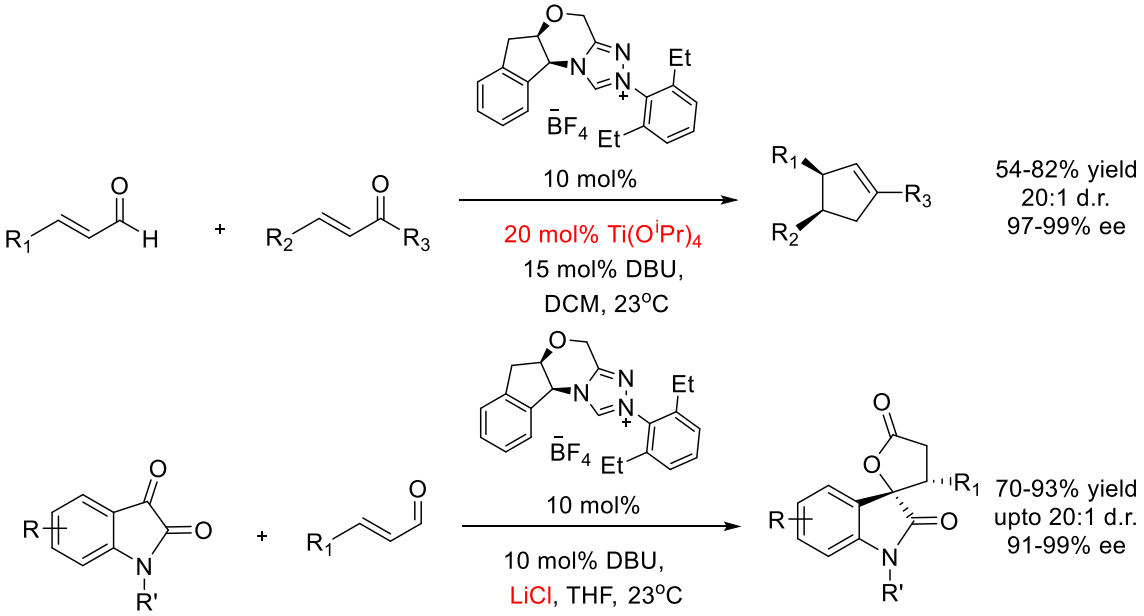
conjugated carbonyl compounds, etc. In most of the cases, excellent yield and enantioselectivities have been obtained.[35-36, 38-44]

In 2013, an enantioselective [4+3] annulation of enals with *o*-quinones has been published by Ye group.[40] Both aromatic and alkyl enals can give the desired products in good yield (79-97%) and excellent enantioselectivity (up to 98% ee) under their reaction condition (Scheme 1.15).



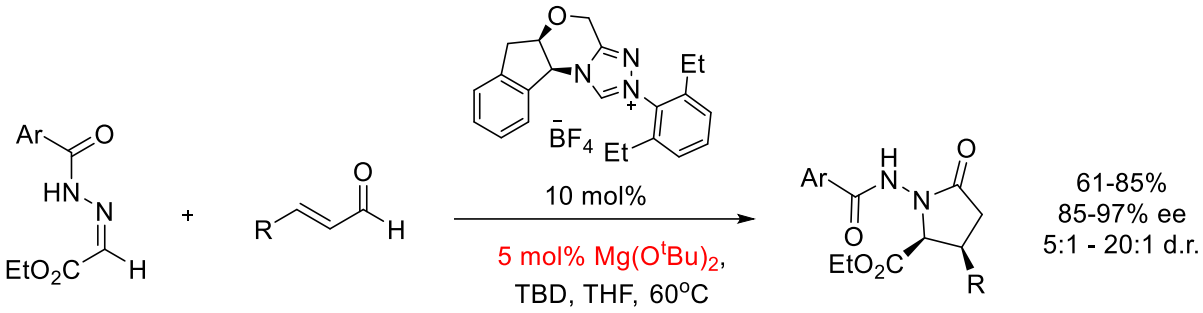
Scheme 1.15 Ye's [4+3] annulation via homoenolate.

Homoenolate intermediate can also be utilized in cooperative Lewis acid/NHC catalysis strategy. Under this new strategy, different kinds of Lewis acids ($Ti(O^iPr)_4$, LiCl, etc.) have used as secondary catalyst with NHC to synthesize complex molecules (Scheme 1.16).



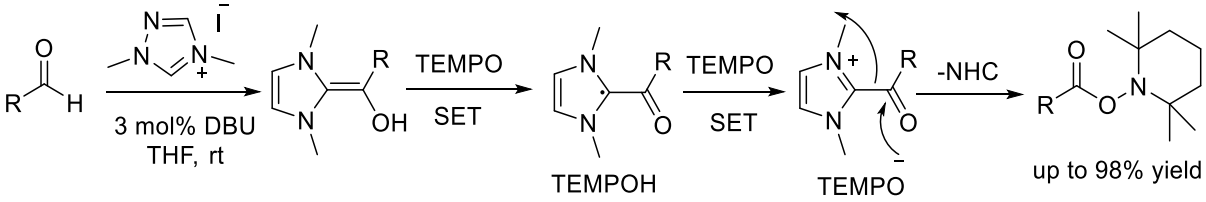
Scheme 1.16 Lewis acid & NHC-carbene cooperative catalysis

As an example, Scheidt[38] demonstrated a Lewis acid (Mg^{2+})/NHC dual catalyzed [3+2] annulation of enals with hydrazones. According to their proposed mechanism, interaction between the nitrogen atom of hydrazones and Lewis acid catalyst, $Mg(O^tBu)_2$, facilitates the addition of homoenolate to hydrazones. In this reaction, the cyclization products catalyzed by an optical active aminoindanane-based NHC were collected in 61-85% yield and 85-97% ee (Scheme 1.17).



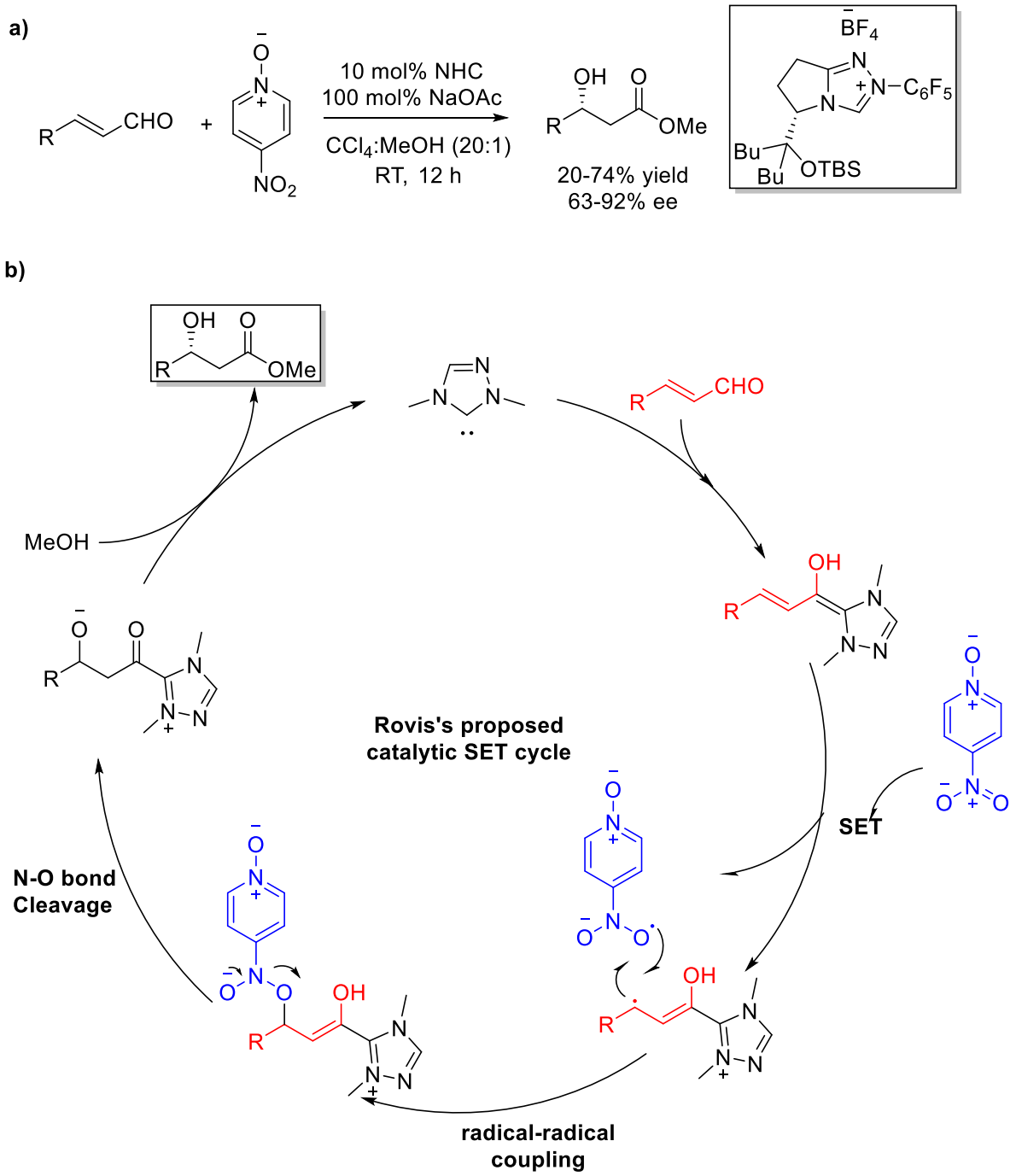
Scheme 1.17 Scheidt's enantioselective [3+2] annulations promoted by $Mg(O^tBu)_2$

In addition to the classical reactivity of homoenolate (via electron pair donation), this extended Breslow intermediate is also competent to show non-classical activity i.e. chemical transformations through the single-electron-transfer (SET) pathway. Inspiring from the nature, Studer and his co-workers[45] first reported this type of reaction. They proposed that the anticipated esters have obtained after two times single-electron transfer processes from Breslow intermediate to TEMPO. Here, TEMPO was used as SET source to oxidize the Breslow intermediate, generated from aldehyde under NHC condition (Scheme 1.18).



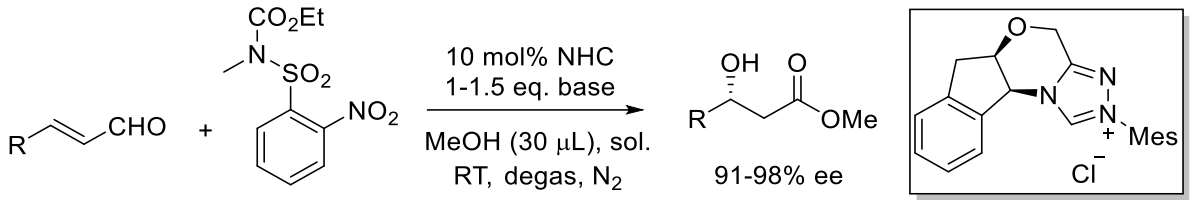
Scheme 1.18 Carbene catalyzed SET oxidation with TEMPO.

In 2014, SET of carbene catalyzed homoenolate has also achieved by both Rovis and Chi groups independently.[46-49] They reported that electron-deficient nitro-compounds can readily act as competent SET oxidants (Scheme 1.19 and Scheme 1.20). Rovis and his coworkers[46] employed 4-nitropyridine N-oxide with homoenolate. First, one electron has abstracted from



Scheme 1.19 a) Rovis' β-hydroxylation of enal via radical process, b) proposed catalytic cycle

homoenolate by the electron-deficient pyridine system to generate NHC-bound radical intermediate. Then, this radical has coupled with the nitro radical and subsequent N-O bond cleavage eventually afforded a β-hydroxyl ester in excellent enantioselectivity (Scheme 1.19a). In seminal work by Chi group[48], they used 2-nitrosulfonamide derivative to capture single electron from extended Breslow intermediate, generated from cinnamaldehyde (Scheme 1.20). Their catalytic system gave the exact product with 98% ee value. Further studies on this radical activation mode have been also investigated thoroughly by Rovis, Chi, Ye, and Sun with other SET sources.[50-52]



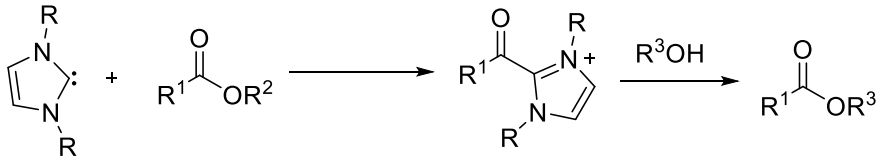
Scheme 1.20 Chi's β-hydroxylation of enal

1.2.3 NHC-catalyzed acyl azolium intermediate involving reactions

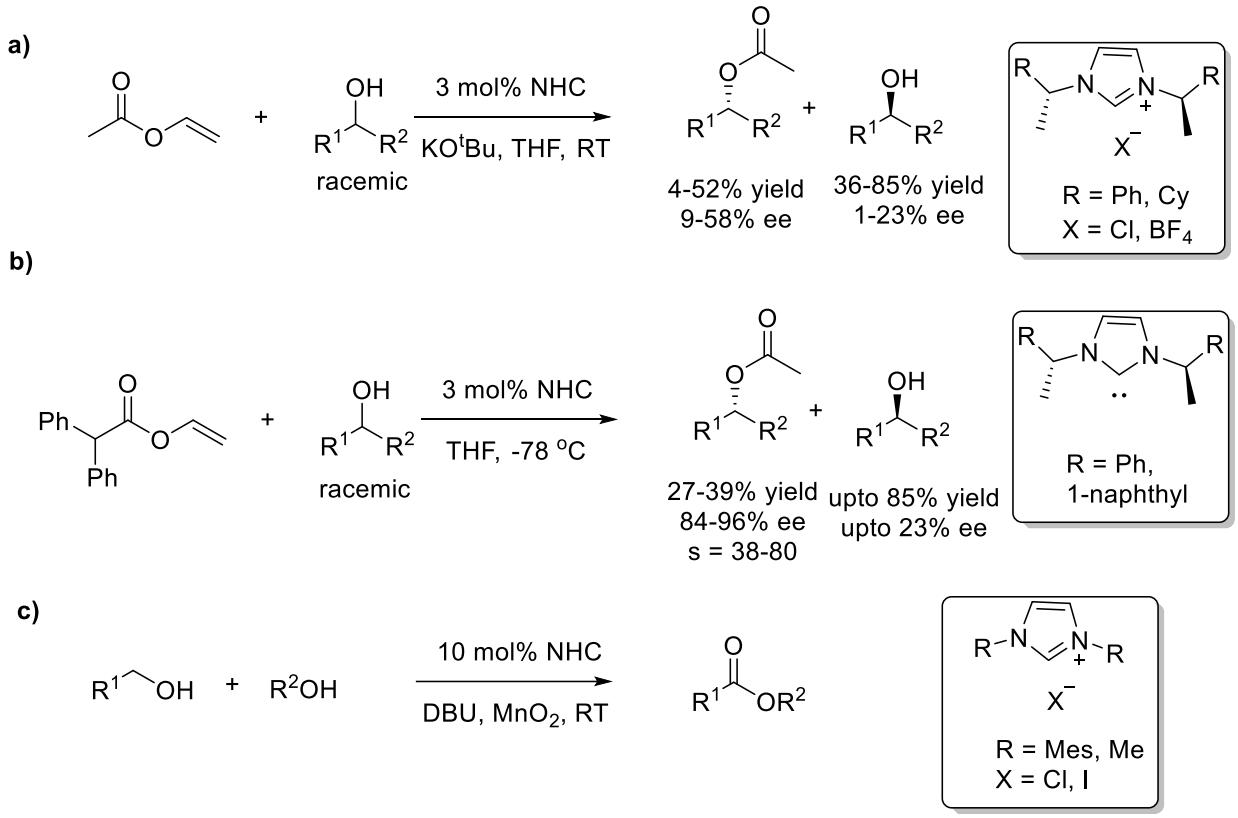
In addition to umpolung chemistry, NHCs are also proficient to furnish several reactions in a non-umpolung manner. For example, acyl azolium and azolium enolate intermediate have gained tremendous attention from chemists over the past decade. Other than these two intermediates, few more reaction modes (activation of β, γ or even remote carbon atom), derived from acyl azoliums intermediate have been achieved. Based on the activation sites, we can categories them into four parts: (a) transesterification; (b) azolium enolate chemistry (α-carbon activation); (c) α,β-unsaturated acyl azolium chemistry (β -carbon activation); (d) γ-functionalization via vinyl azolium enolate.

1.2.3.1 Transesterification reactions

The first transesterification reaction was published by Hedrick and Nolan in 2002 (Scheme 1.21).[53-54] Later, numerous reactions of this type have carried out by different research groups.[55-56] Interestingly, most of the works comprises saturated acyl azoliums as a precursor for transesterifications. In 2004, Suzuki and Maruoka independently used this concept to do the kinetic resolution of secondary alcohols. Suzuki[57-58] used chiral imidazolium NHC catalyst and vinyl acetate as the starting material (Scheme 1.22a). The desired product has been obtained with low to moderate ee value (9-58% ee). A significant improvement in enantioselectivity has found by Maruoka and his coworkers[59] when they simply switched to a bulkier ester (vinyl diphenyl acetate) from vinyl acetate (Scheme 1.22b). In this context, an oxidative NHC-catalysed approach for transesterification has been reported by Scheidt in 2007.[60] In this report, the alcohol, the starting material, was oxidized to aldehyde first by MnO_2. Later, the Breslow intermediate, generated after coupling between aldehyde and NHC, is oxidized to acyl azolium intermediate followed by the addition of alcohol to give the desired ester product (Scheme 1.22c).

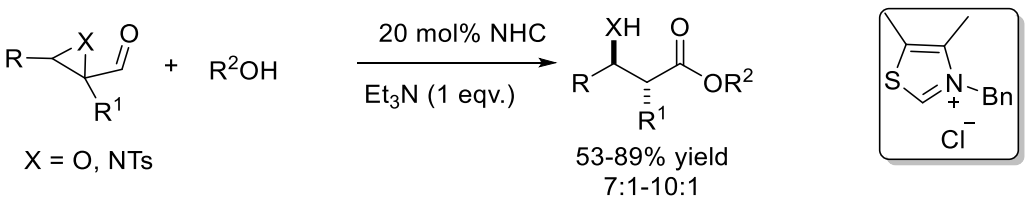


Scheme 1.21 Mechanism of transesterification



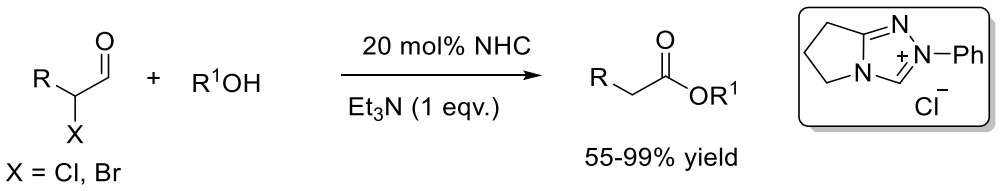
Scheme 1.22 NHC catalyzed transesterification

In this context, chemists found that different kinds of aldehydes could also be a potent substrate for NHC catalyzed transesterifications. In 2004, Bode used epoxy or aziridinyl aldehyde to furnish the transesterification with the concept of the internal redox process. The corresponding β-hydroxy or amino esters were formed in 53-89% yield using thiazolium salt as precatalyst (Scheme 1.23).[61]



Scheme 1.23 Bode's self-redox reaction to form the ester

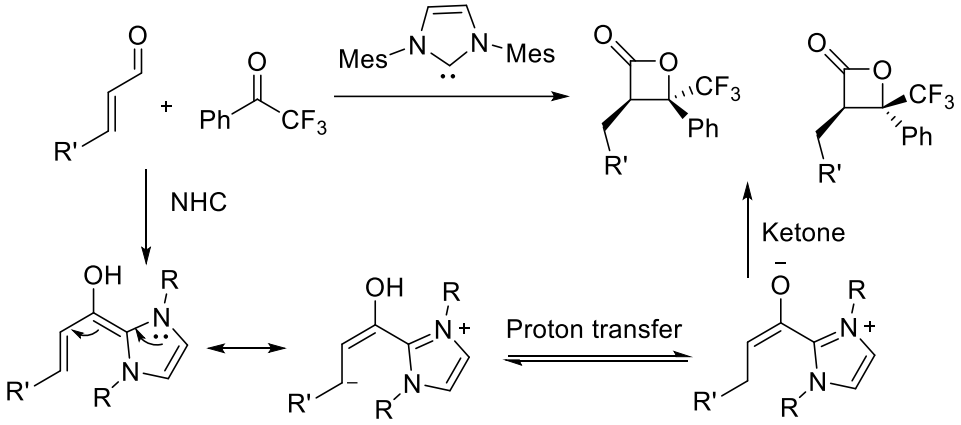
Later, Rovis's group[62] showed that the same type of internal redox reaction from aldehyde to the corresponding ester could be possible with α-bromo or chloro aldehyde as the starting material under the NHC catalysis (Scheme 1.24). In both the catalytic cycles, acyl azolium intermediate was formed by an internal redox process which was started by the elimination of reducible α-functionality.



Scheme 1.24 Rovis' NHC-catalyzed self-redox reaction

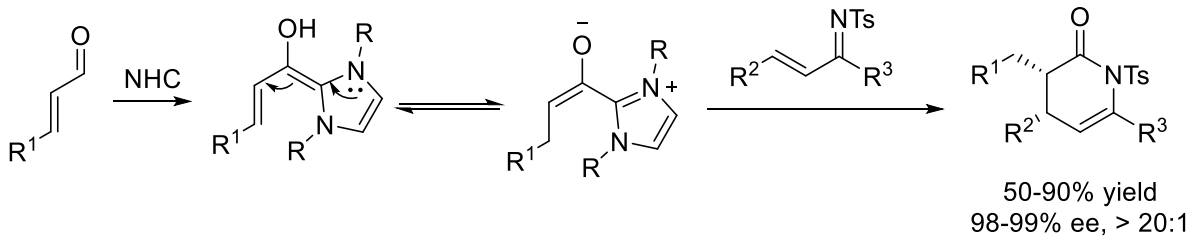
1.2.3.2 NHC-catalyzed α-carbon activation (azolium enolate)

During the initial phase of the homoenolate research, Glorius and his coworker noticed that another cyclization product (β-lactone) was formed as a side product under certain catalytic conditions.[37] Further examination of the β-lactone generation revealed the cause. There was another catalytic process involved, named "enolate activation" in which a proton transfer process has taken place after the generation of homoenolate. The proposed mechanism is depicted below (Scheme 1.25) –

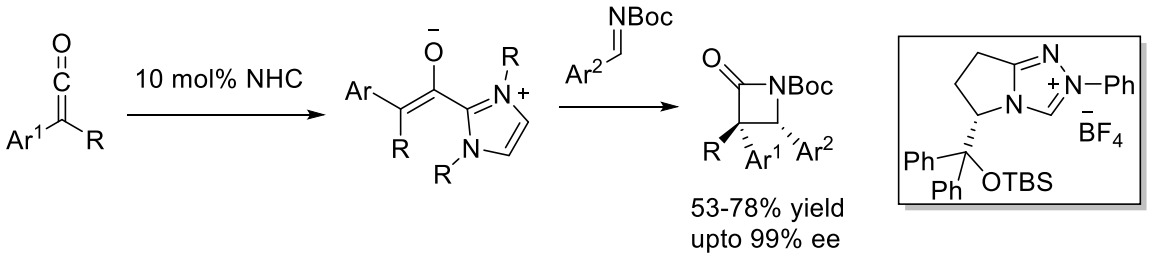


Scheme 1.25 Mechanism of enolate activation

Around the same time, Bode's group[63] has also disclosed the excellent application of enolate activation in [4+2] aza-Diels-Alder reaction. He used α, β-unsaturated aldehydes to synthesize NHC-bound enolate intermediate. Then, the intermediate coupled with α,β-unsaturated aldehyde derived imines (Scheme 1.26). Thereafter, numerous publications have been reported involving this type of activation modes in both racemic and asymmetric versions.[64] Due to substantial applications of enolate chemistry in the formation of complex molecules, different groups tried to develop other approaches to generate enolate intermediate. In 2008, ketene as a precursor of azolium enolate has reported by Ye[65] and Smith[66] groups independently. Ye and his coworkers have used N-protected imines as an electrophile to trap the azolium enolate, the reactive nucleophilic species to get the corresponding [2+2] annulated lactam product (Scheme 1.27). Ye also demonstrated the [4+2] cycloaddition between enone and azolium enolate, generated from the ketene.[67] He got the product with excellent yield and enantioselectivity.



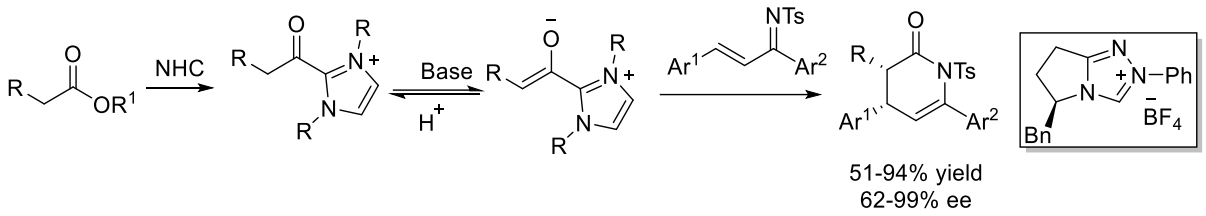
Scheme 1.26 [4+2]-Hetero-Diels-Alder cycloaddition



Scheme 1.27 [2+2] annulation of ketene by Ye

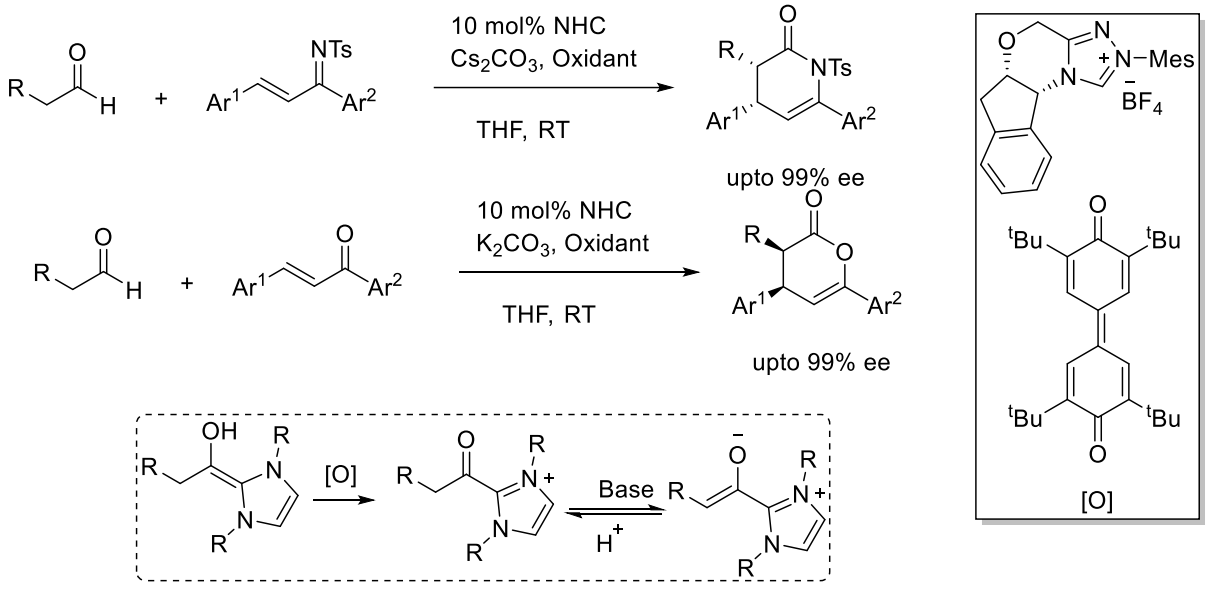
Later, different groups have developed different kinds of precursors of enolate activation in NHC-carbene catalysis.

A unique approach, “backward pathway”, has been adopted by Chi group[68] in the generation of the acyl azolium intermediate from activated carboxylic esters (Scheme 1.28). Because of enhanced acidity, a facile deprotonation of α-CH happens under the basic conditions and provides enolate intermediate which subsequently, couples with chalcone imines to affords the lactam products.



Scheme 1.28 [4+2] cycloadditions of activated esters with chalcone imines

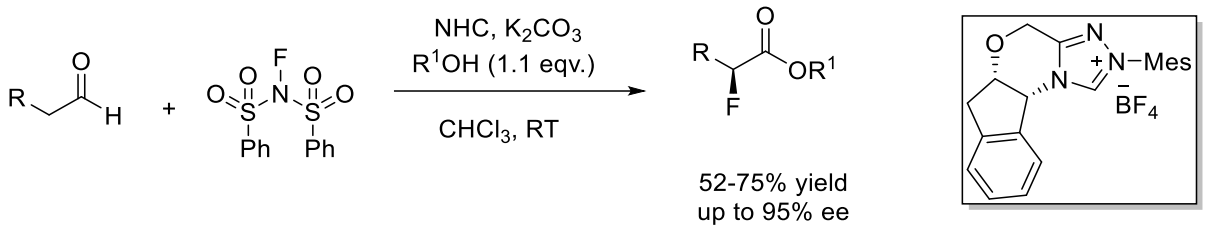
Oxidative NHC catalysis to generate acyl azoliums from saturated aldehydes was also reported. In 2013, Rovis[69] and Chi[70] labs both demonstrated independently that the [4+2] hetero-Diels-Alder annulation could be achieved by employing simple alkyl aldehydes as the source of acyl azoliums (Scheme 1.29). In the catalytic cycle, the Breslow intermediate was



Scheme 1.29 Generation of azolium enolate from alkyl aldehydes

first oxidized to form acyl azoliums followed by α-proton deprotonation. Then, it attacked to an electrophile, α,β- unsaturated imines or enones and provided the corresponding lactam or lactone products in good yield and excellent enantioselectivity.

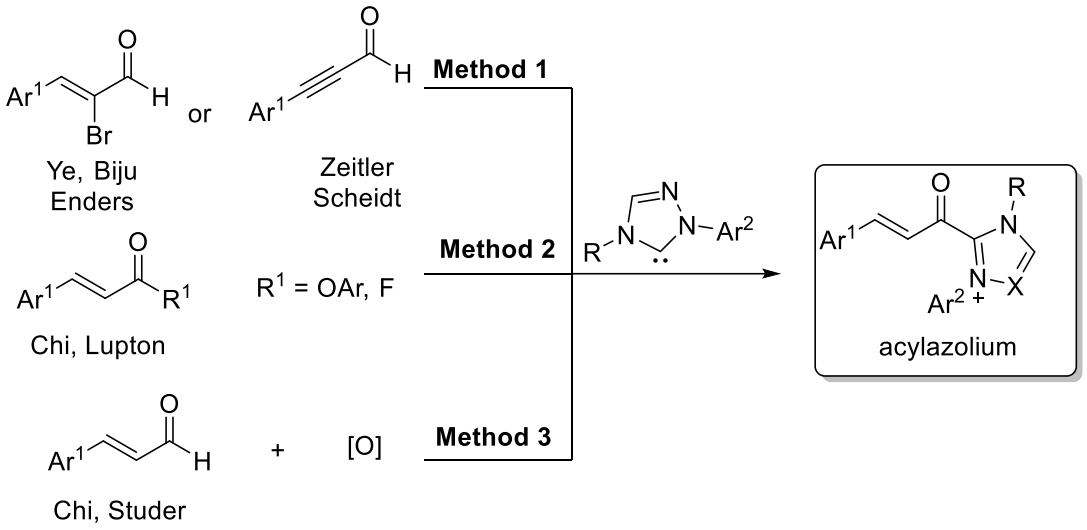
NHC catalyzed enolate intermediate was trapped to produce enantiopure α-fluoroester, reported by Sun[71] and Wang[72] groups independently in 2014 (Scheme 1.30). They employed NFSI to oxidize the Breslow intermediate, generated from aldehyde. After deprotonation of azolium, it coupled with the electrophilic NFSI to obtain the α-fluoroester. Here, NFSI acts as an internal oxidant, as well as a fluorine source.



Scheme 1.30 Enolate generation for α-fluorination of aldehydes using NFSI

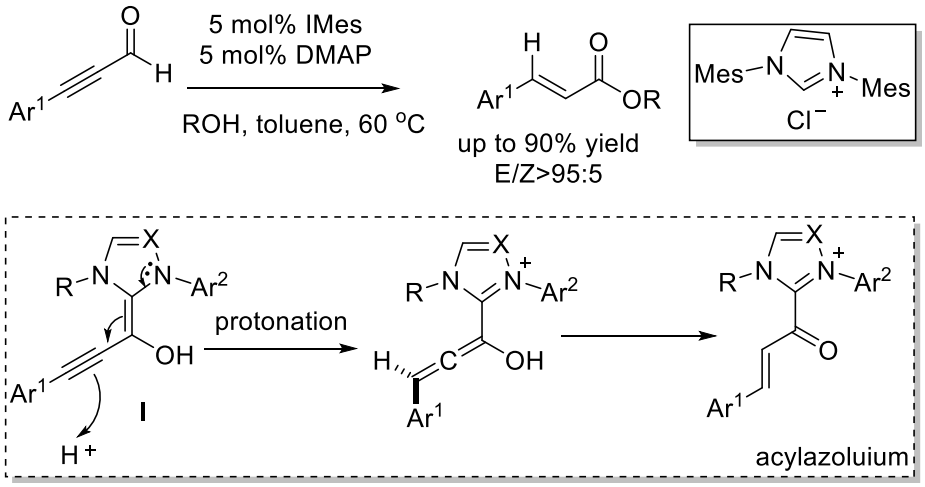
1.2.3.3 NHC-catalyzed β-carbon activation (α, β-unsaturated acyl azoliums reactions).

Other than activation of β-position through homoenolate, there is an alternative approach to activate β-position via formation of α,β-unsaturated acyl azoliums, another example of non-umpolung process. Worthy to note, this activation mode remains the most explored intermediate in NHC catalysis. The typical used methods to access α, β-unsaturated acyl azolium depends on α-oxidizable aldehydes with internal redox functionality (ynals, bromoenals). Alternative approaches include coupling of carbene with unsaturated acyl fluorides, ester, in-situ generated mixed anhydrides, and the oxidation of homoenolate by an external oxidant (Scheme 1.31). The concept of this activation mode is to lower down the LUMO energy of α,β-unsaturated carbonyl compounds, and increase the electrophilicity of the β-positioned carbon.



Scheme 1.31 Different precursors of unsaturated acyl azolium

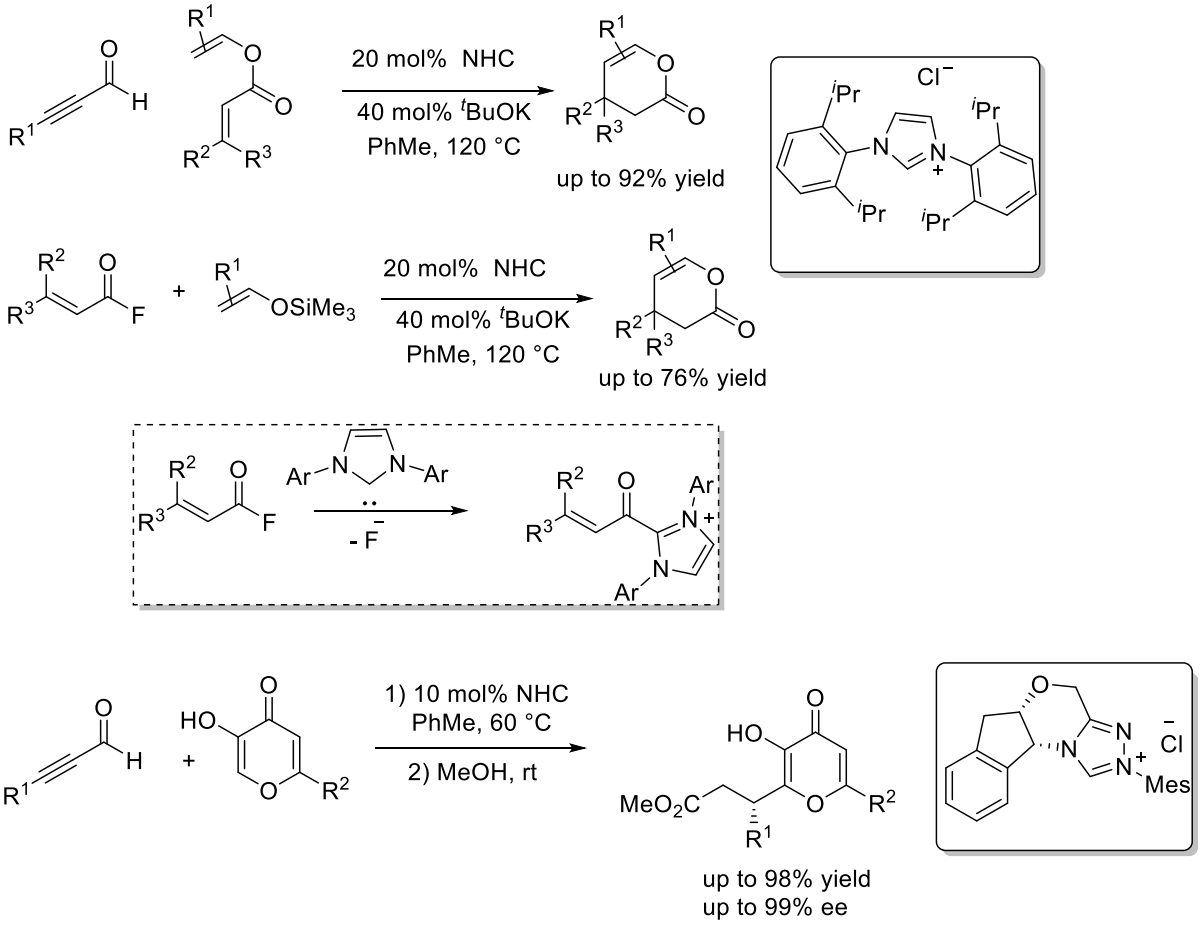
In 2006, Zeitler's group[73] illustrated the formation of unsaturated acyl azolium intermediate from ynals under NHC catalysis. The reaction was initiated by the addition of the carbene to the aldehyde group to afford the Breslow intermediate. Then, a protonation of the intermediate **I** (Scheme 1.32) followed by tautomerization gave the unsaturated acyl azolium, and finally the alcohol trapped the unsaturated to provide the corresponding unsaturated ester.



