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Xiangyu Chen

New Strategies for N-Heterocyclic Carbenes Catalyzed Annulations

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Xiangyu Chen

New Strategies for N-Heterocyclic Carbenes Catalyzed Annulations

Doctoral Thesis accepted by
Institute of Chemistry, Chinese Academy of Sciences,
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Springer

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Supervisor's Foreword

Due to the population of cyclic motifs in pharmaceuticals and natural products, the construction of cyclic molecules is an important topic in organic synthesis. N-heterocyclic carbenes can catalyze various reactions under mild reaction conditions for the rapid construction of cyclic compounds. This thesis focuses on N-heterocyclic carbenes-catalyzed cyclization of nitroalkenes, enals, and α,β-unsaturated carboxylic acids.

(I) It demonstrated that NHC was a powerful catalyst for the [4+2] annulation of β-substituted nitroalkenes with α,β-unsaturated ketones. The scope of Rauhut–Currier reaction was successfully extended to the most challenging β-substituted alkenes by this method.

(II) The NHC-catalyzed [4+2] annulation of enals, having a γ leaving group, with azodicarboxylates by γ addition was developed. This strategy provided a more convenient and easier way to access dihydropyridazinones. Tetrahydropyridazinones and γ-amino acid derivatives could be easily prepared by subsequent transformations of the resulting dihydropyridazinones.

(III) NHC was for the first time proved to be a powerful catalyst to generate α,β-unsaturated acyl azolium from α,β-unsaturated carboxylic acids for annulations with amino ketones and ketimines, giving a range of N-heterocycles in good yields with high to excellent enantioselectivities.

Beijing, China
November 2016

Prof. Song Ye

Parts of this thesis have been published in the following journal articles:

1. Chen X-Y, Sun L-H, Ye S* (2013) N-Heterocyclic Carbene Catalyzed [4+2] Cycloaddition of Nitroalkenes with Oxodienes. Chem Eur J 19:4441–4445. (Reproduced by permission of John Wiley & Sons Ltd)

2. Chen X-Y, Xia F, Cheng J-T, Ye S* (2013) Highly Enantioselective γ-Amination by N-Heterocyclic Carbene Catalyzed [4+2] Annulation of Oxidized Enals and Azodicarboxylates. Angew Chem Int Ed 52:10644–10647. (Reproduced by permission of John Wiley & Sons Ltd)

3. Chen X-Y, Gao Z-H, Song C-Y, Zhang C-L, Wang Z-X*, Ye S* (2014) N-Heterocyclic Carbene Catalyzed Cyclocondensation of α,β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives. Angew Chem Int Ed 53:11611–11615. (Reproduced by permission of John Wiley & Sons Ltd)

Contents

Abbreviations

Bn	Benzyl
Boc	*t*-butoxycarbonyl
Bu	Butyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	Diethyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMAP	N,N-4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereoselective ratio
EA	Ethyl Acetate
equiv.	Equivalent
Et	Ethyl
i-Bu	*i*-butyl
i-Pr	*i*-propyl
LG	Leaving Group
Me	Methyl
Mes	2,4,6-trimethylphenyl
MS	Molecular Sieves
MTsCl	2-mesitylenesulfonyl chloride
n-Bu	*n*-butyl
NHC	N-Heterocyclic Carbenes
OTf	Triflate
PE	Petroleum Ether
PG	Protective Group
Ph	Phenyl
Piv	Pivaloyl
PNBC	*p*-nitrobenzoyl chloride
RT	Room Temperature

TBS	*t*-butyldimethylsilyl
t-Bu	*t*-butyl
TEA	Triethylamine
TFAA	Trifluoroacetic Anhydride
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
Ts	*p*-toluenesulfonyl

Chapter 1
Introduction

1.1 NHC-Catalyzed Annulations Via Homoenolates

1.1.1 Generation Via α,β-Unsaturated Aldehydes for Construction of Heterocycles

Carbenes possessing a bivalent carbon atom with two nonbonding electrons are considered as highly reactive intermediates, and their isolation has been a challenge for a long time. The synthesis of stable imidazolium carbenes was realized by Arduengo and co-workers in 1991 [1]. Independently, the synthesis of phosphinocarbene was reported by Bertrand and co-workers in 1988 [2]. Today, the organocatalytic reactions using carbenes are dominated by triazolium carbenes, the synthesis of which was first described by Enders and co-workers in 1995 [3].

The first example of a N-heterocyclic carbene-catalyzed reaction can date back to 1943, Ukai and co-workers initially reported the thiazolium salts-catalyzed benzoin reaction of aldehydes [4]. In 1958, a breakthrough was made by Breslow and co-workers, they proposed a mechanistic explanation that the thiazolium carbene is generated from the thiazolium salt in the presence of a base, as the catalytically active species to generate the Breslow intermediate **1.2** by the addition of aldehyde **1.1** (Fig. 1.1) [5]. In early 1970s, Stetter and co-workers successfully realized Michael addition of aldehyde via "acyl anion" [6]. Since then, a series of reactions of aldehydes catalyzed by NHC, such as the Stetter reaction and the benzoin reaction, has been well established [7–11].

In 2004, Bode et al. [12] and Glorius et al. [13] independently reported the pioneering work of NHC-catalyzed [3+2] annulation reaction of enals via homoenolate equivalents. The reaction was tolerable for the aromatic aldehydes under the imidazolium salt (**cat.1a**) conditions, giving the corresponding γ-butyrolactones in good yields (Fig. 1.2). After that, NHCs were found to be efficient catalysts for various annulations involving α,β-unsaturated aldehydes. The

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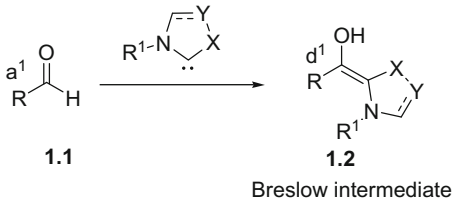
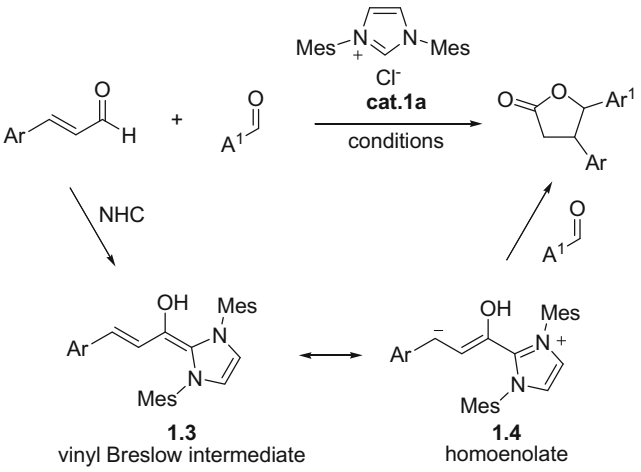


Fig. 1.1 NHC-catalyzed generation of Breslow intermediate



Bode's conditions: cat. (8 mol%), DBU (7 mol%), THF/*t*-BuOH, RT
Glorius' conditions: cat. (5 mol%), *t*-BuOK (10 mol%), THF, RT

Fig. 1.2 NHC-catalyzed [3+2] annulations of enals with aldehydes

conjugate umpolung of α,β-unsaturated aldehydes via homoenolate equivalents opened a new access for the annulation reactions catalyzed by NHC.

In 2006, Nair et al. [14] developed a method for the NHC-catalyzed [3+2] annulation of enals with 1,2-diketones and isatins for the synthesis of spirocyclic oxindole-γ-lactone derivatives (Fig. 1.3a). The enantioselective version was successfully developed by Ye and co-workers in 2011 (Fig. 1.3b) [15]. Later on, Scheidt and co-workers developed an N-heterocyclic carbene/Lewis acid strategy for accessing these spirocyclic structures (Fig. 1.3c). A series of substrates worked well affording desired products with quaternary carbon centers in good yields with high ee [16].

In further investigations, this concept was extended to generate γ-butyrolactones bearing quaternary stereocentres by Glorius and co-workers [17] and You and co-workers [18]. Several electron-deficient ketones as electrophiles worked well under their conditions (Fig. 1.4).

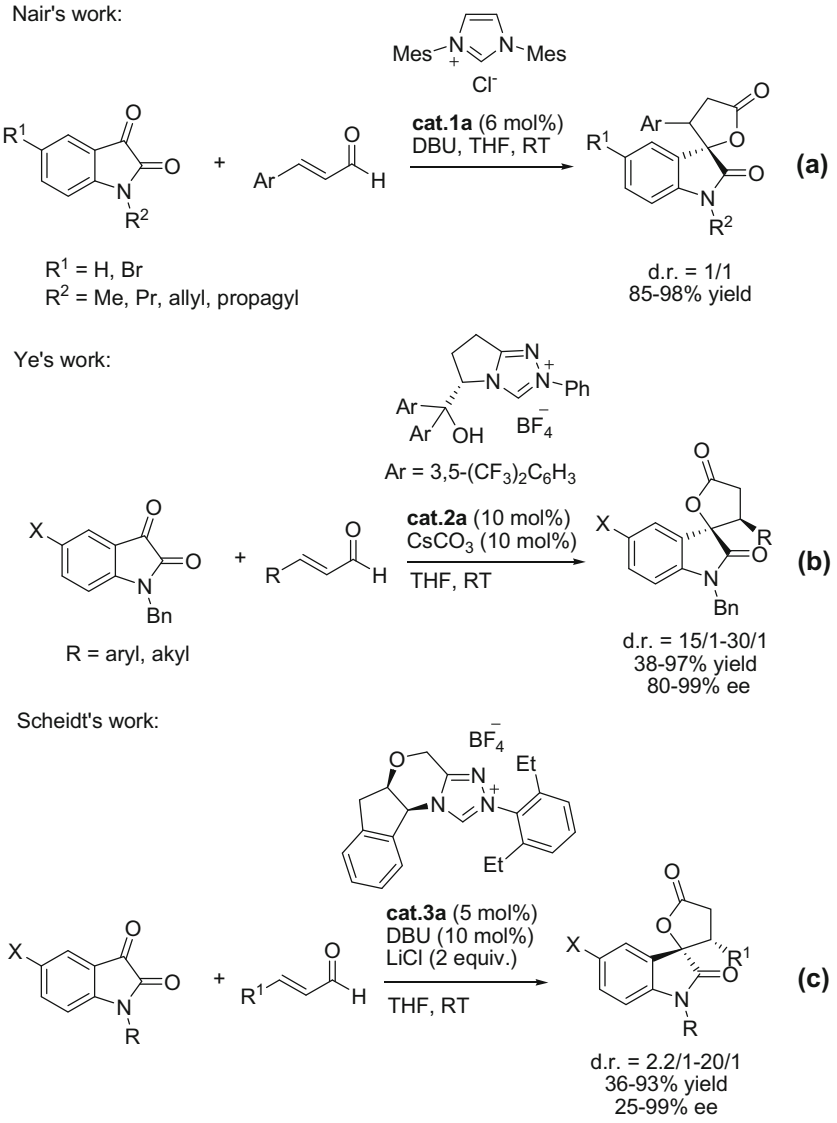


Fig. 1.3 NHC-catalyzed [3+2] annulations of enals with isatins

Employing a similar strategy, Bode and co-workers developed a variation on the reaction system via condensation of imines and homoenolates [19]. Various γ-lactams were constructed in good yields (Fig. 1.5).

The simultaneous use of acid with an NHC is a real challenge. A major breakthrough was made in 2011, Rovis and co-workers introduced the Bronsted acids/NHC co-catalysis, which opens new opportunities for NHC catalysis. They

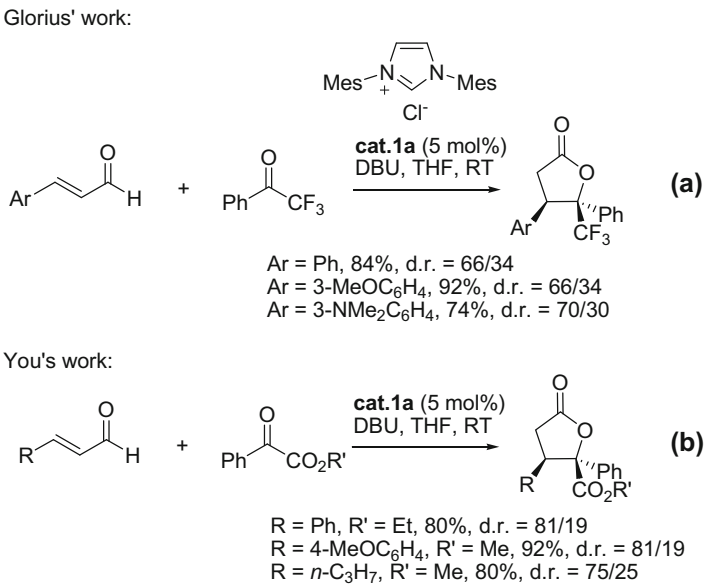


Fig. 1.4 NHC-catalyzed [3+2] annulations of enals with ketones

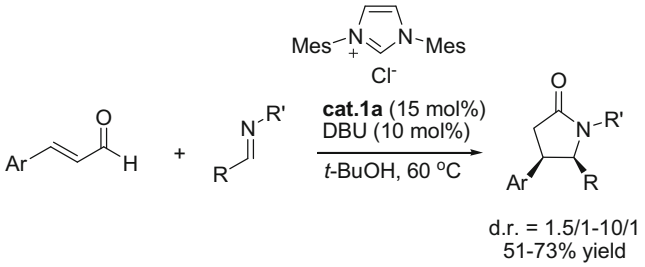


Fig. 1.5 NHC-catalyzed [3+2] annulations of enals with imines

found that the use of the NHC precursor triazolium salt **cat.4a** with catalytic amount of carboxylate **1.6** could activate the imines, improving the enantioselectivity and yield of the reaction (Fig. 1.6) [20].

It's well known that NHCs are good ligands for metals. It's interesting that Scheidt and co-workers reported that the NHC precursor triazolium salt **cat.3a** in combination with catalytic amount of $Mg(O\textit{t}\text{-}Bu)_2$ could afford *cis*-γ-lactams in good to excellent yields and ee via homoenolates (Fig. 1.7) [21].

Besides aldehydes, ketones, imines, NHCs are also powerful catalysts for [3+n] annulations of enals with other electrophiles via homoenolate. For example, Scheidt and co-workers developed NHC-catalyzed [3+2] annulations of enals and

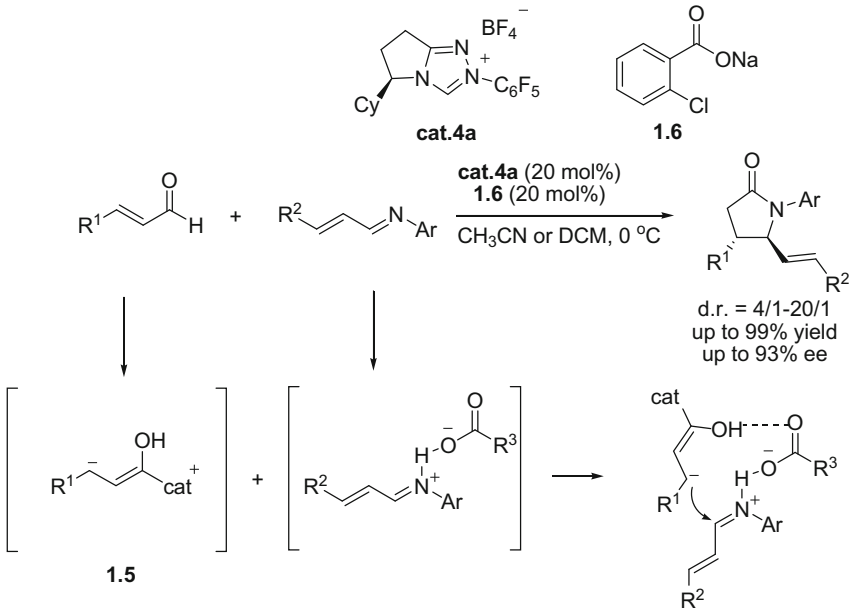


Fig. 1.6 Bronsted acids/NHC co-catalysis for the synthesis of *trans*-γ-lactams

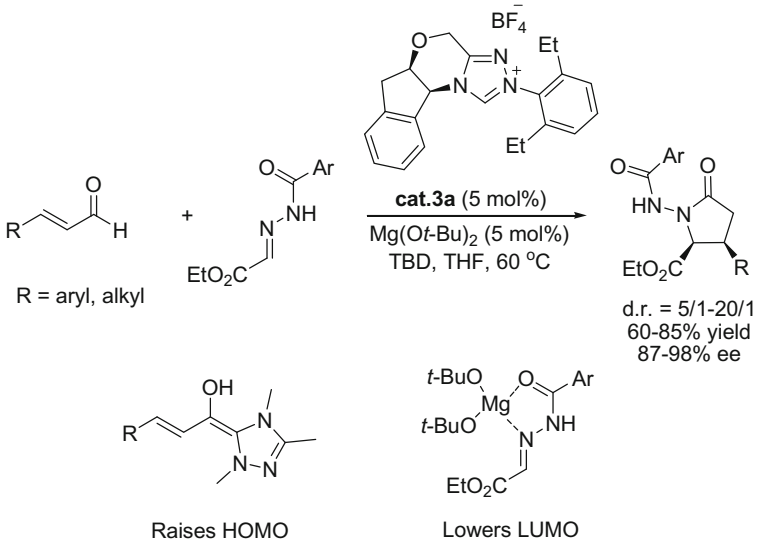


Fig. 1.7 Lewis acids/NHC co-catalysis for the synthesis of *cis*-γ-lactams

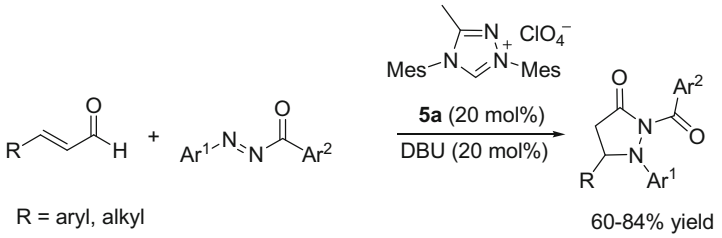


Fig. 1.8 NHC-catalyzed [3+2] annulations of enals with azodicarboxylates

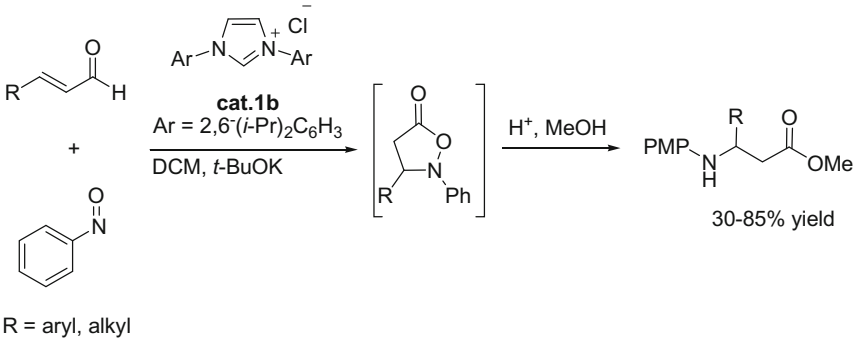


Fig. 1.9 NHC-catalyzed [3+2] annulations of enals with nitroso compounds

azodicarboxylates, giving the corresponding pyrazolidinone products in good yields (Fig. 1.8) [22].

In the same year, The NHC **cat.1b** was demonstrated to be an efficient catalyst for the reaction of enals and nitroso compounds by Ying and co-workers (Fig. 1.9) [23].

The highly selective [3+3] annulation reaction of enals with azomethine imines catalyzed by N-heterocyclic carbenes was also demonstrated by Scheidt and co-workers. The corresponding bicyclic heterocycles were constructed in good yields with excellent diastereoselectivity under the catalysis of **cat.1c** (Fig. 1.10) [24].

Subsequent to these previous reports, Ye et al. [25] and Scheidt et al. [26] independently reported the [3+4] annulations of enals with o-quinone methides (Fig. 1.11).

1.1.2 Generation Via α,β-Unsaturated Aldehydes for Construction of All Carbon Cycles

Furthermore, the homoenolate equivalent could be extended to construct all carbon cycles via homoenolate/enolate domino reactions. In 2006, Nair and co-workers

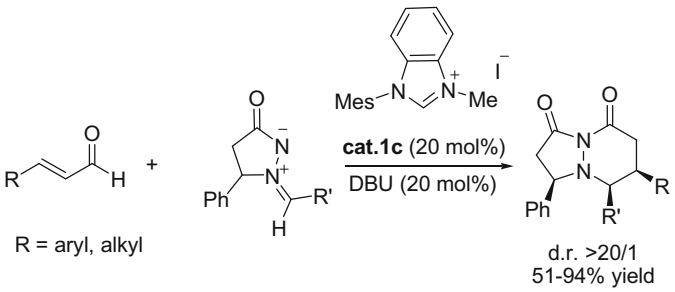


Fig. 1.10 NHC-catalyzed [3+3] annulations of enals with azomethine imines

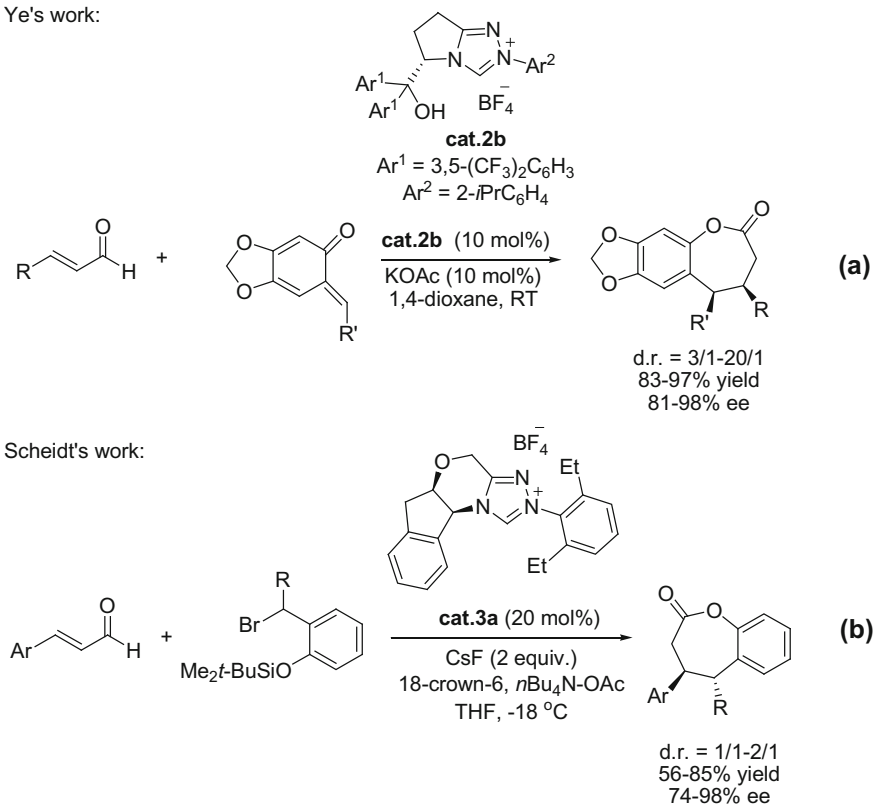


Fig. 1.11 NHC-catalyzed [3+4] annulations of enals

pioneered the NHC-catalyzed [3+2] annulation of enals and chalcones, diverse cyclopentenes were afforded via this method [27]. The key steps was shown in Fig. 1.12, the Michael addition of homoenolate to chalcone gave adduct **1.7**,

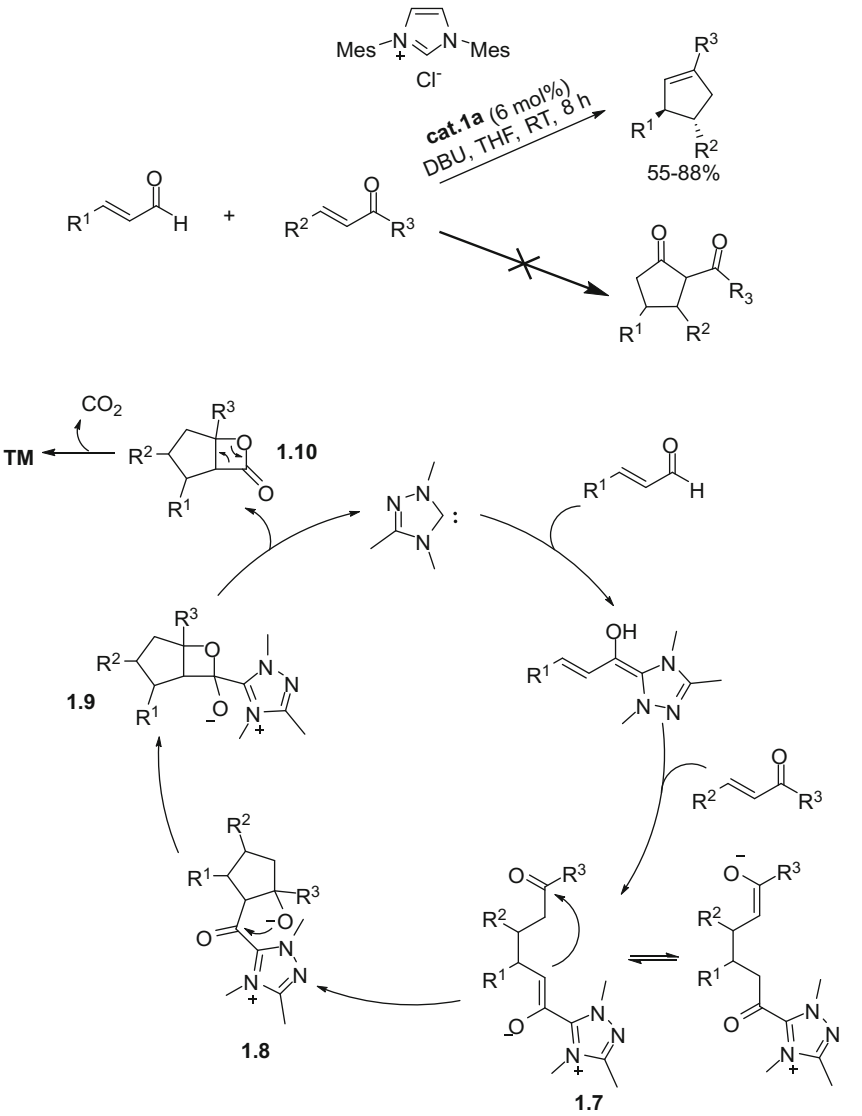


Fig. 1.12 The domino homoenolate/enolate annulations

followed by intramolecular aldol reaction with the activated carbonyl group. The delivered adduct **1.9** led to a β-lactonization and regenerated the catalyst. The decarboxylation of unstable β-lactone **1.10** gave the final cyclopentene via releasing an equivalent of CO_2.

The enantioselective annulation of 4-oxoenones with enals was successfully developed by Bode and co-workers. In the presence of NHC **cat.3b**, the

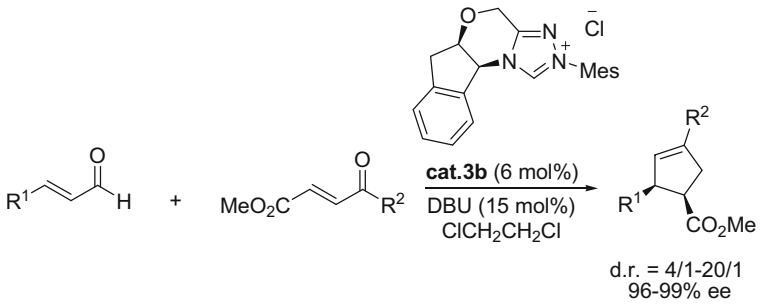


Fig. 1.13 Enantioselective synthesis of *cis*-cyclopentenes

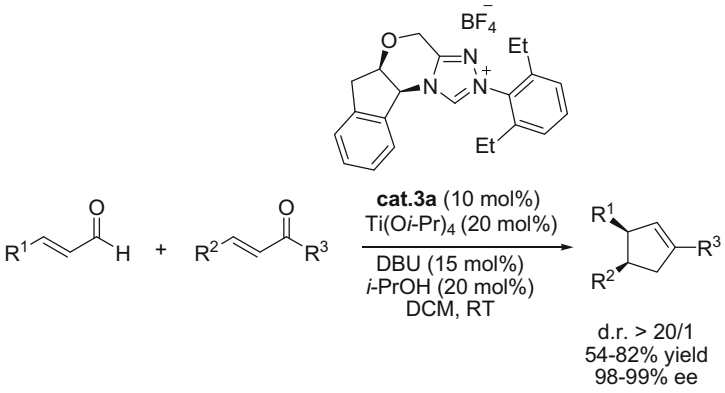


Fig. 1.14 Enantioselective synthesis of *cis*-cyclopentenes

cis-cyclopentenes were afforded in good yields with high ee and good dr (Fig. 1.13) [28].

Later, Scheidt and co-workers further improved this method and they found the use of Ti(O*i*-Pr)$_4$ together with NHC could achieve better results on both the tolerance of substrate scopes and stereoselectivity. Interestingly, in contrast to Nair's work, the *cis* diastereomer was afforded by utilizing cooperative catalysis of NHC and a Lewis acid (Fig. 1.14) [29].

1.1.3 Generation Via Saturated Esters for Construction of Heterocycles

In 2013, Chi and co-workers presented that the homoenolate intermediates could be generated via saturated esters [30]. The β-sp^3 carbon of saturated esters was

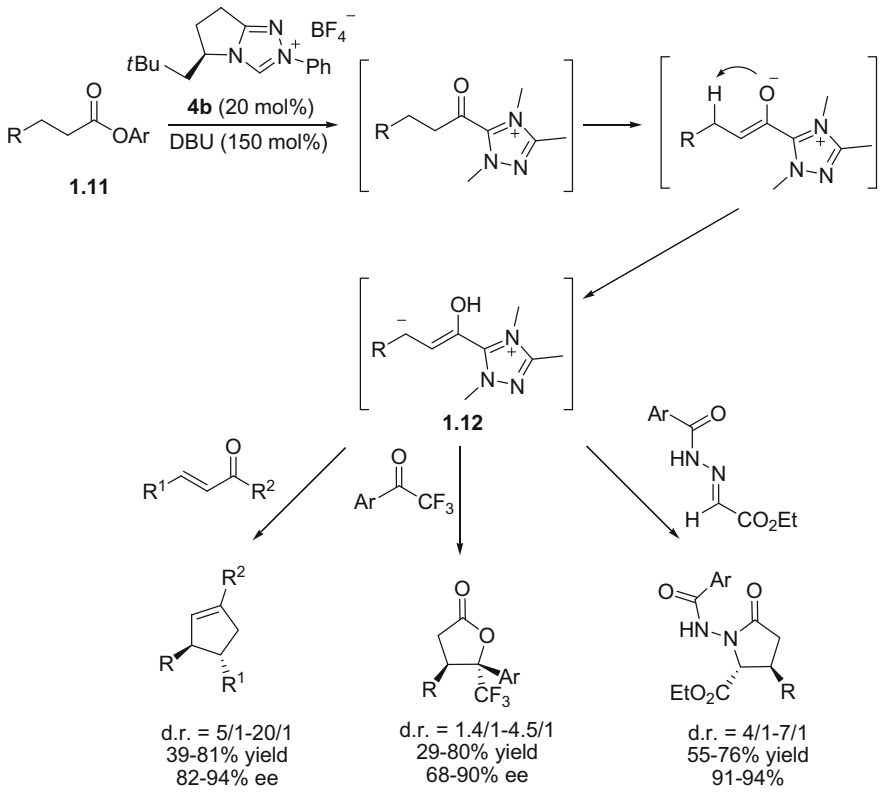


Fig. 1.15 Homoenolate intermediates generated from saturated esters

successfully used as nucleophiles. They showed that the reactions with saturated esters are somehow superior to those with enals. Both enones and imines worked well under their conditions (Fig. 1.15).

1.2 NHC-Catalyzed Annulations Via Azolium Enolates

1.2.1 Generation Via Ketenes

Ketenes, which have adjoining carbon–carbon and carbon–oxygen double bonds, become one of the most powerful reagents in organic synthesis. Catalytic enantioselective annulations of ketenes have been intensively investigated in the past several decades [31–35].

The synthesis of β-lactam motifs has attracted great interest due to their extensive bioactivities. The Staudinger ketene/imine [2+2] annulation provided an

alternative way to construct the β-lactams. In 2008, Ye et al. [36] and Smith et al. [37] independently developed the NHC-catalyzed enantioselective [2+2] annulation of ketenes with imines to afford the β-lactams. Ye and co-workers demonstrated the use of the triazolium precatalyst from L-pyroglutamic acid **cat.6a** could achieve better diastereo- and enantioselectivities (Fig. 1.16).

Later, Ye and co-workers developed aldehydes as electrophiles for the related [2+2] annulations with ketenes. A series of β-lactones was synthesized in good yields with excellent diastereo- and enantioselectivities [38]. The method was then expanded to reactions with ketones. Trifluoromethyl ketones [39] and isatins [40] were found to be appropriate electrophiles, giving β-lactones in good yields with excellent diastereo- and enantioselectivities (Fig. 1.17).