Scheme 1.32 Esterification of ynals

After the success of esterification, the first example of utilization acyl azolium intermediate as a 1,4-Michael acceptor was disclosed by Bode and Lupton independently.[74-75]

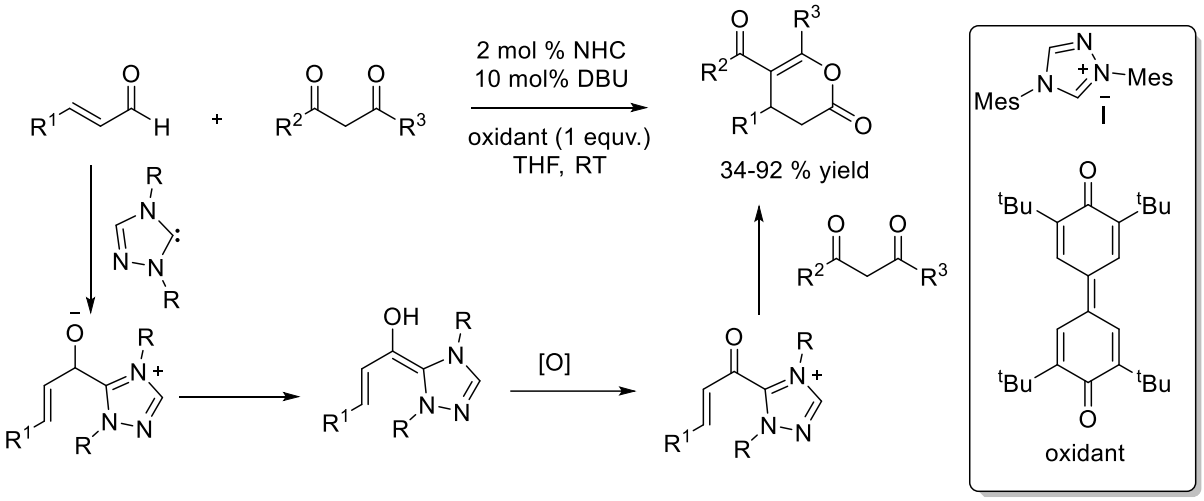
Lupton *et* al. reported the synthesis of the same [4+2] cycloaddition product (dihydropyranones) employing unsaturated acyl fluorides to generate *α,β*-unsaturated acylazolium. Then, nucleophilic addition of trimethyl silyl enol ethers to this intermediate afforded the desired product in 37-76% yield (Scheme 1.33). Later, Bode and co-workers[76] successfully obtained asymmetric version of this type of "Claisen rearrangement'' utilizing aminoindane-based chiral triazolium salt as NHC precatalyst. He used ynals to generate α,β-unsaturated acyl azoluim in the reaction.



Scheme 1.33 Formation of α, β-unsaturated acyl azolium from acyl fluoride and ynals

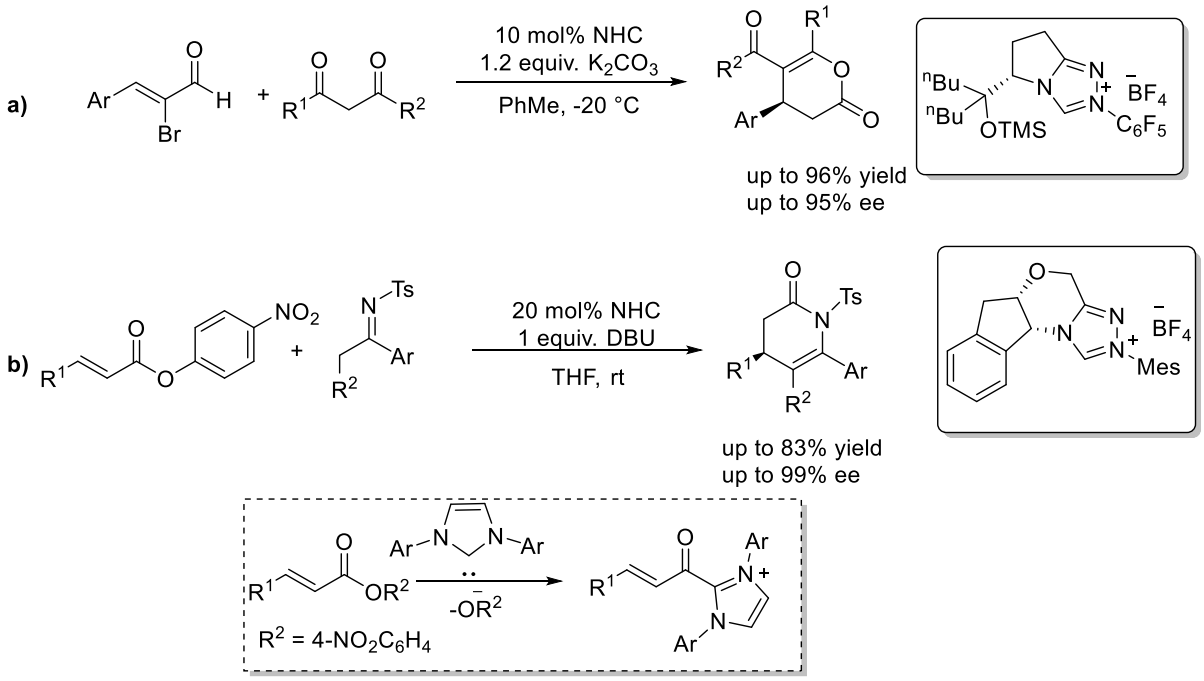
In 2010, Studer group first proposed an oxidative approach with an external oxidant to form unsaturated acyl azoliums directly from readily available unsaturated aldehydes (Scheme 1.34).[77-78] They demonstrated that a mild bulky quinone oxidant could efficiently oxidize the

Breslow intermediate to the unsaturated acyl azolium. Under optimized conditions, various 1,3-dicarbonyl compounds reacted well to furnish 3,4-dihydropyranone products in excellent yield.



Scheme 1.34 Mechanism of acyl azolium Activation pioneered by Studer

Ye and co-workers[79] developed a similar [3+3] cycloaddition reaction where a stable *α*-bromoenals were involved to generate unsaturated acyl azolium intermediate. They have also used 1,3-dicarbonyl compounds for nucleophilic coupling. The asymmetric version was also achieved with chiral triazolium catalyst. The corresponding 3,4-dihydropyranones were obtained with excellent yields and ee (Scheme 1.35a). Later, a wide range of nucleophilic partners was used to couple with acylazolium in an asymmetric fashion. In 2013, Chi group reported the formation of *α,β*-unsaturated acylazolium from *α,β*-unsaturated ester activated by NHC catalyst.[80] They were able to successfully attach various aryl imines with unsaturated acylazolium intermediate to afford lactam ring. In this strategy, the desired products were obtained with excellent yields and ee values in presence of aminoindane-based chiral triazolium catalyst (Scheme 1.35b).

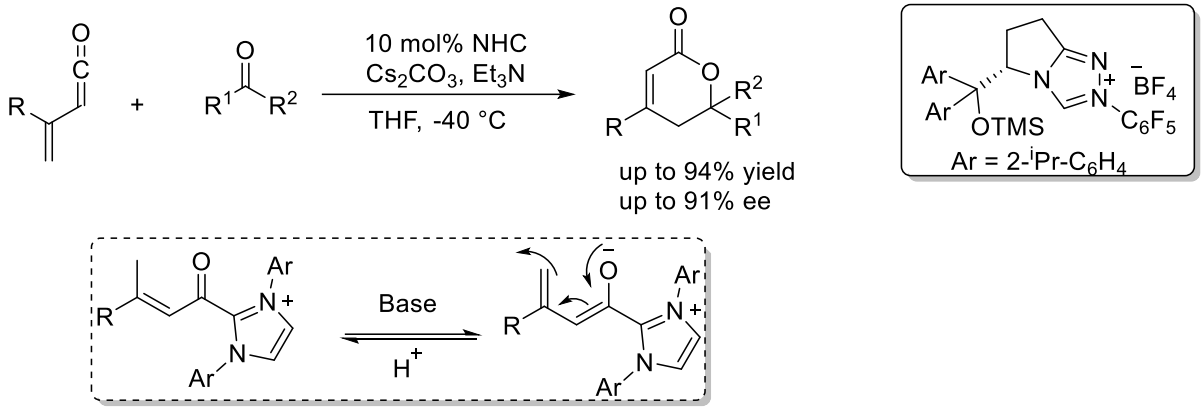


Scheme 1.35 Generation of acylazolium intermediate from bromoenal and *α,β*-unsaturated ester

1.2.3.4 NHC-catalyzed γ-carbon activation (vinyl azolium enolate)

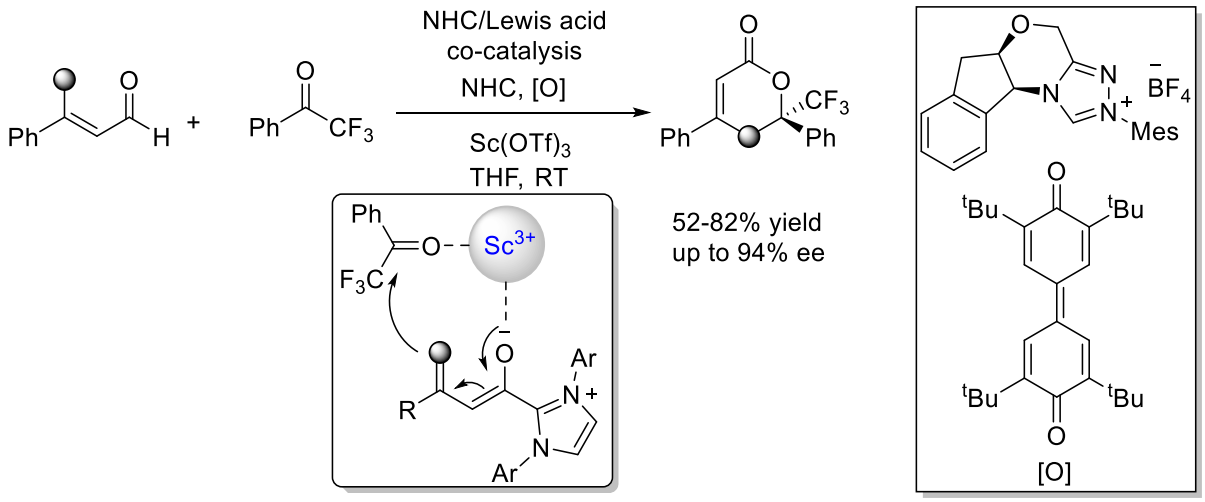
Recently controlling the reactivity of remote carbon center such as γ-carbon through NHC catalyst has also been achieved. Although only a few examples of this type of activation are available in the literature. Under this strategy a β-methyl group of α,β-unsaturated carbonyl compound has been functionalized. First, unsaturated carbonyl compounds need to transform to the α,β-unsaturated acyl azolium intermediated, catalyzed by NHC. Owing to the positive charge on the NHC-moiety, the H-atoms of β-methyl group become more acidic. As a result, a facile deprotonation takes place. The resulted vinyl enolate intermediate was first reported by Ye and co-workers in 2011 (Scheme 1.36).[81-82] They have utilized an in-situ generated α,β-unsaturated ketene to furnish this key intermediate. First, an elimination of HCl from acyl chloride to form the ketene intermediate occurred. Then, NHC addition to this ketene led to formation of the vinyl azolium enolate intermediate. Then, a subsequent [4+2] cycloaddition

between an activated trifluoromethyl ketone would deliver the dihydropyranones motif. However, the controlling of enantioselectivity through this approach remains challenging.



Scheme 1.36 [4+2] Annulations of ketenes with activated ketones

In 2012, Chi lab reported a new duel catalytic strategy (NHC & Lewis acid) to control the enantioselectivity of this type of [4+2] formal cycloaddition product (Scheme 1.37).[83] In the catalytic cycle, azolium enolate intermediate, formed after coupling of carbene with γ-methyl enal was oxidized by bisquinone oxidant (DQ), followed by a proton abstraction would eventually lead to forming vinyl azolium enolate intermediate. Subsequently, a formal [4+2] annulation with active trifluoromethyl ketone afforded γ-lactone products. Interestingly, the jump in enantioselectivity of the product clearly indicated the involvement of Lewis acid in the transition state.



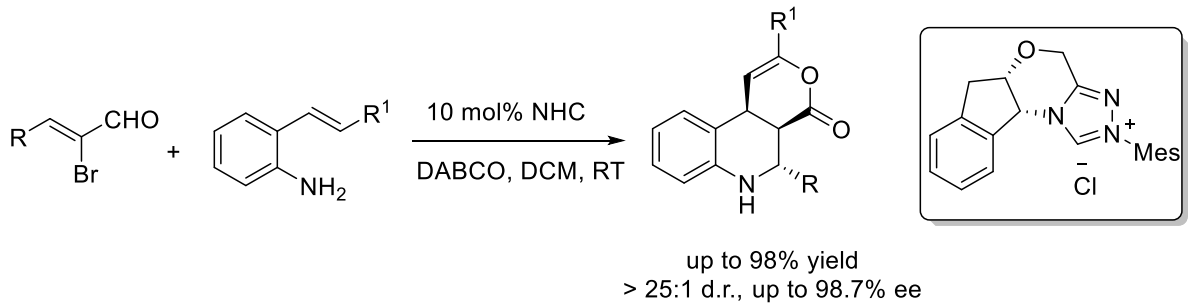
Scheme 1.37 Cooperative catalysis for enantioselective [4+2] reaction

1.3 Carbon-heteroatom (C-X) bond formation using α, β-unsaturated acyl azolium

Many complex molecules have been synthesized by utilizing α, β-unsaturated acyl azolium intermediate over the decade. But most of the typically used reagents to attach with α,β-unsaturated acyl azolium contain carbon-center nucleophile. Because of the relatively poor electrophilic character of β-positioned carbon, this intermediate prefers to couple with a soft center nucleophile and hardly reacts with a hard center nucleophile (such as heteroatom as a nucleophilic center). Although over the years, scientists have tried to resolve this problem by modifying the nucleophilic character of the heteroatom-center nucleophiles, there are only a few successful examples available on the topic of C-heteroatom bond construction involving unsaturated acyl azolium. In this context, the employed heteroatom-center nucleophiles could be divided into two groups – (1) N-center Nucleophile and (2) S-center Nucleophile.

1.3.1 N-center Nucleophile

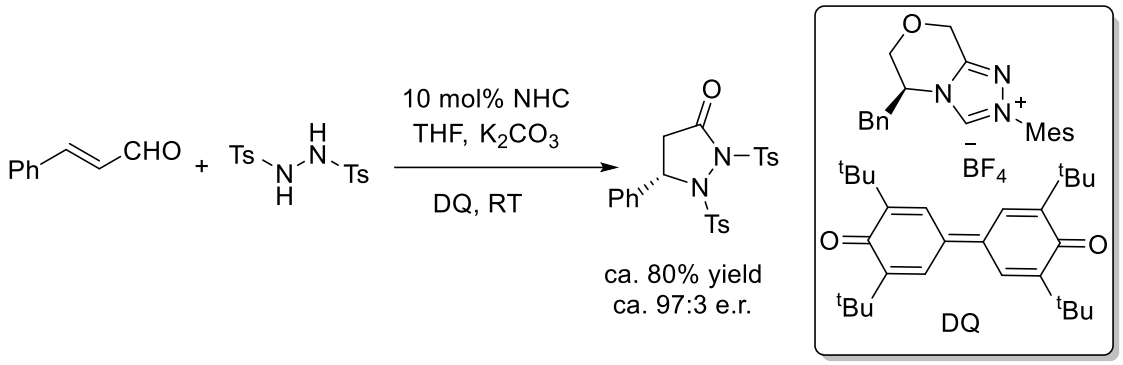
In 2013, Hui and coworkers first reported aza-Michael-Michael-lactonization cascade reaction where 2'-aminophenylenone acts as N-center nucleophiles.[84] They used bromoenal to generate unsaturated acyl azolium, catalyzed by chiral aminoinadane-based triazolium salt as NHC precursor. Then, the NH_2-group of 2'-aminophenylenone was added to the β-positioned carbon and provided the chiral functionalized tetrahydroquinoline scaffold with the excellent result (up to 98% yield, > 25:1 d.r., up to 98.7% ee, Scheme 1.38).



Scheme 1.38 β-amination of bromoenal by Hui

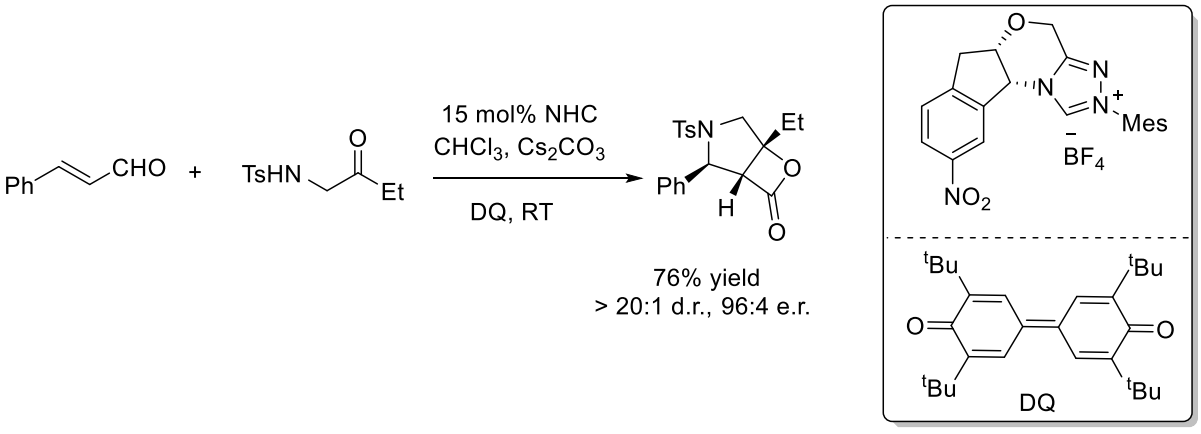
Chi's group has also developed a β-amination process with α, β-unsaturated acyl azolium in 2016.[85] Cinnamaldehyde was transformed to unsaturated acyl azolium under oxidative NHC

catalysis where DQ was used as an oxidant. Chiral morpholine-based NHC catalyst was employed to generate unsaturated acyl azolium intermediate and then, tosyl-protected hydrazine attacked the acyl azolium to form pyrazolidinone adduct with good yield and enantioselectivity (Scheme 39).



Scheme 1.39 Chi's oxidative β-amination

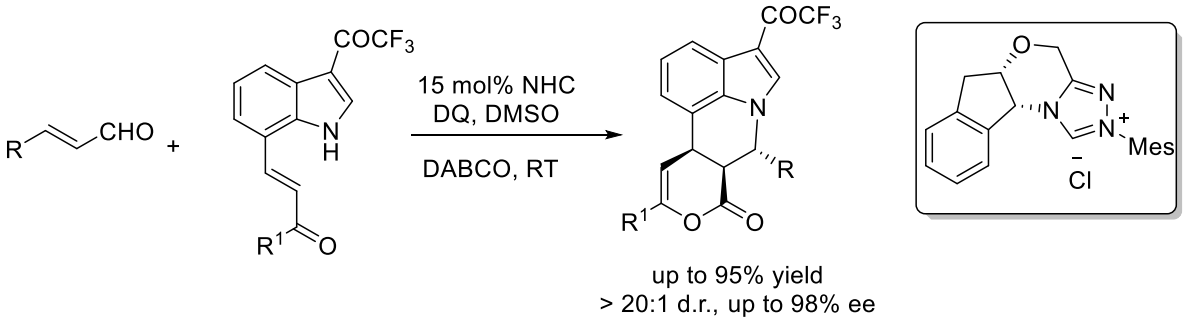
In 2017, a fused pyrrolidine and β -lactone bicyclic motif was synthesized by Chi's group.[86] Under the oxidative condition, unsaturated acyl azolium, generated from cinnamaldehyde was coupled with protected α-amino ketone to afford the biological active motif. A sequence of bond formations (C-N, C-C, C-O) led to the fused bicyclic product in a good result (Scheme 40).



Scheme 1.40 Fused bicyclic ring formation

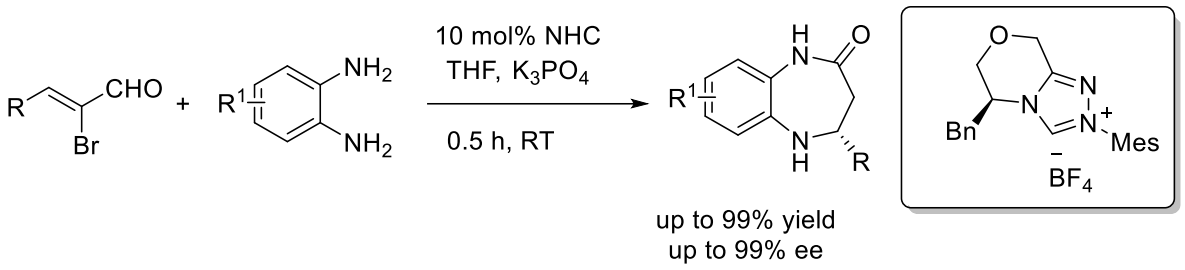
Pyrroloquinoline moiety, one of the most important heterocycles, has also produced through the concept of aza-Michael-Michael-lactonization cascade reaction. This NHC

catalyzed sequence of reactions has been developed by Biju[87] in 2018 (Scheme 41). They applied N-unsubstituted indoles with a Michael acceptor and cinnamaldehyde in the catalytic cycle. Under oxidative NHC condition, first, deprotonation of NH-group, followed by nucleophilic addition to chiral unsaturated acyl azolium intermediate provided the corresponding product with excellent yield and ee (up to 98% yield, > 20:1 d.r., up to 98 % ee).



Scheme 1.41 Biju's oxidative β-amination

In 2018, Wang's group[88] described a β-amination product with unsaturated acyl azolium intermediate using a proton-shuttling strategy. They applied bromoenal with o-phenyldiamine under morpholine-based chiral triazolium NHC. The corresponding [4+3] annulation product was afforded in 99% yield and 99% ee (Scheme 42).

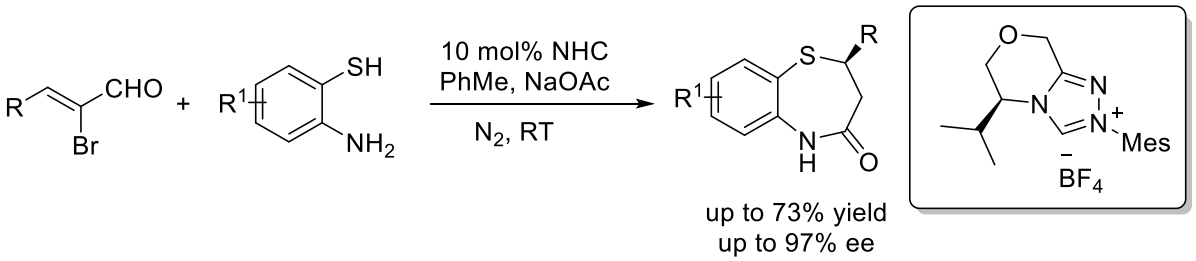


Scheme 1.42 β-amination by Wang

1.3.2 S-center Nucleophile

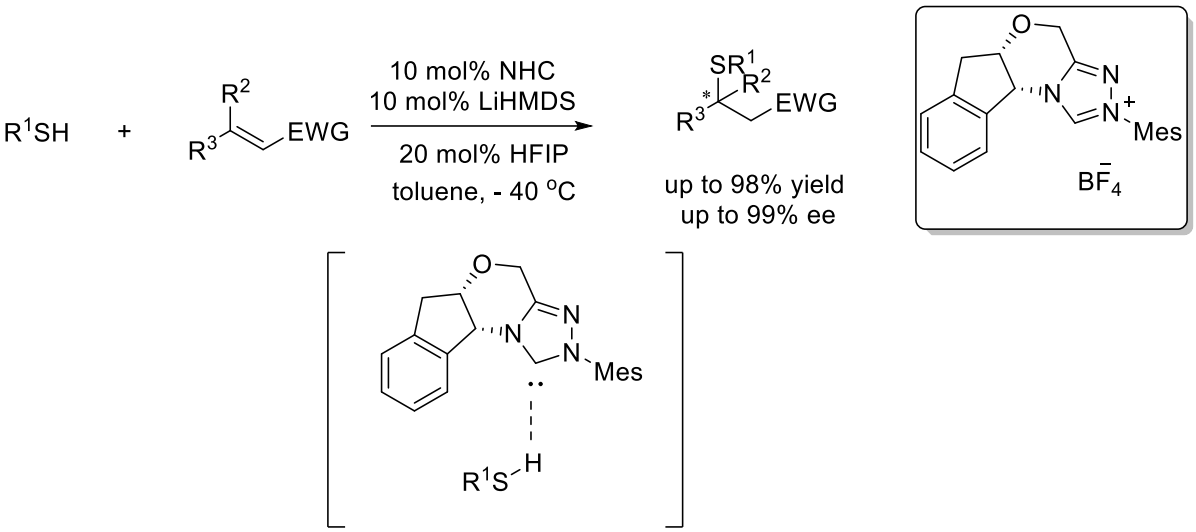
Compare to N-center nucleophiles, the addition of S-centered nucleophiles to the α,β-unsaturated acyl azoliums received even lesser attention. The first example of this kind of transformation has been reported in 2017 by Du's group[89] where the synthesis of biological

active 1,5-benzothiazepine heterocyclic motif has achieved through utilizing unsaturated acyl azolium intermediate as Michael acceptor. First, morpholine-based chiral NHC-catalyzed to synthesize acyl azolium from bromoenal and then [4+3] addition of o-aminobenzenethiol to the NHC-bound Michael acceptor provided the corresponding product (Scheme 43).



Scheme 1.43 Du's [4+3] annulation

Although the first example of an S-centered nucleophile addition to an electrophile, catalyzed by NHC reported back in 2015 by Huang's group.[90] Here, NHC did act as Lewis base rather than classical nucleophile.

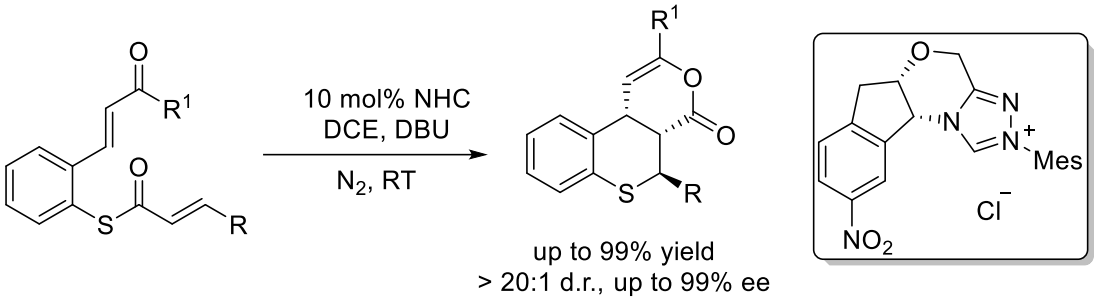


Scheme 1.44 Non-conventional asymmetric NHC-catalyzed sulfa-Michael addition

Under the basic conditions, first, an abstraction of the acidic proton of chiral aminoindane-based triazolium salt took place to form activated NHC species. Then, non-covalent interaction between chiral Lewis base and thiol created an asymmetric acid-base adduct environment.

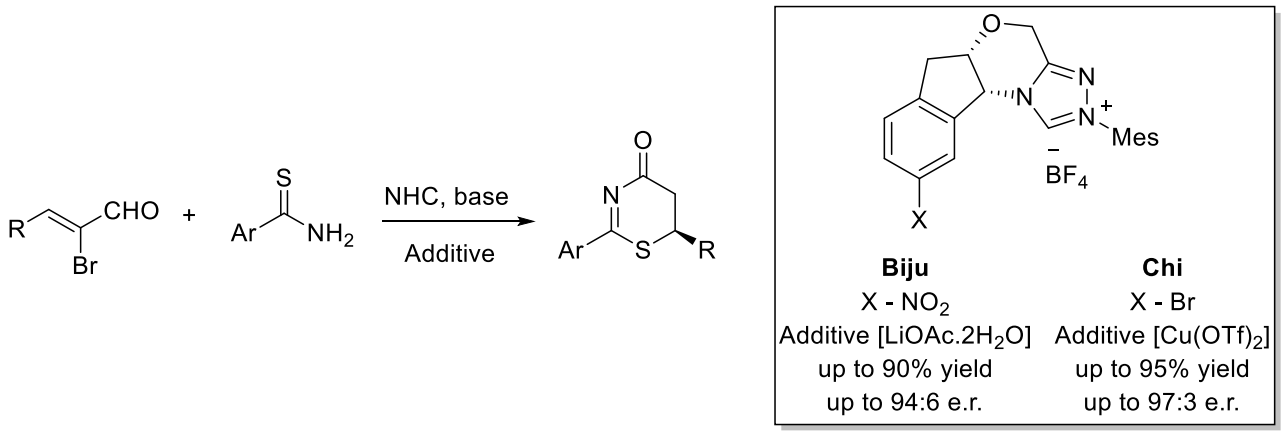
Later, the thiol anion attacked the electron-deficient Michael acceptor to afford S-containing molecules in excellent yield and ee (Scheme 44).

In 2017, Xu and his co-worker[91] reported a paper on C-S bond formation via in-situ generation of unsaturated acyl azolium intermediate from thioester. Later, NHC catalyzed sulfa-Michael/Michael/lactonization cascade reactions led to obtaining the optically active thiochroman scaffold with three continuous stereocenters (Scheme 45).



Scheme 1.45 Xu's functionalized thiochromans synthesis

In 2019, both Biju's group[92] and Chi's group [93] independently developed the strategy of NHC catalyzed enantioselective synthesis of functionalized thiazinones core using thioamide and bromoenal as substrates (Scheme 46). Point to note, Chi's group has used $Cu(OTf)_2$ as an additive to increase the enantioselectivity of the reaction.



Scheme 1.46 Biju's & Chi's [3+3] annulation

1.4 Research Design and Summary of Work

Most of the organic compounds' skeleton is made of C-C bonds, but the presence of a heteroatom (N, S, O, P, etc.) in the framework of these molecules gives the power to display different kinds of functions. For example, C-N bonds are often found in natural products, pharmaceutical compounds, and polymers like plastics with the ability to conduct electricity. Almost every natural product contains C-O bonds (ether, ketone, or ester). Heterocycles, a major class of organic compounds, with C-N, C-O, C-S, C-P, etc. bonds in ring structure often exhibit a wide range of medicinal properties. They are also used as organocatalyst as well as a ligand in metal catalysis. Thus, the development of efficient methods to construct C-heteroatom bonds is an important objective that continues to draw considerable attention from chemists.

Over the past decade, rapid development of NHC catalysis led to furnish a large number of complex molecules with ease that could not be accessed through traditional approaches. As discussed earlier, there are many intriguing activation modes available under NHC catalysis. Among them, α,β-unsaturated acyl azoliums is that privileged intermediate that has been exploited most due to its potential to achieve unprecedented transformations. However, still a few challenges remain in this field to deal with. In particular, α,β-unsaturated acyl azolium has been utilized as a versatile Michael acceptor to couple with the different kinds of nucleophiles. Although the most used reagents that have been coupled with β-position carbon are soft carbon-center nucleophiles, such as 1,3-dicarbonyl compounds, TMS enol ethers, enamine, and ylide. In contrast, this NHC catalyst-derived versatile intermediate has rarely explored in the aspect of C-heteroatom bond formation. Therefore, I aim to extend the list of nucleophiles with heteroatom active centers as the nucleophile and develop a general synthetic approach to access functional molecules with a carbon-heteroatom bond.

In this thesis, first I demonstrated the NHC catalyzed asymmetric construction of biologically active 5,6-dihydropyrimidin-4-one motif. I used S-alkylated isothiourea to couple

with unsaturated acyl azoulim intermediate in high regioselective fashion. Second, I disclosed a general synthetic route to access optically enriched C-centered tertiary phosphine by reacting secondary phosphine to NHC-bound unsaturated acyl azolium, and then the resulted tertiary phosphine products were converted into more diverse tertiary phosphine products like bifunctional phosphine and bidentate bis-phosphine ligand. In the last chapter, I used lesser explored NHC-bound alkynyl acyl azolium intermediate to couple with sulfinic acids to form challenging atroposelective axially chiral styrene derivatives.

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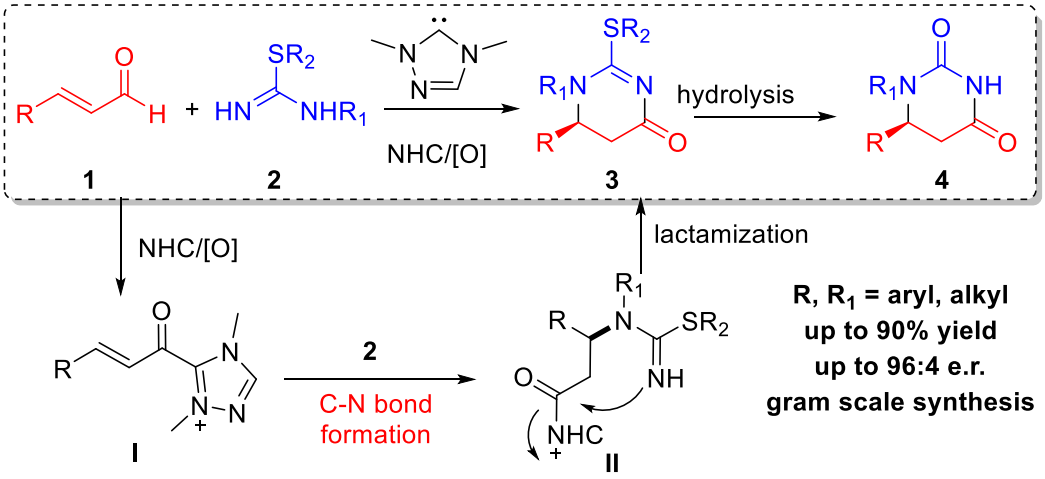
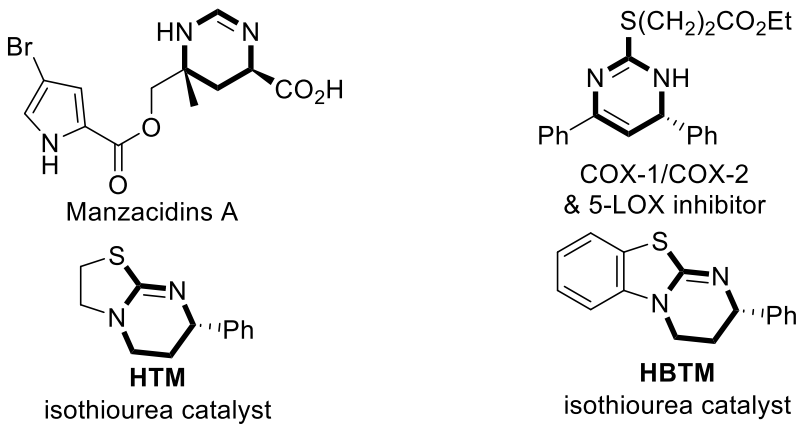
Chapter 2

Carbene-Catalyzed Selective Addition of Isothioureas to Enals for Access to Sulphur-Bearing 5,6-Dihydropyrimidin-4-ones



2.1 Introduction

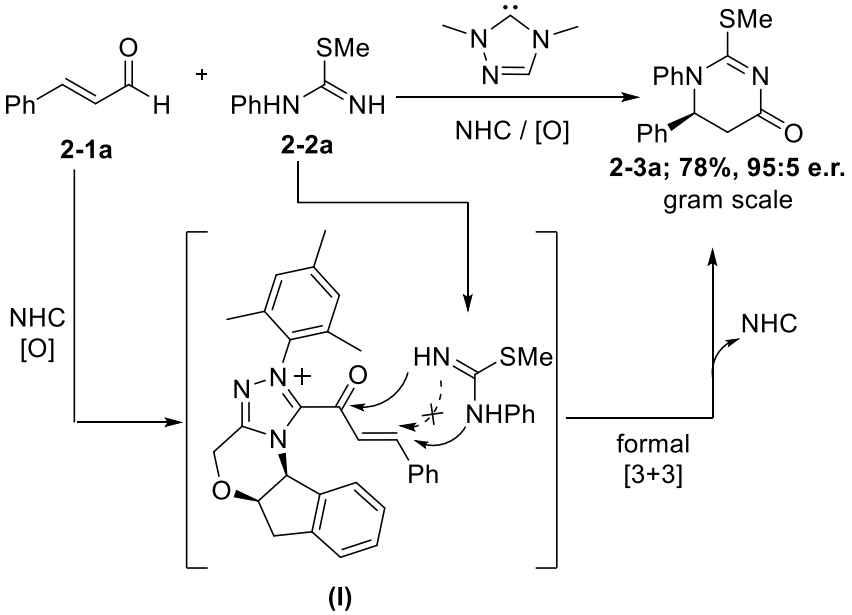
Sulphur and nitrogen are often found in crucial heterocycles with a broad range of applications such as medicines, agricultural chemicals, catalysts, and materials (Scheme 2.1).[1-2] Amidine and isothiourea fragment containing molecules are one of the prime examples of this category. For example, natural product Manzacidin A, an amidine containing moiety, has biologically active potentials to act as an antagonist of the serotonergic receptor, α-adrenoceptor blocker, and actomyosin ATPase activator.[3-4] Dihydropyrimidine compound bearing a sulphur atom and isothiourea derivative displayed inflammatory activity owning to have the potential to make a bond with cyclooxygenase (COX) and 5-lipoxygenase enzymes.[5] Isothiourea fragments containing chiral molecules (HTM and HBTM) (Scheme 1a) have also contributed tremendously to asymmetric organic catalysis.[6-10] Among various sulphur- and nitrogen-containing heterocycles, six-membered 5,6-dihydropyrimidin-4-ones (DHMP) with an S-atom has gained considerable attention. Predominantly to date, most of the traditional approaches to form these moieties were via the Biginelli-Atwal multi-component reactions[11-16] and their asymmetric catalytic variants.[17-21] Notably, optical pure DHMP molecules can also be synthesized from enantiopure beta-amino acids or alcohols through multi-step protocols.[22-23]



Scheme 2.1 Dihydropyrimidin-containing biological active molecules and catalyst

Each of these strategies has its own advantages and limitations depending on the chemical properties and patterns of the substituents on the heterocyclic rings. For example, regio-selectivity remains a daunting challenge in these otherwise elegant Biginelli-Atwal protocols.[16]

Our lab is interested in developing protocols to construct carbon-heteroatom bonds for access to chiral heterocycles by using N-heterocyclic carbene (NHC) as the catalyst.[24-27] One of these approaches is the incorporation of a nitrogen atom to NHC catalyst-bound α,β-unsaturated acyl azolium intermediates.[28-34] The list of the nitrogen nucleophiles in these type of addition reactions contains aryl amines,[35-37] sulfonamides,[24, 25] amidines,[38] and indole,[39] as demonstrated by the group of Hui,[35] our own laboratories, [24, 25, 36] Wang,[37, 38] and Biju.[39] Considering the importance of sulphur atom in N-heterocycles,[3-10] herein, we disclose an enantiomeric NHC-catalyzed [3+3] annulation of S-alkylated isothioureas to enals under oxidative conditions for rapid construction of sulphur atom-containing 5,6-dihydropyrimidin-4-one core. Key steps in this protocol involve a 1,4-addition of one nitrogen atom (phenyl protected) of the isothiourea



Scheme 2.2 NHC-catalyzed addition of isothiourea to enal

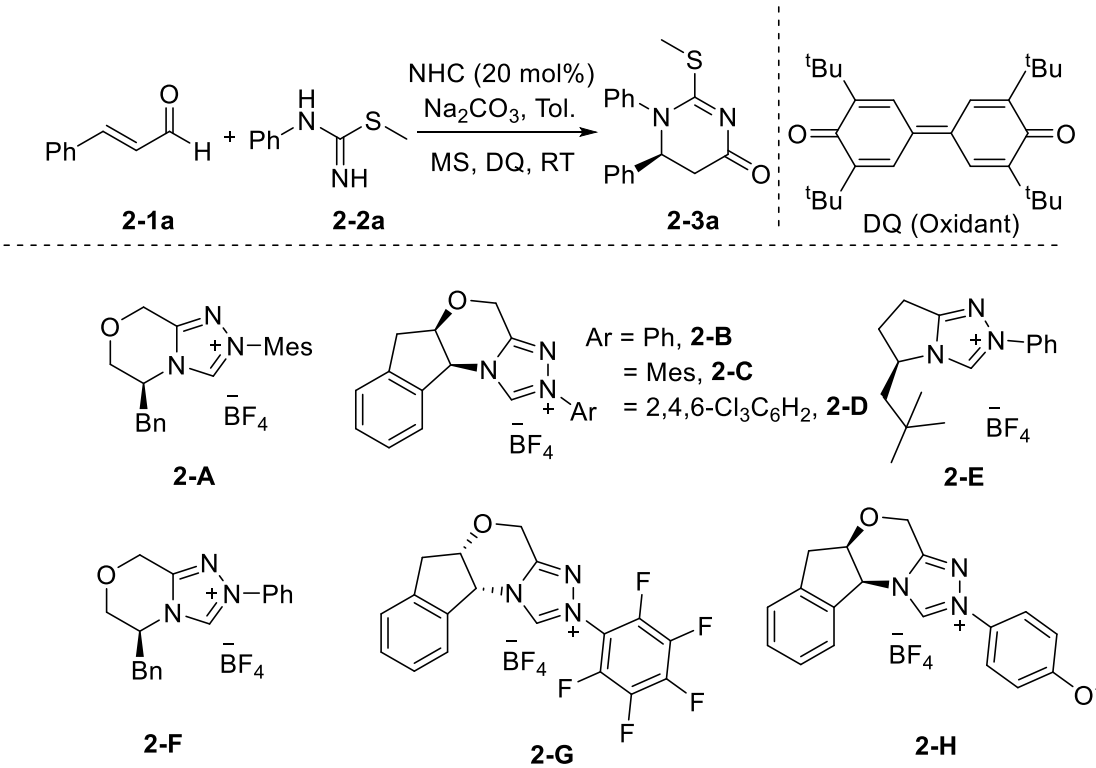
to a catalytically generated α,β-unsaturated acyl azolium intermediate (Scheme 1b) while the other nitrogen atom (unprotected) attacks the carbonyl carbon center of the intermediate (I) to remove the carbene for the next catalytic cycle. Through our NHC-catalytic process, the DHMP products are obtained in essentially a single regio-isomer with excellent optical purities. Additionally, conversion of the DHMP derivatives from our reactions through simple reaction protocols can lead to useful other derivatives such as optically enriched dihydrouracil, guanidine,[11] and 1,6-dihydropyrimidine.