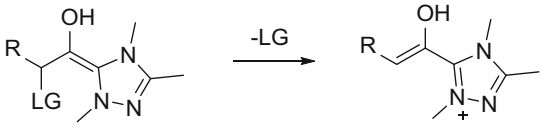
In 2011, the strategy was successfully extended to [2+3] annulations. In the presence of NHC precursor **cat.6c**, the annulation of oxaziridine with ketenes gave the corresponding [2+3] annulation product in good yield and with good diastereoselectivity and high enantioselectivity. Interestingly, the enantioselectivity could be switched when NHC precursor **cat.2b**, containing a free hydroxy group, was employed (Fig. 1.18) [41].

The [2+4] annulation reactions of ketenes are proven to be efficient approaches to six-membered heterocycles. In 2008, Ye and co-workers demonstrated that the acyl azolium enolates could undergo [2+4] annulations with enone in the presence of NHC precursor **cat.6a** (Fig. 1.19) [42].

Later, they expanded the ability of azolium enolate from ketenes to construct oxadiazin-6-ones when *N*-benzoyldiazenes was employed as electrophilic component. Interestingly, NHC precursors **cat.6a** and **cat.2c** could give opposite enantioselectivities. The authors proposed that the triazolium salt **cat.2c**, bearing a free hydroxy group, plays a role in switching the enantioselectivity (Fig. 1.20) [43].

1.2.2 Generation Via Functionalized Aldehydes

α-Functionalized aldehydes were another intensely studied precursor to generate the azolium enolate. It is proposed that after addition of NHC to the α-functionalized aldehydes, the azolium enolate species could be afforded via sequential elimination of the leaving group (Eq. 1.1) [44].



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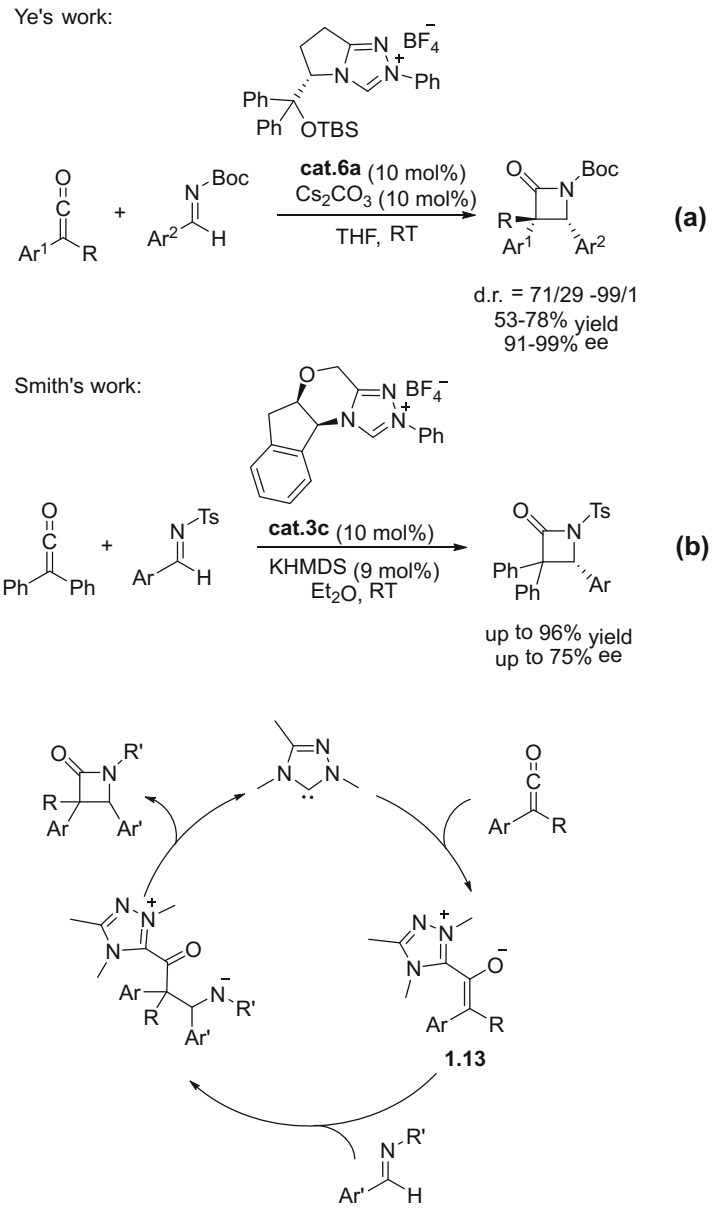

Fig. 1.16 NHC-catalyzed [2+2] annulation of ketenes with imines

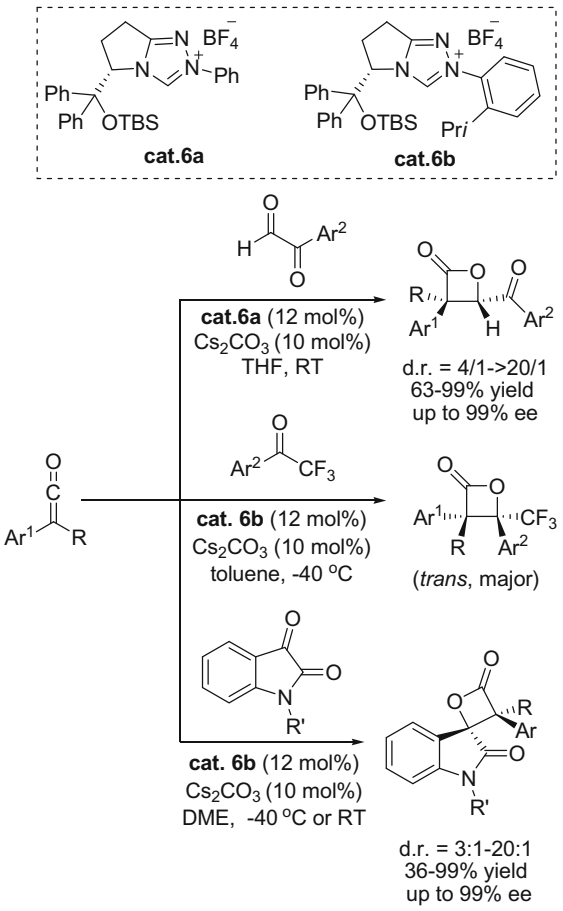

Fig. 1.17 NHC-catalyzed [2+2] annulation of ketenes with aldehydes and ketones

In 2006, Bode and co-workers disclosed the first example of azolium enolates from α-chloroaldehydes to undergo [2+4] annulations [45]. A broad range of enones worked well in the presence of NHC precursor, giving the corresponding product in good yield and with excellent diastereoselectivity and high enantioselectivity (Fig. 1.21).

In 2011, this method was successfully extended to α-aroyloxyaldehydes by Smith and co-workers. Compared to α-chloroaldehydes, α-aroyloxyaldehydes are more stable and easier to handle (Fig. 1.22) [46].

In 2011, Chi and co-workers found formylcyclopropanes were also suitable azolium enolate precursors for [2+4] annulations. In the presence of NHC, highly diastereo- and enantioselective functionalized δ-lactone products were afforded. Then, highly substituted cyclohexanes with good regio- and stereoselectivity were provided via simple transformations (Fig. 1.23) [47].

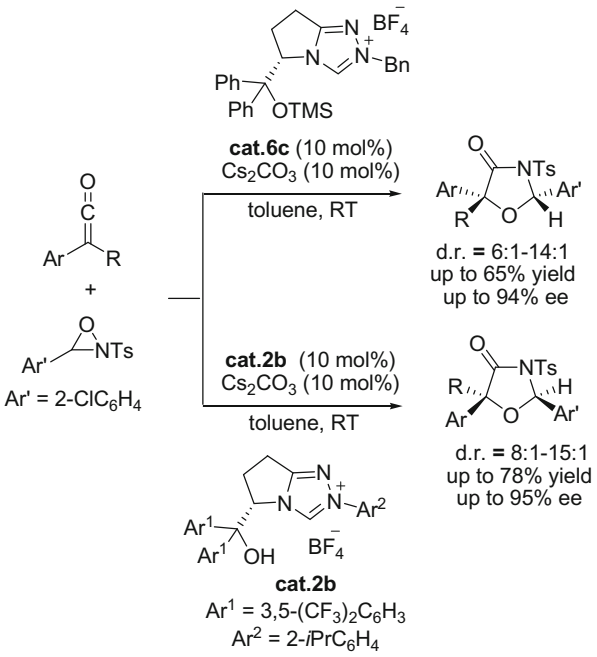

Fig. 1.18 NHC-catalyzed [2+3] annulation of ketenes with oxaziridine

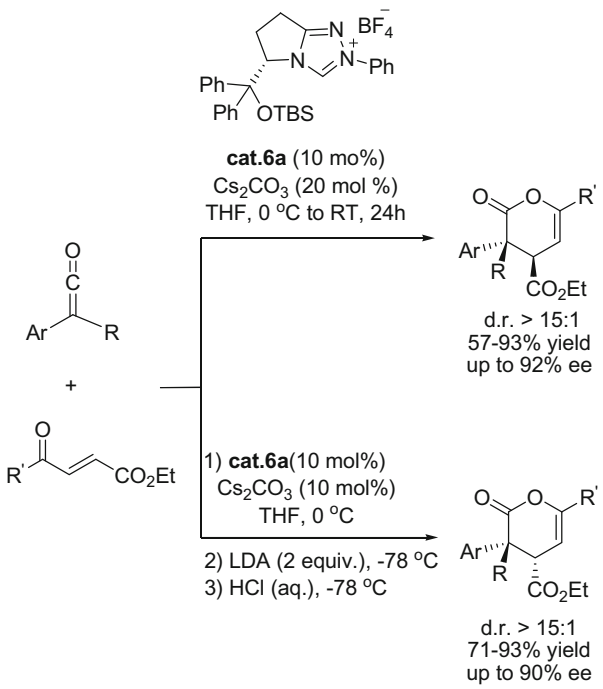

Fig. 1.19 NHC-catalyzed [2+4] annulation of ketenes with enones

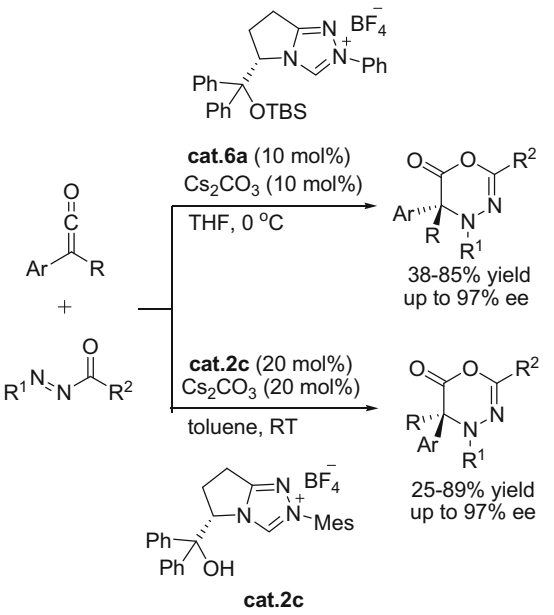

Fig. 1.20 NHC-catalyzed [2+4] annulation of ketenes with *N*-benzoyldiazenes

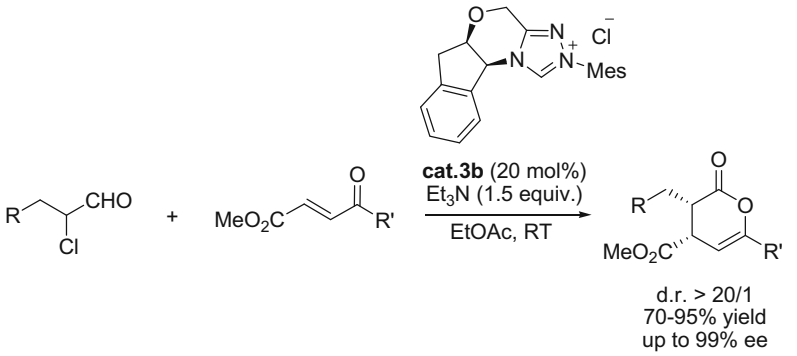

Fig. 1.21 NHC-catalyzed [2+4] annulation of α-chloroaldehydes

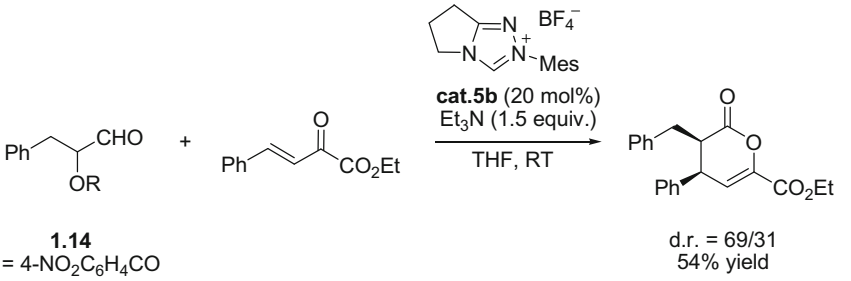

Fig. 1.22 NHC-catalyzed [2+4] annulation of α-aroyloxyaldehydes

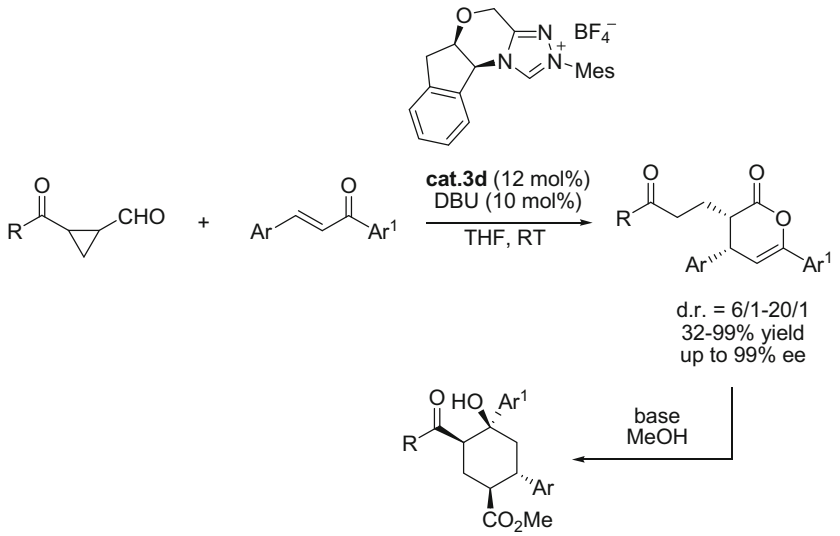

Fig. 1.23 NHC-catalyzed [2+4] annulation of formylcyclopropanes

1.2.3 Generation Via α,β-Unsaturated Aldehydes

Interestingly, the reactive azolium enolate could also be generated via protonation of homoenolate (Fig. 1.24). In 2006, Bode and co-workers pioneered the triazolium catalyst **cat.3b** catalyzed [2+4] annulations of cinnamaldehydes with azadienes, giving the corresponding dihydropyridinones in 90% yield and 99% ee [48].

The NHC-catalyzed [2+4] annulation of enals with enones was then investigated by Chi and co-workers. The use of NHC **cat.3b** as precatalyst, α-modified chalcones as electrophiles led to the Diels–Alder adducts in good yields and excellent stereoselectivities (Fig. 1.25) [49].

Substituted imidazoles commonly appear in a number of biologically natural products and active compounds. In 2013, Scheidt and co-workers reported the NHC-catalyzed formal [2+4] annulation of α,β-unsaturated aldehydes with imidazolidinones via protonation of homoenolate, giving substituted imidazoles in good yields with high ee (up to 98%) and dr (up to 20/1) (Fig. 1.26) [50].

The intramolecular [2+4] annulation of enals was also developed by Scheidt and co-workers. In the presence of triazolium salt, *cis*-bicyclic adducts was provided in good yields with excellent dr and ee (Fig. 1.27) [51].

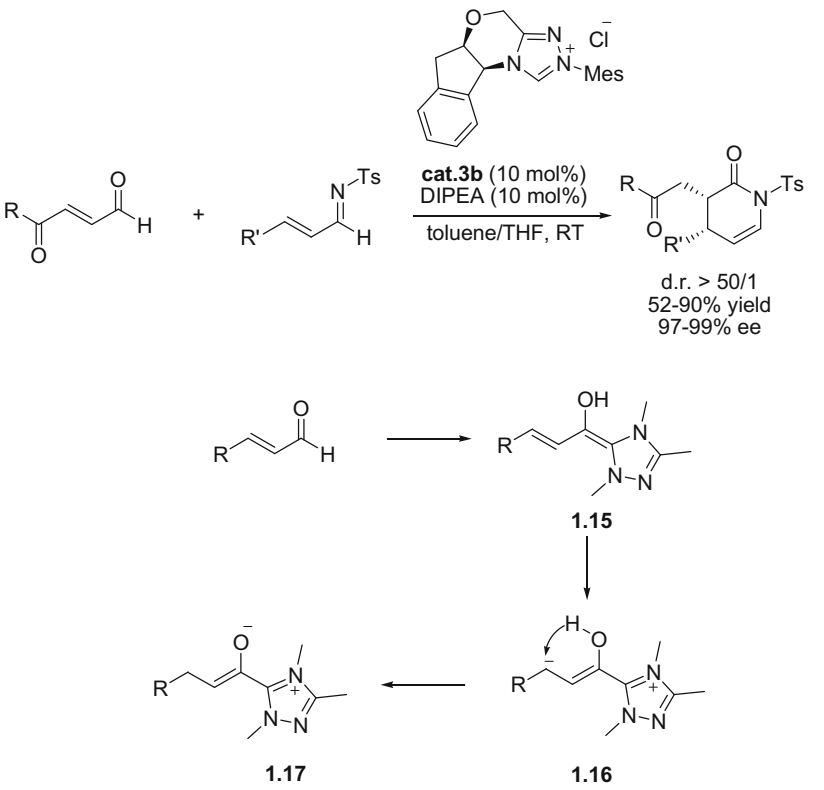

Fig. 1.24 Generation of azolium enolate via protonation of homoenolate

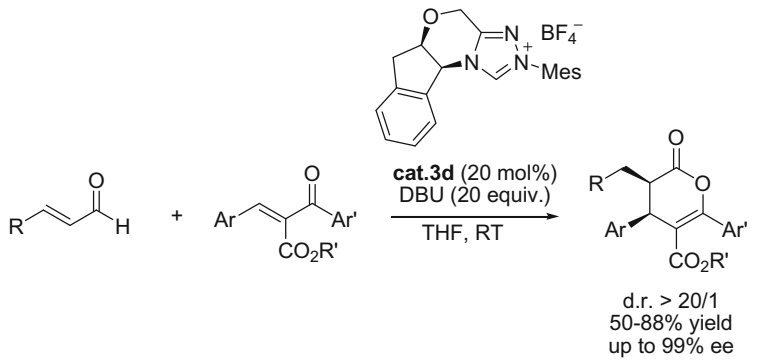

Fig. 1.25 NHC-catalyzed [2+4] annulation of enals with enones

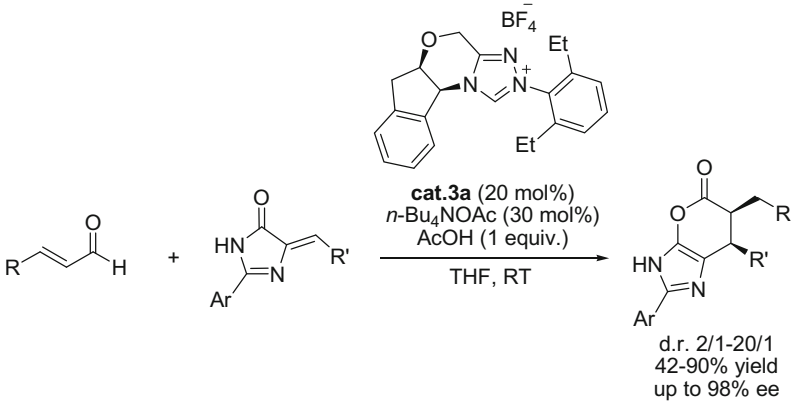

Fig. 1.26 NHC-catalyzed [2+4] annulation of enals with imidazolidinones

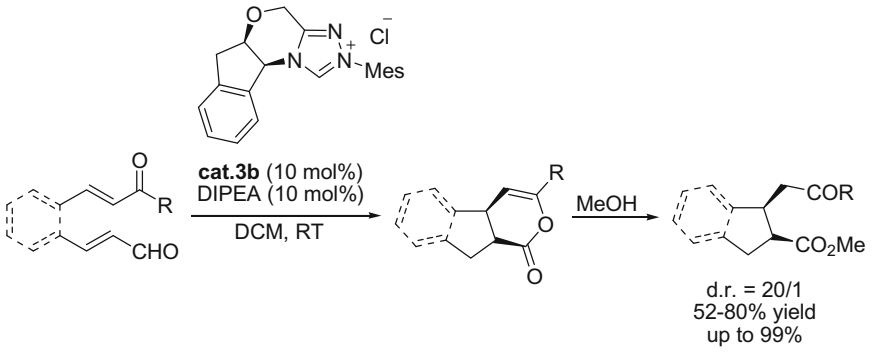

Fig. 1.27 The intramolecular [2+4] annulation of enals

1.2.4 Generation Via Easters and Aldehydes

Chi and co-workers uncovered a new strategy to access azolium enolate in the NHC-catalyzed formal [2+4] annulation. After addition of NHC to esters, the azolium enolates, which underwent an aza-Diels–Alder pathway process with the azadiene, was easily formed in the presence of base, affording the corresponding product in good yields (51–94%) and enantioselectivities (60–92% ee) (Fig. 1.28) [52].

Later on, the strategy was successfully extended to the formal asymmetric [2+4] annulation of simple aliphatic aldehydes with enones by Rovis and co-worker [53]. *cis*-Lactones was afforded in high yields with excellent diastereo- and enantioselectivity. Interestingly, when azadienes were introduced as reaction partners, *trans*-lactams were formed (Fig. 1.29).

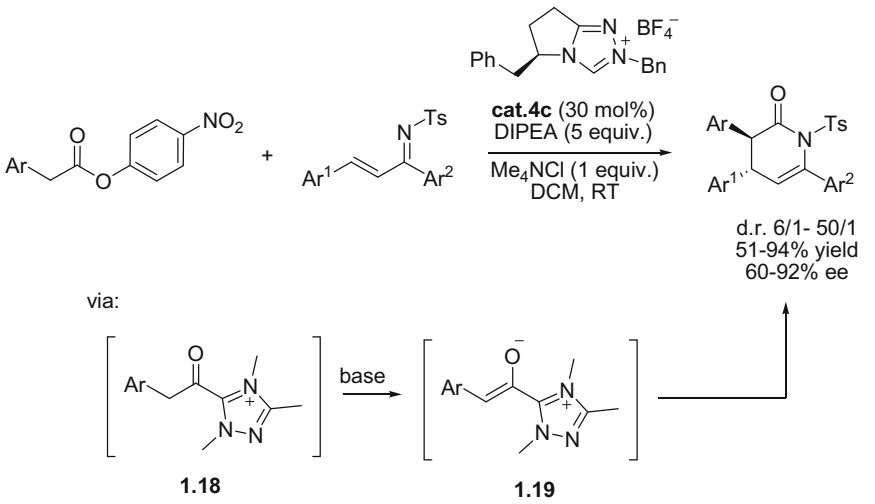

Fig. 1.28 Generation of azolium enolate from esters

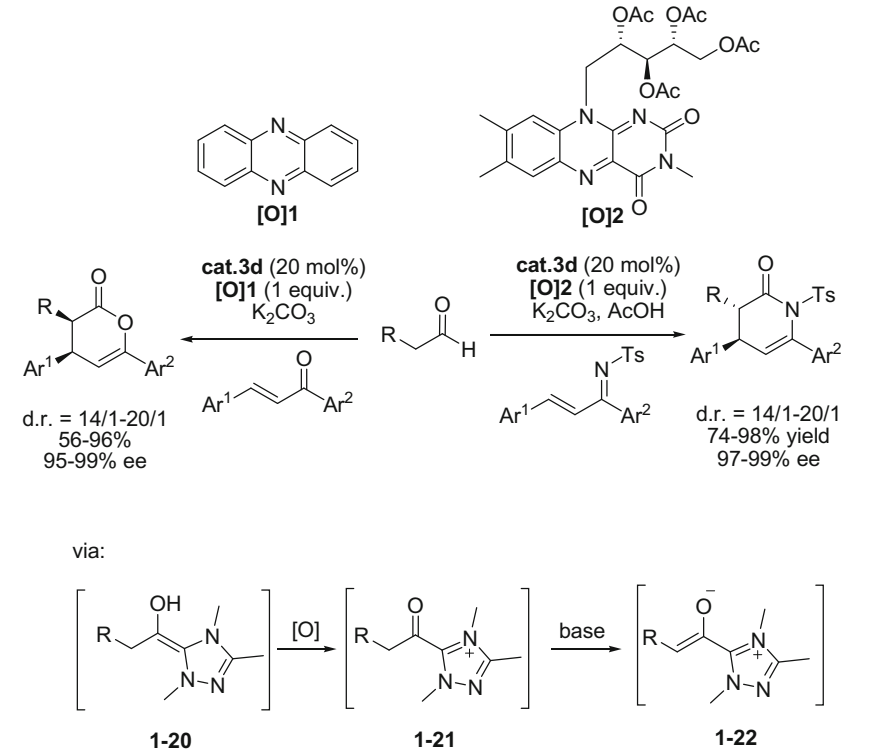

Fig. 1.29 Generation of azolium enolate from aliphatic aldehydes

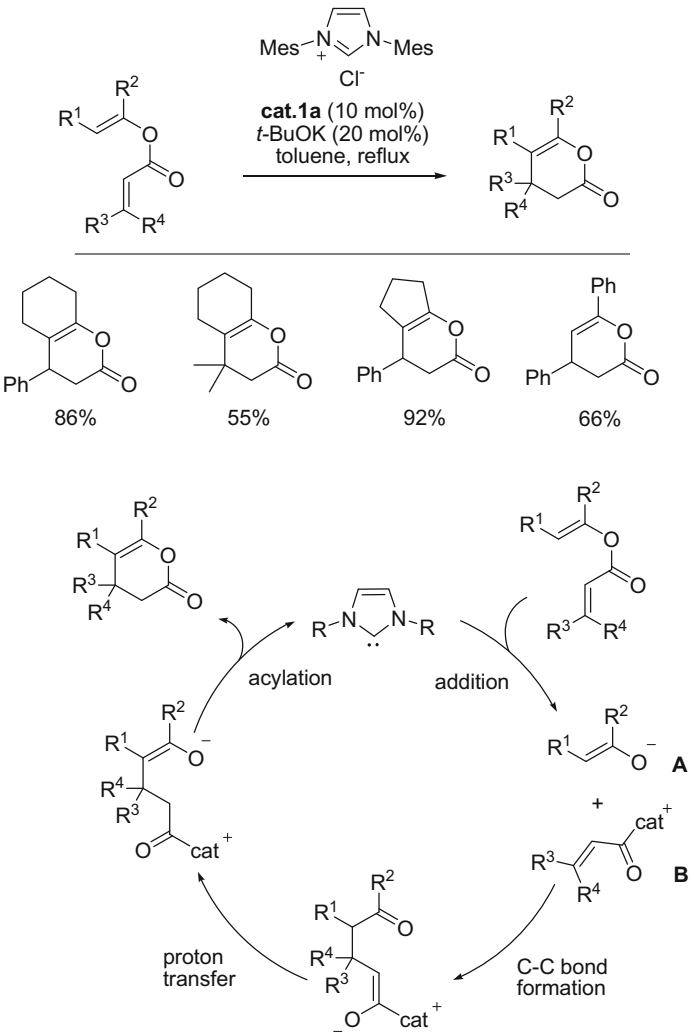

Fig. 1.30 Generation of α,β-unsaturated acyl azolium intermediates from esters

1.3 NHC-Catalyzed Annulations Via α,β-Unsaturated Acyl Azolium Intermediates

1.3.1 Generation Via α,β-Unsaturated Esters

In 2009, Lupton and co-workers initially disclosed the NHC catalyzed rearrangement of cyclopropyl esters to dihydropyranones by using α,β-unsaturated enol esters. They proposed the reaction involved the generation of α,β-unsaturated acyl

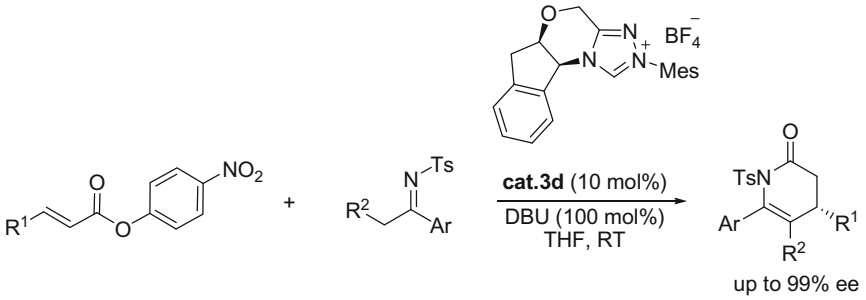

Fig. 1.31 Generation of α,β-unsaturated acyl azolium intermediates from *para*-nitrophenyl esters

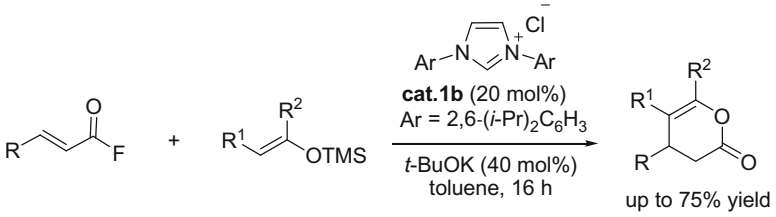

Fig. 1.32 Generation of α,β-unsaturated acyl azolium intermediates from acyl fluorides

azolium intermediates **B** and enolate **A**, following Michael addition, proton *trans*fer and lactonization affords the final products (Fig. 1.30) [54].

In 2013, Chi and co-workers expanded this methodology to the formation of α,β-unsaturated acyl azolium intermediates via *para*-nitrophenyl esters. The [3+3] annulation was developed and good yields with excellent ee were achieved (Fig. 1.31) [55].

1.3.2 Generation Via α,β-Unsaturated Acyl Fluorides

In 2011, Lupton and co-workers reported the NHC catalyzed [2+4] annulation of α,β-unsaturated acyl fluorides and silyl dienol ethers to construct cyclohexadienes (Fig. 1.32). In this case, the α,β-unsaturated acyl azolium was afforded by nucleophilic substitution of imidazolium NHC to acyl fluorides, while the fluoride ion deprotected the enol ethers to reveal dienolate. At last, the annulation of α,β-unsaturated acyl azolium and dienolate afforded the dihydropyranones in good yields [56].

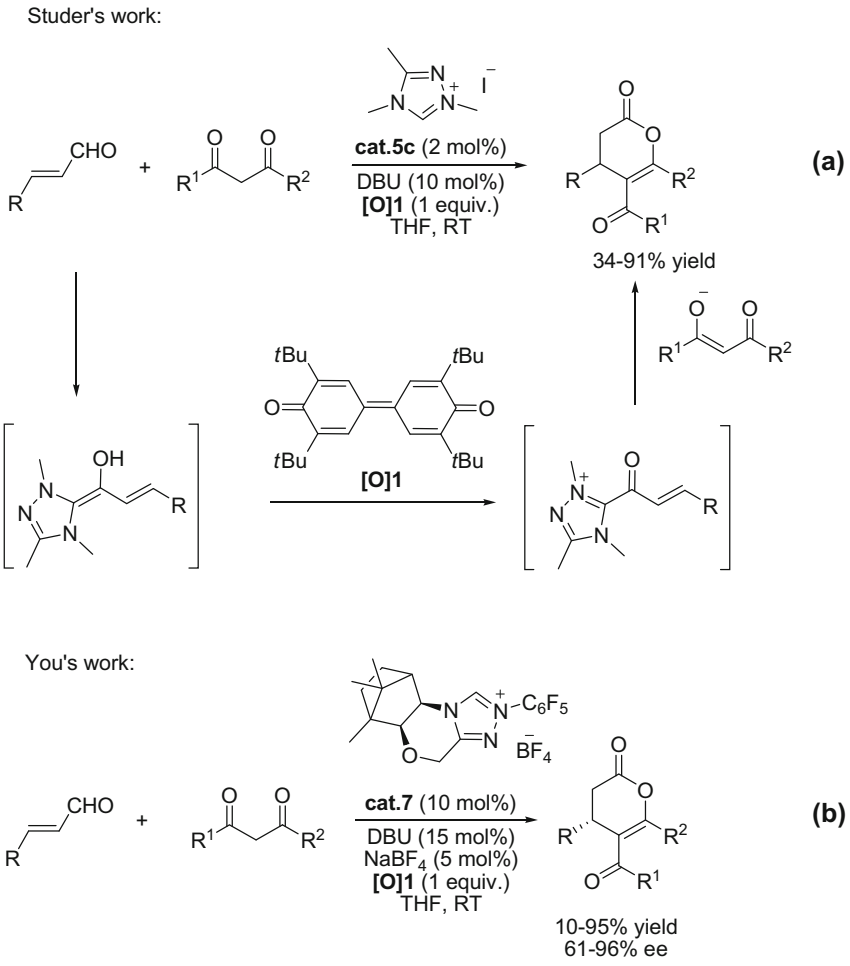

Fig. 1.33 NHC-catalyzed oxidative [3+3] annulation of enals with 1,3-diketones

1.3.3 Generation Via Oxidation of Homoenolate

In 2010, Studer and co-workers pioneered the oxidative NHC-catalyzed [3+3] annulation of enals with 1,3-diketones, giving dihydropyranones in 34–92% yield (Fig. 1.33a). In their system, the key α,β-unsaturated acylazolium intermediate was formed via oxidation of the homoenolate by mild organic oxidants [57]. Later, You and co-worker realized the enantioselective vision, good yields and excellent ee were achieved under the catalysis of camphor-derived triazolium salt **cat.7** (Fig. 1.33b) [58].