2.2 Result and Discussion

2.2.1 Reaction condition optimization

In our initial study, we chose readily available cinnamaldehyde (**2-1a**) and S-methyl phenylisothiourea (**2-2a**) as model substrates to search for suitable conditions. First, several NHC catalysts in toluene were tested for our reaction in presence of Na_2CO_3 as the base and

Table 2.1 Screening of NHC precatalyst[a]



Entry	NHC	Yield (%)[b]	e.r.[c]

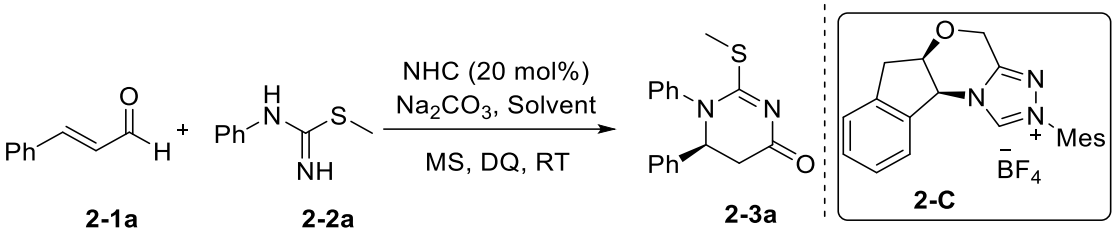
1	**2-A**	63	81:19
2	**2-B**	52	84:16
3	**2-C**	**58**	**93:7**
4	**2-D**	42	84:16
5	**2-E**	65	71:29
6	**2-F**	52	74:26
7	**2-G**	21	36:64
8	**2-H**	43	84:16

[a]Reaction condition: **2-1a** (0.09 mmol.), **2-2a** (0.05 mmol), **NHC** pre-cat. (20 mol%), Na_2CO_3 (1.5 equiv.), **DQ** (1.25 equiv.), AcOH (30 mol%, additive), Tol. (1 mL), MS (50 mg) at RT for 36-48 hrs. [b]Yield determined by ^{1}HNMR, based on **2-2a**, by using the 1,3,5-trimethoxybenzene as internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

DQ as the oxidant. The key results of NHC-catalysts screening are summarized in Table 2.1. 4 Å molecular sieves was employed to inhibit the hydrolysis of α,β-unsaturated acyl azolium. Gratifyingly, triazolium salt **2-A** as the NHC precursor could catalyze the reaction and provided the desired product at room temperature with encouraging results (63% yield, 81:19 e.r., Table 2.1, entry 1). Thus, we continued our survey on chiral NHC with both electron-withdrawing and electron-donating triazolium salts to find an acceptable outcome (entries 2-8). Replacing morpholine-based NHC **2-A** with aminoindole-based NHC **2-B** resulted in a drop in both yield and e.r. (entry 2). Although all the employed NHC catalysts were able to deliver the product in good to moderate yield and e.r., but among all other NHCs, aminoindanol-derived NHC precatalyst **2-C** proved to be offered the best result in terms of e.r. value (58% yield, 93:7 e.r., entry 3). Therefore, NHC **2-C** was selected as an optimal precatalyst for further optimization. Notably, NHC precatalysts with an electron-withdrawing aryl group (**2-D** and **2-G**) did not suitable for the reaction. Next, we assessed the effect of solvents in presence of NHC **2-C** with Na_2CO_3 as the base. Various polar (THF, ACN, EtOAc) and non-polar ($CHCl_3$, DCE, Et_2O)

solvents were used to improve the yield as well as the e.r. value of the desired product. Although most of the cases (except THF and $CHCl_3$) an increased yield was observed, unfortunately, they had little influence on the enantioselectivity of the product. Hence, we focused on the bases screening for better e.r. and yield with toluene as the solvent.

Table 2.2 Screening of solvents[a]



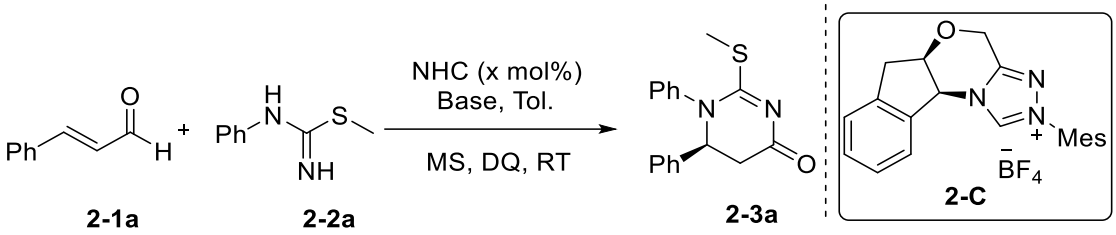
Entry	Solvent	Yield (%)[b]	e.r.[c]
1	THF	50	83:17
2	ACN	63	68:32
3	EtOAc	72	83:17
4	DCE	73	70:30
5	$CHCl_3$	31	87:13
6	Et_2O	77	86:14

[a]Reaction condition: **2-1a** (0.09 mmol.), **2-2a** (0.05 mmol), NHC **2-C** pre-cat. (20 mol%), Na_2CO_3 (1.5 equiv.), **DQ** (1.25 equiv.), AcOH (30 mol%, additive), Solvent (1 mL), MS (50 mg) at RT for 36-48 hrs. [b]Yield determined by ^{1}HNMR, based on **2-2a**, by using the 1,3,5-trimethoxybenzene as internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

Several organic and inorganic bases were employed to the catalytic system in presence of NHC precursor **2-C** to improve the optical purity of the proposed product. The key results are shown in the Table 2.3. In presence of strong inorganic bases like Cs_2CO_3, K_2CO_3 (Table 2.3, entry 1, entry 2) a significant drop in the yield of the product was found, albeit the enantioselectivity was almost intact. Switching to organic bases such as DABCO, DMAP, DIPEA (Table 2.3, entries 4-6) provided more frustrating outcomes in terms of yield. Finally, the use of the weak

inorganic base, NaOAc, afforded the best result with 82% yield (78% iso. yield) and 95:5 e.r (Table 2.3, entry 7). After that, the amount of catalyst loading on this method was investigated (Table 2.3 entries 8-9). A continuous erosion (slight) on both yield and enantioselectivity was observed with lowering down of the catalyst loading.

Table 2.3 Screening of bases and amount of catalyst loading[a]



Entry	NHC (x mol%)	Base	Yield (%)[b]	e.r.[c]
1	**2-C (20)**	K_2CO_3	49	92:8
2	**2-C (20)**	Cs_2CO_3	55	91:9
3	**2-C (20)**	K_3PO_4	61	91:9
4	**2-C (20)**	DABCO	25	87:13
5	**2-C (20)**	DMAP	45	92:8
6	**2-C (20)**	DIPEA	36	92:8
7	**2-C (20)**	**NaOAc**	**82 (78)**	**95:5**
8	**2-C (10)**	NaOAc	77	93:7
9	**2-C (5)**	NaOAc	75	91:9

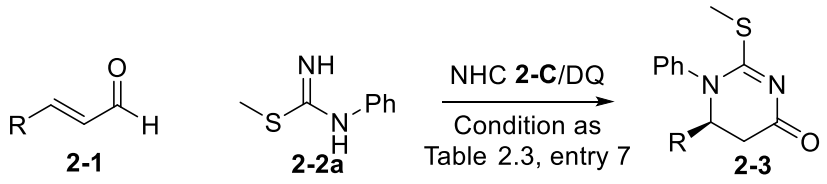
[a]Reaction condition: **2-1a** (0.09 mmol.), **2-2a** (0.05 mmol), NHC **2-C** pre-cat. (x mol%), Base (1.5 equiv.), **DQ** (1.25 equiv.), AcOH (30 mol%, additive), Tol. (1 mL), MS (50 mg) at RT for 36-48 hrs. [b]Yield determined by ^{1}HNMR, based on **2-2a**, by using 1,3,5-trimethoxybenzene as the internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

2.2.2 Substrate scope

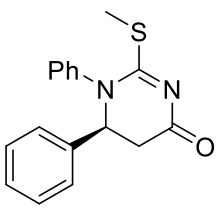
After getting the optimized condition, we assessed the generality of the reaction. The variation in enals is shown in Table 2.4. First, we examined the enals with β-aryl substituents under the optimized standard reaction conditions with **2-2a** as the model substrate. A broad range of substituents (halogen, NO_2, OMe, Me, etc.) at the different positions (*o*-, *m*-, *p*-) of aryl ring of the enal worked well and delivered the desired products in good to excellent yields and enantioselectivities (**2-3a** to **2-3j**). The X-ray analysis of product **2-3a** (CCDC No. - **2025922**) confirmed the absolute structural configuration. Interestingly, with *m*-substituted enal (**2-2j**), the reaction was needed to be heated at 50 °C to afford the corresponding product in moderate yield and e.r value (**2-3j**, 54%, 92:8 e.r.). The β-phenyl ring in the enal (**2-1**) could also be replaced by other aromatic groups like naphthyl and heteroaryl units (pyridine, furfuryl, thiophenyl) (**2-3k** to **2-3n**) without affecting the outcomes significantly. To our delight, enals with β-alkyl substituents (**2-3o** to **2-3r**) were also well-tolerated under the standard oxidative conditions, providing the products with acceptable outcomes. Point to note that bulkier aliphatic group containing enal **2-2q** could lead to the product with better enantioselectivity (90:10 e.r.) than **2-2o** and **2-2p**. Surprisingly, more reactive enal **2-2r** was also compatible under our catalytic conditions and afforded the product **2-3r** in 65% yield and 85:15 e.r.

Next, we moved to explore the substrate scope of S-alkylated isothiourea with respect to **2-1a** as the model substrate (Table 2.5). In general, both electron-donating (OMe, Me) and electron-withdrawing (Cl, Br, F) groups at *p*- position of the phenyl ring of **2-2** proceeded to afford the corresponding products in 70-83% yield and 93:7-96:4 e.r. Notably, a substantial decrease in yields was observed in the case of *m*- substituted bromophenyl enal (**2-4f**, 61%, 95:5 e.r.). Later, the effect of the protecting group on the N-atom of **2-2** had been examined. Remarkably, the corresponding dihydropyrimidinone derivatives (**2-4g** and **2-4h**) were obtained effectively with both benzyl-protected and unprotected substrates (**2-2g** and **2-2h**).

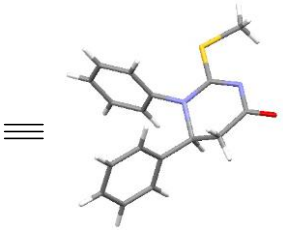
Table 2.4: Examples of the aldehyde substrate scope[a, b]



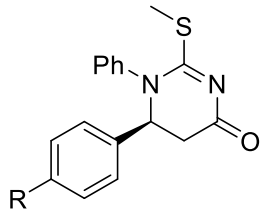
2-1 2-2a 2-3



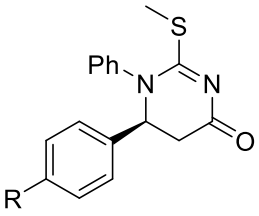
2-3a: 78%, 95:5 e.r.



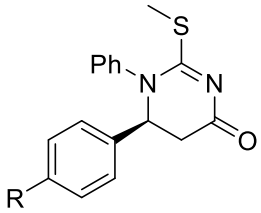
CCDC No. - 2025922



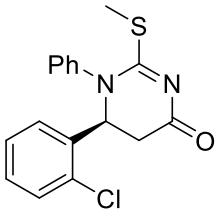
R = OMe, **2-3b:** 77%, 94.5:5.5 e.r.
R = Me, **2-3c:** 78%, 94.5:5.5 e.r.



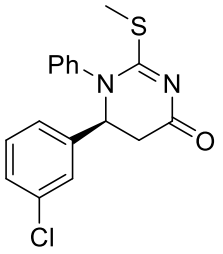
R = Br, **2-3d:** 81%, 96:4 e.r.
R = Cl, **2-3e:** 82%, 95:5 e.r.
R = F, **2-3f:** 86%, 94:6 e.r.



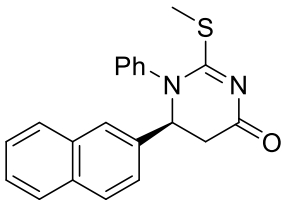
R = NO_2, **2-3g:** 88%, 91.5:8.5 e.r.
R = CO_2Me, **2-3h:** 79%, 95:5 e.r.



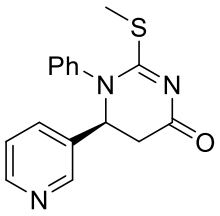
2-3i: 73%, 96:4 e.r.



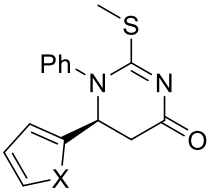
2-3j: 54%, 92:8 e.r.[c]



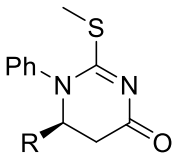
2-3k: 78%, 95.5:4.5 e.r.



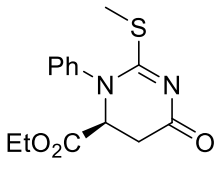
2-3l: 67%, 94.5:5.5 e.r.



X= O, **2-3m:** 63%, 90:10 e.r.
X= S, **2-3n:** 60%, 93:7 e.r.



R = Me, **2-3o:** 85%, 80.5:19.5 e.r.
R = Et, **2-3p:** 81%, 89:11 e.r.
R = ^{n}Pr, **2-3q:** 90%, 90:10 e.r.



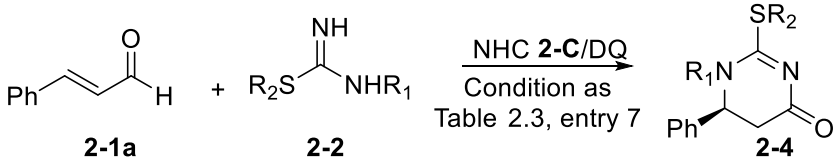
2-3r: 65%, 85:15 e.r.

[a]Isolated yields of **2-3**. Reaction time 30-48 hrs. [b]No additive was added in the case of aliphatic aldehydes**.** [c]Heated at 50°C**.**

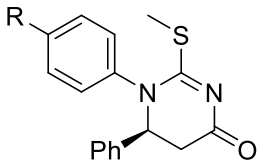
However, to our disappointment, a drastically low e.r. value (76:24 e.r.) was afforded using unprotected S-methylated isothiourea **2-2h**. The loss of the enantioselectivity may cause due to poor electronic and steric effects of the N-protecting group. Therefore, bulkier catalyst **2-I**

was employed to improve the enantioselectivity. Under this condition, the desired product could be achieved in 66% yield with moderate 87:13 e.r. It is worth noting that the methyl group on S-atom could be replaced by the benzyl group, providing the corresponding product (**2-4i** and **2-4j**) in acceptable yields and optical purities.

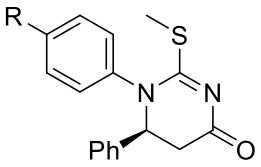
Table 2.5. Example of the S-alkylated isothiourea substrate scope [a]



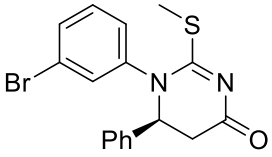
2-1a **2-2** **2-4**



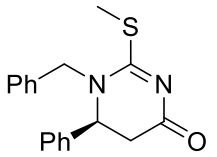
R= OMe, **2-4a:** 83%, 93:7 e.r.
R= Me, **2-4b:** 77%, 95:5 e.r.



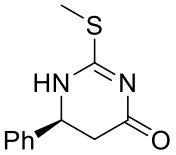
R= Cl, **2-4c:** 70%, 96:4 e.r.
R= F, **2-4d:** 83%, 95:5 e.r.
R= Br, **2-4e:** 83%, 95.5:4.5 e.r.



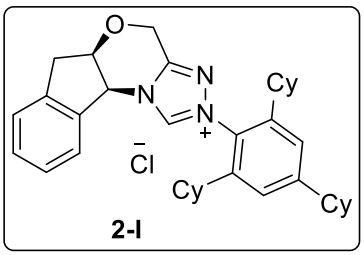
2-4f: 61%, 95:5 e.r.



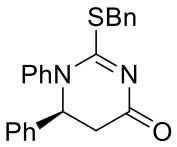
2-4g: 58%, 89.5:10.5 e.r.[b]



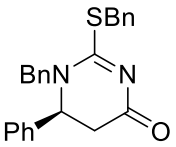
2-4h: 95%, 76:24 e.r[b, c]
66%, 87:13 e.r.[b, c, d]



2-I



2-4i: 51%, 95:5 e.r.

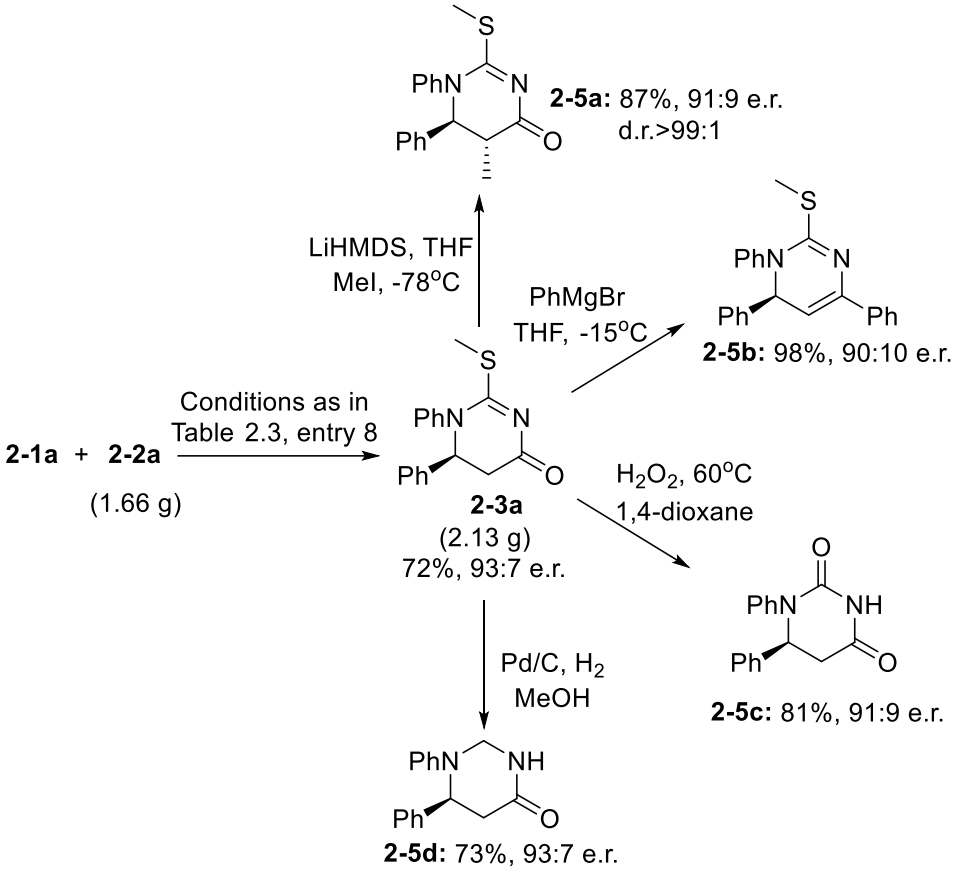


2-4j: 52%, 90:10 e.r.[b]

[a]Isolated yields of **2-4**. Reaction time 30-48 hrs. [b]No additive was used. [c]**2-2**·HI salt and K_2CO_3 were used. [d] 20 mol% NHC **2-I** was used.

2.2.3 Scale-up reaction and synthetic transformations

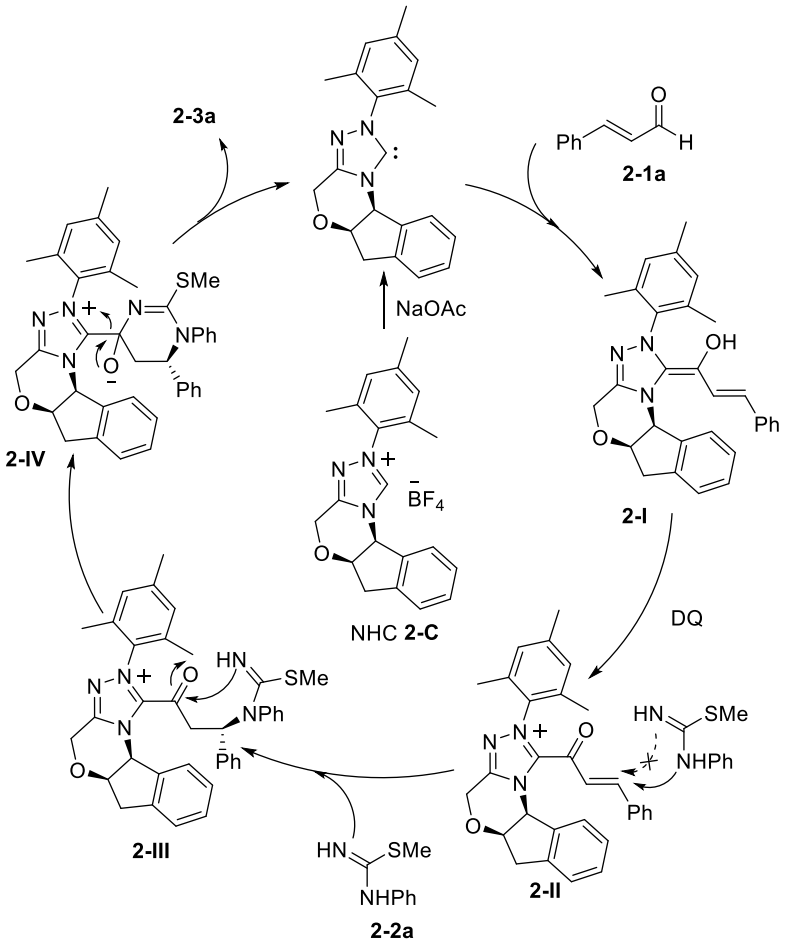
To check the practicality of our method, a large scale (10 mmol) synthesis of 5,6-dihydropyrimidin-4-one core was carried out with 10 mol% catalyst loading. Under the standard condition, the desired product **2-3a** was obtained in 72% isolated yield (2.13 g) and



Scheme 2.3 Scale-up reaction and synthetic transformations

93:7 e.r. value that is comparable to small-scale reaction (Table 2.3, entry 8). The optically enriched DHMP core can readily undergo further synthetic transformations to more complex motifs through simple methods (Scheme 2.3). For instance, direct methylation of **2-3a** using LiHMDS at -78°C afforded the α −monomethylated single diastereomer **2-5a** (87%, 91:9 e.r.). Simple Grignard solution (PhMgBr) addition to **2-3a** in THF led to the extended conjugated system **2-5b** in quantitative yield with slight erosion of e.r. value (98% yield, 90:10 e.r.). The product **2-3a** could undergo simple oxidative hydrolysis by H_2O_2 solution to obtain the optically pure dihydrouracil scaffold **2-5c**. The product **2-5c** was also obtained in 73% yield without losing the enantioselectivity through Pd/C catalyzed hydrogenation of **2-3a**.

2.2.4 Postulated reaction mechanism



Scheme 2.4 Proposed mechanism

Based on previous reports, here we proposed a plausible reaction mechanism (Scheme 2.4). Under basic conditions, NHC precatalyst **2-C** was activated and generated a free carbene species. Subsequently, the free carbene coupled with enal **2-1a** to form the Breslow intermediate **2-I**, followed by oxidation with oxidant DQ led to the unsaturated acyl azoluim **2-II**. Next, selective aza-Michael addition by the phenyl protected N-atom of **2-2a** to **2-II** provided the intermediate **2-III**. Finally, a lactamization process happened by the other N-atom of **2-2a** (i.e., unprotected one), providing the six-membered DHPM core **2-3a** in 78% yield and 95:5 e.r.

2.3 Conclusion

In summary, we have developed an NHC organocatalyzed enantiomeric formal [3+3] annulation strategy for construction of an S-containing 5,6-dihydropyrimidin-4-one core. Our

method employs cheap and easily accessible enals and S-alkylated isothiourea to form an optically active DHPM framework with high enantioselectivity. Our method could also work in scalable preparation of the product. Transformation of our product through simple reaction protocols could also provide more useful molecules efficiently such as chiral 1,6-dihydropyrimidine, dihydrouracil, and guanidine derivatives.[11] Further studies on the bioactivities of the products are ongoing in our lab.

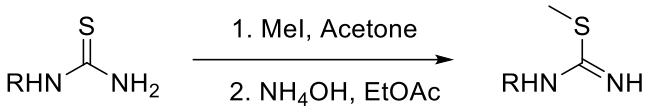
2.4 Experimental section

2.4.1 General information

Commercially available materials purchased from TCI or Sigma Aldrich were used as received. All reactions were carried out under nitrogen atmosphere under anhydrous conditions unless otherwise noted. THF was distilled from sodium-benzophenone. Flash chromatography was performed using silica gel (200-300 mesh). Reactions were monitored by thin-layer chromatography (TLC). Visualization was achieved under a UV lamp (254nm and 365 nm). ^{1}H and ^{13}C NMR were recorded on Bruker BBFO 400 MHz NMR, Bruker AV400 MHz NMR spectrometer with TMS as the internal standard and were calibrated using residual undeuterated solvent as an internal reference ($CDCl_3$: ^{1}H NMR = 7.26, ^{13}C NMR = 77.16). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants (J) are reported in Hertz (Hz). High-resolution Mass spectra (HRMS) were recorded by using 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. 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: $\mathbf{[\alpha]^{21}_D}$ (c in g per 100 mL solvent).

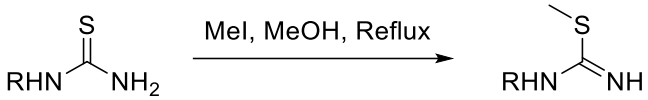
2.4.2 Synthesis of S-alkylated isothiourea

S-Methyl Isothiourea:[40]



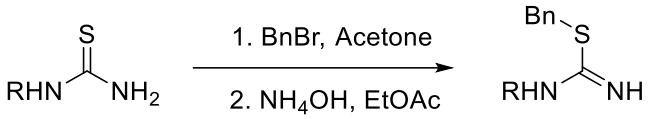
Iodomethane (5 mmol) was added to a solution of thiourea derivative (5 mmol) in acetone and the mixture was continued to stir overnight at room temperature. After that, the mixture was concentrated under vacuum and ethyl acetate (25 mL) was added. Later, H_2O (50 mL) was added and cooled to 0°C. Next, conc. NH_4OH was mixed dropwise until all the solid disappeared and then, stirred for another 30 mins. Organic layer was separated, washed with brine, and concentrated. The product was used directly without further purification.

Synthesis of 2-2h:[41]



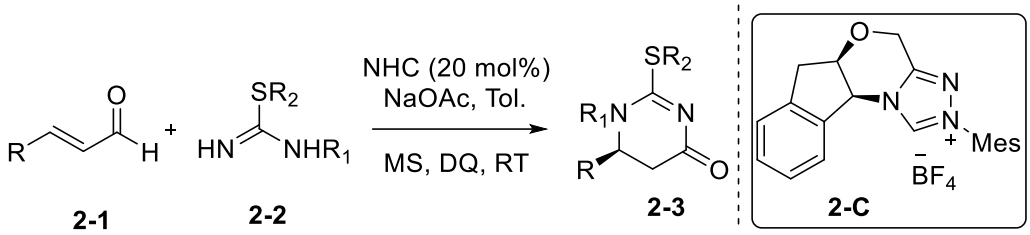
In 100 mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser, thiourea (4.00 g, 51.3 mmol) was dissolved in methanol (40.0 mL). Then, Iodomethane (3.20 mL, 51.3 mmol) was added in one portion and the mixture was continued to reflux for 2 hrs. After the mentioned time, the reaction mixture was cooled to room temperature and concentrated under reduced pressure, giving a yellowish solid. Then, the yellowish solid was mixed with EtOAc (50.0 mL), and the precipitate that did not dissolve was filtered. The precipitate was sequentially washed several times with EtOAc and diethyl ether until it becomes completely colorless. The product was dried under vacuum to provide 8.35 g (38.0 mmol, 74% yield) of white powder.

Synthesis of 2-2i and 2-2j:



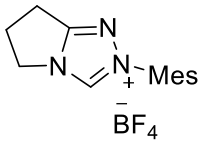
Benzyl Bromide (5 mmol) was added dropwise to a cooled solution of thiourea derivative (5 mmol) in acetone and the mixture was continued to stir overnight at room temperature. After that, the mixture was concentrated under vacuum and ethyl acetate (25 mL) was added. Later, H_2O (50 mL) was added and cooled to 0 ^oC. Next, conc. NH_4OH was mixed dropwise until all the solid disappeared and then, stirred for another 30 mins. Organic layer was separated, washed with brine, and concentrated. The product was used directly without further purification.

2.4.3 General procedure for the catalytic reactions of enal (2-1) with S-alkylated isothioura (2-2) to synthesize Product 2-3



A dry 10 mL Schlenk tube with a stir bar was charged with enal **2-1** (0.18 mmol, 1.8 equiv.), **2-2** (0.1 mmol, 1.0 equiv.), NHC (8.4 mg, 20 mol%), NaOAc (13 mg, 0.15 mmol, 1.5 equiv.), AcOH (1.8 µL, 30 mol%), DQ (51 mg, 0.125 mmol, 1.25 equiv.) and molecular sieves (100 mg). The tube was evacuated and refilled with nitrogen. Then the mixture was dissolved with newly distilled solvent toluene (2.0 mL). Then the mixture was stirred at room temperature for 36-48h. When the substrate was consumed completely (monitored by TLC), the mixture was concentrated under vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1) to afford desired product **2-3**, which was confirmed by ^1H NMR, ^{13}C NMR spectra, and the enantiomeric ratio was determined by chiral HPLC.

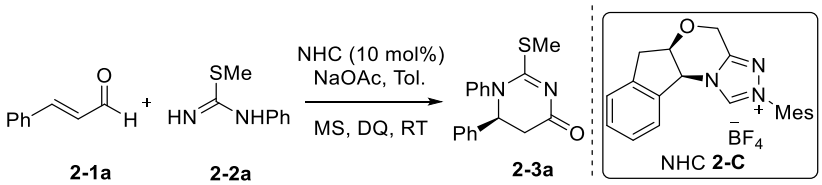
Note: Racemic samples were prepared using NHC below for chiral phase HPLC analysis.



Achiral NHC

2.4.4 Procedures for scale-up reaction and synthetic transformations

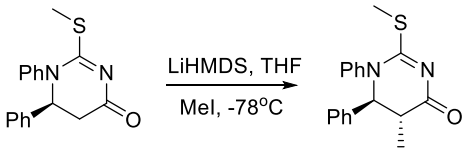
Gram-scale Preparation of 2-3a



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

A dry 100 mL Schlenk tube with stir bar was charged with cinnamaldehyde **2-1a** (12 mmol, 1.2 equiv.), **2-2a** (1.66 g, 10 mmol, 1.0 equiv.), NHC **2-C** (420 mg, 10 mol%), NaOAc (1.23 gm, 15 mmol, 1.5 equiv.), DQ (5.1 gm, 12.5 mmol, 1.25 equiv.) and molecular sieves (1 gm). The tube was evacuated and refilled with nitrogen. Then the mixture was dissolved with newly distilled solvent Toluene (50 mL). Then the mixture was stirred at room temperature for 36 h. After complete consumption of the substrate **2-2a** (monitored by TLC), the mixture was concentrated under vacuum and purified by column chromatography on silica gel (hexane/ethyl acetate = 2:1) to afford desired product **2-3a** (2.13g) with 72% yield and 93:7 e.r.

Preparation of 2-5a[42]

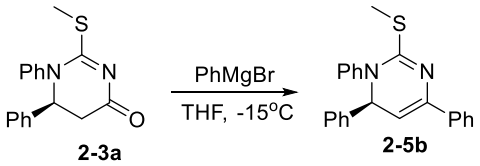


2-3a **2-5a**

To a stirred solution of **3a** (30 mg, 0.1 mmol) in anhydrous THF (1 mL) at −78 °C was added LiHMDS (1 M in THF, 0.15 mL, 0.15 mmol), and the solution was stirred for 2 hrs. The iodomethane (28.4 mg, 0.2 mmol) was added dropwise. After that, the temperature of the reaction mixture was slowly raised to room temperature and continued to stir for 20 h at the same temperature. After completion of the reaction, H_2O (1 mL) was added. The organic layer

was collected, and the aqueous layer was extracted with EtOAc (twice). The combined organic extracts were washed with brine, dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified via silica gel flash chromatography (hexane/ethyl acetate = 5:1) to afford product **2-5a (**27 mg, 87%, 91:9 e.r., >99:1 d.r.).

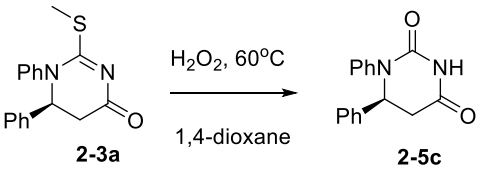
Preparation of 2-5b[43]



2-3a **2-5b**

The product **2-3a** (30 mg, 0.1 mmol) was suspended in dry THF and then cooled −15 °C. Grignard reagent (PhMgBr, 1.2 equiv.) was then added dropwise, and the reaction mixture was stirred at −15 °C for 5 h. Trifluoroacetic acid (3.0 equiv.) was then carefully added, and the reaction was stirred at −15 °C for another 30 minutes. The mixture was concentrated under reduced pressure, diluted with water, and extracted with EtOAc. The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/ethyl acetate = 1:50) to obtain **2-5b** (35 mg, 98%, 90:10 e.r.).

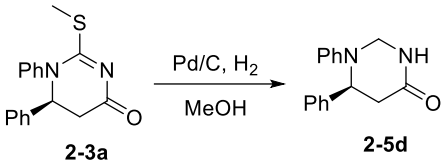
Preparation of 2-5c



2-3a **2-5c**

The product **2-3a** (30 mg, 0.1 mmol) was dissolved in 1,4-dioxane and then H_2O_2 (35% v/v, 1 mL) was added. Then the solution was heated at 60 °C for 6 hrs. Solvent was evaporated and the reaction mixture was extracted with EtOAc. The combined organic layers were dried over MgSO4, filtered, and concentrated under reduced pressure. Pure **2-5c** (21.6 mg, 81%, 91:9 e.r.) was obtained by silica gel column chromatography (hexane/ethyl acetate = 5:1).

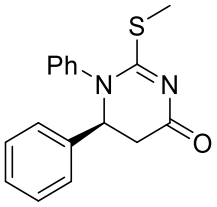
Preparation of 2-5d



2-3a **2-5d**

The product **2-3a** (30 mg, 0.1 mmol) and Pd/C (10 mol%) was added to MeOH (10 ml). Then solution was degassed using a pump and bubbled with H_2 gas (5 times). The reaction mixture was stirred until the starting materials consumed completely. When the reaction was finished, MeOH was evaporated and EtOAc was added to the reaction mixture. Excess Pd/C was filtered through celite, solvent was evaporated and concentrated under reduced pressure. Silica gel column chromatography (hexane/ethyl acetate = 3:1) of the residue provided the pure **2-5d** (18.4 mg, 73%, 93:7 e.r.).

2.4.5 Characterization of products



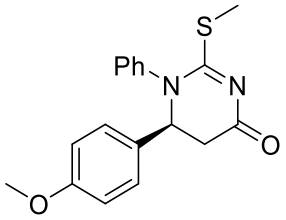
***(S)*-2-(methylthio)-1,6-diphenyl-5,6-dihydropyrimidin-4(1H)-one (2-3a)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.24 (m, 6H), 7.24 – 7.16 (m, 2H), 7.12 (s, 2H), 4.91 (dd, *J* = 7.7, 3.6 Hz, 1H), 3.25 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.88 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.46 (s, 3H).**^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.8, 173.1, 140.7, 138.5, 129.7, 129.5, 129.2, 128.8, 128.7, 126.8, 64.9, 38.6, 15.2 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{16}N_2OSH^+$: 297.1062 $(M+H)^+$, found: 297.1063.