Inspired by this work, Bode and co-workers developed the NHC-catalyzed asymmetric aza-Claisen reactions (Fig. 1.34). The dihydropyridinones were

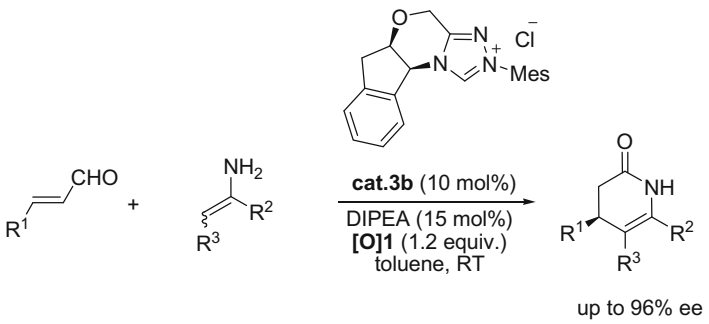

Fig. 1.34 NHC-catalyzed [3+3] annulation of enals with vinylogous amides

afforded in good to excellent yields and enantioselectivities via [3+3] annulation of vinylogous amides with α,β-unsaturated acylazolium intermediates, which were formed via oxidation of the homoenolates [59].

1.3.4 Generation Via Bromoenals

Another efficient approach to generate α,β-unsaturated acyl azoliums is from bromoenals. This method avoided expensive oxidant compared to enals. In 2011, Ye and co-worker uncovered the first [3+3] annulation of bromoenals with 1,3-dicarbonyl compounds under the catalyst of bifunctional triazolium salt **cat.2d**, giving the corresponding dihydropyranones in good yields with excellent enantioselectivities. The aliphatic bromoenals also worked well [60]. They proposed that the addition of NHC to bromoenals afforded the Breslow intermediates. Following tautomerization and elimination of bromide provided the α,β-unsaturated acyl azoliums **1.23** (Fig. 1.35).

1.3.5 Generation Via Ynals

In 2010, Bode [61] and co-workers found that the α,β-unsaturated acyl azoliums could be also formed from ynals, and the kojic acid derivatives were afforded in excellent yields and ee values via this method (Fig. 1.36a). Interestingly, no additional base was needed for the reaction. They proposed the product was formed via Claisen rearrangement after the 1,2 addition of kojic acids to α,β-unsaturated acyl azolium **1.24**. At the same time, a similar work was realized by Xiao and co-workers (Fig. 1.36b) [62].

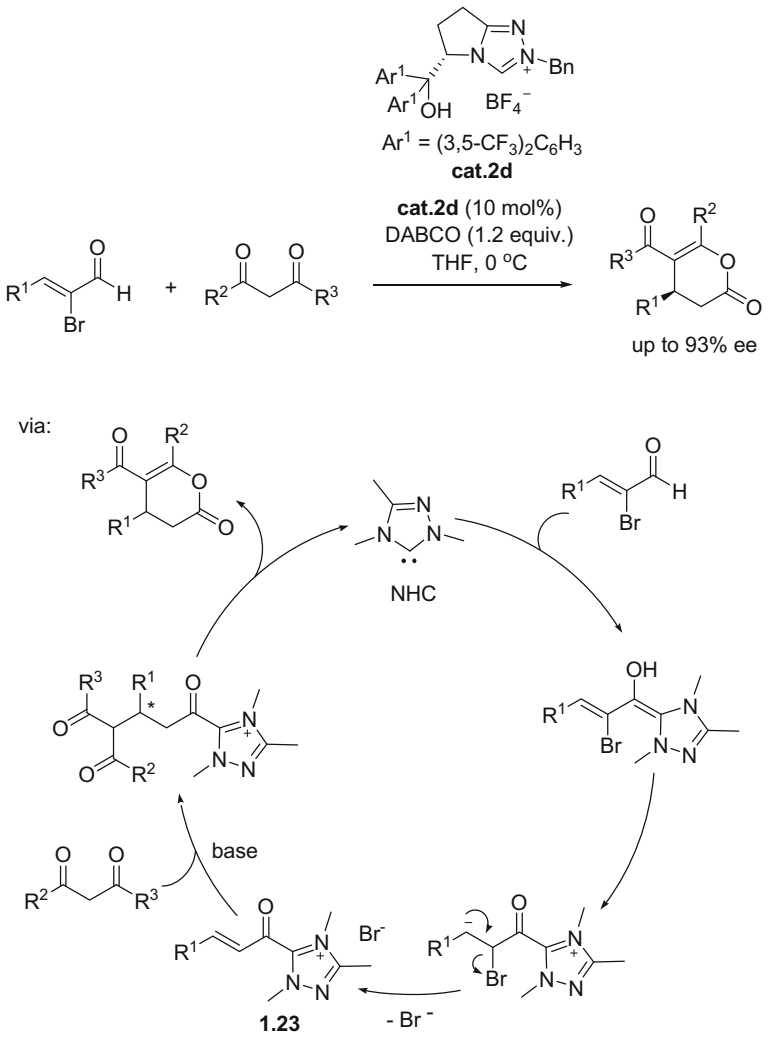

Fig. 1.35 Generation of α,β-unsaturated acyl azolium intermediates from bromoenals

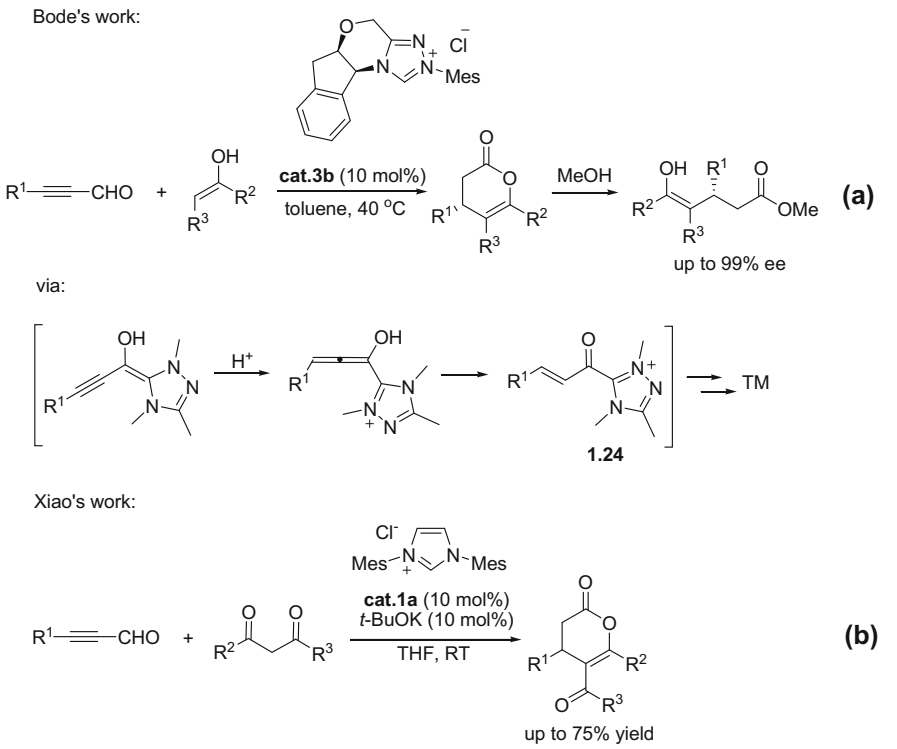

Fig. 1.36 Generation of α,β-unsaturated acyl azolium intermediates from ynals

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Chapter 2
NHC-Catalyzed Annulations of Nitroalkenes

2.1 Introduction

As described in the previous chapter, the NHCs are powerful catalysts for the reaction of C–X (X = O, S, N) bonds, however the reactions of C–C unsaturated bonds catalyzed by NHC are far less developed. In 2006, Fu and coworkers [1] disclosed an NHC-catalyzed umpolung of Michael acceptors. Nucleophilic addition of the triazolium-derived carbene to the Michael acceptor gives the adduct **A**. The sequential proton shift forms a β-anion intermediate **B**. Therefore, the umpolung of Michael acceptors was realized by reversing the polarity of the β-carbon of the Michael acceptor from an acceptor to a donor (Fig. 2.1).

In 2011, Matsuoka and coworkers [2] expanded this method to the dimerization of methacrylates. Later on, a better substrate scope was realized by Glorius and coworkers [3] (Fig. 2.2).

Besides that, the NHC was also a suitable catalyst for Morita–Baylis–Hillman (MBH) reaction. In 2007, Ye and coworkers [4] found that the reaction of cyclic enones with a variety of *N*-tosylarylimines went well under the catalyst of stable NHC **1b**, giving the aza-MBH adduct in good to excellent yields (Fig. 2.3).

In 2011, Scheidt and coworkers [5] reported an NHC-catalyzed [3+2] annulation of nitrones and vinyl sulfone. The [3+2] annulation products were afforded in good yields with high diastereoselectivities in the presence of sodium *tert*-butoxide and 20 mol% of triazolium **cat. 5f** (Fig. 2.4).

1,3-Dipolar annulation reactions of nitrile oxides and alkynes are efficient approaches to obtain isoxazoles. In 2011, Vasam and coworkers [6] demonstrated the [3+2] annulation of nitrile oxides and alkynes catalyzed by NHC. In the presence of NHC **cat.1d**, a variety of nitrile oxides reacted well with the alkynes to provide the desired isoxazoles in good yields (Fig. 2.5).

Nitroalkenes, due to their high reactivity, have become one of the most powerful reagents to construct functionalized cyclic compounds [7–17]. We envision that the

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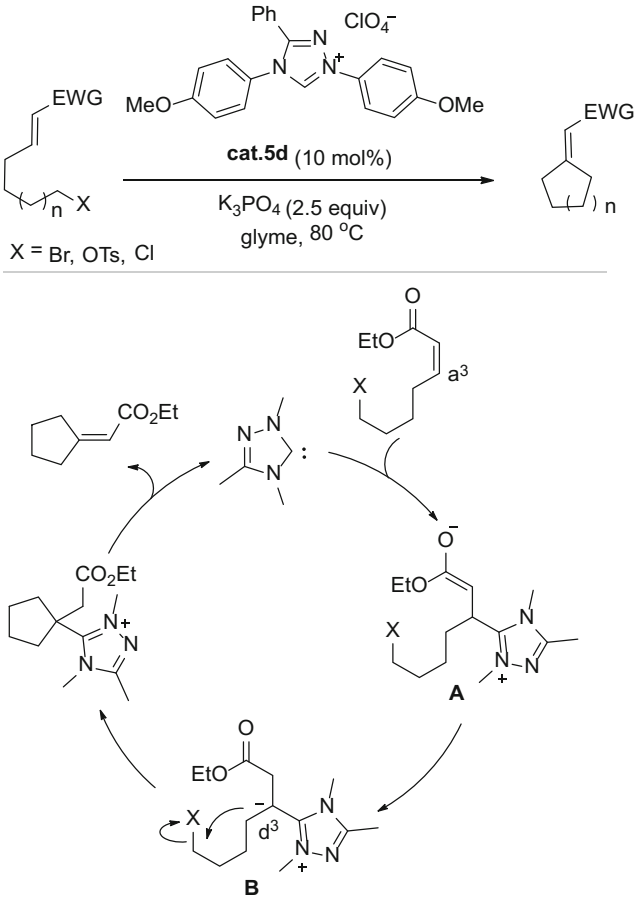


Fig. 2.1 NHC-catalyzed umpolung of Michael acceptors

NHC could attack nitroalkenes and finish the [4+2] annulation with oxodienes (Fig. 2.6).

2.2 Optimization of Conditions

Initially, we evaluated the model reaction of nitroalkene **2.1a** with oxodiene **2.2a** in the presence of various azolium salts. It was found that the use of imidazolium precatalyst **cat.1a** and triazolium precatalyst **cat.5e** gave no reaction (Table 2.1, entries 1 and 2). Gratifyingly, thioazolium **cat.8b–8c** showed reactivity for the reaction. And further solvent screening revealed that the reactions in toluene gave best yields of the desired product (entries 3–6, 9, and 10). It is necessary to note

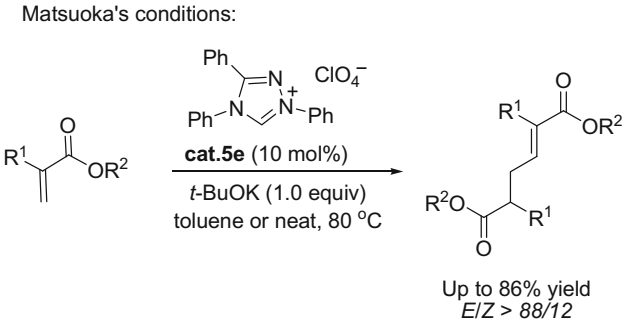


Fig. 2.2 NHC-catalyzed dimerization of Michael acceptors

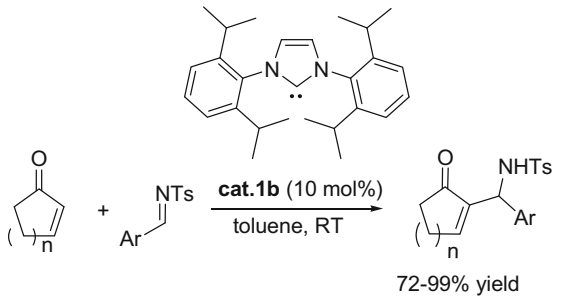


Fig. 2.3 NHC-catalyzed MBH reaction of cyclic enones

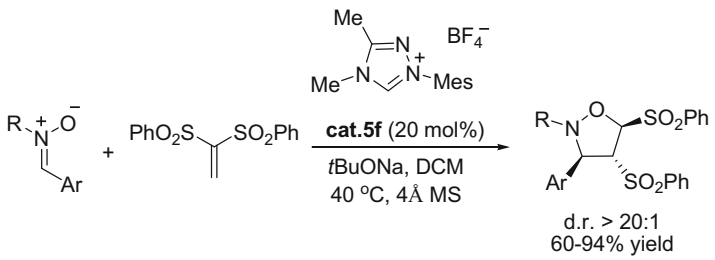


Fig. 2.4 NHC-catalyzed [3+2] annulation of vinyl sulfones with nitrones

that DABCO or PPh_3 offered no or little catalytic activity under current reaction conditions (entries 7 and 8). In the absence of catalyst, no reaction was observed (entry 11).