$[\alpha]^{21}_D$ = +3.6 (c = 1.0 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 22.1 min, R_t (major) = 28.1 min.



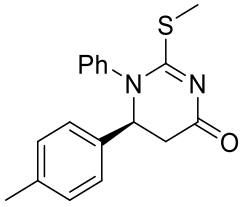
***(S)*-6-(4-methoxyphenyl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3b)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 4.5, 2.1 Hz, 3H), 7.09 (dd, *J* = 6.7, 2.0 Hz, 4H), 6.87 – 6.75 (m, 2H), 4.84 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.77 (s, 3H), 3.21 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.87 (dd, *J* = 15.4, 3.9 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ 173.6, 173.4, 159.9, 140.8, 130.7, 129.6, 129.5, 128.8, 128.3, 114.6, 64.5, 55.4, 38.8, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{18}H_{18}N_2O_2SH^+$: 327.1167 $(M+H)^+$, found: 327.1169.

$[\alpha]^{21}_D$ = -5.3 (c = 1.0 in $CHCl_3$).

HPLC analysis: 94.5:5.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 35.7 min, R_t (major) = 38.9 min.



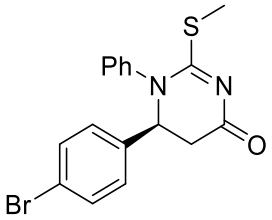
***(S)*-2-(methylthio)-1-phenyl-6-(p-tolyl)-5,6-dihydropyrimidin-4(1H)-one (2-3c)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 3H), 7.18 – 6.97 (m, 6H), 4.86 (dd, *J* = 7.7, 3.7 Hz, 1H), 3.22 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.86 (dd, *J* = 15.4, 3.7 Hz, 1H), 2.45 (s, 3H), 2.30 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.6, 173.2, 140.8, 138.6, 135.6, 129.9, 129.6, 129.4, 128.7, 126.8, 64.8, 38.8, 21.2, 15.2 ppm.

HRMS (ESI, m/z): calculated for $C_{18}H_{18}N_2OSH^+$: 311.1218 $(M+H)^+$, found: 311.1218.

$[\alpha]^{21}_D$ = -1.4 (c = 1.7 in $CHCl_3$).

HPLC analysis: 94.5:5.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 22.0 min, R_t (major) = 28.4 min.



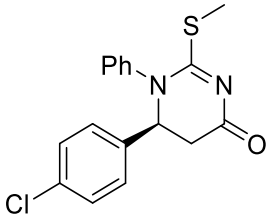
***(S)*-6-(4-bromophenyl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3d)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.39 (m, 2H), 7.39 – 7.30 (m, 3H), 7.16 – 6.99 (m, 4H), 4.87 (dd, *J* = 7.7, 3.4 Hz, 1H), 3.24 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.83 (dd, *J* = 15.4, 3.5 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 172.6, 140.6, 137.7, 132.5, 129.8, 129.7, 128.6, 128.6, 122.9, 64.4, 38.5, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}BrN_2OSH^+$: 375.0167 $(M+H)^+$, found: 375.0167.

$[\alpha]^{21}_D$ = +3.7 (c = 1.7 in $CHCl_3$).

HPLC analysis: 95.5:4.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 26.3 min, R_t (major) = 37.4 min.



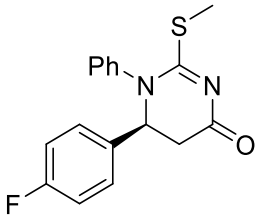
***(S)*-6-(4-chlorophenyl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3e)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 3H), 7.31 – 7.27 (m, 2H), 7.18 – 6.99 (m, 4H), 4.88 (dd, *J* = 7.7, 3.5 Hz, 1H), 3.24 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.84 (dd, *J* = 15.4, 3.5 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 172.7, 140.6, 137.2, 134.8, 129.8, 129.7, 129.5, 128.7, 128.3, 64.4, 38.5, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}ClN_2OSH^+$: 331.0672 $(M+H)^+$, found: 331.0672.

$[\alpha]^{21}_D$ = +12.0 (c = 0.8 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 24.2 min, R_t (major) = 30.7 min.



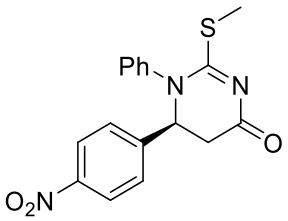
***(S)*-6-(4-fluorophenyl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3f)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 3H), 7.22 – 7.13 (m, 2H), 7.10 (s, 2H), 7.03 – 6.92 (m, 2H), 4.90 (dd, *J* = 7.7, 3.6 Hz, 1H), 3.24 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.85 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.45 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.8, 172.9, 164.1, 161.7, 140.6, 134.5 (d, *J* = 3.3 Hz), 129.7 (d, *J* = 14.8 Hz), 128.8 (d, *J* = 8.6 Hz), 116.2, 116.0, 64.1, 38.5, 15.1 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}FN_2OSH^+$: 315.0967 $(M+H)^+$, found: 315.0967.

$[\alpha]^{21}_D$ = -6.4 (c = 2.2 in $CHCl_3$).

HPLC analysis: 94:6 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 23.5 min, R_t (major) = 29.1 min.



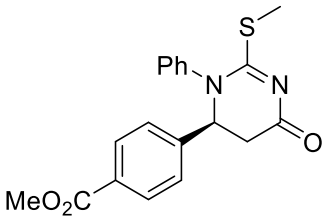
***(S)*-2-(methylthio)-6-(4-nitrophenyl)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3g)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.09 (m, 2H), 7.51 – 7.31 (m, 5H), 7.13 (d, *J* = 5.6 Hz, 2H), 5.06 (dd, *J* = 7.8, 3.2 Hz, 1H), 3.31 (dd, *J* = 15.4, 7.9 Hz, 1H), 2.85 (dd, *J* = 15.4, 3.3 Hz, 1H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.0, 171.7, 148.0, 145.7, 140.4, 130.0, 129.9, 128.4, 127.9, 124.6, 64.2, 38.2, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}N_3O_3SH^+$: 342.0912 $(M+H)^+$, found: 342.0912.

$[\alpha]^{21}_D$ = +51.8 (c = 0.3 in $CHCl_3$).

HPLC analysis: 91.5:8.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 36.3 min, R_t (major) = 71.4 min.



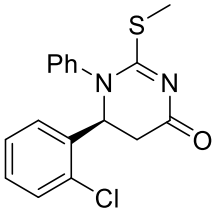
methyl *(S)*-4-(2-(methylthio)-6-oxo-3-phenyl-3,4,5,6-tetrahydropyrimidin-4-yl)benzoate (2-3h)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.90 (m, 2H), 7.34 (dd, *J* = 7.6, 3.9 Hz, 3H), 7.28 (d, *J* = 7.0 Hz, 2H), 7.11 (d, *J* = 5.7 Hz, 2H), 4.98 (dd, *J* = 7.8, 3.5 Hz, 1H), 3.90 (s, 3H), 3.27 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.86 (dd, *J* = 15.4, 3.5 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.0, 172.5, 166.5, 143.5, 140.6, 130.7, 130.5, 129.8, 129.7, 128.6, 126.9, 64.6, 52.3, 38.4, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{19}H_{18}N_2O_3SH^+$: 355.1116 $(M+H)^+$, found: 375.0167.

$[\alpha]^{21}_{D}$ = +15.7 (c = 1.7 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak ORJ-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 34.1 min, R_t (major) = 40.2 min.



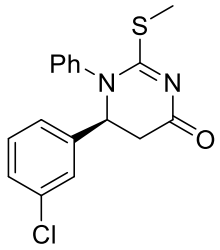
***(S)*-6-(2-chlorophenyl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3i)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 1H), 7.43 – 7.33 (m, 3H), 7.30 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.26 – 7.09 (m, 3H), 5.47 (dd, *J* = 7.9, 2.7 Hz, 1H), 3.23 (dd, *J* = 15.4, 7.9 Hz, 1H), 2.90 (dd, *J* = 15.4, 2.8 Hz, 1H), 2.48 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 172.6, 140.9, 135.4, 132.3, 130.4, 129.9, 129.8, 129.6, 128.3, 127.8, 127.7, 61.2, 37.1, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}ClN_2OSH^+$: 331.0672 $(M+H)^+$, found: 331.0672.

[α]^{21} D = +51.9 (c = 1.9 in $CHCl_3$).

HPLC analysis: 96:4 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 21.9 min, R_t (major) = 53.3 min.



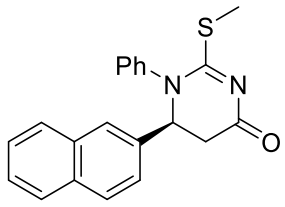
***(S)*-6-(3-chlorophenyl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3j)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.2, 4.1 Hz, 3H), 7.30 – 7.23 (m, 2H), 7.13 (dd, *J* = 5.4, 2.5 Hz, 4H), 4.89 (dd, *J* = 7.7, 3.4 Hz, 1H), 3.24 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.84 (dd, *J* = 15.4, 3.4 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.0, 172.5, 140.6, 140.6, 135.1, 130.6, 129.8, 129.7, 129.1, 128.6, 127.1, 124.9, 64.4, 38.5, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}ClN_2OSH^+$: 331.0672 $(M+H)^+$, found: 331.0672.

[α]^{21} D = +11.9 (c = 1.9 in $CHCl_3$).

HPLC analysis: 92:8 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 21.0 min, R_t (major) = 24.0 min.



***(S)*-2-(methylthio)-6-(naphthalen-2-yl)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3k)**

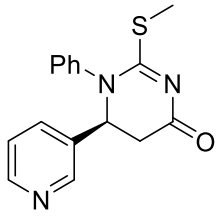
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.86 – 7.69 (m, 3H), 7.59 (s, 1H), 7.52 – 7.40 (m, 2H), 7.38 – 7.27 (m, 4H), 7.14 (s, 2H), 5.07 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.31 (dd, *J* = 15.5, 7.8 Hz, 1H), 2.96 (dd, *J* = 15.5, 3.7 Hz, 1H), 2.49 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 173.0, 140.8,

136.0, 133.4, 133.3, 129.7, 129.5, 129.4, 128.7, 128.2, 127.8, 126.7, 126.7, 126.2, 124.2, 65.2, 38.7, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{21}H_{18}N_2OSH^+$: 347.1218 $(M+H)^+$, found: 347.1218.

[α]^{21} D = +5.2 (c = 1.1 in $CHCl_3$).

HPLC analysis: 95.5:4.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 34.9 min, R_t (major) = 48.2 min.



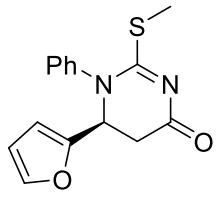
***(S)*-2-(methylthio)-1-phenyl-6-(pyridin-3-yl)-5,6-dihydropyrimidin-4(1H)-one (2-3l)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 3.7 Hz, 1H), 8.35 (s, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.37 (s, 3H), 7.29 (dd, *J* = 8.8, 6.3 Hz, 1H), 7.10 (s, 2H), 4.97 (dd, *J* = 7.4, 3.6 Hz, 1H), 3.29 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.88 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.1, 172.3, 150.4, 148.7, 140.3, 134.3, 130.0, 129.8, 128.6, 124.2, 62.6, 38.3, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{16}H_{15}N_3OSH^+$: 298.1014 $(M+H)^+$, found: 298.1017.

[α]^{21} D = +2.3 (c = 0.9 in $CHCl_3$).

HPLC analysis: 94.5:5.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 45.6 min, R_t (major) = 50.2 min.



***(S)*-6-(furan-2-yl)-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3m)**

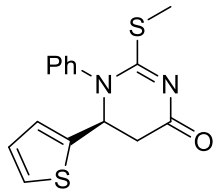
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.1, 4.3 Hz, 3H), 7.35 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.13 (s, 2H), 6.26 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 4.95 (dd, *J* = 7.0, 4.8 Hz,

1H), 3.15 (dd, *J* = 15.6, 7.1 Hz, 1H), 3.04 (dd, *J* = 15.6, 4.8 Hz, 1H), 2.41 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 173.1, 150.4, 143.2, 140.4, 129.7, 129.7, 128.8, 110.6, 109.3, 58.0, 35.9, 15.2 ppm.

HRMS (ESI, m/z): calculated for $C_{15}H_{14}N_2O_2SH^+$: 287.0854 $(M+H)^+$, found: 287.0854.

$[\alpha]^{21}_D$ = -19.1 (c = 1.8 in $CHCl_3$).

HPLC analysis: 90:10 *e.r.* (Chiralpak OD, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 29.2 min, R_t (major) = 31.6 min.



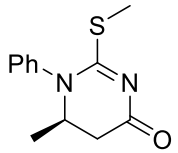
***(S)*-2-(methylthio)-1-phenyl-6-(thiophen-2-yl)-5,6-dihydropyrimidin-4(1H)-one (2-3n)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 5.8 Hz, 3H), 7.23 (dd, *J* = 4.3, 2.0 Hz, 1H), 7.13 (s, 2H), 6.89 (dd, *J* = 5.2, 2.7 Hz, 2H), 5.16 (dd, *J* = 7.1, 4.1 Hz, 1H), 3.26 (dd, *J* = 15.5, 7.1 Hz, 1H), 3.00 (dd, *J* = 15.5, 4.1 Hz, 1H), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 172.8, 140.6, 140.3, 129.7, 128.9, 127.0, 126.8, 126.2, 60.2, 39.05, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{15}H_{14}N_2OS_2H^+$: 303.0626 $(M+H)^+$, found: 303.0626.

$[\alpha]^{21}_D$ = -79.8 (c = 0.9 in $CHCl_3$).

HPLC analysis: 90:10 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 29.2 min, R_t (major) = 31.6 min.



***(R)*-6-methyl-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3o)**

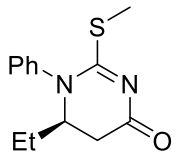
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 3H), 7.32 – 7.21 (m, 2H), 4.10 – 3.86 (m, 1H), 2.95 (dd, *J* = 15.2, 6.4 Hz, 1H), 2.59 (dd, *J* = 15.2, 4.9 Hz, 1H), 2.39 (s, 3H), 1.23 (d, *J* = 6.6

Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 172.6, 140.1, 129.9, 129.6, 128.9, 56.4, 38.3, 18.3, 15.1 ppm.

HRMS (ESI, m/z): calculated for $C_{12}H_{14}N_2OSH^+$: 235.0905 $(M+H)^+$, found: 235.0907.

$[\alpha]^{21}_D$ = +18.1 (c = 1.1 in $CHCl_3$).

HPLC analysis: 80.5:19.5 *e.r.* (Chiralpak AS-H, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 43.6 min, R_t (major) = 80.4 min.



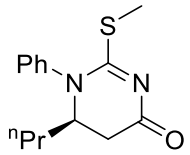
***(R)*-6-ethyl-2-(methylthio)-1-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-3p)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.42 (m, 2H), 7.33 – 7.22 (m, 2H), 3.86 – 3.63 (m, 1H), 2.92 (dd, *J* = 15.4, 6.9 Hz, 1H), 2.72 (dd, *J* = 15.4, 3.8 Hz, 1H), 2.38 (s, 2H), 1.74 – 1.49 (m, 2H), 0.88 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.0, 172.8, 140.4, 129.9, 129.6, 128.9, 61.9, 34.6, 24.6, 15.1, 9.4 ppm.

HRMS (ESI, m/z): calculated for $C_{13}H_{16}N_2OSH^+$: 249.1062 $(M+H)^+$, found: 249.1062.

$[\alpha]^{21}_D$ = +45.6 (c = 1.8 in $CHCl_3$).

HPLC analysis: 89:11 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 17.7 min, R_t (major) = 19.5 min.



***(R)*-2-(methylthio)-1-phenyl-6-propyl-5,6-dihydropyrimidin-4(1H)-one (2-3q)**

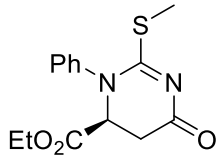
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.39 (m, 3H), 7.34 – 7.21 (m, 2H), 3.96 – 3.63 (m, 1H), 2.92 (dd, *J* = 15.3, 6.8 Hz, 1H), 2.70 (dd, *J* = 15.3, 3.6 Hz, 1H), 2.38 (s, 3H), 1.75 – 1.46 (m, 2H), 1.46 – 1.30 (m, 1H), 1.19 (dddd, *J* = 13.3, 10.5, 9.7, 4.7 Hz, 1H), 0.83 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 172.7, 140.5, 129.8, 129.5, 128.9, 60.6, 35.1, 33.6, 18.3, 15.1, 13.8 ppm.

HRMS (ESI, m/z): calculated for $C_{14}H_{18}N_2OSH^+$: 263.1218 $(M+H)^+$, found: 263.1218.

$[\alpha]^{21}_D$ = +48.0 (c = 2.1 in $CHCl_3$).

HPLC analysis: 90:10 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 35.9 min, R_t (major) = 44.0 min.



Ethyl *(S)*-2-(methylthio)-6-oxo-3-phenyl-3,4,5,6-tetrahydropyrimidine-4-carboxylate (2-3r)

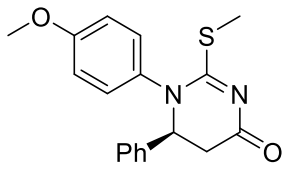
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.32 (m, 5H), 4.48 (dd, *J* = 7.9, 2.8 Hz, 1H), 4.20 (qq, *J* = 10.8, 7.1 Hz, 2H), 3.11 (dd, *J* = 15.9, 7.9 Hz, 1H), 3.03 (dd, *J* = 15.9, 2.8 Hz, 1H), 2.42 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.2, 171.6, 169.0, 140.9, 130.0, 129.9, 128.7, 62.7, 62.6, 34.0, 15.2, 14.1 ppm.

HRMS (ESI, m/z): calculated for C14H16N2O$_3$SH$^+$: 293.0960 $(M+H)^+$, found: 293.0960.

$[\alpha]^{21}_D$ = +43.3 (c = 1.4 in $CHCl_3$).

HPLC analysis: 85:15 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 21.9 min, R_t (major) =

26.6 min.



***(S)*-1-(4-methoxyphenyl)-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4a)**

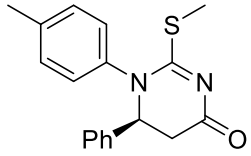
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 3H), 7.22 – 7.12 (m, 2H), 7.00 (s, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 4.85 (dd, *J* = 7.8, 3.5 Hz, 1H), 3.77 (s, 3H), 3.23 (dd, *J* = 15.4, 7.8 Hz, 1H),

2.86 (dd, *J* = 15.4, 3.5 Hz, 1H), 2.44 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.3, 173.1, 160.1, 138.7, 133.3, 129.8, 129.2, 128.7, 126.9, 114.7, 65.06, 55.5, 38.6, 15.2 ppm.

HRMS (ESI, m/z): calculated for $C_{18}H_{18}N_2O_2SH^+$: 327.1167 $(M+H)^+$, found: 327.1167.

$[\alpha]^{21}_D$ = -1.3 (c = 1.9 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 30.6 min, R_t (major) = 35.0 min.



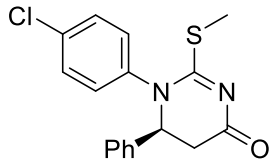
***(S)*-2-(methylthio)-6-phenyl-1-(p-tolyl)-5,6-dihydropyrimidin-4(1H)-one (2-4b)**

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.30 (ddd, *J* = 10.7, 4.2, 2.7 Hz, 3H), 7.23 – 7.15 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 7.1 Hz, 2H), 4.87 (dd, *J* = 7.8, 3.4 Hz, 1H), 3.23 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.86 (dd, *J* = 15.4, 3.4 Hz, 1H), 2.45 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 173.1, 139.7, 138.7, 138.2, 130.3, 129.2, 128.7, 128.3, 126.8, 65.0, 38.6, 21.3, 15.2 ppm.

HRMS (ESI, m/z): calculated for $C_{18}H_{18}N_2OSH^+$: 311.1218 $(M+H)^+$, found: 311.1218.

$[\alpha]^{21}_D$ = +0.1 (c = 1.9 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 20.7 min, R_t (major) = 24.2 min.



***(S)*-1-(4-chlorophenyl)-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4c)**

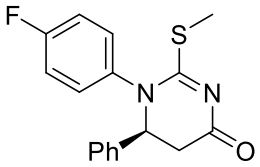
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.37 – 7.27 (m, 1H), 7.17 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 4.86 (dd, *J* = 7.6, 3.9 Hz, 1H), 3.23 (dd, *J* = 15.5, 7.7 Hz, 1H), 2.88 (dd, *J* =

15.5, 3.9 Hz, 1H), 2.46 (s, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.5, 172.9, 139.1, 138.3, 135.5, 130.1, 129.9, 129.3, 129.0, 126.8, 65.05, 38.6, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}ClN_2OSH^+$: 331.0672 $(M+H)^+$, found: 331.0672.

$[\alpha]^{21}_D$ = -3.3 (c = 1.8 in $CHCl_3$).

HPLC analysis: 96:4 *e.r.* (Chiralpak OD, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 29.4 min, R_t (major) = 32.0 min.



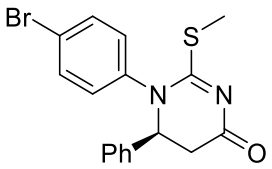
***(S)*-1-(4-fluorophenyl)-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4d)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 3H), 7.17 (dd, *J* = 7.2, 2.3 Hz, 2H), 7.08 (d, *J* = 3.0 Hz, 2H), 7.00 (t, *J* = 8.1 Hz, 2H), 4.86 (dd, *J* = 7.7, 3.9 Hz, 1H), 3.23 (dd, *J* = 15.5, 7.7 Hz, 1H), 2.88 (dd, *J* = 15.5, 3.9 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.9, 172.9, 164.0, 161.5, 138.4, 136.6, 130.7 (d, *J* = 8.9 Hz), 129.1 (d, *J* = 38.8 Hz), 126.9, 116.7 (d, *J* = 22.9 Hz), 65.1, 38.6, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}FN_2OSH^+$: 315.0967 $(M+H)^+$, found: 315.0967.

$[\alpha]^{21}_D$ = -14.5 (c = 2.0 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 22.6 min, R_t (major) = 25.6 min.



***(S)*-1-(4-bromophenyl)-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4e)**

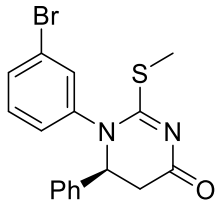
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.45 (d, *J* = 8.7 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.22 – 7.11 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 4.86 (dd, *J* = 7.7, 3.8 Hz, 1H), 3.23 (dd, *J* = 15.5, 7.7 Hz, 1H),

2.88 (dd, *J* = 15.5, 3.8 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 172.8, 139.7, 138.3, 132.9, 130.4, 129.3, 129.0, 126.8, 123.6, 65.0, 38.6, 15.2 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}BrN_2OSH^+$: 375.0167 $(M+H)^+$, found: 375.0167.

[α]^{21} D = -0.6 (c = 2.3 in $CHCl_3$).

HPLC analysis: 95.5:4.5 *e.r.* (Chiralpak OD, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 30.5 min, R_t (major) = 32.9 min.



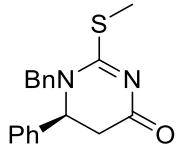
***(S)*-1-(3-bromophenyl)-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4f)**

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.53 – 7.42 (m, 1H), 7.38 – 7.27 (m, 4H), 7.24 – 7.10 (m, 3H), 7.03 (d, *J* = 7.5 Hz, 1H), 4.89 (dd, *J* = 7.6, 3.8 Hz, 1H), 3.23 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.88 (dd, *J* = 15.4, 3.8 Hz, 1H), 2.47 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.4, 172.8, 141.9, 138.2, 132.7, 131.9, 130.8, 129.3, 129.0, 127.5, 126.8, 122.8, 65.0, 38.7, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{17}H_{15}BrN_2OSH^+$: 375.0167 $(M+H)^+$, found: 375.0166.

[α]^{21} D = +8.9 (c = 1.8 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 23.6 min, R_t (major) = 28.5 min.



***(S)*-1-benzyl-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4g)**

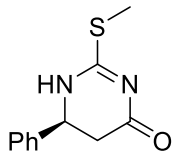
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.44 – 7.29 (m, 6H), 7.26 – 7.19 (m, 2H), 7.16 – 7.05 (m, 2H), 5.12 (d, *J* = 16.3 Hz, 1H), 4.56 (dd, *J* = 7.9, 2.7 Hz, 1H), 4.08 (d, *J* = 16.3 Hz, 1H), 2.96 (dd, *J* = 15.4, 8.0 Hz, 1H), 2.70 (dd, *J* = 15.4, 2.8 Hz, 1H), 2.62 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$)

δ 172.8, 172.6, 138.0, 135.1, 129.5, 129.3, 128.8, 128.5, 127.5, 126.4, 59.6, 53.0, 38.5, 15.0 ppm.

HRMS (ESI, m/z): calculated for $C_{18}H_{18}N_2OSH^+$: 311.1218 $(M+H)^+$, found: 311.1218.

[α]^{21} D = +26.4 (c = 0.8 in $CHCl_3$).

HPLC analysis: 89.5:10.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 25.2 min, R_t (major) = 28.3 min.



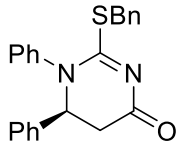
***(S)*-2-(methylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4h)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.48 – 7.34 (m, 4H), 7.34 – 7.26 (m, 1H), 4.84 (dd, *J* = 12.2, 5.2 Hz, 1H), 2.82 (dd, *J* = 16.7, 5.2 Hz, 1H), 2.61 – 2.43 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.8, 152.5, 142.3, 128.8, 127.5, 126.4, 58.8, 38.4, 13.4.

HRMS (ESI, m/z): calculated for $C_{11}H_{12}N_2OSH^+$: 221.0749 $(M+H)^+$, found: 221.0746.

[α]^{21} D = +67.0 (c = 0.5 in $CHCl_3$).

HPLC analysis: 87:13 *e.r.* (Chiralpak ID, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 17.9 min, R_t (minor) = 21.7 min.



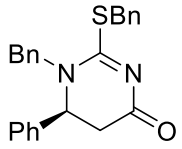
***(S)*-2-(benzylthio)-1,6-diphenyl-5,6-dihydropyrimidin-4(1H)-one (2-4i)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.14 (m, 12H), 7.10 (s, 2H), 4.90 (dd, *J* = 7.7, 3.6 Hz, 1H), 4.39 (s, 2H), 3.25 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.89 (dd, *J* = 15.4, 3.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 173.0, 172.9, 140.6, 138.5, 136.3, 129.7, 129.6, 129.5, 129.3, 128.8, 128.7, 128.7, 127.6, 126.9, 65.0, 38.7, 37.1 ppm.

HRMS (ESI, m/z): calculated for $C_{23}H_{20}N_2OSH^+$: 373.1375 $(M+H)^+$, found: 373.1372.

[α]$^{21}_{D}$ = -15.3 (c = 0.3 in $CHCl_3$).

HPLC analysis: 95.5:4.5 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 28.0 min, R_t (major) = 34.2 min.



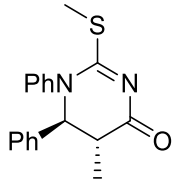
***(S)*-1-benzyl-2-(benzylthio)-6-phenyl-5,6-dihydropyrimidin-4(1H)-one (2-4j)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.40 (m, 2H), 7.40 – 7.26 (m, 9H), 7.24 – 7.16 (m, 2H), 7.13 (dd, *J* = 7.5, 1.8 Hz, 2H), 5.10 (d, *J* = 16.2 Hz, 1H), 4.69 – 4.42 (m, 3H), 4.06 (t, *J* = 16.6 Hz, 1H), 2.96 (dd, *J* = 15.4, 8.0 Hz, 1H), 2.70 (dd, *J* = 15.4, 2.8 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.6, 172.0, 137.9, 136.2, 135.0, 129.6, 129.5, 129.3, 128.9, 128.5, 127.8, 127.5, 126.4, 59.5, 53.1, 38.5, 36.9 ppm.

HRMS (ESI, m/z): calculated for $C_{24}H_{22}N_2OSH^+$: 387.1531 $(M+H)^+$, found: 387.1529.

[α]$^{21}_{D}$ = -1.6 (c = 0.7 in $CHCl_3$).

HPLC analysis: 90:10 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 21.2 min, R_t (major) = 24.9 min.



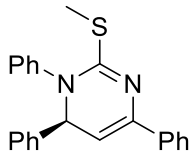
(5*R*,6*S*)-5-methyl-2-(methylthio)-1,6-diphenyl-5,6-dihydropyrimidin-4(1H)-one (2-5a)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 6H), 7.20 – 7.14 (m, 2H), 7.11 (d, *J* = 3.1 Hz, 2H), 4.50 (d, *J* = 4.0 Hz, 1H), 2.88 (qd, *J* = 7.1, 4.1 Hz, 1H), 2.47 (s, 3H), 1.44 (d, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.4, 172.7, 140.9, 138.2, 129.7, 129.4, 129.2, 128.7, 126.9, 71.8, 42.9, 17.0, 15.3 ppm.

HRMS (ESI, m/z): calculated for $C_{18}H_{18}N_2OSH^+$: 311.1218 $(M+H)^+$, found: 311.1212.

[α]$^{21}_{D}$ = -26.4 (c = 1.2 in $CHCl_3$).

HPLC analysis: 91:9 *e.r.* (Chiralpak IA, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 20.7 min, R_t (minor) = 25.4 min.



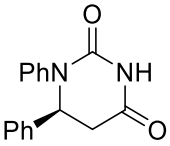
***(S)*-2-(methylthio)-1,4,6-triphenyl-1,6-dihydropyrimidine (2-5b)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.84 (m, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.33 – 7.26 (m, 9H), 7.11 – 7.00 (m, 2H), 5.71 (d, *J* = 5.0 Hz, 1H), 5.30 (d, *J* = 4.9 Hz, 1H), 2.50 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.7, 143.6, 142.3, 140.6, 138.5, 129.3, 129.2, 128.8, 128.3, 128.3, 128.2, 127.9, 127.7, 125.6, 103.1, 65.8, 14.8 ppm.

HRMS (ESI, m/z): calculated for $C_{23}H_{20}N_2SH^+$: 357.1425 $(M+H)^+$, found: 357.1425.

$[\alpha]^{21}_D$ = +12.7 (c = 1.4 in $CHCl_3$).

HPLC analysis: 90:10 *e.r.* (Chiralpak AD-H, 3:97 ^{i}PrOH/Hexane, 0.3 mL/min), R_t (minor) = 21.1 min, R_t (major) = 25.2 min.



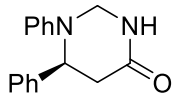
***(S)*-1,6-diphenyldihydropyrimidine-2,4(1H,3H)-dione (2-5c)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.43 – 7.29 (m, 5H), 7.28 – 7.14 (m, 5H), 5.08 (dd, *J* = 6.7, 2.6 Hz, 1H), 3.34 (dd, *J* = 16.6, 6.8 Hz, 1H), 2.95 (dd, *J* = 16.6, 2.6 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2, 151.8, 140.7, 138.6, 129.4, 129.3, 128.7, 127.2, 126.0, 125.9, 60.0, 39.4 ppm.

HRMS (ESI, m/z): calculated for $C_{16}H_{14}N_2O_2H^+$: 267.1134 $(M+H)^+$, found: 267.1126.

$[\alpha]^{21}_D$ = +139.8 (c = 0.4 in $CHCl_3$).

HPLC analysis: 91:9 *e.r.* (Chiralpak AD-H, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 30.7 min, R_t (major) = 43.9 min.



***(S)*-1,6-diphenyltetrahydropyrimidin-4(1H)-one (2-5d)**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 4H), 7.33 – 7.19 (m, 3H), 6.97 – 6.84 (m, 3H), 6.71 (s, 1H), 4.97 (t, *J* = 5.7 Hz, 1H), 4.81 (dd, *J* = 12.2, 2.9 Hz, 1H), 4.63 (dd, *J* = 12.1, 2.8 Hz, 1H), 2.93 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.76 (dd, *J* = 16.4, 5.0 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.2, 148.3, 141.0, 129.6, 129.1, 127.9, 126.6, 120.8, 116.6, 59.6, 56.0, 36.9 ppm.

HRMS (ESI, m/z): calculated for $C_{16}H_{16}N_2OH^+$: 253.1341 $(M+H)^+$, found: 253.1341.

$[\alpha]^{21}_D$ = +94.8 (c = 0.8 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 16.3 min, R_t (minor) = 17.9 min.

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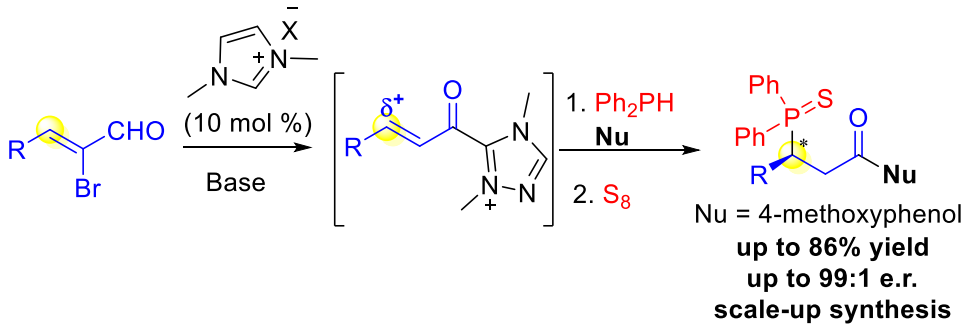
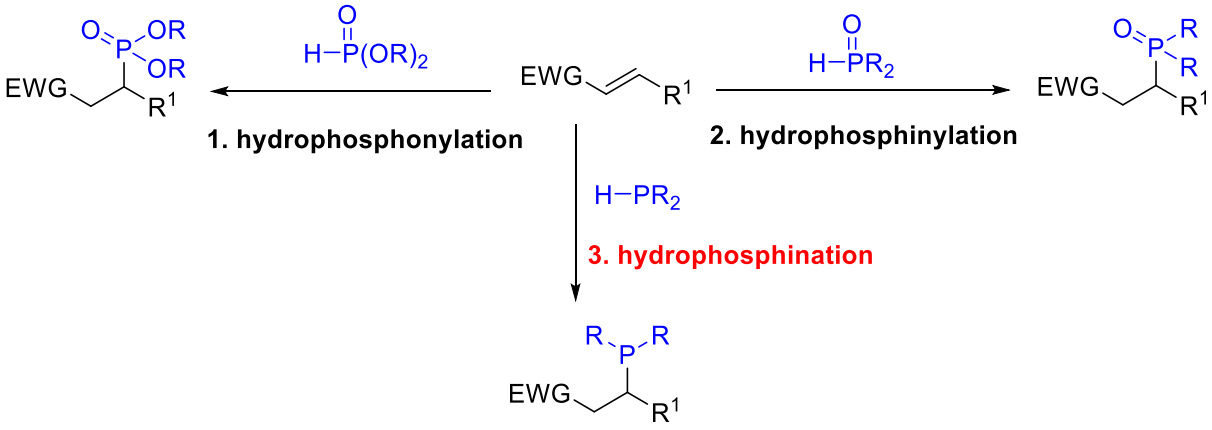
Chapter 3

Carbene-Catalyzed Asymmetric Hydroph-osphination of Bromoenals



3.1 Introduction

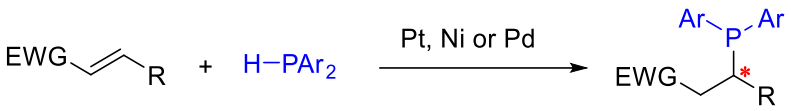
Optically pure organophosphorus compounds, one of the most versatile building blocks are frequently found in pharmaceutical compounds, natural products, and other functional molecules like polymeric materials etc.[1-6] Indeed, they are also highly in demand because of their crucial role as a ligand in metal catalyzed asymmetric transformations.[7-16] In addition to this, a chiral organophosphorus compounds such as phosphine or phosphonate can be utilized as a organocatalyst.[17-18] For example, the infamous asymmetric Morita–Baylis–Hillman (MBH) reaction can be achieved by using chiral tertiary phosphine.[19-20] One more example, chiral phosphonates are applied in the synthesis of enantiopure phosphonic acids, and later, they can be used as pharmaceuticals and pesticides.[21-24] Therefore, the development of an efficient, atom economy synthetic approach in the construction of compounds with chiral C-P bond continues to draw tremendous attention from chemists over the past decade. Construction of C-P bond from nucleophilic addition to C=C bond of unsaturated carbonyl compounds could be classified into three major types: (1) hydrophosphonylation (addition of dialkyl phosphites); (2) hydrophosphinylation (addition of secondary phosphine oxides); and (3) hydrophosphination (addition of secondary phosphines) (Scheme 3.1).[25] Among these three categories, asymmetric hydrophosphination (AHP), the addition of secondary phosphine



Scheme 3.1: Classification of P-H bond addition reactions

containing one P-H group to electron-deficient olefin is the most straightforward approach to access optically pure tertiary phosphines, which are employed numerous times in asymmetric catalysis.

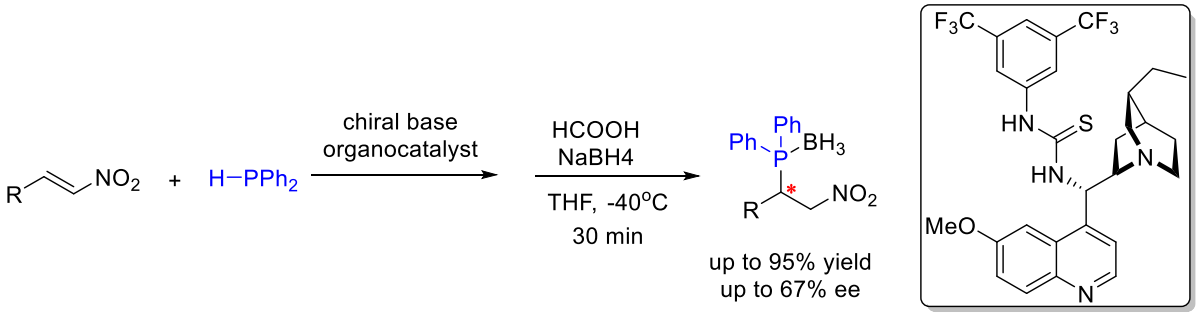
As expected, the development of synthetic methodologies for the formation of C-P bond through metal catalysis has started first (Scheme 3.2). Scientists have achieved excellent results via metal catalyzed transformation.[10, 26-42] However, several intrinsic challenges have been faced during the synthesis of organophosphorus compounds through metal catalysis. The most dominant challenge among them is arising from the coordination between the newly formed phosphine compound and the original metal complex. This phenomenon resulted a negative effect on catalyst efficiency and chiral induction ability.



1. Pt(Me-Duphos), acrylonitrile and acrylate esters, up to 27% ee, 2000
2. Ni(Pigiphos), methylacetonitrile, up to 94% ee, 2004
3. Pincer-Pd, enones, enals, enamides, nitroalkenes, carboxylic and sulfonic esters, up to 94% ee, since 2010

Scheme 3.2: Examples of transition metal catalyzed hydrophophination reactions

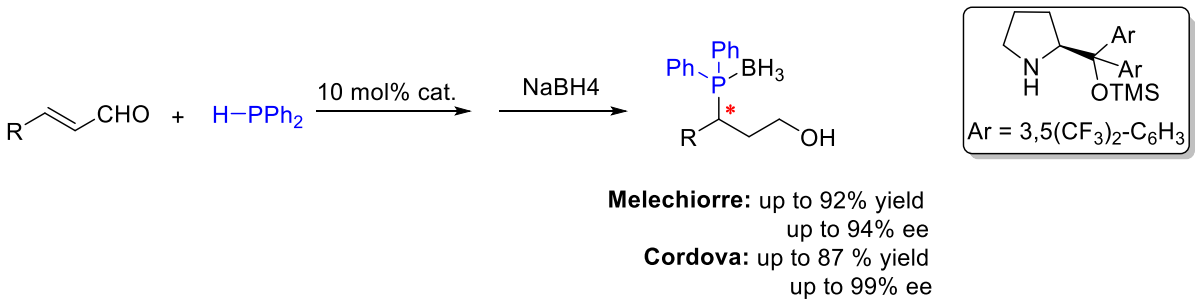
To overcome the catalyst poisoning effect by phosphine (product), scientists switched to organocatalyzed approach to develop an asymmetric hydrophosphination (AHP) reaction. In absence of metal, organocatalyst controls the chirality of the product by its chiral environment and offers an additional advantage i.e., reaction cannot be inhibited by either the substrate or the product. The first example of organocatalyzed asymmetric hydrophosphination (AHP),



Scheme 3.3: Melechiorre's chiral base organocatalyzed hydrophosphination of nitroalkene

the stereo-controlled addition of secondary phosphine compounds to electron-deficient olefins, was reported by Melchiorre in 2007 (Scheme 3.3).[43] They demonstrated that a bifunctional Cinchona alkaloid can catalyze the enantioselective nucleophilic addition of diphenylphosphine to nitroalkenes. They obtained the anticipated enantiopure β-nitrophosphines in excellent yield (>95%) with moderate ee value (67%).

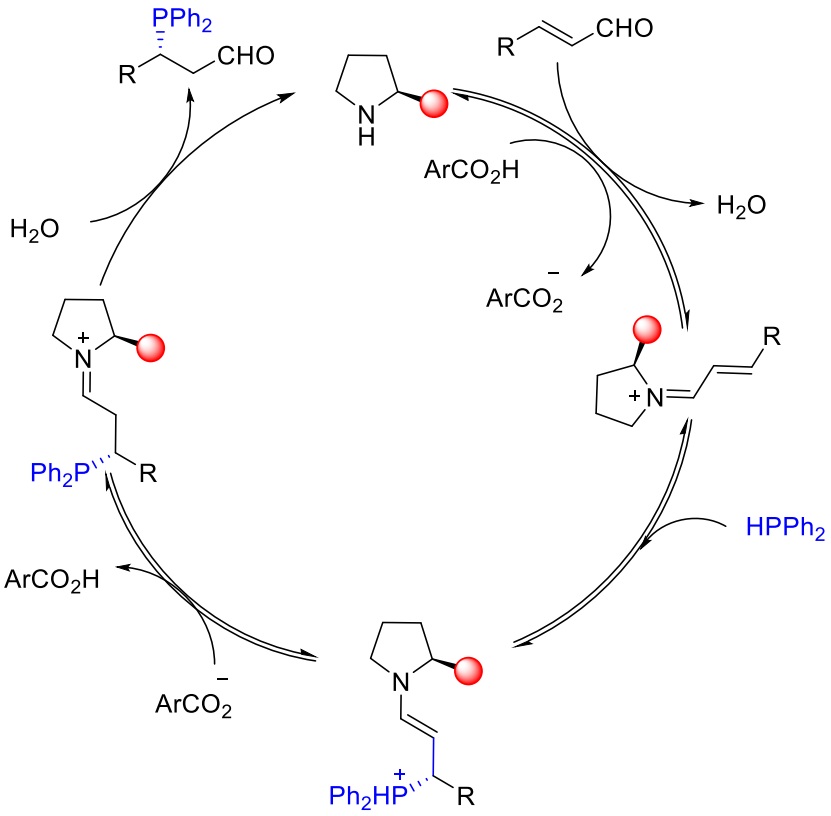
After this report, two back-to-back articles have been published by Melchiorre[44] and Cordova[45] simultaneously in 2007 on asymmetric hydrophophination of unsaturated aldehyde catalyzed by pyrrolidine derivative (Scheme 3.4). Firstly, Melechiorre showed that a chemo- and enantioselective reaction between cinnamaldehyde derivatives and diphenylphosphine,



Scheme 3.4: Pyrrolidine catalyzed hydrophosphination of unsaturated aldehyde

controlled by pyrrolidine derivative can provide the anticipated product with excellent yield and ee value (up to 92% yield, up to 94% ee). The unsaturated aldehydes with different kinds of functional groups were well-tolerated under the catalytic conditions. Next, Cordova

demonstrated an identical reaction with better enantioselectivity (up to 99% ee). He and his co-workers have also used the same pyrrolidine catalyst. But they employed 2-fluorobenzoic acid as an additive to accelerate the reaction. Enhancement in the reaction rate of iminium ion, formed in presence of 2-fluorobenzoic acid, can be reasoned with less reaction time for AHP reaction.



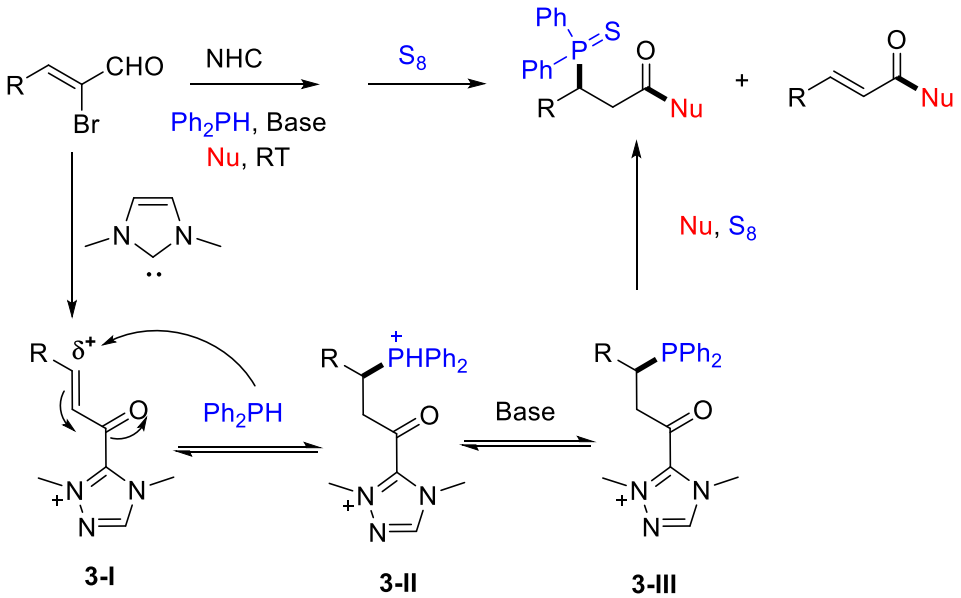
Scheme 3.5: Proposed catalytic cycle

According to their proposed mechanism, the catalytic cycle (Scheme 3.5) started with the formation of an iminium ion when cinnamaldehyde derivative couples with the catalyst (chiral pyrrolidine derivative). Due to extended conjugation, the LUMO energy of C=C of unsaturated aldehyde lowered down and facilitated the nucleophilic addition of diphenylphophine. After deprotonation, followed by the release of the catalyst by the in-situ generated H_2O afforded the product.

Till to date, only these two organocatalytic systems for asymmetric hydrophosphination reaction have been developed with limited substrates scope and applications. Therefore, a new atom-efficient catalytic system with the capability to synthesize a wide range of enantiopure hydrophophine product (other than β-phosphine alcohol and β-phosphine nitroalkane) is highly desirable.

Our proposal

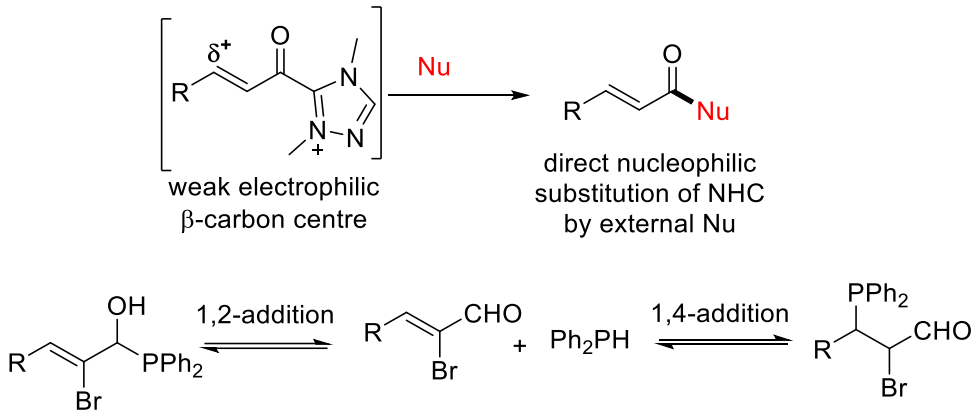
Inspired by the previous reports, herein we proposed a unique approach of asymmetric C-P bond construction between diphenylphosphine and bromoenal catalyzed by NHC (Scheme 3.6). Nucleophilic addition of NHC to the bromoenal generated NHC-bound α,β-unsaturated acyl azolium intermediate (**3-I**) and as a result, it ultimately activated the LUMO of the substrate. Therefore, the coupling of diphenylhydrophosphine to **3-I** was facilitated and formed intermediated **3-II**. After deprotonation of **3-II** by the base, followed by nucleophilic substitution of NHC with an external nucleophile (alcohol) provided the tertiary phosphine product. Due to the air sensitivity, we converted the corresponding product into a stable phosphine sulfide derivative by oxidizing the phosphorous atom with S_8.



Scheme 3.6 Hydrophosphination of bromoenal

However, few inherent challenges were experienced during the reaction (Scheme 3.7). The challenges are as follows –

1. Direct addition of an external nucleophile (alcohol) to unsaturated acyazolium.
2. Two reversible competing nucleophilic 1,2- and 1,4-addition of diphenylphosphine to bromoenal.



Scheme 3.7 Challenges of the strategy

Here, the present study of asymmetric NHC-catalysed hydrophosphination displayed a new enantiomeric methodology to access chiral tertiary phosphine with up to >99:1 e.r. value. In addition, the phosphine product from the catalytic cycle was transformed into more valuable compounds like bidentate-phosphine ligand and bifunctional phosphine organocatalyst.

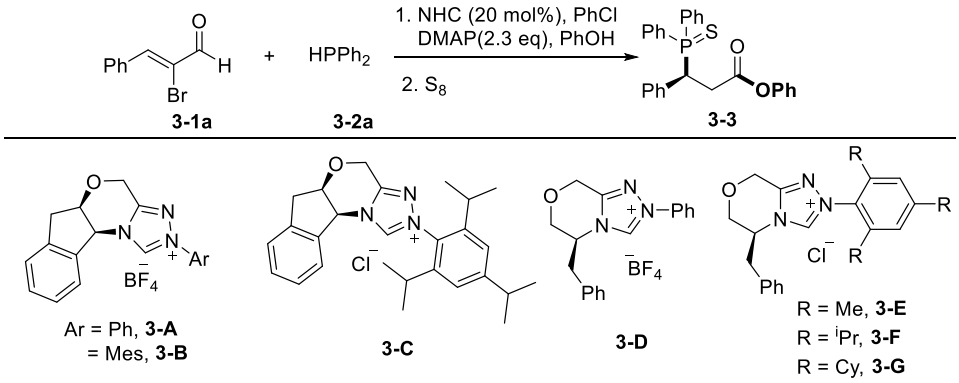
3.2 Result and Discussion

3.2.1 Reaction condition optimization

We started our search for a suitable NHC-catalyst for the reaction by using α-bromocinnamaldehyde (**3-1a**) and diphenylphosphine (**3-2a**) to form the proposed product **3-3a**. Key results are briefed in Table 3.1. We first used triazolium salt **A** as a NHC pre-catalyst for our model reaction in PhCl and DMAP as the base to activate **3-1a**. PhOH was added to the reaction as an external nucleophile to remove the NHC and complete the catalytic cycle. Under this condition, product **3-3a** was obtained in a low yield although there was no

enantioselectivity (Table 3.1, entry 1, 29%, 50:50 e.r.). Replacing the NHC precursor **3-A** with chiral aminoindane-based NHC pre-catalyst **3-B** gave the product **3-3a** in 78% yield. Although,

Table 3.1 Screening of NHC precatalyst[a]



Entry	NHC	Yield (%)[b]	e.r.[c]
1	**3-A**	29	50:50
2	**3-B**	78	56:44
3	**3-C**	50	90:10
4	**3-D**	46	66:34
5	**3-E**	97	63:37
6	**3-F**	95	90:10
7	**3-G**	**95**	96:4

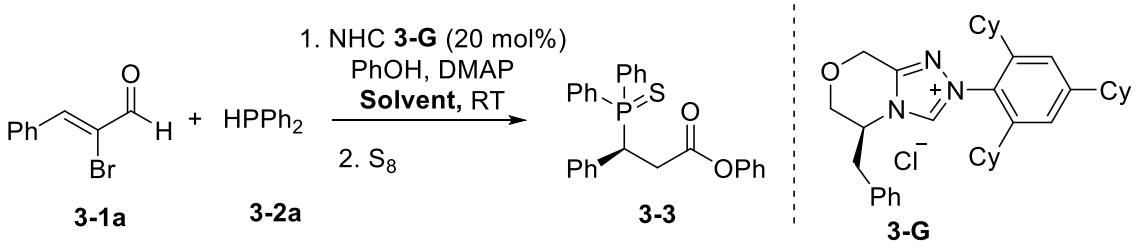
[a]Reaction condition: **3-1a** (0.09 mmol.), **3-2a** (0.05 mmol), **NHC** pre-cat. (20 mol%), DMAP (2.3 equiv.), PhCl (1 mL), at RT for 12-24 hrs. [b]Yield was determined by ^{1}HNMR analysis with the 1,3,5-trimethoxybenzene as internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

the e.r. value of the product showed no real improvement (Table 3.1, entry 2, 56:44 e.r.). Further replacement NHC pre-catalyst with more bulky isopropyl group substituent in N-aryl position (NHC **3-C**) resulted in an encouraging improvement in the e.r. (entry 3, 80% ee). An additional survey of NHC catalyst's effect on the product **3-3a** revealed that morpholine-based NHC had much more control in enantioselectivity over aminoindane-based NHC pre-catalyst

(comparing Table 3.1, entry 1 & 4). Thus, we next focused our investigation on morpholine-based NHC pre-catalysts. Additional screening of morpholine-based pre-catalysts **3-D**, **3-E**, **3-F**, and **3-G** led to satisfactory yield and e.r. values (Table 3.1, entries 5-7). We found that the bulkier cyclohexyl group substituted NHC precursor **3-G** could promote the formation of **3-3a** with the excellent yield and optical purity (Table 3.1, entry 7).

We next moved to screen the solvent to improve the enantiomeric ratio of the product further (Table 3.2). First, the polar aprotic solvents (THF, EtOAc) were checked by changing the PhCl under the standard conditions (i.e. NHC-G precatalyst, DMAP base). Both the e.r. and yield dropped quite a bit (Table 3.2, entries 1-2). So, we concentrated our survey on the non-polar solvents. Interestingly, chlorinated solvents (CH_2Cl_2, $CHCl_3$, DCE) were not suitable for the reaction (Table 3.2, entries 3-5). Later, a polar solvent like 1,4-dioxane was employed in the reaction. Under this condition, the desired product was also obtained in a much lower yield with 96:4 e.r. value (Table 3.2, entry 6). When toluene as a solvent was introduced to the reaction, the catalytic system provided the product in 86% yield with excellent e.r. value (98:2 e.r., Table 3.2, entry 7).

Table 3.2 Screening of solvents[a]



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

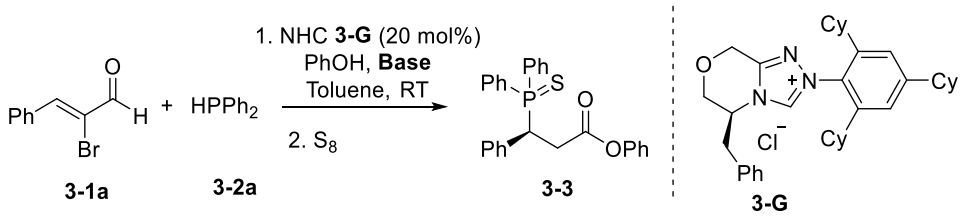
Entry	Solvent	Yield (%)[b]	e.r.[c]
1	THF	53	94:6
2	EtOAc	56	95:5
3	CH_2Cl_2	20	78:22

4	$CHCl_3$	>10	83:17
5	DCE	28	78:22
6	1,4-dioxane	68	96:4
7	**Toluene**	**86**	**98:2**

[a]Reaction condition: **3-1a** (0.09 mmol.), **3-2a** (0.05 mmol), NHC **3-G** pre-cat. (20 mol%), DMAP (2.3 equiv.), Solvent (1 mL), at RT for 12-24 hrs. [b]Yield was determined by ^{1}HNMR analysis with the 1,3,5-trimethoxybenzene as internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

Therefore, we chose the solvent toluene as our optimized solvent and went for the base screening to find a better result. All the key results for base screening are tabulated in Table 3.3. Both organic and inorganic bases were examined. Surprisingly, all the bases gave discouraging results on both the accounts i.e., yield and e.r. value, except DBACO. Therefore, we considered DMAP as our optimal base.

Table 3.3 Screening of bases[a]

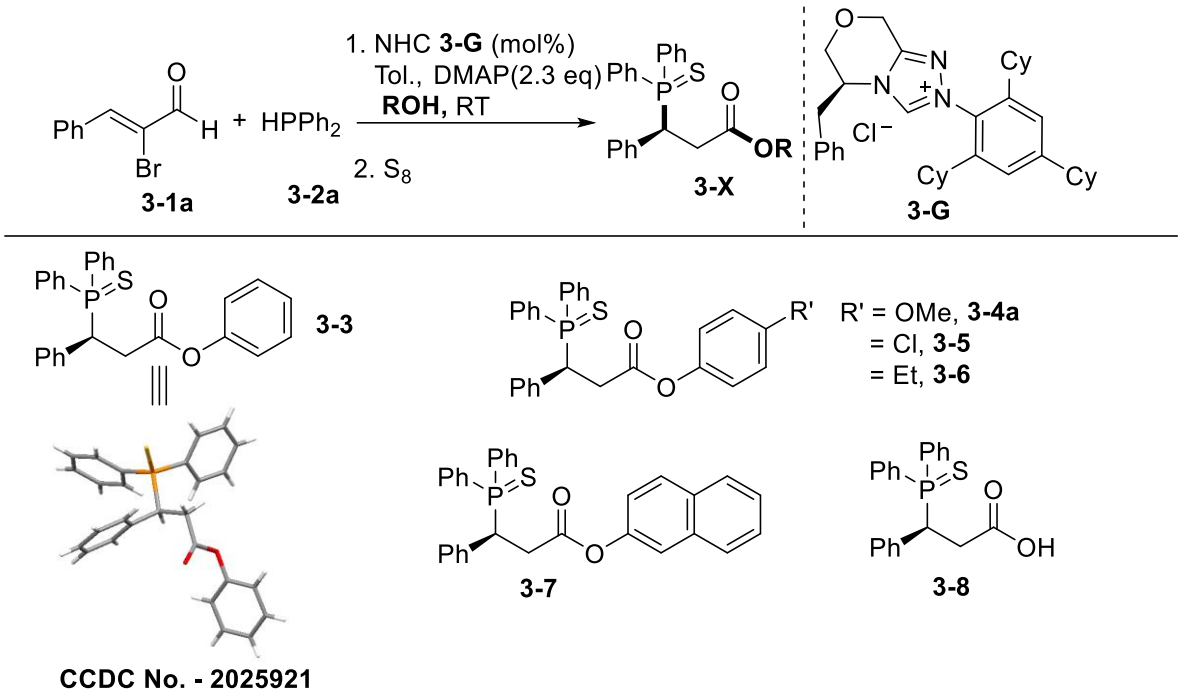


Entry	Base	Yield (%)[b]	e.r.[c]
1	Cs_2CO_3	39	87:13
2	K_2CO_3	39	71:29
3	NaOAc	>10	77:23
4	DABCO	62	98:2
5	Et_3N	14	87:13
6	DIPEA	14	80:20
7	DBU	39	87:13

[a]Reaction condition: **3-1a** (0.09 mmol.), **3-2a** (0.05 mmol), NHC **3-G** pre-cat. (20 mol%), Base (2.3 equiv.), toluene (1 mL), at RT for 12-24 hrs. [b]Yield was determined by ^{1}HNMR analysis with the 1,3,5-trimethoxybenzene as internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

As we discussed earlier in this chapter, one of the concerns of this APH reaction under our strategy is the formation of direct ester (reaction between alcohol and NHC-bound unsaturated acyl azolium intermediate). Thus, we redirected our attention to the influence of the external nucleophile (alcohol) and later the amount of catalyst loading (Table 3.4). First, we conducted the reaction with different kinds of alcohols and H_2O using 20 mol% catalyst (**3-G**) loading.

Table 3.4 Screening of alcohol and the amount of cat. loading[a,b]



Entry	ROH	NHC (x mol%)	3-X (Yield%)	e.r.
1	phenol	G (20)	**3-3** (82%)	98:2
2	4-methoxyphenol	G (20)	**3-4a** (83%)	97:3
3	4-chlorophenol	G (20)	**3-5** (35%)	90:10
4	4-ethylphenol	G (20)	**3-6** (65%)	93:7

5	2-naphthol	G (20)	**3-7** (80%)	96:4
6	H_2O	G (20)	**3-8** (87%)	89:11
7	phenol	G (10)	**3-3** (40%)	93:7
8	**4-methoxyphenol**	**G (10)**	**3-4a (81%)**	**98:2**
9	4-methoxyphenol	G (5)[c]	**3-4a** (73%)	96:4

[a]Reaction condition: **3-1a** (0.18 mmol.), **3-2a** (0.1 mmol), NHC **3-G** pre-cat., DMAP (2.3 equiv.), solvent (2 mL), at RT for 24 hrs. [b]Isolated yield. The e.r. was determined via chiral-phase HPLC analysis. [c]heated at 50°C.

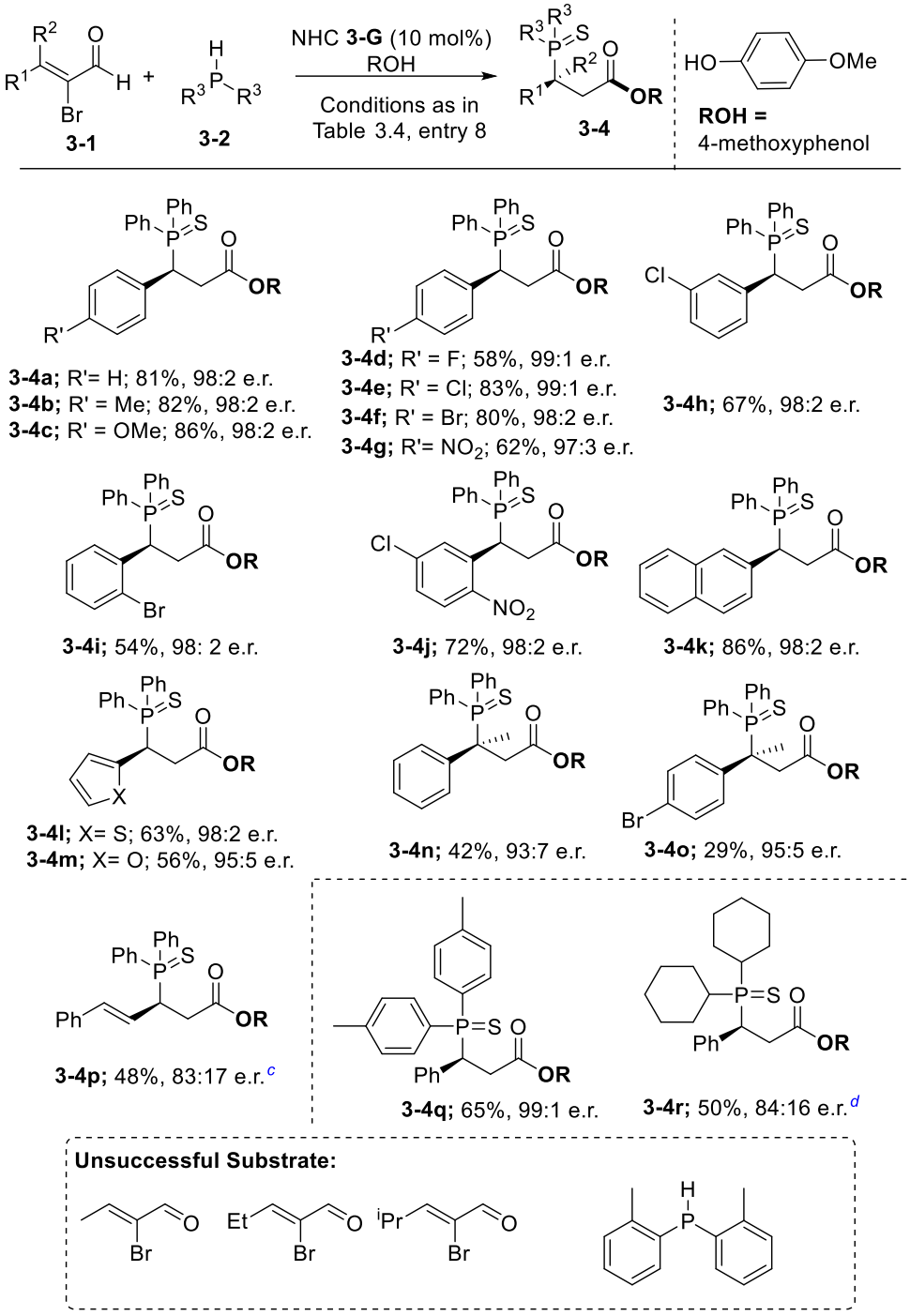
Screening results indicated that neutral phenol and the electron-donating group-containing phenol (Table 3.4, entries 1-4) promoted the reaction more efficiently in terms of both ythe ield and ee value. More bulkier alcohol, 2-naphthol (Table 3.4, entry 5) was also competent to furnish the desired product in an acceptable outcomes. Astonishingly, H_2O is also skilled to terminate this catalytic cycle proficiently and deliver the hydrophosphination product in excellent yield with 89:11 e.r. (Table 3.4, entry 6). Next, we wanted to lower down the amount of the catalyst for the reaction so that later we can use it for scale-up synthesis of the desired product. We found that the catalyst loading could be reduced up to 5 mol% employing 4-methoxyphenol as the nucleophilic external alcohol with a little effect on the enantioselectivity (Table 3.4, entry 9), although the reaction was required to be heated at 50°C for acceptable yield. We finally discovered that the use of 10 mol% NHC **3-G** in toluene gave the optically active carbon-centered tertiary phosphine product in 81% isolated yield with 98:2 e.r. at room temperature in presence of DMAP as the base and 4-methoxyphenol as the nucleophilic external alcohol (Table 3.4, entry 8).

3.2.2 Substrate scope

After having the acceptable conditions in hand, we moved to explore the substrate scope (Table 3.5) with various bromoenals and phosphines. Different substituents [such as Me, OMe,

halogen, NO_2] and their patterns [*ortho*-, *meta*-, *para*-] on phenyl ring of the *α*-bromocinnamaldehyde were all well-tolerated and provided the desired products with excellent yields and e.r. values (**3-4a - 3-j**). Notably, bromoenal with strong withdrawing groups (**3-4d**

Table 3.5 Substrate Scope[a, b]



[a]Reaction condition: **3-1** (0.18 mmol.), **3-2** (0.1 mmol), NHC **3-G** pre-cat. (10 mol%), DMAP (2.3 equiv.), toluene (2 mL), at RT for 24 hrs. [b]Isolated yield. The e.r was determined via chiral-phase HPLC analysis. [c]the reaction was carried out at 0°C for 48hrs. [d]Reaction was performed at 50°C.

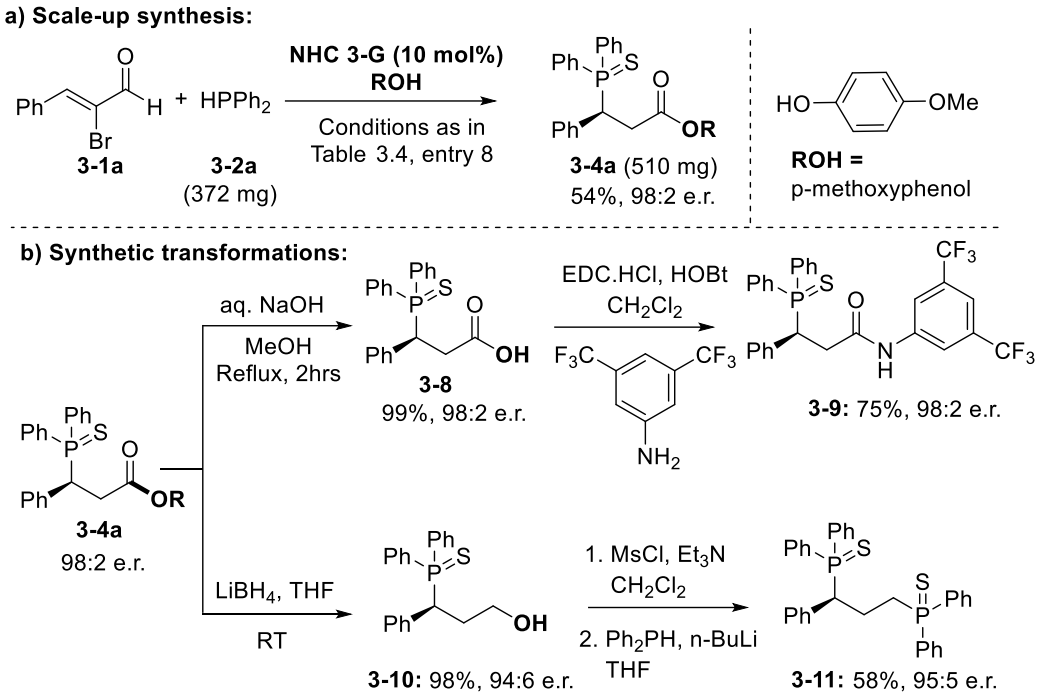
and **3-4g**) on the benzene ring had lowered down the yield quite visibly, possibly owing to facilitate the direct ester formation reaction. The negative effect of steric hindrance on yield could also be affirmed with the result of **3-4i**. Replacement of phenyl ring with naphthyl (**3-4k**) and heteroaryl (**3-4l** and **3-4m**) could also give the desired product in moderate yields and excellent optical purities. To our delight, asymmetric hydrophosphination of bulkier β-methyl substituted bromoenals (**3-1n** and **3-1o**) were also successful under our catalytic conditions, providing the adduct with an acceptable outcome. Unfortunately, this protocol was not suitable for bromoenals having a β-alkyl substituent. Although, to our surprise, a bromoenal containing a further transferable alkenyl group was compatible and afforded the product **3-4p** in 50% yield and 83:17 e.r.

With **3-1a** as the model substrate, we then evaluated the scope of the phosphine **3-2**. Both *para*-methyl substituted diphenyl phosphine and dicyclohexyl phosphine (alkyl substituted secondary phosphine) were also enabled to deliver the phosphine products **3-4q** and **3-4r** in acceptable yields and optical purities. Unfortunately, bulkier aryl group substituted **3-2** were not suitable to furnish the corresponding products in acceptable results under our catalytic system.

3.2.3 Scale-up reaction and synthetic transformations

For practicality purpose of the catalytic method, a scale-up (2 mmol) reaction was carried out and obtained the product **3-4a** in 54% yield (510 mg) with 98:2 e.r. (Scheme 3.8a). We also demonstrated that under mild conditions, the optically enriched tertiary phosphine could be transformed into more valuable chemicals. Simple hydrolysis of the product from our catalytic

cycle under basic condition, followed by amide bond formation could lead to a bifunctional phosphine **3-9** without erosion in enantioselectivity (Scheme 3.8b). We also disclosed a synthetic route to access important bidentate phosphine ligand **3-11** using a sequence of few mild reaction strategies (Scheme 3.8b).



Scheme 3.8 Scale-up reaction and synthetic transformations

3.3 Conclusion

In summary, an NHC-catalyzed asymmetric hydrophosphination of bromoenals has been developed. The reaction proceeds via 1,4-addition of secondary phosphine bearing one P-H group to the NHC-bound unsaturated acyl azolium. This unique strategy allows to form a carbon-center tertiary phosphine in high optical purity (up to 99:1 e.r.). The reaction strategy applies to a wide range of bromoenals as well as secondary phosphine (both aromatic and aliphatic). In addition, we also converted the product into more valuable molecules such as bidentate phosphine ligand and bifunctional phosphine which can act as organocatalyst and ligand in metal catalysis, respectively. Currently, the application of the bifunctional phosphine **3-9** as organocatalyst and the reaction mechanism are being investigated in our lab.

3.4 Experimental section

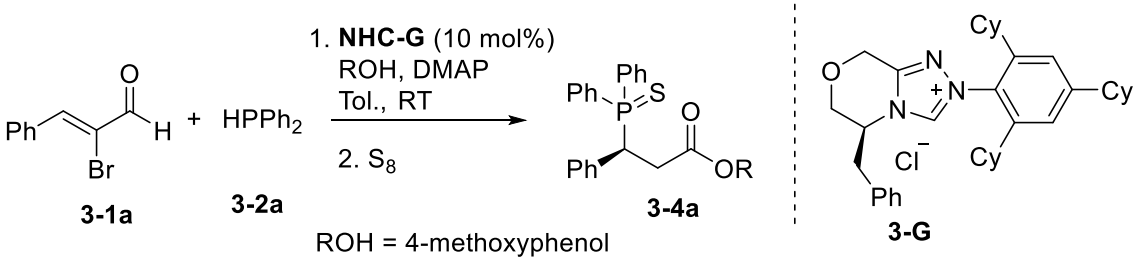
3.4.1 General information

Please refer to Chapter 2, Section 2.4.1

3.4.2 Synthesis of bormoenals

Bromoenals were prepared according to the previously published method.[46]

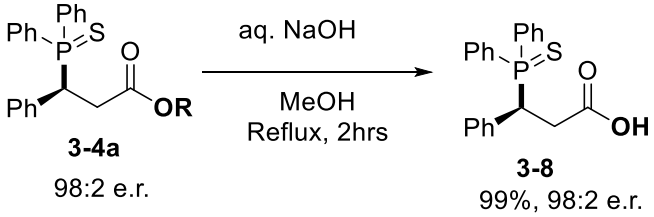
3.4.3 General procedure: asymmetric hydrophosphination



To a 25 mL test tube equipped with a magnetic stirring bar was added α- bromocinnamaldehyde **3-1a** (0.15 mmol), NHC precursor **3-G** (0.01 mmol), DMAP (0.02 mmol), 4-methoxyphenol (0.12 mmol). The tube was closed with a septum, evacuated, and refilled with nitrogen (3 cycles). After that, diphenyl phosphine **3-2a** (0.1 mmol) was added using syringe. Again, the tube was evacuated, and refilled with nitrogen (3 cycles). Freshly distilled toluene (2 mL) was added to the reaction mixture at room temperature for 12-24 hrs. Upon the reaction completed (monitored by TLC) sulphur (S_8, 2 equiv.) was poured into the tube and stirred for another 30 mins. Then, the solvent was evaporated, and the reaction mixture was purified using silica gel column chromatography with hexane/ethyl acetate as eluent.

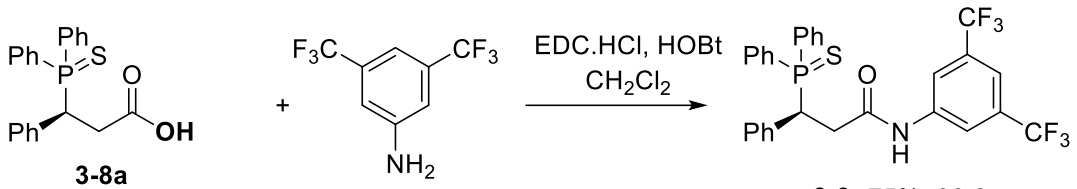
3.4.4 Synthetic transformations

Synthesis of **3-8**:



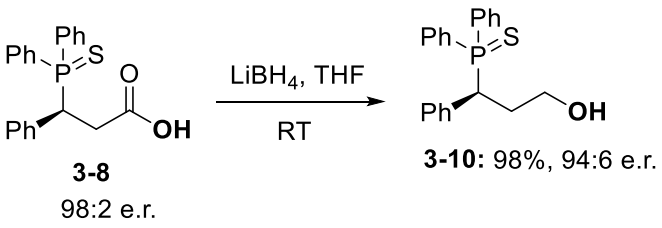
NaOH (40 mg, 1 mmol) was added to a solution of **3-8a** (118 mg, 0.25 mmol) in MeOH/H_2O (2 mL/2mL) and the resulting mixture was refluxed for 2 hrs. When the reaction was finished, the solution was cooled to room temperature and conc. HCl was added to make the pH 1-2. The MeOH was evaporated and H_2O (10 mL) was added. After extraction with dichloromethane, the organic phase was washed with brine and concentrated under vacuum. The pure product (91 mg, 98:2 e.r.) was obtained after silica gel column chromatography (MeOH/ DCM = 1:50).

Synthesis of **3-9**:



3,5-bis(trifluoromethyl)aniline (32μL, 0.2 mmol) was added to the solution of **3-8a** (62 mg, 0.17 mmol) in dichloromethane. Then, HOBt (28 mg, 0.2 mmol), and EDC·HCl (39 mg, 0.2 mmol) were mixed into the solution. The mixture was continued to stir until all the starting materials were consumed (monitor by TLC). The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (EtOAc/Hexane = 1:5) to obtain **3-9** (74 mg, 98:2 e.r.).