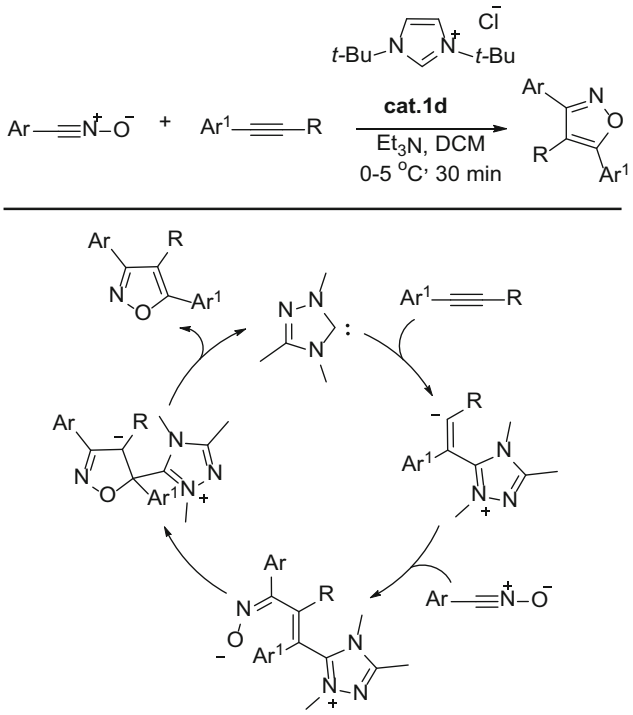


Fig. 2.5 NHC-catalyzed [3+2] annulation of alkynes

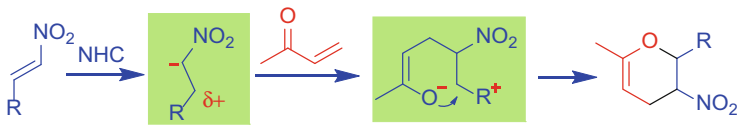
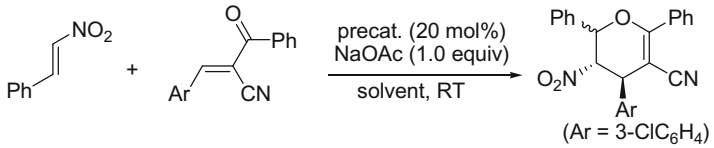


Fig. 2.6 Reaction design

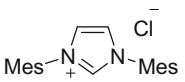
2.3 Substrate Scope

Under the optimized reaction conditions, we conducted the reactions of nitroalkene **2.1** with oxodiene **2.2**. As shown in Table 2.2, in the presence of precatalyst **cat.8b** (20 mol%). Both electron-rich (4-Me, 4-MeO) and electron-poor (4-Cl, 4-Br) *para*-substituted nitroalkenes were tolerated, giving the cycloadducts **2.3b–2.3f** in good yield with good diastereoselectivity. *meta*-Substituted aromatic nitroalkenes also worked well (**2.3g** and **2.3h**). Moreover, introducing a heterocyclic thienyl group on the nitroalkene gave the corresponding dihydropyran **2.3i** in 76% yield with a

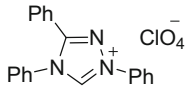
Table 2.1 Optimization of the reaction conditions



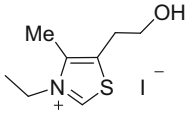
2.1a **2.2a** (Ar = 3-ClC_6H_4) **2.3a** (2,3-*trans*) **2.4a** (2,3-*cis*)



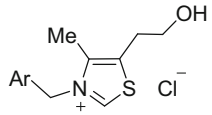
cat.1a



cat.5e



cat.8a



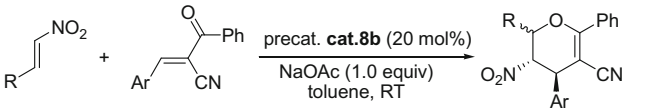
cat.8b Ar = Mes
cat.8c Ar = 3,5-$(CF_3)_2C_6H_3$

Entry	Cat	Solvent	Yield (%)[a]	**2.3a**:**2.4a**[b,c]
1	**Cat.1a**	DCM	Trace	/
2	**Cat.5e**	DCM	Trace	/
3	**Cat.8a**	DCM	Trace	/
4	**Cat.8b**	DCM	33	4:1
5	**Cat.8c**	DCM	84	1:2
6	**Cat.8b**	THF	55	5:1
7	DABCO[d]	THF	Trace	/
8	PPh_3[d]	THF	13	2:1
9	**Cat.8b**	Toluene	88	18:1
10	**Cat.8c**	Toluene	90	1:3
11	None	Toluene	NR	/

[a]Isolated yield of the mixture of stereoisomers
[b]Determined by ^1H NMR (300 MHz) of the raw product
[c]Beside **2.3a** and **2.4a**, another stereoisomer was also observed in the reaction mixture but not isolable
[d]No base of NaOAc was added when DABCO or PPh_3 was used

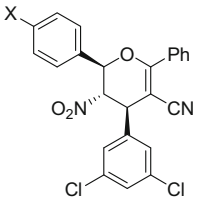
diastereomeric ratio (d.r.) of 7:1. It is worth noting that good results were also obtained when β-alkyl nitroalkenes (R = cyclohexyl, *n*-butyl, *n*-propyl; cycloadducts **2.3j**, **2.3k** and **2.3l**) were employed. The α-cyano-β-aryl-α,β-unsaturated ketones were also varied. Different aryl groups (Ar = Ph, 4-ClC_6H_4, 4-BrC_6H_4)

Table 2.2 NHC-precursor **cat.8b** catalyzed [4+2] cycloadditions of nitroalkenes with oxodienes

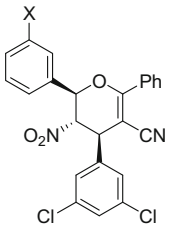


2.1 **2.2** **2.3** (2,3-*trans,* major)

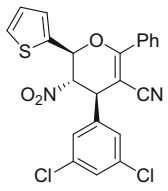
Isolated yield,[a] followed by dr (*trans*/*cis*) of the reaction mixture[b]



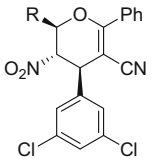
2.3b (X = H), 70%, dr = 7:1[c]
2.3c (X = Me), 74%, dr = 9:1
2.3d (X = MeO), 72%, dr = 8:1
2.3e (X = Cl), 68%, dr = 6:1
2.3f (X = Br), 64%, dr = 5:1



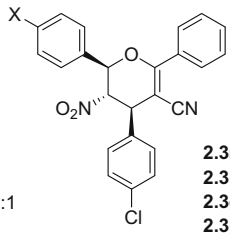
2.3g (X = Cl), 70%, dr = 6:1
2.3h (X = MeO), 71%, dr = 6:1



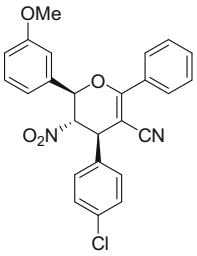
2.3i, 76%, dr = 7:1



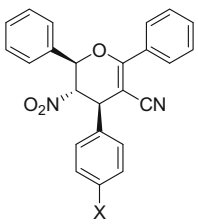
2.3j (R = cyclohexyl), 50%,[d] dr = 3:1
2.3k (R = *n*-Bu), 72%,[e] dr = 5:1
2.3l (R = *n*-Pr),[f] 64%, dr = 6:1



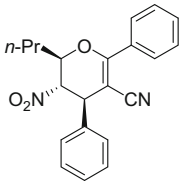
2.3m (X = H), 52%, dr = 7:1[c]
2.3n (X = Me), 64%, dr = 5:1
2.3o (X = MeO), 55%, dr = 7:1
2.3p (X = Cl), 64%, dr = 4:1
2.3q (X = Br), 73%, dr = 6:1[c]



2.3r, 76%, dr = 6:1



2.3s, (X = H), 81%,[f] dr = 3:1[c]
2.3t, (X = Br), 65%, dr = 5:1[c]



2.3u, 60%, dr = 4:1

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[a]Unless otherwise noted, isolated yield of pure 2,3-*trans* isomer (**2.3**) is shown
[b]Determined by ^{1}H NMR spectroscopy (300 MHz)
[c]As well as the 2,3-*trans* (**2.3**) and 2,3-*cis* isomers (**2.4**), another stereoisomer was observed by ^{1}H NMR analysis of the reaction mixture, although it was not isolable
[d]Isolated yield of a mixture of **2.3j** and **2.4j** (d.r. = 14:1)
[e]Isolated yield of a mixture of **2.3k** and **2.4k** (d.r. = 7:1)
[f]Isolated yield of the mixture of stereoisomers

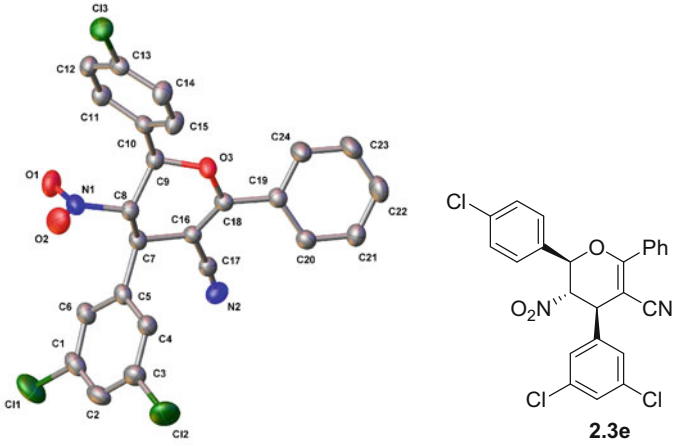


Fig. 2.7 X-ray structure of **2.3e**

were tolerable under current reaction conditions, giving the desired dihydropyrans **2.3m**–**2.3u** in good yield with moderate-to-good diastereoselectivity.

The structure of dihydropyrans **2.3e** was confirmed by the X-ray analysis of its crystal (Fig. 2.7).

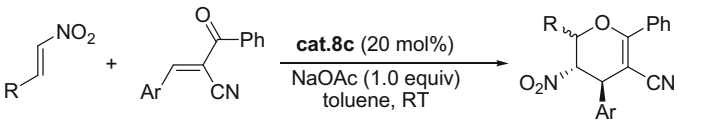
The synthesis of *cis*-cycloadduct **2.4** as the major product using NHC-precursor **cat.8c** was also investigated (Table 2.3). Both electron-donating and electron-withdrawing substituents at the *para* or *meta* positions of the β-phenyl group were well tolerated (**2.4m**–**2.4q**, **2.4r**, and **2.4v**). Moreover, the variation on the oxodienes was also investigated. Both *para* and *meta*-substituents on the aryl group of the oxodienes were well tolerated (**2.4s**–**2.4t** and **2.4a**). Much better diastereoselectivity was achieved when *ortho* cholorphenyl-substituted nitroalkenes were employed (**2.4w**).

The structure of dihydropyran **2.4s** was unambiguously established by the X-ray analysis of its crystal (Fig. 2.8).

2.4 Reduction of the Nitro Group of Dihydropyran

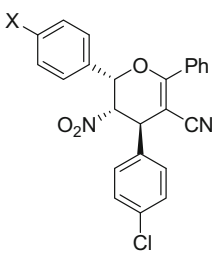
Some possible chemical transformations could be provided by the resulted highly functionalized dihydropyrans. For example, the nitro group in dihydropyrans **2.3** could be easily reduced by Zn/HCl, giving the corresponding 3-amino dihydropyrans **2.5** in good yield (Table 2.4).

Table 2.3 NHC-precursor **cat.8c** catalyzed [4+2] cycloadditions of nitroalkenes with oxodienes

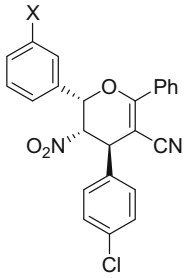


2.1 **2.2** **2.4** (2,3-*cis*, major)

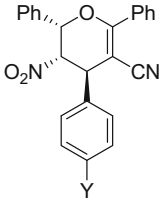
Isolated yield,[a] followed by dr (*cis*/*trans*) of the reaction mixture[b,c]



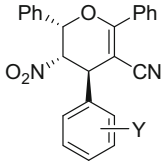
2.4m (X = H), 87%, dr = 3:1
2.4n (X = Me), 91%, dr = 3:1
2.4o (X = MeO), 85%, dr = 2:1
2.4p (X = Cl), 92%, dr = 2:1
2.4q (X = Br), 83%, dr = 2:1



2.4r (X = OMe), 90%, dr = 4:1
2.4v (X = Cl), 88%, dr = 2:1



2.4s (Y = H), 89%, dr = 5:1
2.4t (Y = Br), 93%, dr = 4:1



2.4a (Y = *m*-Cl), 90%, dr = 3:1
2.4w (Y = *o*-Cl), 44%, dr > 20:1

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[a]Isolated yield of mixture of diastereomers
[b]Determined by ^{1}H NMR spectroscopy (300 MHz)
[c]As well as the 2,3-*trans* (**2.3**) and 2,3-*cis* isomers (**2.4**), another stereoisomer was observed by ^{1}H NMR analysis of the reaction mixture, although it was not isolable

2.5 Studies on the Enantioselectivity of the Annulation Process

We envisioned that a thiourea may be suitable catalyst to activate nitroalkenes. Therefore, a catalytic enantioselective variant of the annulation process was further studied with a series thioureas as co-catalysts. However, most of the thioureas have

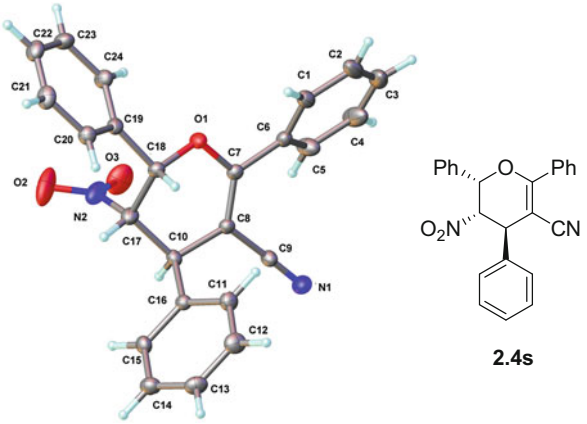


Fig. 2.8 X-ray structure of **2.4s**

no catalytic effects and only gave trace of products. Thiourea **2.7d** could provide good yield but without enantioselectivity (Table 2.5).

Although further optimization was extensively studied by a series of chiral NHCs, no more improvement could be achieved so far. Only chiral triazolium NHC **cat.2d** could catalyze the reaction, providing the desired dihydropyran **2.3b** in 24% yield with 29% ee (Table 2.6).

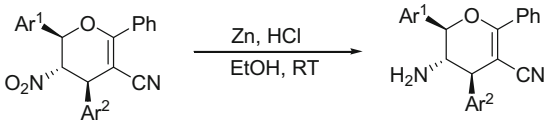
In order to improve the enantioselectivity, a series of additives and bases were also examined, but no further improvement was achieved (Table 2.7).

2.6 Mechanistic Studies

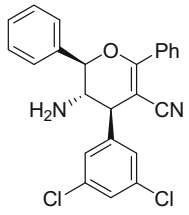
A plausible mechanism for the reaction is suggested in Fig. 2.9. Addition of the NHC catalyst to the nitroalkenes delivers the carbon anion intermediate **I**, this species could feasibly react with the electron-deficient oxodiene via Michael addition, providing adduct **II**. Intramolecular alkoxide attack at the carbonyl group leads to the desired dihydropyrans and regenerates the NHC catalyst.

The deuterium experiment was then carried out to investigate the mechanism. It was found that in the presence of NHC-precursor **cat.8b** (20 mol%), 1.0 equivalent of base, and D_2O, 19 and 14% deuteration of the α- and β-position of nitroalkene was observed. We proposed that the α-deuterium nitroalkenes were afforded via deuteration of adduct **I** followed by elimination. The acidity of the β-proton was enhanced by the addition of NHC to the β-position of nitroalkenes, and thus led to the β-deuterium nitroalkenes (Fig. 2.10).

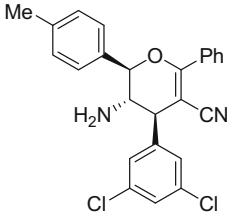
Table 2.4 Reduction of the nitro group of dihydropyran **2.3**



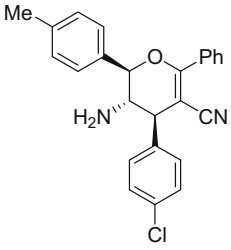
2.3 **2.5**



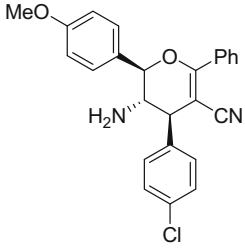
2.5b, 79%



2.5c, 86%



2.5n, 90%



2.5o, 70%

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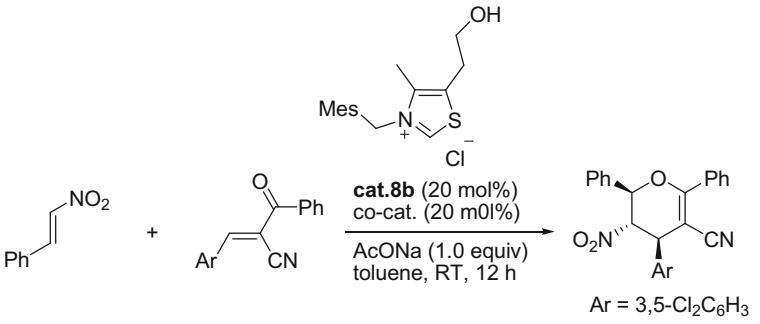
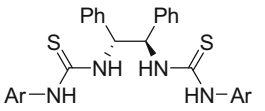
2.7 Summary

In this chapter, *N*-heterocyclic carbene-catalyzed [4+2] annulation of nitroalkenes and oxodienes was developed, affording the corresponding dihydropyrans in good yield with good diastereoselectivity [18]. The reaction is possibly initiated by the addition of an *N*-heterocyclic carbene to nitroalkenes, which was revealed by deuteration experiments.