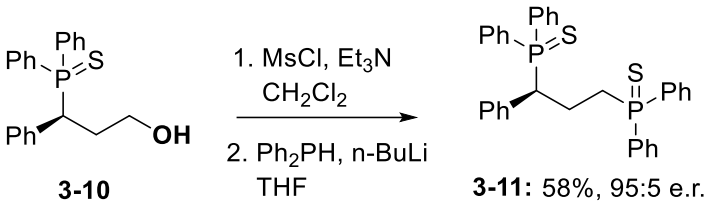
Synthesis of **3-10**:



A mixture of **3-8a** (145 mg, 0.31 mmol) and $LiBH_4$ (25 mg, 1.1 mmol) was continued to stir in THF until all the starting materials disappeared. The reaction was quenched with H_2O and

extracted with EtOAc. The solvent was evaporated and purified in silica gel column chromatography (EtOAc/Hexane = 1:3) to afford **3-10** (107 mg, 94:6 e.r.).

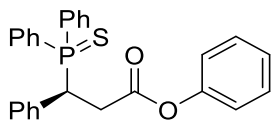
Synthesis of **3-11**:



3-10 **3-11:** 58%, 95:5 e.r.

Compound **3-10** (35 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1 mL) under N_2 atmosphere and cooled to 0 ^oC with an ice-bath. Then, Et_3N (0.15 mmol) was added dropwise to the solution. After stirring for 15 mins, MsCl (0.12 mmol) was mixed with rection mixture and continued to stir for another 2 h at the same temperature. After completion of the reaction, H_2O was added and extracted with EtOAc. Then, the solvent was evaporated, and the residue was passed through a small pad of silica gel. Solvent was evaporated under vacuum again and used for further transformation. Under N_2 atmosphere, Ph_2PH (0.2 mmol) was placed into 10 mL round bottle flask and THF was added. The temperature of the flask was cooled down to 0 ^oC and then, n-BuLi (0.2 mmol) was added. An orange-colored solution was formed and continued to stir at this temperature for another 15 mis. Then, a THF solution of the residue from previous step was prepared under N_2 atmosphere and added to the Ph_2PH solution dropwise. After the addition, the reaction was placed for over-night at 0 ^oC. When the reaction had completed, S_8 was added and purified with column chromatography (EtOAc/Hex = 1:3) to obtain pure **3-11** (32 mg, 95:5 e.r.).

3.4.5 Characteristization of products



Phenyl *(S)*-3-(diphenylphosphorothioyl)-3-phenylpropanoate (3-3):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (ddd, *J* = 12.0, 7.3, 2.1 Hz, 2H), 7.59 (dt, *J* = 8.0, 3.6 Hz, 3H), 7.51 (dd, *J* = 12.7, 7.3 Hz, 2H), 7.35 (dd, *J* = 7.7, 5.9 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.26 – 7.07 (m, 8H), 6.67 (d, *J* = 7.8 Hz, 2H), 4.53 (td, *J* = 11.1, 3.5 Hz, 1H), 3.49 (ddd, *J* = 16.4, 11.5, 7.7 Hz, 1H), 3.07 (ddd, *J* = 16.3, 8.8, 3.5 Hz, 1H).

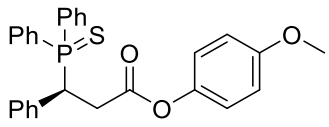
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 (d, *J* = 20.5 Hz, 1C, *C*(O)), 150.5 – 121.4 (Ar, 16C), 43.6 (d, *J* = 51.9 Hz, 1C, P*C*H), 35.8 (d, *J* = 3.9 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.12 (s).

HRMS (ESI, m/z): calculated for $C_{27}H_{23}O_2PSH^+$: 443.1235 $(M+H)^+$, found: 443.1235.

[α]$^{21}_{D}$ = +153.3 (c = 0.3 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IB, 5:95 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 16.3 min, R_t (minor) = 21.6 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-phenylpropanoate (3-4a):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 – 8.10 (m, 2H), 7.66 – 7.55 (m, 3H), 7.55 – 7.45 (m, 2H), 7.34 (dt, *J* = 7.3, 3.7 Hz, 1H), 7.32 – 7.10 (m, 7H), 6.82 – 6.69 (m, 2H), 6.64 – 6.52 (m, 2H), 4.52 (td, *J* = 11.2, 3.5 Hz, 1H), 3.73 (s, 3H), 3.47 (ddd, *J* = 16.3, 11.5, 7.8 Hz, 1H), 3.04 (ddd, *J* = 16.3, 8.8, 3.6 Hz, 1H).

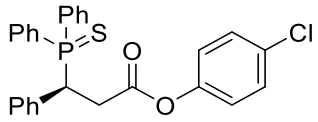
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (d, *J* = 20.2 Hz, 1C, *C*(O)), 157.4 – 114.4 (Ar, 16C), 55.6 (s, 1C, O(CH_3)), 43.6 (d, *J* = 51.8 Hz, 1C, P*C*H), 35.7 (d, *J* = 3.9 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.15 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{25}O_3PSH^+$: 473.1340 $(M+H)^+$, found: 473.1340.

[α]$^{21}_{D}$ = +144.5 (c = 0.6 in $CHCl_3$).

HPLC analysis: 97:3 *e.r.* (Chiralpak IB, 5:95 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 22.2 min, R_t (minor) = 25.2 min.



4-chlorophenyl *(S)*-3-(diphenylphosphorothioyl)-3-phenylpropanoate (3-5):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (ddd, *J* = 12.0, 7.3, 2.1 Hz, 2H), 7.71 – 7.56 (m, 3H), 7.55 – 7.45 (m, 2H), 7.35 (dd, *J* = 7.7, 5.9 Hz, 1H), 7.32 – 7.11 (m, 9H), 6.72 – 6.51 (m, 2H), 4.50 (td, *J* = 11.1, 3.6 Hz, 1H), 3.49 (ddd, *J* = 16.3, 11.5, 8.0 Hz, 1H), 3.06 (ddd, *J* = 16.3, 8.6, 3.7 Hz, 1H).

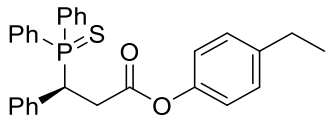
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (d, *J* = 20.4 Hz, 1C, *C*(O)), 149.0 – 122.8 (Ar, 16C), 43.6 (d, *J* = 51.8 Hz, 1C, P*C*H), 35.8 (d, *J* = 3.9 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.08 (s).

HRMS (ESI, m/z): calculated for $C_{27}H_{22}ClO_2PSH^+$: 477.0845 $(M+H)^+$, found: 477.0845.

$[\alpha]^{21}_D$ = +138.7 (c = 0.8 in $CHCl_3$).

HPLC analysis: 90:10 *e.r.* (Chiralpak IB, 5:95 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 14.2 min, R_t (major) = 15.2 min.



4-ethylphenyl *(S)*-3-(diphenylphosphorothioyl)-3-phenylpropanoate (3-6):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (ddd, *J* = 12.0, 7.3, 2.1 Hz, 2H), 7.59 (dt, *J* = 8.1, 3.6 Hz, 3H), 7.51 (dd, *J* = 12.7, 7.3 Hz, 2H), 7.34 (dd, *J* = 7.8, 6.0 Hz, 1H), 7.32 – 7.11 (m, 7H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 4.53 (td, *J* = 11.1, 3.5 Hz, 1H), 3.48 (ddd, *J* = 16.3, 11.5, 7.7 Hz, 1H), 3.05 (ddd, *J* = 16.3, 8.8, 3.5 Hz, 1H), 2.56 (q, *J* = 7.6 Hz, 2H), 1.16 (t, *J* = 7.6 Hz, 3H).

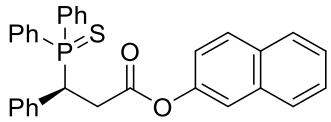
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, *J* = 20.3 Hz, 1C, *C*(O)), 151.0– 117.5 (Ar, 16C), 43.7 (d, *J* = 51.9 Hz, 1C, P*C*H), 35.8 (d, *J* = 3.8 Hz, *J* = 3.9 Hz, 1C, C(O)*C*H_2), 28.3 (s, 1C, Ar*C*H_2CH_3), 15.6 (s, 1C, $ArCH_2$*C*H_3).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 50.16 (s).

HRMS (ESI, m/z): calculated for $C_{29}H_{27}O_2PSH^+$: 471.1548 $(M+H)^+$, found: 471.1548.

$[\alpha]^{21}_D$ = +71. 4 (c = 1.1 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 23.2 min, R_t (minor) = 29.7 min.



Naphthalen-2-yl *(S)*-3-(diphenylphosphorothioyl)-3-phenylpropanoate (3-7):

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 – 8.13 (m, 2H), 7.86 – 7.08 (m, 19H), 6.78 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.57 (td, *J* = 11.1, 3.6 Hz, 1H), 3.55 (ddd, *J* = 16.3, 11.5, 7.9 Hz, 1H), 3.13 (ddd, *J* = 16.3, 8.8, 3.6 Hz, 1H).

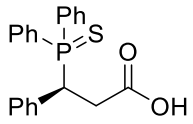
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, *J* = 20.2 Hz, 1C, *C*(O)), 148.2 – 118.4 (Ar, 22C), 43.7 (d, *J* = 51.9 Hz, 1C, P*C*H), 35.9 (d, *J* = 4.0 Hz, 1C, C(O)*C*H_2).

$^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$): δ 50.19 (s).

HRMS (ESI, m/z): calculated for $C_{31}H_{25}O_2PSH^+$: 493.1391 $(M+H)^+$, found: 493.1391.

$[\alpha]^{21}_D$ = +55.0 (c = 2.4 in $CHCl_3$).

HPLC analysis: 96:4 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 42.4 min, R_t (major) = 50.8 min.



***(S)*-3-(diphenylphosphorothioyl)-3-phenylpropanoic acid (3-8):**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 – 8.05 (m, 2H), 7.53 (d, *J* = 2.1 Hz, 3H), 7.44 (dd, *J* = 12.6, 7.6 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.24 – 7.02 (m, 7H), 4.38 (td, *J* = 10.9, 2.7 Hz, 1H), 3.20 (ddd, *J* = 17.5, 11.0, 6.8 Hz, 1H), 2.85 (ddd, *J* = 17.0, 10.4, 2.6 Hz, 1H).

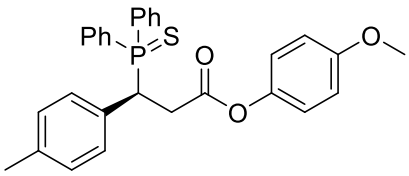
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5 (d, *J* = 16.6 Hz, 1C, *C*(O)), 134.1 – 127.8 (Ar, 12C), 43.0 (d, *J* = 52.2 Hz, 1C, P*C*H), 35.4 (d, *J* = 3.1 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.46 (s).

HRMS (ESI, m/z): calculated for $C_{21}H_{19}O_2PSH^+$: 367.0922 $(M+H)^+$, found: 367.0920.

$[\alpha]^{21}_D$ = +165.6 (c = 0.9 in $CHCl_3$).

HPLC analysis: 89:11 *e.r.* (Chiralpak AD-H, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 22.4 min, R_t (major) = 25.0 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(p-tolyl)propanoate (3-4b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (ddd, *J* = 12.0, 7.3, 2.0 Hz, 2H), 7.55 (ddd, *J* = 13.9, 6.3, 1.7 Hz, 5H), 7.35 (dd, *J* = 7.7, 6.0 Hz, 1H), 7.25 (td, *J* = 7.3, 3.0 Hz, 2H), 7.16 (dd, *J* = 8.0, 1.8 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.74 (dd, *J* = 7.3, 5.1 Hz, 2H), 6.61 (dd, *J* = 9.7, 2.7 Hz, 2H), 4.51 (td, *J* = 11.2, 3.4 Hz, 1H), 3.72 (s, 3H), 3.43 (ddd, *J* = 16.3, 11.5, 7.8 Hz, 1H), 3.03 (ddd, *J* = 16.3, 8.8, 3.5 Hz, 1H), 2.25 (d, *J* = 1.0 Hz, 3H).

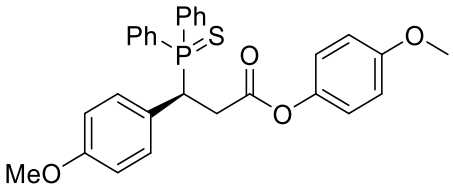
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (d, *J* = 20.4 Hz, 1C, *C*(O)), 157.3 – 114.4 (Ar, 16C), 55.6 (s, 1C, O*C*H_3), 43.2 (d, *J* = 52.2 Hz, 1C, P*C*H), 35.7 (d, *J* = 4.1 Hz, 1C, C(O)*C*H_2), 21.2 (s, 1C, Ar*C*H_3).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.04 (s).

HRMS (ESI, m/z): calculated for $C_{29}H_{27}O_3PSH^+$: 487.1497 $(M+H)^+$, found: 487.1497.

$[\alpha]^{21}_D$ = +141.4 (c = 3.5 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 31.5 min, R_t (major) = 41.0 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(4-methoxyphenyl)propanoate (3-4c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 – 8.04 (m, 2H), 7.65 – 7.45 (m, 5H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.31 – 7.14 (m, 4H), 6.73 (dd, *J* = 16.7, 8.7 Hz, 4H), 6.61 (d, *J* = 8.9 Hz, 2H), 4.49 (td, *J* = 11.3, 3.2 Hz, 1H), 3.73 (d, *J* = 6.7 Hz, 6H), 3.41 (ddd, *J* = 16.3, 11.6, 7.7 Hz, 1H), 3.01 (ddd, *J* = 16.1, 8.3, 3.3 Hz, 1H).

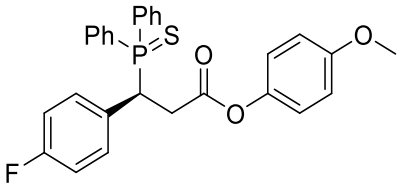
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4 (d, *J* = 20.6 Hz, 1C, *C*(O)), 159.3 – 113.5 (Ar, 16C), 55.7 (s, 1C, O*C*H$_3$), 55.3 (s, 1C, O*C*H$_3$), 42.8 (d, *J* = 52.5 Hz, 1C, P*C*H), 35.8 (d, *J* = 4.5 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 49.99 (s).

HRMS (ESI, m/z): calculated for $C_{29}H_{27}O_4PSH^+$: 503.1446 $(M+H)^+$, found: 503.1446.

$[\alpha]^{21}_D$ = +102.0 (c = 2.3 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 38.2 min, R_t (major) = 45.7 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(4-fluorophenyl)propanoate (3-4d)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (ddd, *J* = 12.1, 7.4, 2.0 Hz, 2H), 7.68 – 7.56 (m, 3H), 7.57 – 7.45 (m, 2H), 7.36 (dd, *J* = 7.6, 5.9 Hz, 1H), 7.32 – 7.21 (m, 4H), 6.86 (t, *J* = 8.6 Hz, 2H), 6.80 – 6.71 (m, 2H), 6.68 – 6.57 (m, 2H), 4.51 (td, *J* = 11.4, 3.4 Hz, 1H), 3.73 (s, 3H), 3.42 (ddd, *J* = 16.4, 11.6, 7.5 Hz, 1H), 3.01 (ddd, *J* = 16.4, 8.5, 3.5 Hz, 1H).

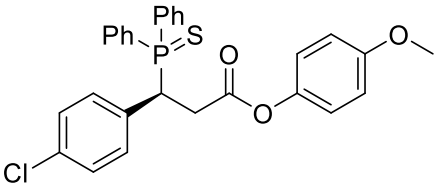
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, *J* = 20.3 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 16C), 55.7 (s, 1C, O*C*H$_3$), 42.8 (d, *J* = 52.3 Hz, 1C, P*C*H), 35.8 (d, *J* = 4.0 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.06 (d, *J* = 5.3 Hz).

HRMS (ESI, m/z): calculated for $C_{28}H_{24}FO_3PSH^+$: 491.1246 $(M+H)^+$, found: 491.1246.

[α]$^{21}_D$ = +78.3 (c = 1.7 in $CHCl_3$).

HPLC analysis: 99:1 *e.r.* (Chiralpak AD-H, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 30.6 min, R_t (major) = 37.4 min.



4-methoxyphenyl *(S)*-3-(4-chlorophenyl)-3-(diphenylphosphorothioyl)propanoate (3-4e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (ddd, *J* = 12.1, 7.4, 1.9 Hz, 2H), 7.56 (ddd, *J* = 12.8, 10.9, 4.8 Hz, 5H), 7.37 (dd, *J* = 7.7, 5.9 Hz, 1H), 7.33 – 7.19 (m, 4H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.83 – 6.71 (m, 2H), 6.69 – 6.56 (m, 2H), 4.51 (td, *J* = 11.2, 3.4 Hz, 1H), 3.73 (s, 3H), 3.42 (ddd, *J* = 16.6, 11.6, 7.4 Hz, 1H), 3.02 (ddd, *J* = 16.5, 8.7, 3.4 Hz, 1H).

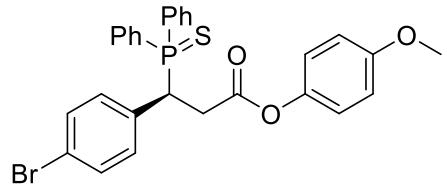
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (d, *J* = 20.1 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 16C), 55.7 (s, 1C, O*C*H$_3$), 42.9 (d, *J* = 51.8 Hz, 1C, P*C*H), 35.6 (d, *J* = 3.9 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 49.92 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{24}ClO_3PSH^+$: 507.0951 $(M+H)^+$, found: 507.0951.

[α]$^{21}_D$ = +106.2 (c = 2.4 in $CHCl_3$).

HPLC analysis: 99:1 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 19.1 min, R_t (major) = 20.3 min.



4-methoxyphenyl *(S)*-3-(4-bromophenyl)-3-(diphenylphosphorothioyl)propanoate (3-4f)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (ddd, *J* = 12.1, 7.4, 1.9 Hz, 2H), 7.67 – 7.48 (m, 5H), 7.38 (dd, *J* = 7.7, 5.9 Hz, 1H), 7.34 – 7.23 (m, 4H), 7.17 (dd, *J* = 8.5, 2.0 Hz, 2H), 6.83 – 6.72 (m, 2H), 6.70 – 6.56 (m, 2H), 4.50 (td, *J* = 11.2, 3.4 Hz, 1H), 3.73 (s, 3H), 3.41 (ddd, *J* = 16.6, 11.6, 7.4 Hz, 1H), 3.02 (ddd, *J* = 16.5, 8.8, 3.4 Hz, 1H).

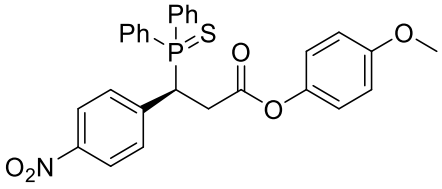
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (d, *J* = 20.1 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 16C), 55.7 (s, 1C, O*C*H_3), 43.0 (d, *J* = 51.8 Hz, 1C, P*C*H), 35.6 (d, *J* = 3.8 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 49.81 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{24}BrO_3PSH^+$: 551.0445 $(M+H)^+$, found: 551.0446.

$[\alpha]^{21}_D$ = +85.3 (c = 3.5 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 20.0 min, R_t (major) = 21.3 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(4-nitrophenyl)propanoate (3-4g)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (ddd, *J* = 12.3, 7.5, 1.8 Hz, 2H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.71 – 7.52 (m, 5H), 7.47 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.39 (dd, *J* = 7.5, 5.7 Hz, 1H), 7.34 – 7.21 (m, 2H), 6.82 – 6.72 (m, 2H), 6.70 – 6.60 (m, 2H), 4.66 (td, *J* = 11.1, 3.3 Hz, 1H), 3.73 (s, 3H), 3.50 (ddd, *J* = 17.1, 11.5, 7.2 Hz, 1H), 3.08 (ddd, *J* = 17.0, 8.9, 3.4 Hz, 1H).

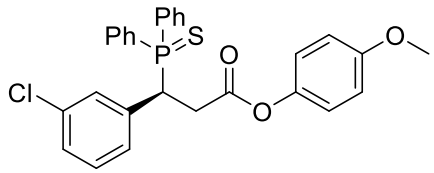
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8 (d, *J* = 19.5 Hz, 1C, *C*(O)), 157.5 – 114.5 (Ar, 16C), 55.7 (s, 1C, O*C*H_3), 43.5 (d, *J* = 50.5 Hz, 1C, P*C*H), 35.5 (d, *J* = 3.2 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 49.98 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{24}NO_5PSH^+$: 518.1191 $(M+H)^+$, found: 518.1191.

$[\alpha]^{21}_D$ = +104.2 (c = 1.9 in $CHCl_3$).

HPLC analysis: 97:3 *e.r.* (Chiralpak AD-H, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 22.6 min, R_t (major) = 29.4 min.



4-methoxyphenyl *(S)*-3-(3-chlorophenyl)-3-(diphenylphosphorothioyl)propanoate (3-4h)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (ddd, *J* = 12.2, 7.5, 1.9 Hz, 2H), 7.68 – 7.57 (m, 3H), 7.57 – 7.46 (m, 2H), 7.38 (dd, *J* = 7.7, 5.8 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.19 (dt, *J* = 8.1, 4.6 Hz, 3H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.85 – 6.72 (m, 2H), 6.71 – 6.60 (m, 2H), 4.48 (td, *J* = 11.1, 3.4 Hz, 1H), 3.73 (s, 3H), 3.43 (ddd, *J* = 16.7, 11.5, 7.5 Hz, 1H), 3.04 (ddd, *J* = 16.6, 9.0, 3.5 Hz, 1H).

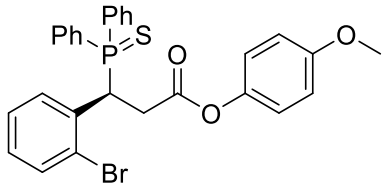
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (d, *J* = 19.9 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 18C), 55.7 (s, 1C, O*C*H$_3$), 43.3 (d, *J* = 51.5 Hz, 1C, P*C*H), 35.5 (d, *J* = 3.7 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.10 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{24}ClO_3PSH^+$: 507.0951 $(M+H)^+$, found: 507.0951.

$[\alpha]^{21}_D$ = +101.7 (c = 1.7 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 19.1 min, R_t (major) = 29.0 min.



4-methoxyphenyl *(S)*-3-(2-bromophenyl)-3-(diphenylphosphorothioyl)propanoate (3-4i)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 – 8.20 (m, 3H), 7.80 – 7.59 (m, 5H), 7.38 (dd, *J* = 13.3, 7.3 Hz, 3H), 7.30 (dd, *J* = 7.9, 6.6 Hz, 1H), 7.14 (td, *J* = 7.7, 3.2 Hz, 2H), 6.75 (dd, *J* = 9.5, 2.6

Hz, 2H), 6.72 – 6.64 (m, 2H), 5.96 (td, *J* = 11.3, 3.6 Hz, 1H), 3.72 (s, 3H), 3.57 (ddd, *J* = 16.9, 11.5, 8.1 Hz, 1H), 3.00 (ddd, *J* = 16.8, 8.1, 3.7 Hz, 1H).

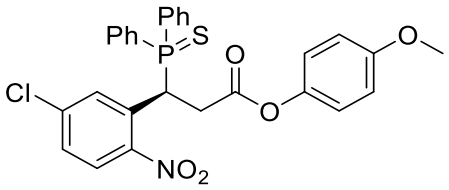
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5 (d, *J* = 20.1 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 18C), 55.7 (s, 1C, O*C*H$_3$), 36.5 (d, *J* = 3.3 Hz, 1C, P*C*H), 35.8 (d, *J* = 50.2 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 51.84 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{24}BrO_3PSH^+$: 551.0445 $(M+H)^+$, found: 551.0445.

$[\alpha]^{21}_D$ = +111.2 (c = 1.0 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 30.5 min, R_t (major) = 33.2 min.



4-methoxyphenyl *(S)*-3-(5-chloro-2-nitrophenyl)-3-(diphenylphosphorothioyl)-propanoate (3-4j)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 13.5, 6.4 Hz, 3H), 7.66 (dd, *J* = 5.3, 3.0 Hz, 4H), 7.44 (dd, *J* = 13.0, 7.7 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.17 (td, *J* = 7.7, 3.1 Hz, 2H), 6.89 – 6.62 (m, 4H), 5.98 (td, *J* = 11.3, 3.4 Hz, 1H), 3.72 (s, 3H), 3.52 (ddd, *J* = 17.5, 11.5, 7.9 Hz, 1H), 3.01 (ddd, *J* = 17.2, 8.2, 3.5 Hz, 1H).

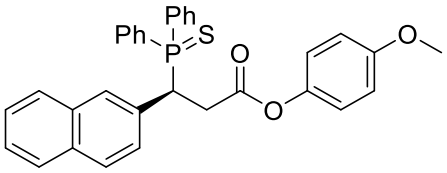
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4 (d, *J* = 19.8 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 18C), 55.7 (s, 1C, O*C*H$_3$), 36.4 (d, *J* = 3.2 Hz, 1C, P*C*H), 35.6 (d, *J* = 49.6 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 51.86 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{23}ClNO_5PSH^+$: 552.0801 $(M+H)^+$, found: 552.0800.

$[\alpha]^{21}_D$ = +101.3 (c = 4.4 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 21.4 min, R_t (major) = 29.8 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(naphthalen-2-yl)propanoate (3-4k)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (ddd, *J* = 12.0, 7.2, 2.2 Hz, 2H), 7.82 – 7.66 (m, 3H), 7.66 – 7.55 (m, 4H), 7.55 – 7.47 (m, 2H), 7.47 – 7.34 (m, 3H), 7.29 (dd, *J* = 7.7, 6.0 Hz, 1H), 7.17 (td, *J* = 7.7, 3.1 Hz, 2H), 6.75 – 6.63 (m, 2H), 6.61 – 6.49 (m, 2H), 4.70 (td, *J* = 11.1, 3.4 Hz, 1H), 3.68 (s, 3H), 3.58 (ddd, *J* = 16.5, 11.5, 7.5 Hz, 1H), 3.15 (ddd, *J* = 16.5, 9.0, 3.4 Hz, 1H).

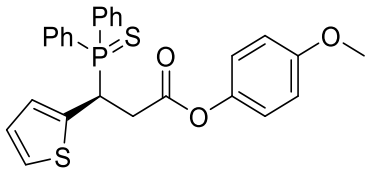
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3 (d, *J* = 20.1 Hz, 1C, *C*(O)), 157.3 – 114.4 (Ar, 22C), 55.6 (s, 1C, O*C*H_3), 43.8 (d, *J* = 51.6 Hz, 1C, P*C*H), 35.9 (d, *J* = 3.9 Hz, 1C, C(O)*C*H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.05 (s).

HRMS (ESI, m/z): calculated for $C_{32}H_{27}O_3PSH^+$: 523.1497 $(M+H)^+$, found: 523.1497.

$[\alpha]^{21}_D$ = +92.4 (c = 2.6 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 28.4 min, R_t (major) = 36.9 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(thiophen-2-yl)propanoate (3-4l)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (ddd, *J* = 12.2, 7.6, 1.7 Hz, 2H), 7.73 – 7.62 (m, 2H), 7.62 – 7.50 (m, 3H), 7.40 (dd, *J* = 7.7, 5.8 Hz, 1H), 7.31 (td, *J* = 7.5, 3.1 Hz, 2H), 7.12 (d, *J* = 5.1 Hz, 1H), 7.00 (t, *J* = 3.0 Hz, 1H), 6.90 – 6.82 (m, 1H), 6.82 – 6.75 (m, 2H), 6.73 – 6.63 (m, 2H), 4.88 (td, *J* = 11.1, 3.3 Hz, 1H), 3.74 (s, 3H), 3.37 (ddd, *J* = 16.3, 11.5, 6.9 Hz, 1H), 3.06 (ddd, *J* = 16.2, 8.4, 3.3 Hz, 1H).

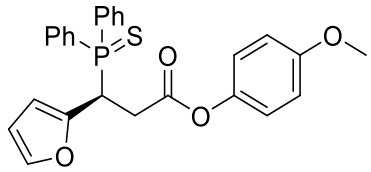
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (d, *J* = 19.6 Hz, 1C, <u>*C*</u>(O)), 157.4 – 114.5 (Ar, 16C), 55.7 (s, 1C, O<u>*C*</u>H_3), 40.0 (d, *J* = 54.5 Hz, 1C, P<u>*C*</u>H), 37.2 (d, *J* = 5.0 Hz, 1C, C(O)<u>*C*</u>H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 49.62 (s).

HRMS (ESI, m/z): calculated for $C_{26}H_{23}O_3PS_2H^+$: 479.0904 $(M+H)^+$, found: 479.0905.

$[\alpha]^{21}_D$ = +85.4 (c = 1.8 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 32.3 min, R_t (major) = 46.6 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-(furan-2-yl)propanoate (3-4m)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 – 7.94 (m, 2H), 7.74 – 7.62 (m, 2H), 7.61 – 7.50 (m, 3H), 7.46 (dd, *J* = 7.7, 5.8 Hz, 1H), 7.37 (td, *J* = 7.5, 3.2 Hz, 2H), 7.19 (s, 1H), 6.90 – 6.69 (m, 4H), 6.23 (dt, *J* = 12.7, 3.3 Hz, 2H), 4.75 (td, *J* = 11.4, 3.7 Hz, 1H), 3.75 (s, 3H), 3.28 (ddd, *J* = 16.7, 11.5, 7.2 Hz, 1H), 3.14 (ddd, *J* = 16.6, 8.8, 3.8 Hz, 1H).

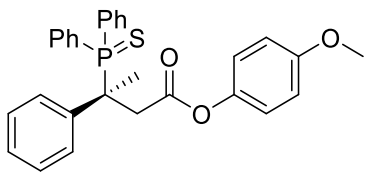
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2 (d, *J* = 19.2 Hz, 1C, <u>*C*</u>(O)), 157.4 – 109.7 (Ar, 16C), 55.7 (s, 1C, O<u>*C*</u>H_3), 39.3 (d, *J* = 54.1 Hz, 1C, P<u>*C*</u>H), 34.1 (d, *J* = 4.5 Hz, 1C, C(O)<u>*C*</u>H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 48.55 (s).

HRMS (ESI, m/z): calculated for $C_{26}H_{23}O_4PSH^+$: 463.1133 $(M+H)^+$, found: 463.1133.

$[\alpha]^{21}_D$ = +25.2 (c = 1.4 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 24.4 min, R_t (major) = 30.0 min.



4-methoxyphenyl *(S)*-3-(diphenylphosphorothioyl)-3-phenylbutanoate (3-4n)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.65 (m, 4H), 7.58 – 7.46 (m, 2H), 7.39 (td, *J* = 7.7, 3.1 Hz, 4H), 7.34 – 7.27 (m, 1H), 7.19 (t, *J* = 7.7 Hz, 2H), 7.04 – 6.91 (m, 2H), 6.71 (dd, *J* = 9.8, 2.8 Hz, 2H), 6.57 – 6.46 (m, 2H), 3.71 (s, 3H), 3.63 (dd, *J* = 15.3, 5.3 Hz, 1H), 3.52 (dd, *J* = 15.3, 9.9 Hz, 1H), 1.94 (d, *J* = 18.7 Hz, 3H).

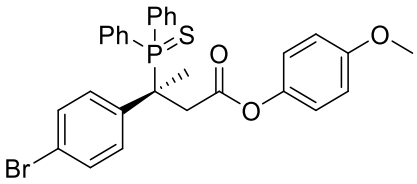
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (d, *J* = 23.8 Hz, 1C, *C*(O)), 157.3 – 114.4 (Ar, 16C), 55.7 (s, 1C, O*C*H_3), 47.5 (d, *J* = 45.5 Hz, 1C, P*C*H), 41.6 (d, *J* = 5.1 Hz, 1C, C(O)*C*H_2), 20.8 (s, 1C, P(C)*C*H_3).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 59.29 (s).

HRMS (ESI, m/z): calculated for $C_{29}H_{27}O_3PSH^+$: 487.1497 $(M+H)^+$, found: 487.1497.

$[\alpha]^{21}_D$ = +9.9 (c = 1.5 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 34.9 min, R_t (major) = 41.0 min.



4-methoxyphenyl *(S)*-3-(4-bromophenyl)-3-(diphenylphosphorothioyl)butanoate (3-4o)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.68 (m, 4H), 7.54 (dt, *J* = 7.6, 6.0 Hz, 2H), 7.43 (qd, *J* = 7.7, 3.2 Hz, 4H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.86 (dd, *J* = 8.8, 2.1 Hz, 2H), 6.81 – 6.69 (m, 2H), 6.67 – 6.50 (m, 2H), 3.72 (s, 3H), 3.55 (qd, *J* = 15.7, 7.5 Hz, 2H), 1.91 (d, *J* = 18.3 Hz, 3H).

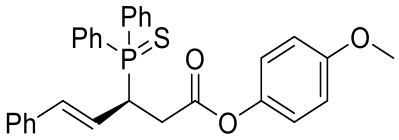
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3 (d, *J* = 23.4 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar, 16C), 55.7 (s, 1C, O*C*H_3), 47.2 (d, *J* = 45.2 Hz, 1C, P*C*H), 41.3 (d, *J* = 5.0 Hz, 1C, C(O)*C*H_2), 20.9 (s, P(C)*C*H_3).

^{31}P NMR (162 MHz, $CDCl_3$): δ 58.90 (s).

HRMS (ESI, m/z): calculated for $C_{29}H_{26}BrO_3PSH^+$: 565.0602 $(M+H)^+$, found: 565.0601.

[α]$^{21}_{D}$ = +21.3 (c = 1.1 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak AD-H, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 29.9 min, R_t (major) = 38.5 min.



4-methoxyphenyl *(S,E)*-3-(diphenylphosphorothioyl)-5-phenylpent-4-enoate (3-4p)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (ddd, *J* = 12.3, 7.6, 1.7 Hz, 2H), 7.97 – 7.80 (m, 2H), 7.64 – 7.50 (m, 3H), 7.49 – 7.35 (m, 3H), 7.34 – 7.11 (m, 5H), 6.92 – 6.69 (m, 4H), 6.41 (dd, *J* = 15.9, 4.6 Hz, 1H), 6.21 (ddd, *J* = 15.8, 9.1, 6.5 Hz, 1H), 4.14 (td, *J* = 12.5, 3.0 Hz, 1H), 3.75 (s, 3H), 3.16 – 2.98 (m, 1H), 2.92 (ddd, *J* = 15.9, 9.9, 3.1 Hz, 1H).

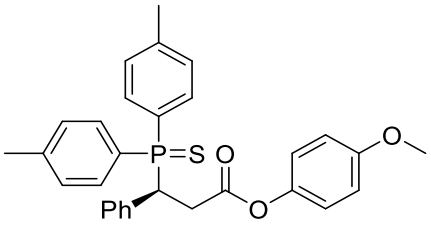
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (d, *J* = 20.3 Hz, 1C, *C*(O)), 157.4 – 114.5 (Ar and *C*H=CH, 18C), 55.7 (s, 1C, O*C*H$_3$), 42.1 (d, *J* = 54.8 Hz, 1C, P*C*H), 34.6 (d, *J* = 2.2 Hz, 1C, C(O)*C*H$_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 48.40 (s).

HRMS (ESI, m/z): calculated for $C_{30}H_{27}O_3PSH^+$: 499.1497 $(M+H)^+$, found: 499.1497.

[α]$^{21}_{D}$ = +49.2 (c = 1.1 in $CHCl_3$).

HPLC analysis: 83:17 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 26.6 min, R_t (minor) = 50.9 min.



4-methoxyphenyl *(S)*-3-(di-p-tolylphosphorothioyl)-3-phenylpropanoate (3-4q)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 11.9, 8.1 Hz, 2H), 7.38 (dd, *J* = 12.4, 8.1 Hz, 4H), 7.34 – 7.27 (m, 2H), 7.23 – 7.11 (m, 3H), 7.03 (dd, *J* = 8.0, 2.5 Hz, 2H), 6.79 – 6.67 (m,

2H), 6.62 – 6.51 (m, 2H), 4.47 (td, *J* = 11.1, 3.6 Hz, 1H), 3.72 (s, 3H), 3.43 (ddd, *J* = 16.2, 11.5, 7.9 Hz, 1H), 3.03 (ddd, *J* = 16.2, 8.7, 3.6 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H).

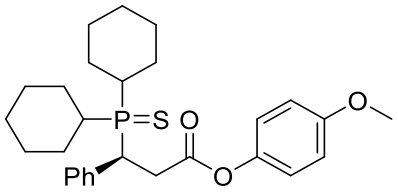
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5 (d, *J* = 20.1 Hz, 1C, *C*(O)), 157.3 – 114.4 (Ar, 16C), 55.6 (s, 1C, O*C*H_3), 43.8 (d, *J* = 52.0 Hz, 1C, P*C*H), 35.8 (d, *J* = 3.8 Hz, 1C, C(O)*C*H_2), 21.6 (d, *J* = 1.1 Hz, 1C, P(Ar)*C*H_3), 21.5 (d, *J* = 1.1 Hz, 1C, P(Ar)*C*H_3).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 49.57 (s).

HRMS (ESI, m/z): calculated for $C_{30}H_{29}O_3PSH^+$: 501.1653 $(M+H)^+$, found: 501.1653.

$[\alpha]^{21}_D$ = +101.8 (c = 2.0 in $CHCl_3$).

HPLC analysis: 99:1 *e.r.* (Chiralpak IC, 10:90 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 37.6 min, R_t (minor) = 40.3 min.



4-methoxyphenyl *(S)*-3-(dicyclohexylphosphorothioyl)-3-phenylpropanoate (3-4r)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.41 – 7.28 (m, 3H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.65 (t, *J* = 6.0 Hz, 2H), 3.93 (td, *J* = 10.6, 4.1 Hz, 1H), 3.74 (d, *J* = 0.5 Hz, 3H), 3.50 – 3.22 (m, 2H), 2.36 – 0.63 (m, 22H).

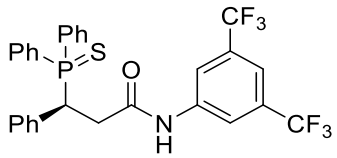
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7 (d, *J* = 17.4 Hz, 1C, *C*(O)), 157.3 – 114.4 (Ar, 8C), 55.7 (s, 1C, O*C*H_3), 40.2 (d, *J* = 41.3 Hz, 1C, P*C*H), 39.1 (d, *J* = 30.0 Hz, 1C, P*C*H$(CH_2)_2$), 38.7 (d, *J* = 31.6 Hz, 1C, P*C*H$(CH_2)_2$), 37.5 (d, *J* = 1.8 Hz, 1C, C(O)*C*H_2), 27.6 – 26.0 (6C, Cy).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 64.14 (s).

HRMS (ESI, m/z): calculated for $C_{28}H_{37}O_3PSH^+$: 485.2279 $(M+H)^+$, found: 485.2279.

$[\alpha]^{21}_D$ = -5.9 (c = 2.1 in $CHCl_3$).

HPLC analysis: 84:16 *e.r.* (Chiralpak IC, 30:70 ^{i}PrOH/Hexane, 0.3 mL/min), R_t (minor) = 19.9 min, R_t (major) = 29.1 min.



***(S)*-N-(3,5-bis(trifluoromethyl)phenyl)-3-(diphenylphosphorothioyl)-3-phenylpropanamide (3-9)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.19 – 8.02 (m, 2H), 7.70 (s, 2H), 7.48 (s, 1H), 7.44 – 7.32 (m, 5H), 7.31 – 7.26 (m, 3H), 7.22 – 7.04 (m, 5H), 4.60 (q, *J* = 7.4 Hz, 1H), 3.35 (ddd, *J* = 14.3, 11.5, 7.2 Hz, 1H), 3.14 (ddd, *J* = 19.1, 14.4, 7.3 Hz, 1H).

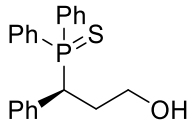
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1 (d, *J* = 10.3 Hz, 1C, <u>*C*</u>(O)), 138.8 – 117.5 (Ar, 16C and <u>*C*</u>F_3), 42.9 (d, *J* = 50.7 Hz, 1C, P<u>*C*</u>H), 39.8 (d, *J* = 1.7 Hz, 1C, C(O)<u>*C*</u>H_2).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 51.10 (s).

HRMS (ESI, m/z): calculated for $C_{29}H_{22}F_6NOPSH^+$: 578.1142 $(M+H)^+$, found: 578.1142.

$[\alpha]^{21}_D$ = +178.9 (c = 1.0 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak IB, 3:97 ^{i}PrOH/Hexane, 0.3 mL/min), R_t (major) = 37.6 min, R_t (minor) = 40.3 min.



***(S)*-(3-hydroxy-1-phenylpropyl)diphenylphosphine sulfide (3-10)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 – 8.05 (m, 2H), 7.54 (d, *J* = 2.0 Hz, 3H), 7.44 (dd, *J* = 12.5, 7.4 Hz, 2H), 7.35 – 7.21 (m, 3H), 7.21 – 7.06 (m, 5H), 4.30 – 4.12 (m, 1H), 3.68 – 3.47 (m, 1H), 3.34 (td, *J* = 10.3, 3.8 Hz, 1H), 2.38 (dddd, *J* = 15.0, 11.3, 7.5, 3.7 Hz, 1H), 2.09 (tdd, *J* = 14.3, 5.5, 2.9 Hz, 1H).

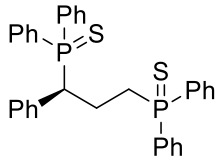
^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5 – 127.5 (Ar, 12C), 59.8 (d, *J* = 14.7 Hz, 1C, $CH_2\underline{C}HOH$), 43.0 (d, *J* = 52.0 Hz, 1C, $P\underline{C}H$), 32.8 (s, 1C, $PCH\underline{C}H_2CH_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.71 (s).

HRMS (ESI, m/z): calculated for $C_{21}H_{21}OPSH^+$: 353.1129 $(M+H)^+$, found: 353.1129.

[α]$^{21}_D$ = +80.2 (c = 1.0 in $CHCl_3$).

HPLC analysis: 94:6 *e.r.* (Chiralpak IC, 15:85 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 17.9 min, R_t (major) = 31.1 min.



***(S)*-(1-phenylpropane-1,3-diyl)bis(diphenylphosphine sulfide) (3-11)**

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 – 8.06 (m, 2H), 7.58 (td, *J* = 11.6, 7.9 Hz, 4H), 7.52 – 7.32 (m, 11H), 7.30 – 7.19 (m, 3H), 7.19 – 7.06 (m, 5H), 4.51 (t, *J* = 9.8 Hz, 1H), 2.58 (ddd, *J* = 18.9, 14.0, 6.2 Hz, 1H), 2.29 – 2.12 (m, 2H), 2.13 – 1.96 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4 – 127.5 (Ar, 20C), 45.9 (dd, *J* = 50.6, 6.4 Hz, 1C, $P\underline{C}HCH_2$), 26.4 (dd, *J* = 71.8, 13.9 Hz, 1C, $CH_2\underline{C}H_2P$), 23.0 (t, *J* = 2.8 Hz, 1C, $CH\underline{C}H_2CH_2$).

^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ 50.54 (s), 32.72 (s).

HRMS (ESI, m/z): calculated for $C_{33}H_{30}P_2S_2H^+$: 553.1342 $(M+H)^+$, found: 553.1346.

[α]$^{21}_D$ = +37.1 (c = 1.8 in $CHCl_3$).

HPLC analysis: 95:5 *e.r.* (Chiralpak IC, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 31.3 min, R_t (minor) = 43.3 min.

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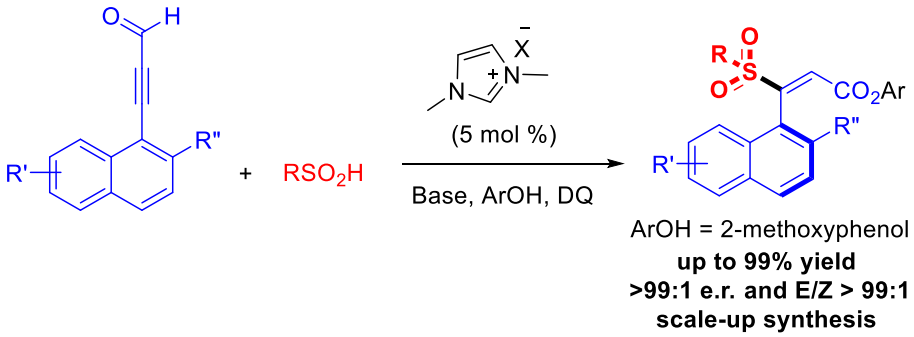
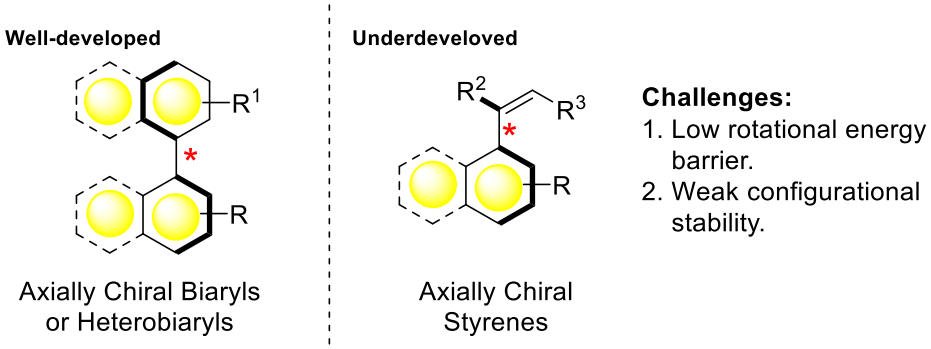
Chapter 4

Carbene-Catalyzed Atroposelective Access to Axially Chiral Sulfone-containing Styrenes



4.1 Introduction

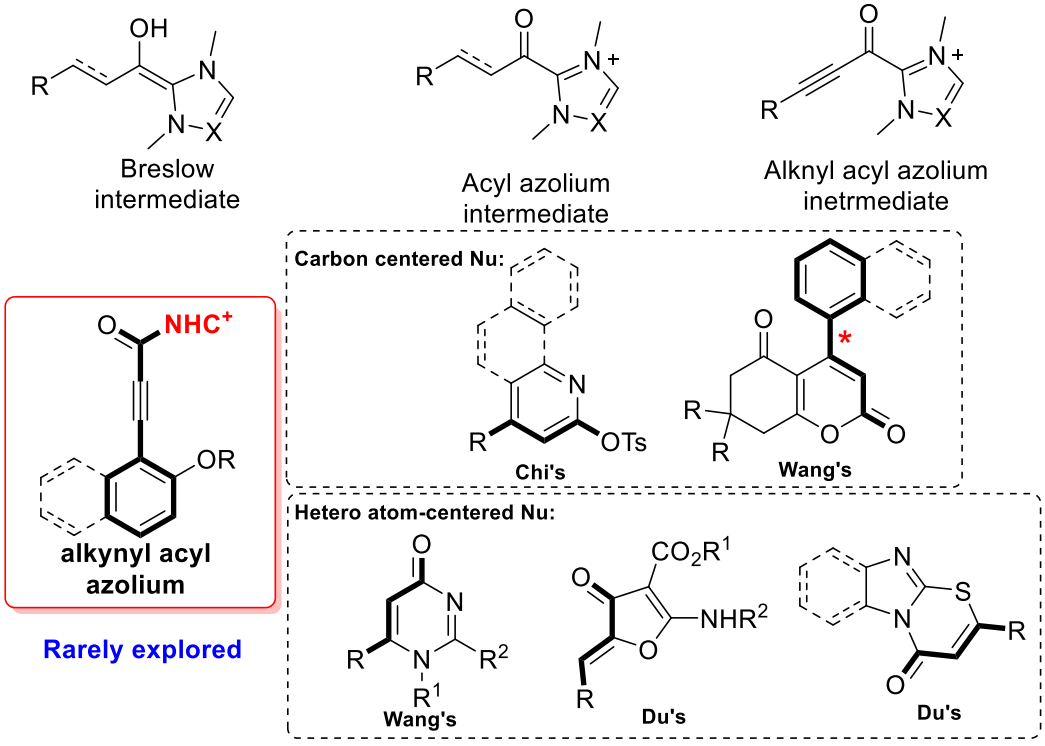
Axially chiral motifs, especially aryl-based atropoisomeric systems are a privileged class of organic molecules which are potent to act as chiral organic catalysts or ligands.[1] Besides, they are also ubiquitous in many natural products[2-3] and biologically active compounds.[4-7] Therefore, a substantial attention has been directed towards the development of catalytic asymmetric routes for access to these axially chiral aryl-based moieties such as biaryls,[8-17] heterobiaryls,[18-24] anilides,[25-28] benzamides,[29-30] etc. Particularly, enantioselective synthetic paths for biaryls and heterobiaryl systems have been developed in a rapid pace over the past decade. On the contrary, synthetic protocols for axially chiral styrenes or vinyl arenes, another member of this family, have been less developed, although the concept of axially chiral styrene has been demonstrated long back in 1991 by Kawabata *et al*[31] (Scheme 4.1). The challenges faced by chemists for atroposelective axially styrenes synthesis include mainly two factors – 1) low rotational energy barrier and 2) weak configurational stability of the axially chiral styrenes. To date, only a few methods for the enantioselective construction of axially chiral styrenes have been demonstrated by the groups of Baker,[32] Smith,[33] Gu,[34] and Miyano.[35] Recently, few successes through organocatalysis have also been achieved. For example, Tan and his coworkers[36] have synthesized axially chiral styrene using amine catalysis to couple a carbon nucleophile with the alkyne aldehyde. Yan,[37] and Shi[38] have also reported the procedures for



Scheme 4.1 Profile of axially chiral systems

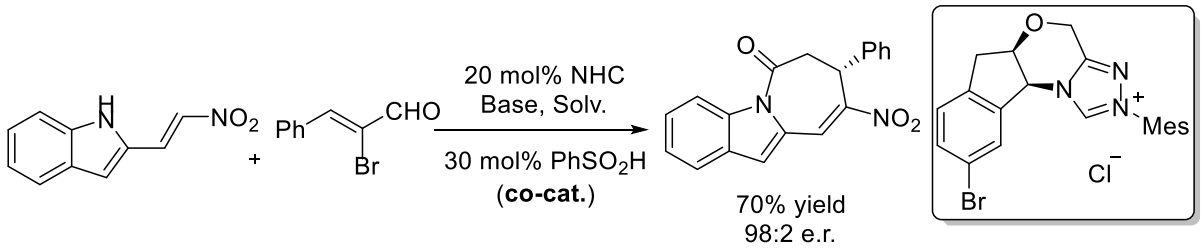
access to axially chiral styrenes using isothiourea-proline dual catalytic and phosphoric acid catalytic strategies, respectively. Despite these progresses, a practical pathway to achieve these molecules with various substitutions is still in demand.

Our group is interested in the asymmetric construction of the carbon-hetero atom bonds using N-heterocyclic carbene (NHC) catalysis. Over the years, different kinds of activation modes (Breslow intermediate, homoenolate, enolate, acyl azolium, etc.), generated by NHC catalyst, have successfully employed in the enantioselective construction of complex molecules from readily available molecules. However, unlike other activation modes, alkynyl acyl azolium intermediate has been rarely explored in asymmetric NHC catalysis (Scheme 4.2). In 2017, Chi's group made pyridine derivatives using this intermediate, generated from a carbon-carbon triple bond containing ester.[39] Subsequently, in 2018, Wang's group has demonstrated the utilization of this intermediate to form an axial chiral pyrone system.[40] In this context, it is worthy to mention that Du's group was also fascinated by this alkynyl acyl azolium intermediate and employed it to construct achiral heterocyclic moieties.[41]



Scheme 4.2 Backgrounds of alkynyl acyl azolium

In 2019, we demonstrated sulfinate ion as a co-catalyst with NHC for access to the enantioselective azepino[1,2-*a*]indole moieties (Scheme 4.3).[42] In this report, sulfinate ion activated the α-positioned carbon of the electron-deficient NHC-derived unsaturated α,β-acyl azolium by attacking the β-positioned carbon and facilitated the intermediate to couple with nitrovinyl indole.

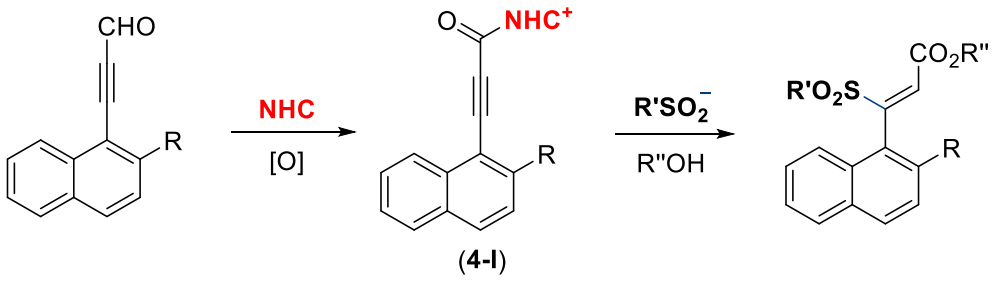


Scheme 4.3 Sulfinate as co-catalyst in NHC-catalysis

As part of an ongoing effort to develop synthetic approach to access carbon-heteroatom bond, we presumed that sulfinic acid is also potent to couple with alkynyl acyl azolium intermediate and as a result, it can lead to an axially chiral styrene system, bearing a C-S bond. Sulfones are versatile synthetic intermediate in organic chemistry. In addition, they are getting considerable attention due to their wide range of biological activities, primarily as antimicrobial, anticancer, anti-HIV, antimalarial, and anti-inflammatory. Recently, methodologies to afford hybrid molecules with more than one biological property has gained momentum. In this context, integration of two features i.e. axially chirality and sulfones in a single motif may enhance the possibility to have new pharmacological activities. By now, only Yan's approach[37] could asymmetrically access the axially chiral sulfone-containing styrenes. But one of the limitations of this method is that an OH group is necessary in the 2-position of the alkyne substrate to control the stereoselectivities. Therefore, it constrains the substrate scope.

Our proposal

Herein, we report an alternative pathway to afford enantioselective axially chiral sulfone-containing styrene via NHC-catalyzed reaction of alkynyl aldehydes (Scheme 4.4). Key steps include the generation of an alkynyl acyl azolium intermediate under oxidative NHC conditions.



Scheme 4.4 NHC-catalyzed 1,4-addition of sulfinate to alkynyl acyl azolium

Later, a 1,4-coupling of sulfinate ion to the β-positioned carbon of the NHC-bound intermediate **4-I**, followed by removal of NHC by an external nucleophile (alcohol) led to the proposed axially chiral styrene derivatives with diverse substituents in 2-position of the axially chiral styrene.

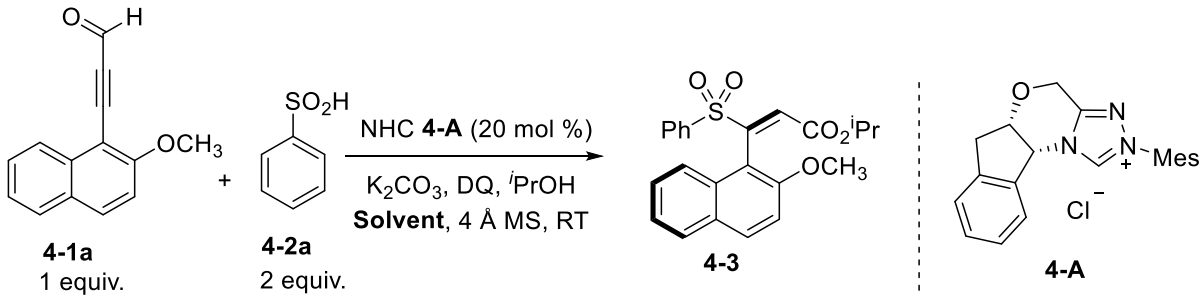
4.2 Result and Discussion

4.2.1 Reaction condition optimization

We initiated our investigation with **4-1a** and **4-2a** as the model substrates for finding the optimized conditions. We started our screening for a suitable solvent for the reaction in presence of the amidoindole-based triazolium salt **4-A** as the NHC precursor and K_2CO_3 as the base. The results are shown in Table 4.1. Chlorinated solvents (Table 4.1, entries 1-2) were giving the product in low yields and e.r. values. Thus, we shifted to polar solvents (Table 4.1, entries 3-5). But, unfortunately, they were not providing the product at all. Later, when non-polar solvents (toluene and Et_2O) were introduced to the reaction, the product was afforded in encouraging results. The solvent Et_2O proved to be the optimal one for this reaction, giving the

product in 42% yield and 30:70 e.r (Table 4.1, entry 7). Therefore, we moved to the base screening with Et_2O as the solvent to obtain a better result.

Table 4.1 Screening of solvents[a]



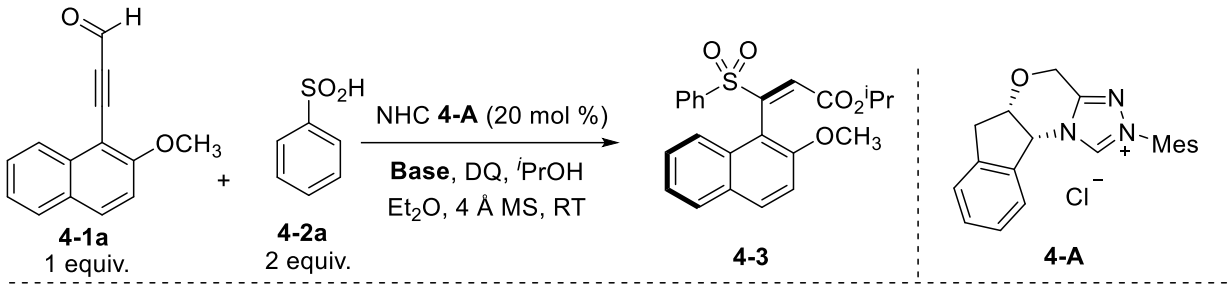
Entry	Solvent	Yield (%)[b]	e.r.[c]
1	DCM	37	35:65
2	DCE	41	34:66
3	THF	NP	-
4	DME	NP	-
5	MeCN	NP	-
6	Toluene	27%	36:64
7	**Et_2O**	**42%**	**30:70**

[a]Standard reaction condition: **4-1a** (0.05 mmol), **4-2a** (0.1 mmol), NHC **4-E** (20 mol%), NaOAc (0.15 mmol), DQ (0.1 mmol), ^{i}PrOH (0.055 mmol) and solvent (1 mL). [b]Yield was determined by ^{1}HNMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis.

Both the organic and inorganic bases were checked for this catalytic reaction protocol. All the screening results are enlisted in Table 4.2. Strong bases like Cs_2CO_3, DBU (Table 4.2, entry 1 and entry 2) were not compatible with this reaction and gave a trace amount of the proposed product. According to the results, shown in Table 4.2, the weak inorganic base, NaOAc (Table 4.2, entry 4) led to the product with the best result (54% yield and 22:78 e.r.). Therefore, we focused our further studies with NaOAc as the optimal base. To improve the yield and

enantioselectivity further, we started to screen the catalysts. The results are briefed in Table 4.3. We found out that NHC **4-D** bearing 2,4,6-isopropyl substituted aryl group in its triazolium

Table 4.2 Screening of bases[a]



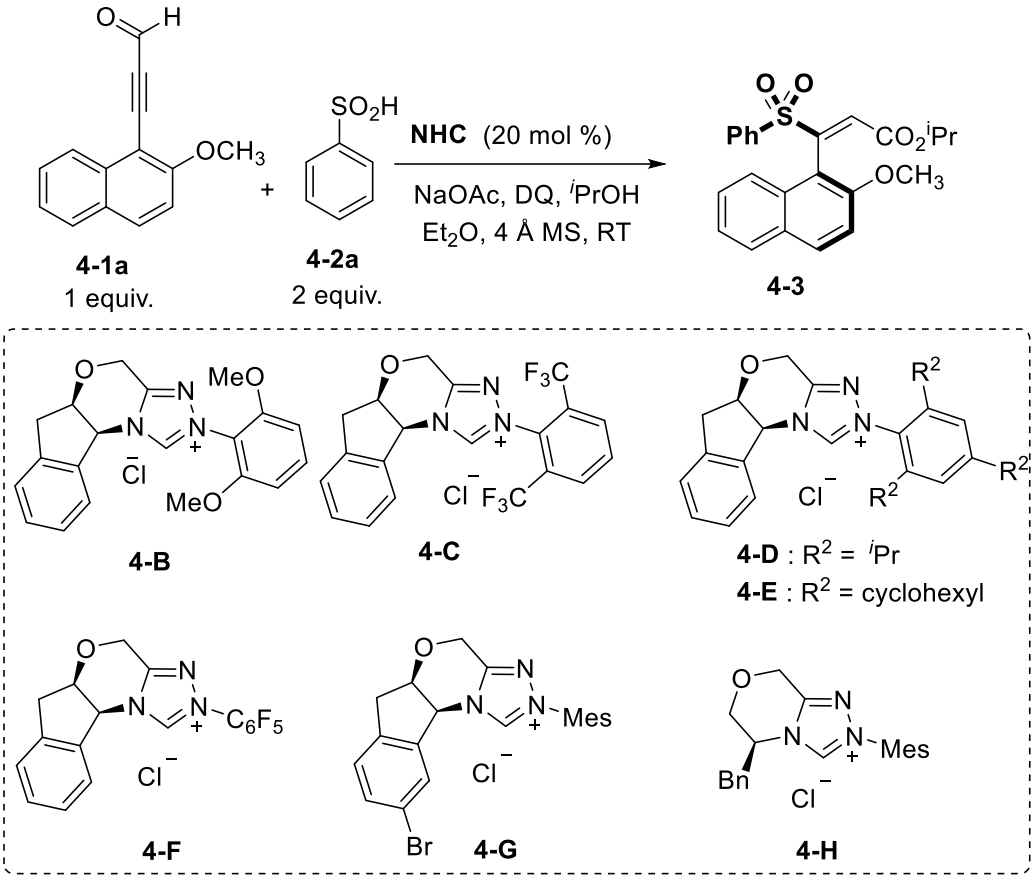
Entry	Base	Yield (%)[b]	e.r.[c]
1	Cs_2CO_3	trace	-
2	Na_2CO_3	24	28:72
3	KOAc	40	25:75
4	**NaOAc**	**54**	**22:78**
5	DIPEA	trace	-
6	DBU	trace	-

[a]Standard reaction condition: **4-1a** (0.05 mmol), **4-2a** (0.1 mmol), NHC **4-E** (20 mol%), Base (0.15 mmol), DQ (0.1 mmol), ^{i}PrOH (0.055 mmol) and Et_2O (1 mL). [b]Yield was determined by ^{1}HNMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis

ring, gave the product in 37% yield and 85:15 e.r. Therefore, we employed the bulkier NHC **4-E**, comparing to **4-D** in the hope to get a better result. And indeed, the product was obtained in 40% yield with 87:13 e.r. under these conditions. We have also tried morpholine-based NHC **4-H** (Table 4.3, entry 7). Although yield was improved to an acceptable value, but the enantioselectivity was not satisfactory. Therefore, we chose **4-E** as the optimal catalyst for further examinations. We envisioned that external alcohol and temperature had critical roles in the determination of the enantioselectivity as well as the yield of the product. Thus, we applied

bulkier alcohol (aromatic) in our reaction at different temperatures. First, we repeated the reaction with ^{i}PrOH at 0 °C to see the influence of the temperature on the reaction.

Table 4.3 Screening of NHC precatalysts[a]

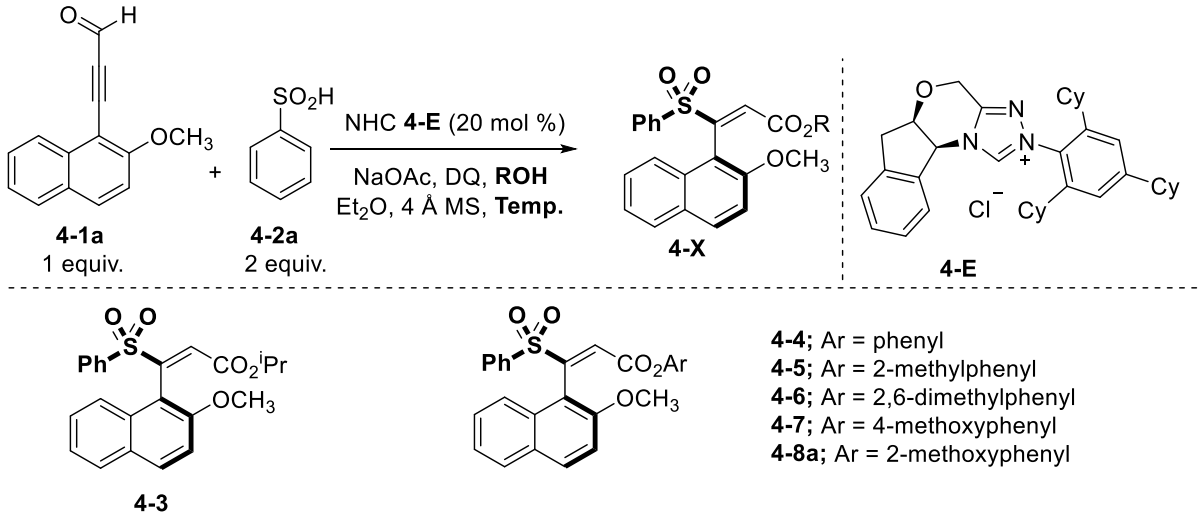


Entry	NHC	Yield (%)[b]	e.r.[c]
1	**4-B**	40	78:22
2	**4-C**	22	83:17
3	**4-D**	37	85:15
4	**4-E**	**40**	**87:13**
5	**4-F**	29	60:40
6	**4-G**	10	76:24
7	**4-H**	63	52:48

[a]Standard reaction condition: **4-1a** (0.05 mmol), **4-2a** (0.1 mmol), **NHC** (20 mol%), NaOAc (0.15 mmol), DQ (0.1 mmol), [i]PrOH (0.055 mmol) and Et_2O (1 mL). [b]Yield was determined by ^{1}HNMR analysis with 1,3,5-trimethoxybenzene as the internal standard. [c]The e.r. was determined via chiral-phase HPLC analysis

To our surprise, both yield and the e.r. value had elevated slightly (Table 4.4, entry 1). When aromatic alcohols (Table 4.4, entries 2-6) were added to the reaction mixture, in most of the cases, a sharp increase in the yield of the desired product was observed. Among various aromatic alcohols, 2-methoxyphenol behaved as the most suitable one for the reaction, affording the product in 97% yield with >99:1 e.r. and 50:1 E/Z value (Table 4.4, entry 6).

Table 4.4 Screening of alcohol, temperature, and the amount of catalyst loading [a, b]



Entry	ROH	Temp. (°C)	4-X (Yield%)	e.r.	E/Z
1	[i]PrOH	0	**4-3** (48)	91:9	>99:1
2	phenol	0	**4-4** (90)	86:14	30:1
3	2-methylphenol	0	**4-5** (91)	83:17	>99:1
4	2,6-dimethylphenol	0	**4-6** (65)	84:16	>99:1
5	4-methoxyphenol	0	**4-7** (97)	>99:1	15:1
6	2-methoxyphenol	0	**4-8a** (97)	>99:1	50:1
7[c]	2-methoxyphenol	-20	**4-8a** (93)	>99:1	>99:1

8[d]	**2-methoxyphenol**	**-20**	**4-8a (94)**	>99:1	**>99:1**
9[e]	2-methoxyphenol	0	**4-8a** (78)[f]	>99:1	>99:1

[a]Standard reaction condition: **4-1a** (0.1 mmol), **4-2a** (0.2 mmol), NHC **4-E** (20 mol%), NaOAc (0.3 mmol), DQ (0.2 mmol), ROH (0.11 mmol) and Et_2O (2 mL). [b]Isolated yield. The e.r. was determined via chiral-phase HPLC analysis. The E/Z value was calculated using ^{1}HNMR analysis. [c]Reaction was performed at -20 °C for 3 days. [d]5 mol% catalyst was loaded, and reaction was continued for 6 days. [e]1 mol% catalyst was loaded, and reaction was done at 0 °C for 10 days. [d]Isolated yield based on recycle of starting material.

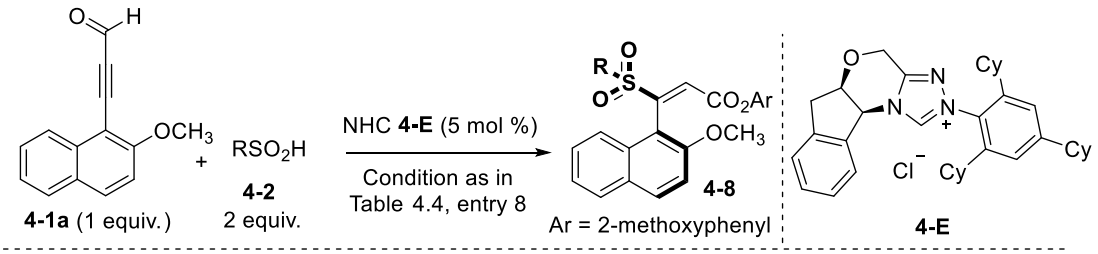
Further improvement was obtained in the E/Z value with lowering down the temperature to -20 °C. For the practicality purpose of scale-up synthesis, a few experiments on the amount of the catalyst loading (**4-E**) were carried out. It was found that the catalyst loading could be reduced up to 1 mol% without affecting the enantioselectivity and E/Z value (Table 4.4, entries 9), although the yield was severely lowered down in case of 1 mol% catalyst loading (Table 4.4, entry 9). After extensive screenings, we found out the optimized conditions. In presence of 5 mol% NHC **4-E** at -20 °C temperature, the desired product was afforded in 94% isolated yield with > 99:1 e.r. and >99:1 E/Z where Et_2O, NaOAc were the solvent and the base, respectively (Table 4.4, entry 8).

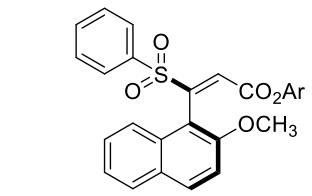
4.2.2 Substrate scope

With optimized reaction conditions in hand, we assessed the generality of our reaction. We first examined the substate scope of various aromatic and alkyl sulfinic acids by using **4-1a** as the model substrate. The substrate scope of sulfinic acids is shown in Table 4.5. Both electron-donating and electron-withdrawing groups (Me, CF_3, CN, halogens) in the *para*-position of the phenyl ring are well tolerated and provided the desired products (**4-8a** to **4-8g**) in excellent yields and optical purities. Replacement of phenyl ring by heteroaryl group (thiophenyl, **4-8h**) had also little effect on the outcome. Notably, although alkyl sulfinic acids were compatible with this catalytic system, they were giving the proposed products (**4-8i-j**) in much less E/Z value.

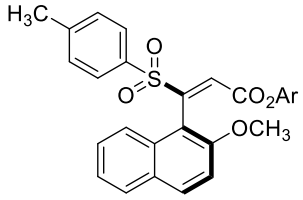
With **4-2a** as the model substrate, we next explored the substrate scope of alkynyl aldehydes **4-1**. The substrate scope of various alkynyl aldehydes is shown in Table 4.6. To our delight, a wide range of electron-donating, as well as electron-withdrawing groups (OMe, OBn, OEt, Br, Cl, etc.) in the different position (2-, 3-, 6-, 7-) of the alkynyl aldehydes performed well, affording the corresponding adducts in moderate to excellent yields and enantioselectivities. Point to note, alkynyl aldehydes containing either 6-substituted CN or CO_2Me group afforded the products in much less yields and e.r. values. This phenomenon may cause due to the low

Table 4.5 Variation in sulfinic acid [a, b]

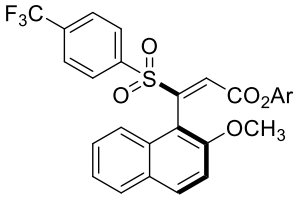




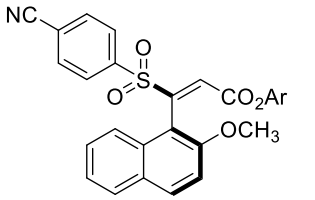
4-8a; 91%, >99:1 e.r., E/Z > 99:1



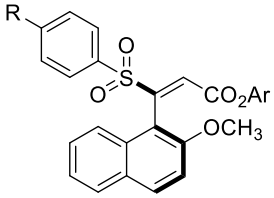
4-8b; 87%, >99:1 e.r., E/Z > 99:1



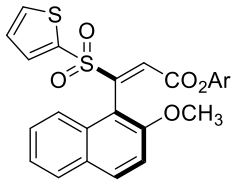
4-8c; 98%, 87:13 e.r., E/Z >60:1[c]



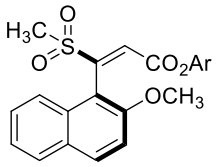
4-8d; 96%, 93:7 e.r., E/Z >60:1[c]



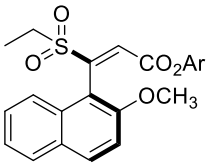
4-8e; R = F, 75%, 98:2 e.r., E/Z > 99:1[d]
4-8f; R = Cl, 77%,>99:1 e.r., E/Z > 99:1[c]
4-8g; R = Br, 85%, >99:1 e.r., E/Z >30:1[c]



4-8h; 99%, 98:2 e.r. E/Z > 60:1



4-8i; 90%, 93:7 e.r., E/Z = 5:1

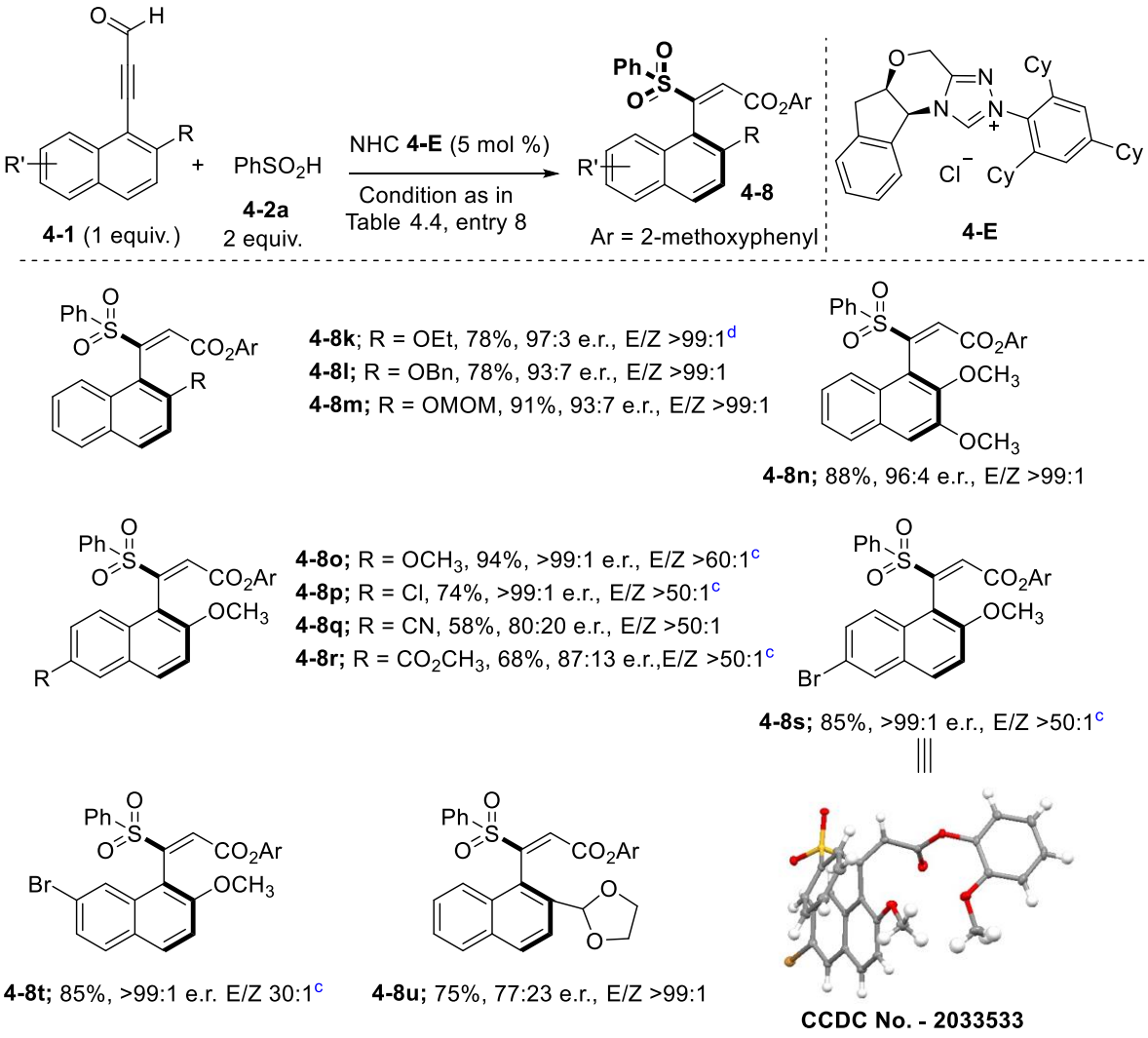


4-8j; 83%, 93:7 e.r., E/Z = 25:1

[a]Standard reaction condition: **4-1a** (0.1 mmol), **4-2** (0.2 mmol), NHC **4-E** (5 mol%), NaOAc (0.3 mmol), DQ (0.2 mmol), ROH (0.11 mmol) and Et_2O (2 mL), -20 °C for 3 days. [b]Isolated yield. The e.r. was determined via chiral-phase HPLC analysis. The E/Z value was calculated using ^{1}HNMR analysis. [c]20 mol% catalyst was used. [d]The reaction was continued for 9 days.

solubility of these corresponding alkyne aldehydes in Et_2O. Another point to note, bulkier groups (OEt, OBn, OMOM) had a negative effect on the yield of the products (**4-8k**, **4-8l**, **4-8m**), with a slight effect on the enantioselectivity. In this context when acetal bearing alkynyl aldehyde **4-1u** was used to furnish the desired product, both yield and e.r. value dropped quite sharply.