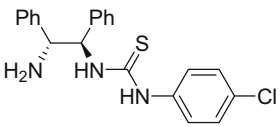
Table 2.5 Screening of co-catalysts



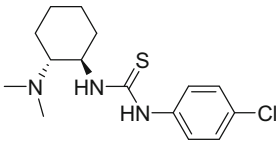
co-cat.:



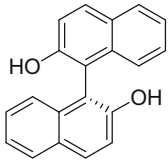
2.7a Ar = 4-ClC_6H_4
2.7b Ar = 3,5-$F_2C_6H_3$



2.7c



2.7d

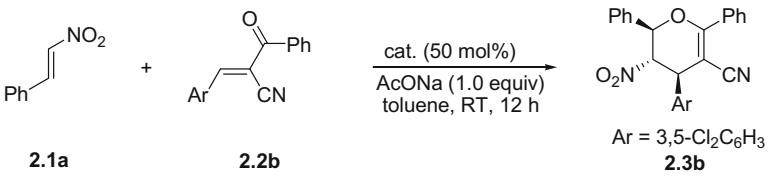


2.6

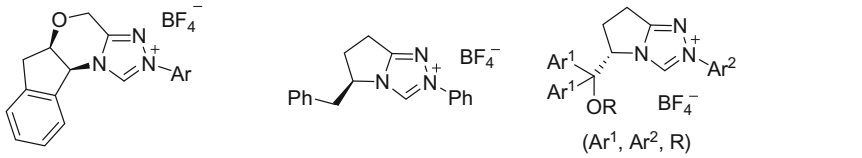
Entry	Solvent	Co-cat.	Yield (%)[a]	**2.3b**:**2.4b**[b]	Ee[c]
1	Toluene	**2.7a**	Trace	/	/
2	Toluene	**2.7b**	Trace	/	/
3	Toluene	**2.7c**	Trace	/	/
4	Toluene	**2.7d**	76	7/1	0%
5	Toluene	**2.6**	Trace	/	/

[a]Isolated yield of pure 2,3-*trans* isomer **2.3a**
[b]Determined by ^{1}H NMR spectroscopy (300 MHz)
[c]Determined by chiral-phase HPLC analysis

Table 2.6 Screening of chiral NHCs



2.1a **2.2b** **2.3b**



cat.3c Ar = Ph, trace
cat.3d Ar = Mes, trace

cat.4d
trace

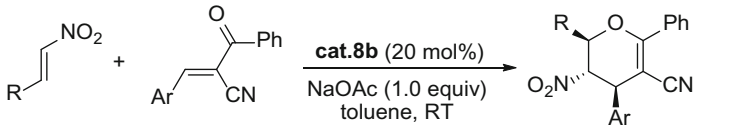
cat.6a (Ph, Ph, TBS), trace
cat.2a (3,5-$(CF_3)_2C_6H_3$, Ph, H), trace
cat.2d (3,5-$(CF_3)_2C_6H_3$, Bn, H)
24% yield, d.r. = 5/1, 29% ee
cat.2e (Ph, Ph, H), trace
cat.2f (3,5-$(CF_3)_2C_6H_3$, Mes, H), trace

2.8 Experimental Part

2.8.1 Materials

The nitroalkenes were prepared according to literature methods [19], purified by chromatography and recrystallization from ethanol. α-cyano-α,β-unsaturated ketones were prepared according to literature methods [20], purified by chromatography.

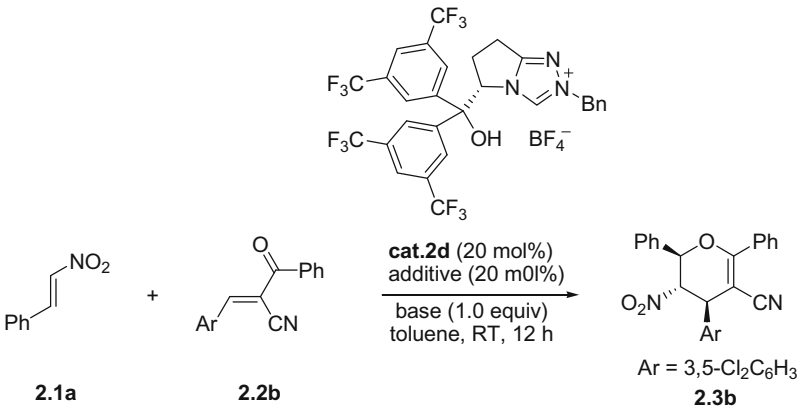
2.8.2 [4+2] Annulation of Nitroalkenes with α-Cyano-α,β-Unsaturated Ketones Catalyzed by NHC-Precursor Cat.8b



2.1 **2.2** **2.3** (2,3-*trans*, major)

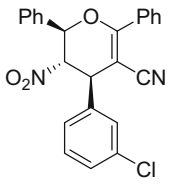
An oven-dried 50 mL Schlenk tube was charged with nitroalkenes **2.1** (0.4 mmol, 2.0 eq.), α-cyano-α,β-unsaturated ketones **2.2** (0.2 mmol, 1.0 eq.), **cat.8b** (0.04 mmol, 12 mg, 0.2 eq.), and AcONa (0.2 mmol, 16 mg, 1.0 eq.).

Table 2.7 Screening of additives and bases



Entry	Base	Additive	Yield (%)	**2.3b**:**2.4b**	Ee (%)
1	AcONa	LiBr	Trace	/	/
2	AcONa	AcOH	Trace	/	/
3	AcONa	PhOH	Trace	/	/
4	AcONa	Diphenyl thiourea	Trace	/	/
5	AcONa	$Ti(OEt)_4$	Trace	/	/
6	AcONa	$Zn(AcO)_2$	Trace	/	/
7	AcONa	$Mg(t\text{BuO})_2$	Trace	/	/
8	*t*BuOK	/	Trace	/	/
9	Cs_2CO_3	/	Trace	/	/
10	DABCO	/	Trace	/	/
11	K_2CO_3	/	Trace	/	/

To this mixture was added freshly distilled toluene (2 mL). The reaction mixture was stirred at room temperature until the full consumption of the α-cyano-α,β-unsaturated ketones (typically, 18 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleumether/EtOAc as the eluent, typically 20:1-0:100) to furnish the corresponding cycloadduct.



2.3a

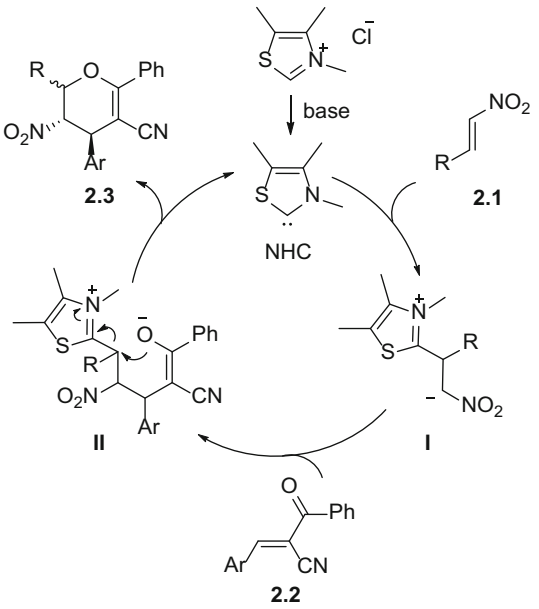


Fig. 2.9 Possible catalytic cycle. Reproduced from Ref. [18] by permission of John Wiley & Sons Ltd.

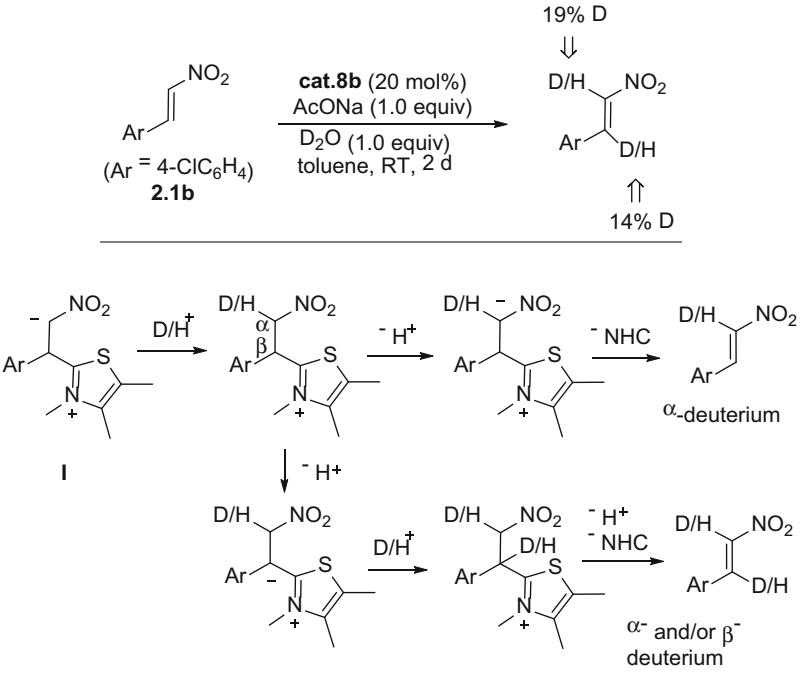
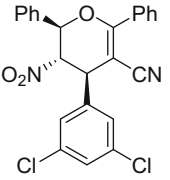


Fig. 2.10 Deuteration experiment. Reproduced from Ref. [18] by permission of John Wiley & Sons Ltd.

(2R*,3S*,4R*)-4-(3-chlorophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

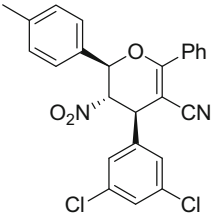
Yield: 73 mg, 88%; yellow solid; mp 174–176 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, DMSO) δ 7.74 (d, *J* = 8.0 Hz, 3H), 7.65–7.61 (m, 2H), 7.56–7.44 (m, 9H), 5.85–5.83 (m, 2H), 4.78 (dd, *J* = 6.9, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 165.4, 138.4, 133.7, 133.4, 131.6, 131.5, 130.9, 130.2, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 127.7, 117.7, 87.9, 86.6, 79.6, 45.8; IR (KBr) 2211, 1616, 1556, 1277, 1149, 778, 696; HRMS (ESI) calcd for $C_{24}H_{18}ClN_2O_3$ $[M+H]^+$ 417.10005, found 417.09998.



2.3b

(2R*,3S*,4R*)-4-(3,5-dichlorophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 63 mg, 70%; yellow solid; mp 211–213 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.1 Hz, 2H), 7.53–7.25 (m, 9H), 7.19 (d, *J* = 1.7 Hz, 2H), 5.45 (d, *J* = 9.7 Hz, 1H), 4.89 (t, *J* = 10.0 Hz, 1H), 4.58 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 139.0, 136.4, 132.4, 132.3, 130.8, 130.8, 130.0, 129.4, 128.9, 128.6, 127.3, 126.6, 117.2, 90.3, 86.0, 80.4, 46.6; IR (KBr) 2360, 2210, 1622, 1556, 1297, 1161, 804, 694; HRMS (ESI) calcd for $C_{24}H_{17}Cl_2N_2O_3$ $[M+H]^+$ 451.06107, found 451.06161.

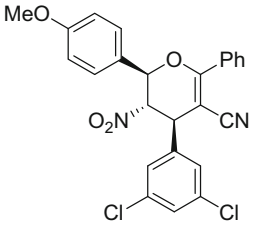


2.3c

(2R*,3S*,4R*)-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-2-p-tolyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 68 mg, 74%; yellow solid; mp 238–240 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.51–7.37 (m, 4H), 7.30–7.18 (m, 6H), 5.41 (d, *J* = 9.7 Hz, 1H), 4.89 (t, *J* = 9.9 Hz, 1H), 4.56 (d, *J* = 10.2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 140.9, 139.1, 136.3, 132.3, 130.9, 130.0, 129.8, 129.4, 128.8, 128.6, 127.3, 126.6,

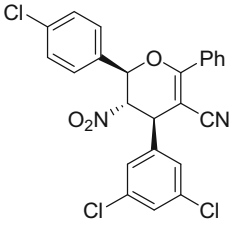
117.3, 90.2, 85.9, 80.3, 46.6, 21.4; IR (KBr) 2360, 2211, 1557, 1273, 1151, 805, 694; HRMS (ESI) calcd for $C_{25}H_{19}Cl_2N_2O_3$ $[M+H]^+$ 465.07672, found 465.07685.



2.3d

(2R*,3S*,4R*)-4-(3,5-dichlorophenyl)-2-(4-methoxyphenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

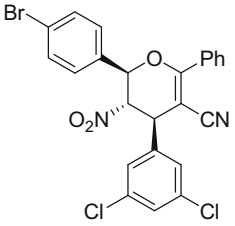
Yield: 69 mg, 72%; yellow solid; mp 242–244 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, J = 6.9 Hz, 2H), 7.52–7.25 (m, 6H), 7.19 (d, J = 1.8 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 5.39 (d, J = 9.7 Hz, 1H), 4.88 (t, J = 10.0 Hz, 1H), 4.56 (d, J = 10.2 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 161.3, 139.1, 136.3, 132.2, 130.9, 129.9, 128.9, 128.8, 128.6, 126.5, 124.2, 117.3, 114.7, 90.2, 85.9, 80.2, 55.5, 46.7; IR (KBr) 2210, 1613, 1557, 1516, 1250, 1150, 833, 694; HRMS (ESI) calcd for $C_{25}H_{19}Cl_2N_2O_4$ $[M+H]^+$ 481.07164, found 481.07241.



2.3e

(2R*,3S*,4R*)-2-(4-chlorophenyl)-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

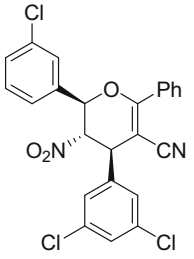
Yield: 66 mg, 68%; yellow solid; mp 227–230 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83–7.80 (m, 2H), 7.54–7.25 (m, 8H), 7.18 (d, J = 1.7 Hz, 2H), 5.43 (d, J = 9.7 Hz, 1H), 4.85 (t, J = 10.0 Hz, 1H), 4.56 (d, J = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 138.7, 136.9, 136.4, 132.4, 130.9, 130.6, 130.0, 129.7, 128.9, 128.7, 128.6, 126.5, 117.1, 90.1, 86.2, 79.7, 46.6; IR (KBr) 2212, 1616, 1557, 1272, 1151, 830, 694; HRMS (ESI) calcd for $C_{24}H_{16}Cl_3N_2O_3$ $[M+H]^+$ 485.02210, found 485.02224.



2.3f

(2R*,3S*,4R*)-2-(4-bromophenyl)-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

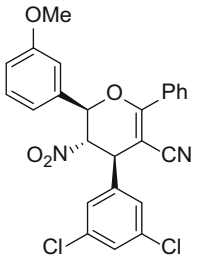
Yield: 68 mg, 64%; yellow solid; mp 230–233 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.5 Hz, 2H), 7.57–7.39 (m, 6H), 7.28–7.25 (m, 2H), 7.18 (d, *J* = 1.6 Hz, 2H), 5.42 (d, *J* = 9.7 Hz, 1H), 4.84 (t, *J* = 10.0 Hz, 1H), 4.55 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 138.7, 136.4, 132.6, 132.4, 131.4, 130.6, 130.0, 128.9, 128.6, 126.5, 125.1, 117.1, 90.0, 86.2, 79.7, 46.5; IR (KBr) 2359, 2212, 1617, 1557, 1264, 1151, 805, 695; HRMS (ESI) calcd for $C_{24}H_{16}BrCl_2N_2O_3$ $[M+H]^+$ 528.97159, found 528.97161.



2.3g

(2R*,3S*,4R*)-2-(3-chlorophenyl)-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

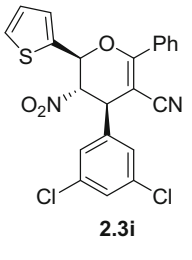
Yield: 67 mg, 70%; yellow solid; mp 191–193 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.2 Hz, 2H), 7.55–7.35 (m, 7H), 7.26 (d, *J* = 5.7 Hz, 1H), 7.19 (d, *J* = 1.5 Hz, 2H), 5.43 (d, *J* = 9.7 Hz, 1H), 4.86 (t, *J* = 10.0 Hz, 1H), 4.56 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 138.7, 136.5, 135.4, 134.4, 132.4, 131.0, 130.6, 130.6, 130.0, 128.9, 128.6, 127.4, 126.5, 125.6, 117.0, 90.0, 86.3, 79.5, 46.5; IR (KBr) 2212, 1610, 1557, 1301, 1151, 862, 805, 694; HRMS (ESI) calcd for $C_{24}H_{16}Cl_3N_2O_3$ $[M+H]^+$ 485.02210, found 485.02232.