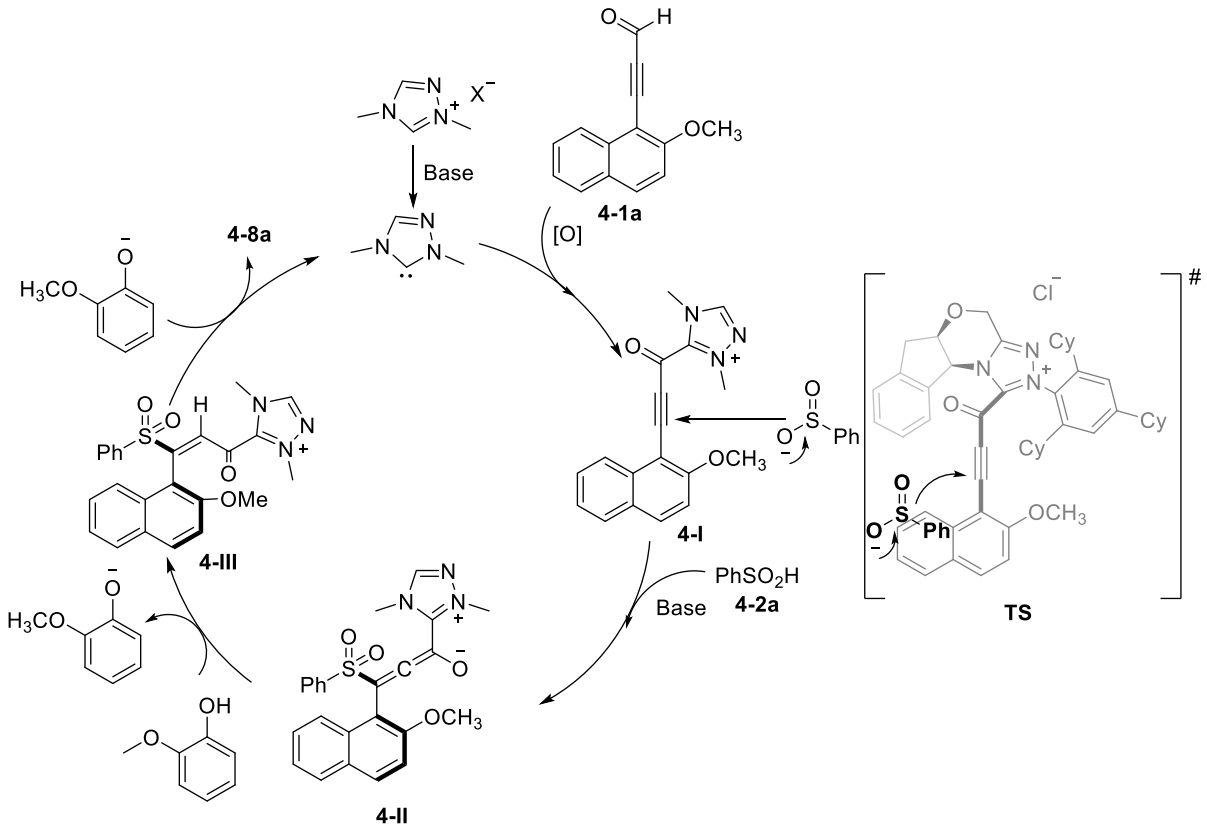
Table 4.6 Variation in aldehyde [a, b]



[a]Standard reaction condition: **4-1a** (0.1 mmol), **4-2a** (0.2 mmol), NHC **4-E** (5 mol%), NaOAc (0.3 mmol), DQ (0.2 mmol), ROH (0.11 mmol) and Et_2O (2 mL), -20 °C for 3 days. [b] Isolated yield. The e.r. was determined via chiral-phase HPLC analysis. The E/Z value was calculated using ^{1}HNMR analysis. [c]20 mol% catalyst was used. [d]The reaction was continued for 9 days.

4.2.3 Proposed reaction mechanism

Based on previous studies, a plausible catalytic cycle is disclosed in Scheme 4.5. First, free NHC was generated in the presence of the base (NaOAc). Then, the starting material **4-1a** was attacked by this free carbeen species, followed by an oxidation with the oxidant DQ, the alkynyl acyl azolium intermediate **4-I** was formed. Under the basic conditions, a sulfinate ion was produced from phenyl sulfinic acid (**4-2a**) and then, it coupled with the intermediate **4-I,** resulted in the formation of the intermediate **4-II.** Subsequently, a protonation of the intermediate **4-II** by 2-methoxyphenol occurred to generate the intermediate **4-III**. Finally, the esterification process by 2-methoxyphenoxide ion removed the NHC from the intermediate **4-III** and led to obtaining the corresponding product **4-8a** in an essentially one enantiomer with excellent yield (91%, >99:1, E/Z >99:1). The stereochemical-outcome of the product could be explained from the depicted **TS**.



Scheme 4.5 Proposed reaction pathway

4.3 Conclusion

In conclusion, we have developed an enantioselective general synthetic approach for access to atroposelective axially chiral styrene. Through this procedure, challenging axially chiral styrene with different substituents in 2-position of the alkyne aldehyde can be achieved in excellent yields and optical purities (up to 99% yield, >99:1 e.r., E/Z >99:1). Further study on reaction mechanism is an ongoing process in our lab.

4.4 Experimental section

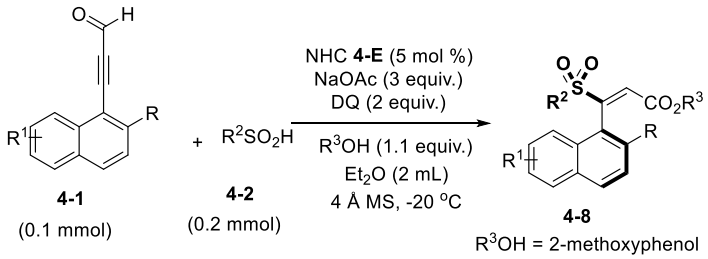
4.4.1 General information

Please refer to Chapter 2, Section 2.4.1

4.4.2 Synthesis of starting materials (4-1 and 4-2)

Alkynyl aldehydes and sulfinic acids were prepared according to previously published method.[40, 43]

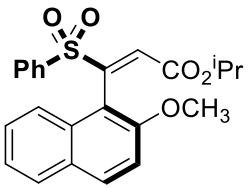
4.4.3 General Procedure: synthesis axially chiral styene



NHC **4-E** (2.86 mg, 5 mol%), alkynyl aldehyde **4-1** (0.1 mmol, 1 equiv), sulfinic acid **4-2** (0.2 mmol, 2 equiv.), NaOAc (25 mg, 3 equiv.), DQ (82 mg, equiv.), and 100 mg 4Å MS were added in a dry 10 mL Schlenk tube with stir bar. Then, the tube was evacuated using a pump and refilled with nitrogen (3 times). After that, 2-methoxyphenol (12.5 µL, 0.11 equiv.) was added to the reaction mixture. At the end, the reaction mixture was dissolved in dry Et_2O (2 mL) and allowed to stir for 3 days at -20 °C. After completion of the reaction (monitored by TLC), solvent was evaporated under vacuum and purified by column chromatography on silica gel with Hexane/EtOAc (20:1) as eluent to obtain the corresponding product **4-8**. The product

was confirmed by ^{1}H NMR, ^{13}C NMR spectra. The enantiomeric ratio (e.r.) was determined by chiral HPLC and E/Z value was determined by ^{1}H NMR analysis of the pure product.

4.4.4 Characteristization of products



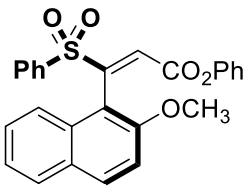
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.57 – 7.50 (m, 2H), 7.48 (s, 1H), 7.33 (ddd, *J* = 22.6, 13.3, 7.4 Hz, 4H), 7.01 (d, *J* = 9.1 Hz, 1H), 4.68 (hept, *J* = 6.2 Hz, 1H), 3.34 (s, 3H), 0.72 (d, *J* = 6.2 Hz, 3H), 0.65 (d, *J* = 6.2 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 163.2, 154.3, 151.2, 138.4, 133.7, 133.1, 131.8, 131.6, 129.6, 128.5, 127.8, 127.1, 124.8, 124.0, 113.0, 111.8, 68.7, 55.6, 21.2, 21.0 ppm.

HRMS (ESI, m/z): calculated for $C_{23}H_{22}O_5SH^+$: 411.1266 $(M+H)^+$, found: 411.1263.

$[\alpha]^{21}_D$ = -27.5 (c = 0.6 in $CHCl_3$).

HPLC analysis: 91:9 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 15.5 min, R_t (major) = 22.8 min.



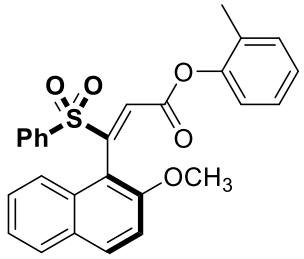
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.1 Hz, 1H), 7.73 (d, *J* = 10.4 Hz, 2H), 7.60 (dd, *J* = 12.2, 4.9 Hz, 3H), 7.57 – 7.50 (m, 1H), 7.42 – 7.34 (m, 3H), 7.34 – 7.28 (m, 1H), 7.16 (dt, *J* = 10.6, 2.1 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.70 – 6.61 (m, 2H), 3.35 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9, 154.3, 153.7, 150.1, 138.0, 133.9, 132.8, 132.1, 130.2, 129.7, 129.3, 128.6, 128.0, 127.4, 126.0, 124.6, 124.1, 121.0, 112.3, 111.8, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{26}H_{20}O_5SH^+$: 445.1110 $(M+H)^+$, found: 445.1110.

$[\alpha]^{21}_D$ = -19.4 (c = 2.0 in $CHCl_3$).

HPLC analysis: 86:14 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 19.1 min, R_t (minor) = 20.8 min.



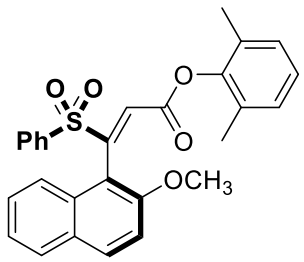
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.76 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.33 – 7.27 (m, 1H), 7.09 – 6.90 (m, 4H), 6.68 – 6.57 (m, 1H), 3.34 (s, 3H), 1.73 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 154.3, 153.4, 148.8, 138.0, 133.9, 132.9, 132.2, 131.1, 130.1, 129.9, 129.7, 128.6, 128.6, 128.0, 127.4, 126.8, 126.3, 124.7, 124.1, 121.4, 112.3, 111.8, 55.6, 15.8 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{22}O_5SH^+$: 459.1266 $(M+H)^+$, found: 459.1267.

$[\alpha]^{21}_D$ = -15.5 (c = 2.1 in $CHCl_3$).

HPLC analysis: 83:17 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 18.2 min, R_t (minor) = 22.5 min.



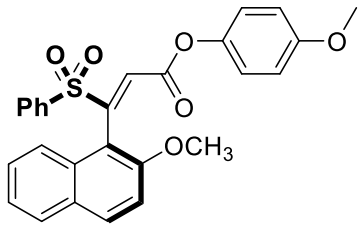
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.78 (s, 1H), 7.69 (dd, *J* = 12.1, 8.3 Hz, 2H), 7.64 – 7.58 (m, 2H), 7.55 (dd, *J* = 10.7, 4.3 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.33 – 7.27 (m, 1H), 6.97 (d, *J* = 9.1 Hz, 1H), 6.92 – 6.80 (m, 3H), 3.33 (s, 3H), 1.74 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 154.2, 153.2, 147.6, 138.0, 133.8, 133.0, 132.2, 130.0, 129.9, 129.8, 128.6, 128.5, 128.5, 127.9, 127.3, 126.0, 124.8, 124.1, 112.3, 111.6, 55.4, 15.9 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{24}O_5SH^+$: 473.1423 $(M+H)^+$, found: 473.1423.

$[\alpha]^{21}_D$ = -1.8 (c = 4.3 in $CHCl_3$).

HPLC analysis: 84:16 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 15.8 min, R_t (minor) = 18.4 min.



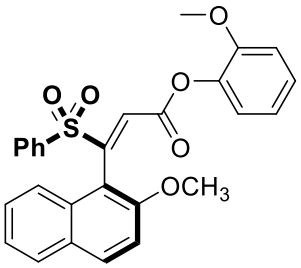
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.70 (s, 1H), 7.64 – 7.57 (m, 3H), 7.57 – 7.49 (m, 1H), 7.41 – 7.34 (m, 3H), 7.32 (ddd, *J* = 8.4, 8.0, 5.0 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.71 – 6.63 (m, 2H), 6.62 – 6.50 (m, 2H), 3.67 (s, 3H), 3.35 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 162.3, 157.4, 154.3, 153.5, 143.6, 138.1, 133.8, 132.8, 132.1, 130.3, 129.7, 128.6, 128.0, 127.4, 124.6, 124.1, 121.8, 114.8, 114.3, 112.4, 111.9, 55.7, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{22}O_6SH^+$: 475.1215 $(M+H)^+$, found: 475.1215.

$[\alpha]^{21}_D$ = -19.3 (c = 2.3 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 24.6 min, R_t (minor) = 25.8 min.



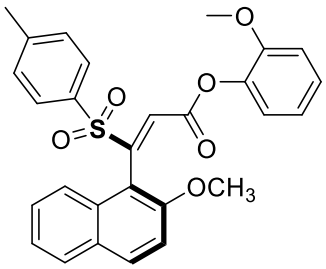
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.77 (s, 1H), 7.71 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.37 (ddd, *J* = 21.2, 11.2, 4.4 Hz, 3H), 7.32 – 7.26 (m, 1H), 7.04 (td, *J* = 8.2, 1.6 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 1H), 6.80 – 6.69 (m, 2H), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.49 (s, 3H), 3.36 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4, 154.5, 153.5, 150.9, 139.1, 138.1, 133.8, 132.9, 132.0, 130.0, 129.7, 128.6, 128.6, 127.9, 127.2, 127.1, 124.7, 123.9, 122.3, 120.6, 112.5, 112.3, 111.9, 55.7, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{22}O_6SH^+$: 475.1215 $(M+H)^+$, found: 475.1215.

$[\alpha]^{21}_D$ = -13.4 (c = 4.9 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 18.0 min, R_t (minor) = 23.0 min.



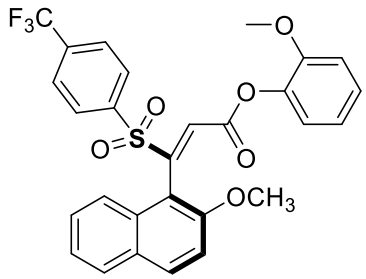
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.1 Hz, 1H), 7.73 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.33 (m, 1H), 7.29 (dd, *J* = 11.1, 3.8 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.03 (ddd, *J* = 12.4, 9.6, 5.3 Hz, 2H), 6.79 – 6.71 (m, 2H), 6.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.49 (s, 3H), 3.39 (s, 3H), 2.37 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4, 154.5, 153.8, 150.9, 144.9, 139.2, 135.0, 132.9, 131.9, 129.8, 129.5, 129.2, 128.6, 127.9, 127.1, 124.8, 123.9, 122.1, 120.6, 112.5, 112.0, 55.7, 55.6, 21.7 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{24}O_6SH^+$: 489.1372 $(M+H)^+$, found: 489.1372.

$[\alpha]^{21}_D$ = -8.5 (c = 3.7 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 22.5 min, R_t (minor) = 30.3 min.



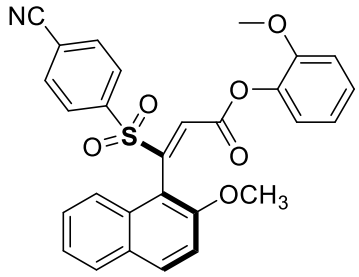
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.79 (m, 1H), 7.72 (dd, *J* = 8.2, 3.2 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.09 – 7.01 (m, 1H), 6.98 (d, *J* = 9.1 Hz, 1H), 6.82 – 6.69 (m, 1H), 6.63 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.48 (s, 1H), 3.34 (s, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 154.4, 152.5, 150.8, 141.6, 139.0, 135.4 (q, *J* = 33.0 Hz), 132.8, 132.4, 131.0, 130.3, 128.6, 128.0, 127.4, 127.2, 125.5 (q, *J* = 3.6 Hz), 124.6, 124.1, 122.2, 121.9, 120.6, 112.5, 111.8, 111.7, 55.6, 55.5 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{21}F_3O_6SH^+$: 543.1089 $(M+H)^+$, found: 543.1089.

$[\alpha]^{21}_D$ = -15.2 (c = 3.5 in $CHCl_3$).

HPLC analysis: 87:13 *e.r.* (Chiralpak AD-H, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 21.8 min, R_t (minor) = 29.4 min.



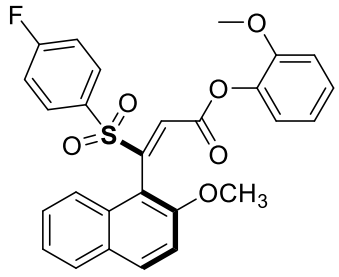
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.1 Hz, 1H), 7.80 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 3H), 7.41 (dd, *J* = 11.1, 4.1 Hz, 1H), 7.33 (dd, *J* = 11.0, 3.9 Hz, 1H), 7.09 – 7.02 (m, 1H), 6.99 (d, *J* = 9.1 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.48 (s, 3H), 3.40 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 154.4, 152.1, 150.8, 142.4, 138.9, 132.7, 132.6, 132.1, 131.3, 130.3, 128.7, 128.1, 127.5, 127.3, 124.5, 124.3, 122.2, 120.6, 117.3, 117.3, 112.5, 111.9, 111.6, 55.8, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{21}NO_6SH^+$: 500.1168 $(M+H)^+$, found: 500.1169.

$[\alpha]^{21}_D$ = +6.6 (c = 4.3 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 30:70 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 35.8 min, R_t (minor) = 39.8 min.



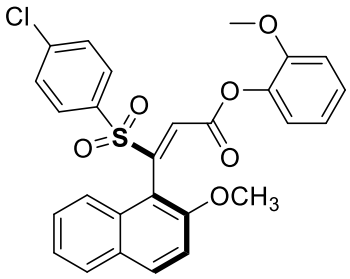
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.1 Hz, 1H), 7.76 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.40 (t, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.04 (ddd, *J* = 12.1, 8.8, 2.1 Hz, 4H), 6.81 – 6.70 (m, 2H), 6.64 (dd, *J* = 7.8, 1.3 Hz, 1H), 3.49 (s, 3H), 3.45 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 164.8, 161.3, 154.5, 153.1, 150.8, 139.1, 133.9 (d, *J* = 3.1 Hz), 132.8, 132.6 (d, *J* = 9.7 Hz), 132.2, 130.0, 128.6, 127.9, 127.2 (d, *J* = 11.5 Hz), 124.7, 124.0, 122.3, 120.6, 115.8 (d, *J* = 22.6 Hz), 112.5, 112.2, 111.9, 55.6, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{21}FO_6SH^+$: 493.1121 $(M+H)^+$, found: 493.1121.

$[\alpha]^{21}_D$ = -18.7 (c = 3.4 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 18.7 min, R_t (minor) = 22.8 min.



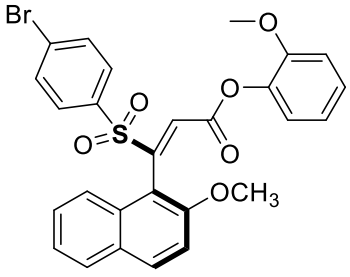
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.1 Hz, 1H), 7.76 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.46 – 7.37 (m, 1H), 7.31 (dd, *J* = 11.1, 4.7 Hz, 3H), 7.05 (td, *J* = 8.3, 1.6 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.81 – 6.69 (m, 2H), 6.64 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.49 (s, 3H), 3.41 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2, 154.4, 153.0, 150.8, 140.7, 139.1, 136.4, 132.8, 132.2, 131.2, 130.2, 128.8, 128.6, 128.0, 127.3, 127.2, 124.7, 124.1, 122.3, 120.6, 112.5, 112.0, 111.9, 55.7, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{21}ClO_6SH^+$: 509.0826 $(M+H)^+$, found: 509.0826.

$[\alpha]^{21}_D$ = +1.2 (c = 3.9 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 22.0 min, R_t (minor) = 28.3 min.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.1 Hz, 1H), 7.76 (s, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.48 – 7.37 (m, 3H), 7.33 (dd, *J* = 11.0, 3.9 Hz,

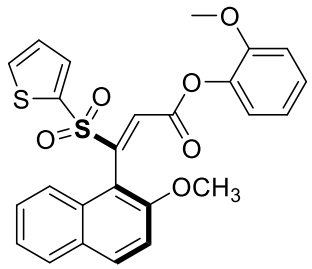
1H), 7.04 (ddd, *J* = 12.7, 9.6, 5.3 Hz, 2H), 6.85 – 6.70 (m, 2H), 6.64 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.49 (s, 3H), 3.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 154.4, 152.9, 150.8, 139.1, 137.0, 132.8, 132.2, 131.8, 131.2, 130.3, 129.3, 128.6, 128.0, 127.3, 127.2, 124.7, 124.1, 122.3, 120.6, 112.5, 112.0, 111.8, 55.7, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{21}BrO_6SH^+$: 553.0320 $(M+H)^+$, found: 553.0318.

$[\alpha]^{21}_D$ = +9.6 (c = 4.2 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 27.8 min, R_t (minor) = 39.1 min.



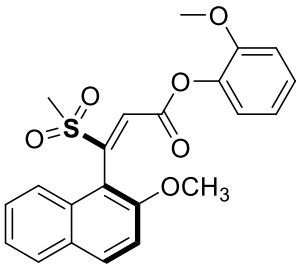
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 9.1 Hz, 1H), 7.76 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.61 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.33 – 7.26 (m, 2H), 7.10 (d, *J* = 9.1 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.95 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.81 – 6.68 (m, 2H), 6.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.57 (s, 3H), 3.48 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 155.2, 153.6, 150.9, 139.1, 138.8, 136.2, 135.5, 133.1, 132.2, 129.7, 128.6, 128.0, 127.8, 127.2, 127.1, 124.4, 123.9, 122.3, 120.6, 112.5, 112.2, 56.2, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{25}H_{20}O_6S_2H^+$: 481.0780 $(M+H)^+$, found: 481.0779.

$[\alpha]^{21}_D$ = -34.1 (c = 4.9 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 24.8 min, R_t (minor) = 29.3 min.



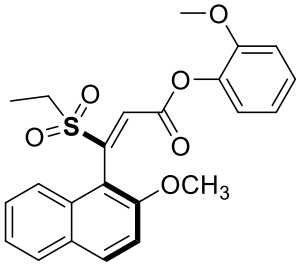
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.1 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.50 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 7.09 – 7.03 (m, 1H), 6.81 – 6.71 (m, 2H), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.95 (s, 3H), 3.49 (s, 3H), 2.94 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2, 154.5, 152.2, 150.8, 139.0, 133.0, 132.4, 130.6, 129.1, 128.1, 127.6, 127.2, 124.8, 124.4, 122.3, 120.6, 112.9, 112.8, 112.5, 56.8, 55.6, 40.6 ppm.

HRMS (ESI, m/z): calculated for $C_{22}H_{20}O_6SH^+$: 413.1059 $(M+H)^+$, found: 413.1058.

$[\alpha]^{21}_D$ = -54.3 (c = 3.7 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 25:75 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 25.8 min, R_t (minor) = 37.6 min.



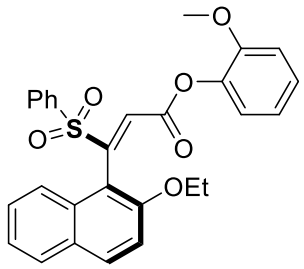
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.1 Hz, 1H), 7.82 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.63 (s, 1H), 7.51 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.0, 6.9, 1.0 Hz, 1H), 7.28 (d, *J* = 9.1 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.82 – 6.72 (m, 2H), 6.64 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.95 (s, 3H), 3.49 (s, 3H), 3.13 (dq, *J* = 14.8, 7.4 Hz, 1H), 3.02 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.40 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.2, 154.6, 151.1, 150.8, 139.0, 133.1, 132.3, 131.8, 129.1, 128.1, 127.5, 127.2, 125.0, 124.4, 122.3, 120.6, 113.1, 112.7, 112.5, 56.7, 55.6, 47.0, 6.4 ppm.

HRMS (ESI, m/z): calculated for $C_{23}H_{22}O_6SH^+$: 427.1215 $(M+H)^+$, found: 427.1211.

$[\alpha]^{21}_D$ = -38.2 (c = 2.0 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 23.6 min, R_t (minor) = 29.2 min.



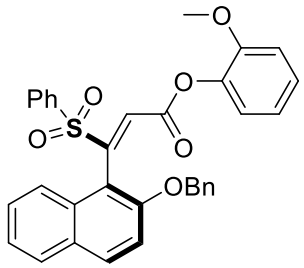
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 9.0 Hz, 1H), 7.74 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.52 (dd, *J* = 10.7, 4.3 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.31 – 7.26 (m, 1H), 7.05 (td, *J* = 8.2, 1.6 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 1H), 6.82 – 6.69 (m, 2H), 6.63 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.85 (tt, *J* = 7.0, 5.2 Hz, 1H), 3.57 – 3.45 (m, 4H), 1.10 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4, 154.2, 153.7, 150.9, 139.1, 138.2, 133.8, 132.9, 131.9, 129.9, 129.7, 128.6, 128.5, 127.8, 127.1, 127.0, 124.9, 123.8, 122.3, 120.6, 112.9, 112.5, 112.5, 64.2, 55.6, 14.8 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{24}O_6SH^+$: 489.1372 $(M+H)^+$, found: 489.1373.

$[\alpha]^{21}_D$ = -24.1 (c = 2.8 in $CHCl_3$).

HPLC analysis: 97:3 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 16.5 min, R_t (minor) = 20.7 min.



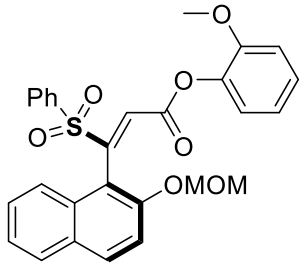
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (t, *J* = 4.5 Hz, 2H), 7.71 (dd, *J* = 8.3, 3.5 Hz, 2H), 7.55 – 7.46 (m, 2H), 7.46 – 7.36 (m, 2H), 7.35 – 7.25 (m, 4H), 7.20 (d, *J* = 6.4 Hz, 2H), 7.15 (dd, *J* = 8.1, 7.7 Hz, 2H), 7.04 (td, *J* = 8.2, 1.6 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 1H), 6.81 – 6.68 (m, 2H), 6.58 (dd, *J* = 7.9, 1.6 Hz, 1H), 4.82 (d, *J* = 12.2 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 3.43 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4, 153.9, 153.7, 150.9, 139.1, 137.8, 137.0, 133.7, 133.0, 132.0, 129.9, 129.6, 128.8, 128.6, 128.5, 127.9, 127.8, 127.2, 127.2, 126.8, 125.1, 124.1, 122.3, 120.6, 113.2, 112.9, 112.4, 70.4, 55.6 ppm.

HRMS (ESI, m/z): calculated for $C_{33}H_{26}O_6SH^+$: 551.1528 $(M+H)^+$, found: 551.1528.

$[\alpha]^{21}_D$ = -13.4 (c = 4.5 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 22.5 min, R_t (minor) = 26.8 min.



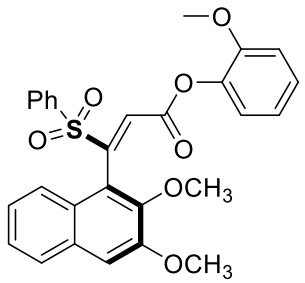
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 9.1 Hz, 1H), 7.77 (s, 1H), 7.74 – 7.67 (m, 1H), 7.62 – 7.57 (m, 2H), 7.53 (dd, *J* = 13.6, 7.4 Hz, 2H), 7.38 – 7.26 (m, 5H), 7.04 (td, *J* = 8.2, 1.6 Hz, 1H), 6.79 – 6.68 (m, 2H), 6.57 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 7.1 Hz, 1H), 3.46 (s, 3H), 3.30 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4, 153.2, 153.0, 150.8, 139.0, 138.0, 133.9, 132.7, 132.0, 130.1, 129.7, 129.1, 128.7, 127.9, 127.2, 127.0, 124.9, 124.3, 122.2, 120.6, 115.2, 113.3, 112.5, 94.9, 56.0, 55.5 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{24}O_7SH^+$: 505.1321 $(M+H)^+$, found: 505.1320.

$[\alpha]^{21}_D$ = -7.3 (c = 4.6 in $CHCl_3$).

HPLC analysis: 93:7 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 17.8 min, R_t (minor) = 20.2 min.



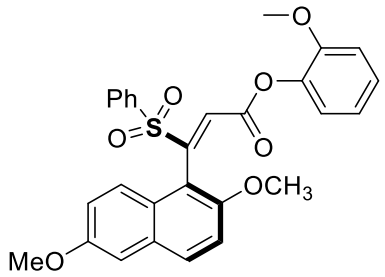
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (s, 1H), 7.68 – 7.63 (m, 2H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 2H), 7.26 (dd, *J* = 8.2, 5.4 Hz, 2H), 7.15 (s, 1H), 7.14 – 7.08 (m, 1H), 7.05 (td, *J* = 8.2, 1.6 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.63 (dd, *J* = 7.9, 1.5 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.49 (s, 3H) ppm.

^{13}C NMR (126 MHz, $CDCl_3$): δ 161.3, 154.4, 151.6, 150.8, 147.6, 139.0, 137.8, 134.1, 130.7, 129.6, 129.4, 128.9, 127.4, 127.2, 126.6, 125.2, 124.4, 122.3, 120.6, 119.2, 112.4, 109.7, 60.8, 55.7, 55.5 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{24}O_7SH^+$: 505.1321 $(M+H)^+$, found: 505.1315.

$[\alpha]^{21}_D$ = -41.0 (c = 1.3 in $CHCl_3$).

HPLC analysis: 96:4 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 21.0 min, R_t (minor) = 23.5 min.



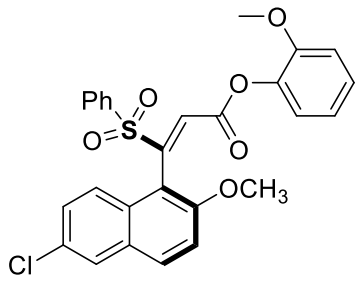
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (s, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.56 (ddd, *J* = 15.0, 9.4, 7.4 Hz, 4H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.05 (ddd, *J* = 11.6, 10.0, 2.5 Hz, 3H), 6.95 (d, *J* = 9.1 Hz, 1H), 6.82 – 6.70 (m, 2H), 6.65 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.85 (s, 3H), 3.53 (s, 3H), 3.32 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 156.3, 153.6, 153.0, 150.9, 139.2, 138.0, 133.8, 130.6, 129.8, 129.7, 129.6, 128.6, 128.3, 127.1, 126.3, 122.4, 120.6, 120.0, 112.6, 112.5, 112.5, 106.0, 55.8, 55.7, 55.4 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{24}O_7SH^+$: 505.1321 $(M+H)^+$, found: 505.1321.

$[\alpha]^{21}_D$ = -22.5 (c = 4.7 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 20:80 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 36.5 min, R_t (minor) = 38.5 min.



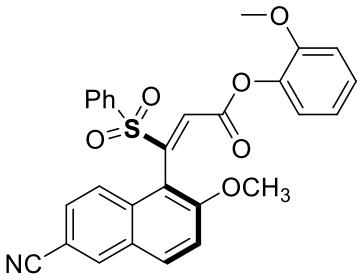
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.71 (dd, *J* = 10.8, 5.6 Hz, 2H), 7.64 – 7.52 (m, 4H), 7.41 – 7.35 (m, 2H), 7.33 (dd, *J* = 9.1, 2.2 Hz, 1H), 7.06 (ddd, *J* = 8.3, 7.5, 1.7 Hz, 1H), 7.01 (d, *J* = 9.1 Hz, 1H), 6.81 – 6.73 (m, 2H), 6.68 (dd, *J* = 7.9, 1.6 Hz, 1H), 3.53 (s, 3H), 3.34 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 154.6, 152.9, 150.8, 139.0, 137.8, 133.9, 131.2, 131.1, 130.1, 129.7, 129.1, 128.6, 128.0, 127.2, 126.6, 126.5, 122.3, 120.6, 113.0, 112.6, 112.5, 55.7, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{21}ClO_6SH^+$: 509.0826 $(M+H)^+$, found: 509.0827.

$[\alpha]^{21}_D$ = -5.2 (c = 0.1 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 21.5 min, R_t (minor) = 25.2 min.



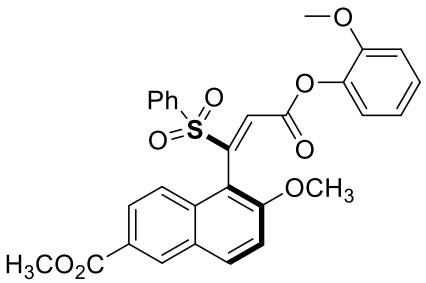
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.89 (d, *J* = 9.1 Hz, 1H), 7.78 (s, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 3H), 7.50 (dd, *J* = 8.9, 1.5 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.10 (dd, *J* = 17.4, 8.3 Hz, 2H), 6.79 (t, *J* = 7.7 Hz, 2H), 6.72 (d, *J* = 7.5 Hz, 1H), 3.54 (s, 3H), 3.41 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 156.8, 152.4, 150.7, 138.9, 137.7, 134.2, 134.1, 132.6, 130.5, 129.7, 128.8, 127.5, 127.3, 126.1, 122.2, 120.7, 119.3, 113.6, 112.5, 107.4, 55.9, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{28}H_{22}NO_6SH^+$: 500.1168 $(M+H)^+$, found: 500.1166.

$[\alpha]^{21}_D$ = -5.3 (c = 1.4 in $CHCl_3$).

HPLC analysis: 80:20 *e.r.* (Chiralpak AS-H, 25:75 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 52.3 min, R_t (major) = 66.2 min.



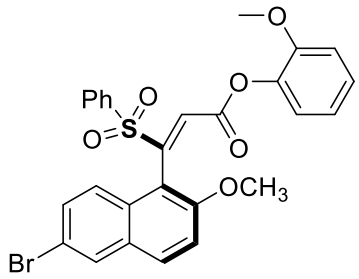
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 7.94 (d, *J* = 9.0 Hz, 2H), 7.78 (s, 1H), 7.71 – 7.48 (m, 4H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.06 (t, *J* = 8.7 Hz, 2H), 6.76 (t, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 7.6 Hz, 1H), 3.95 (s, 3H), 3.51 (s, 3H), 3.42 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 161.3, 156.4, 153.0, 150.8, 139.0, 137.9, 135.2, 134.0, 133.6, 131.2, 130.2, 129.7, 128.7, 127.6, 127.2, 126.5, 125.6, 124.9, 122.3, 120.6, 112.7, 112.5, 55.8, 55.7, 52.3 ppm.

HRMS (ESI, m/z): calculated for $C_{29}H_{24}NO_8SH^+$: 533.1270 $(M+H)^+$, found: 533.1271.

$[\alpha]^{21}_D$ = -40.0 (c = 0.3 in $CHCl_3$).

HPLC analysis: 87:13 *e.r.* (Chiralpak AD-H, 28:72 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 36.9 min, R_t (minor) = 43.1 min.



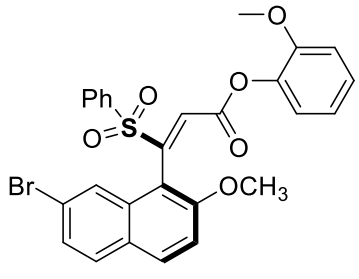
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.10, 155.37, 153.17, 150.71, 139.00, 137.75, 134.08, 133.71, 131.86, 130.10, 129.52, 129.44, 128.66, 127.23, 127.11, 126.81, 126.41, 122.21, 121.74, 120.52, 112.47, 112.38, 111.74, 55.92, 55.63 ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 154.7, 152.9, 150.8, 139.0, 137.8, 134.0, 131.4, 131.1, 130.4, 130.2, 129.8, 129.7, 129.6, 128.6, 127.2, 126.7, 122.3, 120.6, 117.8, 113.0, 112.7, 112.5, 55.7, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{21}BrO_6SH^+$: 553.0320 $(M+H)^+$, found: 553.0314.

$[\alpha]^{21}_D$ = -15.2 (c = 0.7 in $CHCl_3$).

HPLC analysis: 98:2 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 23.5 min, R_t (minor) = 26.7 min.



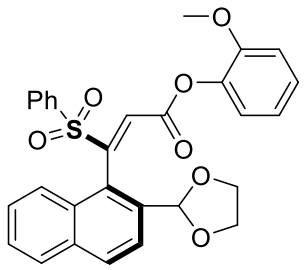
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (t, *J* = 4.5 Hz, 1H), 7.63 – 7.48 (m, 2H), 7.37 (q, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.12 – 7.00 (m, 1H), 6.85 – 6.67 (m, 1H), 3.56 (s, 1H), 3.48 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 155.5, 153.3, 150.8, 139.1, 137.8, 134.2, 133.8, 132.0, 130.2, 129.6, 129.5, 128.8, 127.3, 127.2, 126.9, 126.5, 122.3, 121.8, 120.6, 112.6, 112.5, 111.8, 56.0, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{27}H_{21}BrO_6SH^+$: 553.0320 $(M+H)^+$, found: 553.0320.

$[\alpha]^{21}_D$ = +19.5 (c = 4.9 in $CHCl_3$).

HPLC analysis: >99:1 *e.r.* (Chiralpak AD-H, 24:76 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (major) = 19.7 min, R_t (minor) = 21.4 min.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.7 Hz, 1H), 7.80 (s, 1H), 7.69 (dd, *J* = 11.1, 8.4 Hz, 2H), 7.52 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.49 – 7.40 (m, 1H), 7.37 – 7.19 (m, 4H), 7.13 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.02 (ddd, *J* = 8.2, 7.5, 1.7 Hz, 1H), 6.80 – 6.67 (m, 2H), 6.64 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.83 (s, 1H), 4.21 – 4.09 (m, 1H), 4.04 (ddd, *J* = 10.4, 7.1, 5.1 Hz, 1H), 4.00 – 3.89 (m, 2H), 3.50 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 154.0, 150.8, 139.1, 136.7, 135.6, 134.3, 133.3, 131.2, 130.6, 130.4, 129.8, 129.0, 127.9, 127.1, 126.3, 126.3, 125.5, 123.6, 122.4, 120.6, 112.5, 102.0, 65.8, 65.4, 55.7 ppm.

HRMS (ESI, m/z): calculated for $C_{29}H_{24}O_7SH^+$: 517.1321 $(M+H)^+$, found: 517.1318.

$[\alpha]^{21}_D$ = -18.0 (c = 3.9 in $CHCl_3$).

HPLC analysis: 77:23 *e.r.* (Chiralpak AD-H, 28:72 ^{i}PrOH/Hexane, 0.5 mL/min), R_t (minor) = 27.9 min, R_t (minor) = 34.2 min.

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