2.3h

(2R*,3S*,4R*)-4-(3,5-dichlorophenyl)-2-(3-methoxyphenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

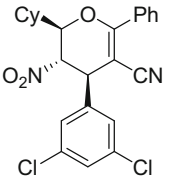
Yield: 68 mg, 71%; yellow solid; mp 224–226 °C; R_f = 0.5 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.53–7.43 (m, 3H), 7.38–7.25 (m, 2H), 7.19 (d, *J* = 1.5 Hz, 2H), 6.97–6.91 (m, 3H), 5.42 (d, *J* = 9.6 Hz, 1H), 4.88 (t, *J* = 9.9 Hz, 1H), 4.56 (d, *J* = 10.2 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 160.2, 139.0, 136.4, 133.8, 132.3, 130.8, 130.5, 129.9, 128.9, 128.6, 126.6, 119.5, 117.2, 116.0, 113.1, 90.2, 86.0, 80.2, 55.5, 46.6; IR (KBr) 2211, 1611, 1557, 1274, 1149, 862, 774, 695; HRMS (ESI) calcd for $C_{25}H_{19}Cl_2N_2O_4$ $[M+H]^+$ 481.07164, found 481.07206.



2.3i

(2R*,3S*,4R*)-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-2-(thiophen-2-yl)-3,4-dihydro-2H-pyran-5-carbonitrile

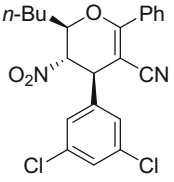
Yield: 69 mg, 76%; yellow solid; mp 218–220 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.54–7.39 (m, 5H), 7.19–7.15 (m, 3H), 7.04–7.01 (m, 1H), 5.79 (d, *J* = 9.6 Hz, 1H), 4.92 (t, *J* = 9.9 Hz, 1H), 4.54 (d, *J* = 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 138.8, 136.4, 134.2, 132.4, 130.6, 130.0, 128.9, 128.8, 128.6, 128.5, 127.5, 126.6, 117.1, 90.4, 86.2, 76.3, 46.7; IR (KBr) 2359, 2214, 1558, 1276, 1149, 807, 697; HRMS (ESI) calcd for $C_{22}H_{15}Cl_2N_2O_3S$ $[M+H]^+$ 457.01749, found 457.01795.



2.3j

(2R*,3S*,4R*)-2-cyclohexyl-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

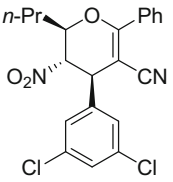
Yield: 46 mg, 50%; **2.3j/2.4j** = 14/1, yellow solid; R_f = 0.5 (**2.3j**), R_f = 0.51 (**4j**) (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ (**2.3j**) 7.79 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.55–7.47 (m, 3H), 7.40 (t, *J* = 1.8 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 2H), 4.81 (t, *J* = 10.0 Hz, 1H), 4.42 (d, *J* = 10.2 Hz, 1H), 4.35 (d, *J* = 10.0 Hz, 1H), 1.82–1.62 (m, 7H), 1.33–1.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (**2.3j**) 166.4, 139.4, 136.4, 132.2, 131.2, 129.9, 128.9, 128.4, 126.6, 117.4, 86.2, 85.5, 81.7, 46.5, 38.3, 29.8, 26.3, 26.0, 25.8, 25.1; IR (KBr) 2210, 1619, 1556, 1282, 1162, 805, 694; HRMS (ESI) calcd for $C_{24}H_{23}Cl_2N_2O_3$ $[M+H]^+$ 457.10802, found 457.10883.



2.3k

(2R*,3S*,4R*)-2-butyl-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

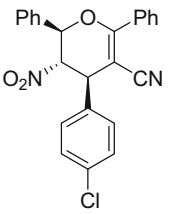
Yield: 62 mg, 72%; **2.3k/2.4k** = 7/1; yellow solid; R_f = 0.5 (**2.3k** and **2.4k**) (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ (**2.3k**) 7.79 (d, *J* = 6.9 Hz, 2H), 7.54–7.46 (m, 3H), 7.39 (s, 1H), 7.15 (d, *J* = 1.6 Hz, 2H), 4.65 (t, *J* = 9.9 Hz, 1H), 4.50–4.38 (m, 2H), 1.78–1.68 (m, 3H), 1.43–1.37 (m, 3H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (**2.3k**) 166.1, 139.3, 136.3, 132.2, 131.1, 129.8, 128.9, 128.4, 126.6, 117.3, 88.8, 85.7, 77.9, 46.1, 30.6, 26.4, 22.3, 13.9; IR (KBr) 2354, 2210, 1616, 1556, 1281, 1162, 805, 693; HRMS (ESI) calcd for $C_{22}H_{21}Cl_2N_2O_3$ $[M+H]^+$ 431.09237, found 431.09312.



2.3l

(2R*,3S*,4R*)-4-(3,5-dichlorophenyl)-3-nitro-6-phenyl-2-propyl-3,4-dihydro-2H-pyran-5-carbonitrile

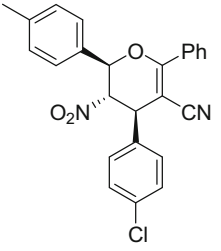
Yield: 53 mg, 64%; **2.3l/2.4l** = 5/1; yellow solid; R_f = 0.6 (**2.3l** and **2.4l**) (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ (**2.3l**) 7.79 (d, *J* = 6.9 Hz, 2H), 7.55–7.46 (m, 3H), 7.39 (s, 1H), 7.15 (d, *J* = 1.6 Hz, 2H), 4.64 (t, *J* = 9.9 Hz, 1H), 4.68–4.39 (m, 2H), 1.78–1.67 (m, 2H), 1.62–1.53 (m, 2H), 1.00 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (**2.3l**) 166.1, 139.3, 136.4, 132.2, 131.1, 129.8, 128.9, 128.4, 126.6, 117.3, 88.8, 85.7, 77.7, 46.1, 32.9, 17.9, 13.7; IR (KBr) 2213, 1616, 1556, 1306, 1189, 735, 697; HRMS (ESI) calcd for $C_{21}H_{19}Cl_2N_2O_3$ $[M+H]^+$ 417.07672, found 417.07700.



2.3m

(2R*,3S*,4R*)-4-(4-chlorophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 44 mg, 52%; yellow solid; mp 223–225 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.52–7.39 (m, 10H), 7.27–7.25 (m, 2H), 5.46 (d, *J* = 9.8 Hz, 1H), 4.88 (t, *J* = 10.1 Hz, 1H), 4.62 (d, *J* = 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 135.5, 134.0, 132.7, 132.1, 131.1, 130.7, 130.1, 129.3, 128.8, 128.6, 127.4, 117.5, 90.8, 87.0, 80.5, 46.8; IR (KBr) 2359, 2210, 1616, 1557, 1275, 1150, 835, 694; HRMS (ESI) calcd for $C_{24}H_{18}ClN_2O_3$ $[M+H]^+$ 417.10005, found 417.09991.

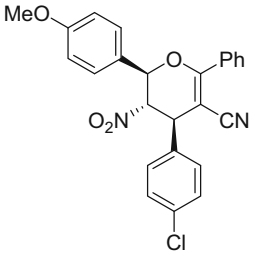


2.3n

(2R*,3S*,4R*)-4-(4-chlorophenyl)-3-nitro-6-phenyl-2-p-tolyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 55 mg, 64%; yellow solid; mp 197–199 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.1 Hz, 2H),

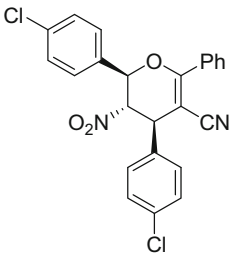
7.50–7.37 (m, 5H), 7.29–7.19 (m, 6H), 5.41 (d, J = 9.8 Hz, 1H), 4.88 (t, J = 10.1 Hz, 1H), 4.59 (d, J = 10.4 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 140.8, 135.4, 134.1, 132.1, 131.1, 130.0, 130.0, 129.7, 129.3, 128.8, 128.6, 127.3, 117.5, 90.7, 86.9, 80.4, 46.8, 21.4; IR (KBr) 2359, 2211, 1615, 1557, 1274, 1149, 818, 695; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_3$ $[M+H]^+$ 431.11570, found 431.11616.



2.3o

(2R*,3S*,4R*)-4-(4-chlorophenyl)-2-(4-methoxyphenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 52 mg, 58%; yellow solid; mp 194–196 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.2, 1.2 Hz, 2H), 7.50–7.23 (m, 9H), 6.91 (d, J = 8.7 Hz, 2H), 5.40 (d, J = 9.8 Hz, 1H), 4.87 (t, J = 10.1 Hz, 1H), 4.58 (d, J = 10.4 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 161.3, 135.4, 134.1, 132.1, 131.1, 130.0, 129.3, 128.9, 128.8, 128.6, 124.5, 117.6, 114.7, 90.7, 86.8, 80.3, 55.5, 46.9; IR (KBr) 2210, 1614, 1556, 1252, 1178, 1148, 737, 698; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_4$ $[M+H]^+$ 447.11061, found 447.11091.

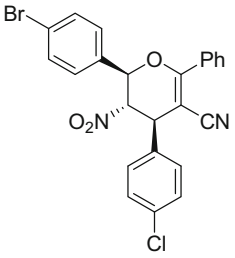


2.3p

(2R*,3S*,4R*)-2,4-bis(4-chlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 58 mg, 64%; yellow solid; mp 189–191 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.80 (m, 2H), 7.53–7.32 (m, 9H), 7.26–7.23 (m, 2H), 5.44 (d, J = 9.8 Hz, 1H), 4.84 (t, J = 10.1 Hz, 1H), 4.59 (d, J = 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 136.8, 135.5,

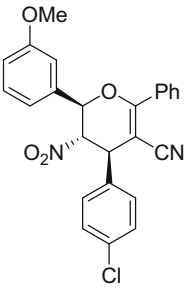
133.8, 132.2, 131.2, 130.9, 130.1, 129.6, 129.3, 128.9, 128.7, 128.5, 117.3, 90.6, 87.2, 79.7, 46.7; IR (KBr) 2360, 2211, 1616, 1557, 1272, 1149, 827, 696; HRMS (ESI) calcd for $C_{24}H_{17}Cl_2N_2O_3$ $[M+H]^+$ 451.06107, found 451.06121.



2.3q

(2R*,3S*,4R*)-2-(4-bromophenyl)-4-(4-chlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 72 mg, 73%; yellow solid; mp 194–196 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.55–7.37 (m, 7H), 7.27–7.22 (m, 4H), 5.41 (d, *J* = 9.8 Hz, 1H), 4.84 (t, *J* = 10.1 Hz, 1H), 4.58 (d, *J* = 10.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 135.5, 133.7, 132.5, 132.2, 131.7, 130.8, 130.0, 129.3, 128.9, 128.8, 128.5, 125.0, 117.3, 90.5, 87.1, 79.7, 46.7; IR (KBr) 2360, 2211, 1617, 1557, 1271, 1149, 824, 695; HRMS (ESI) calcd for $C_{24}H_{17}BrClN_2O_3$ $[M+H]^+$ 495.01056, found 495.01025.

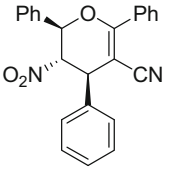


2.3r

(2R*,3S*,4R*)-4-(4-chlorophenyl)-2-(3-methoxyphenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 69 mg, 76%; yellow solid; mp 192–194 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2H), 7.52–7.24 (m, 8H), 6.97–6.92 (m, 3H), 5.42 (d, *J* = 9.8 Hz, 1H), 4.87 (t, *J* = 10.1 Hz, 1H), 4.60 (d, *J* = 10.3 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 160.2, 135.5, 134.1, 134.0, 132.1, 131.1, 130.5, 130.1, 129.3, 128.8, 128.6, 119.6, 117.5, 115.8, 113.2, 90.7, 87.0, 80.4, 55.5, 46.8; IR (KBr) 2359, 2210, 1614,

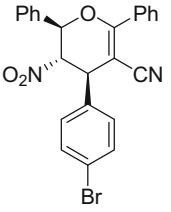
1557, 1273, 1151, 778, 697; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_4$ $[M+H]^+$ 447.11061, found 447.11115.



2.3s

(2R*,3S*,4R*)-3-nitro-2,4,6-triphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

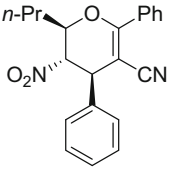
Yield: 62 mg, 81%; **2.3s/2.4s** = 3/1; yellow solid. A small amount of **2.3s** was obtained by carful recrystallization. Analytical data for **2.3s**: mp 238–240 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, DMSO) δ 7.73 (d, *J* = 6.8 Hz, 2H), 7.63–7.39 (m, 13H), 5.83 (d, *J* = 9.7 Hz, 1H), 5.71 (t, *J* = 10.0 Hz, 1H), 4.70 (d, *J* = 10.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 165.2, 136.0, 133.4, 131.7, 131.5, 130.2, 129.1, 128.8, 128.6, 128.5, 128.4, 128.3, 117.8, 88.5, 87.3, 79.8, 46.5; IR (KBr) 2211, 1617, 1556, 1273, 1148, 773, 697. HRMS (ESI) calcd for $C_{24}H_{19}N_2O_3$ $[M+H]^+$ 383.13902, found 383.13993.



2.3t

(2R*,3S*,4R*)-4-(4-bromophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 60 mg, 65%; yellow solid; mp 220–222 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84–7.81 (m, 2H), 7.57–7.39 (m, 10H), 7.19 (dd, *J* = 8.8, 2.2 Hz, 2H), 5.45 (d, *J* = 9.8 Hz, 1H), 4.88 (t, *J* = 10.1 Hz, 1H), 4.60 (d, *J* = 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 134.6, 133.0, 132.7, 132.1, 131.1, 130.7, 129.6, 129.3, 128.8, 128.6, 127.4, 123.6, 117.5, 90.7, 86.9, 80.5, 46.9; IR (KBr) 2210, 1616, 1556, 1276, 1149, 830, 696; HRMS (ESI) calcd for $C_{24}H_{18}BrN_2O_3$ $[M+H]^+$ 461.04953, found 461.05042.

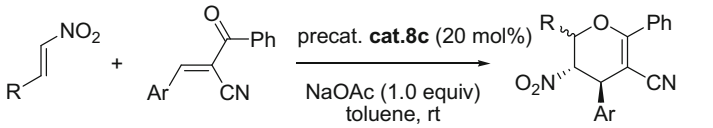


2.3u

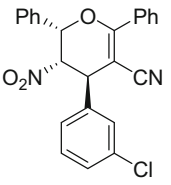
(2R*,3S*,4R*)-3-nitro-4,6-diphenyl-2-propyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 42 mg, 60%; yellow solid; mp 173–175 °C; R_f = 0.5 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.51–7.37 (m, 6H), 7.26 (dd, *J* = 7.4, 1.5 Hz, 2H), 4.69 (t, *J* = 9.9 Hz, 1H), 4.53–4.42 (m, 2H), 1.81–1.52 (m, 4H), 0.99 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 135.9, 131.8, 131.5, 129.7, 129.3, 128.8, 128.4, 127.9, 117.7, 89.6, 87.2, 77.7, 46.7, 33.0, 17.9, 13.7; IR (KBr) 2359, 2209, 1616, 1556, 1306, 1159, 761, 697; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.15467, found 349.15506.

2.8.3 *[4+2] Annulation of Nitroalkenes with α-Cyano-α,β-Unsaturated Ketones Catalyzed by NHC-Precursor Cat.8c*



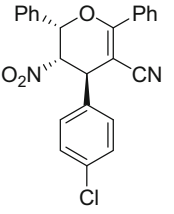
An oven-dried 50 mL Schlenk tube was charged with nitroalkenes **2.1** (0.4 mmol, 2.0 eq.), α-cyano α,β-unsaturated ketones **2.2** (0.2 mmol, 1.0 eq.), **cat.8c** (16 mg, 0.04 mol, 0.2 eq.), and AcONa (0.2 mmol, 16 mg, 1.0 eq.). To this mixture was added freshly distilled toluene (2 mL). The reaction mixture was stirred at room temperature until the full consumption of the α-cyano α,β-unsaturated ketones (typically, 18 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleumether/EtOAc as the eluent, typically 20:1-0:100) to furnish the corresponding cycloadduct as a mixture of *trans*- and *cis* isomers.



2.4a

(2S*,3S*,4R*)-4-(3-chlorophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

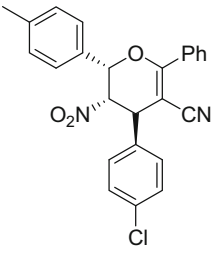
Total yield: 74 mg, 90%; **2.4a/2.3a** = 3/1; yellow solid. A small amount of **2.4a** was obtained by recrystallization. Analytical data for **2.4a**: R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, DMSO) δ 7.91 (dd, *J* = 7.4, 2.1 Hz, 2H), 7.79 (s, 1H), 7.62–7.59 (m, 3H), 7.53–7.49 (m, 3H), 7.38 (d, *J* = 1.6 Hz, 5H), 5.75 (d, *J* = 2.0 Hz, 1H), 5.55 (d, *J* = 1.3 Hz, 1H), 4.85 (s, 1H); ^{13}C NMR (75 MHz, DMSO) δ 165.6, 140.5, 134.1, 133.7, 132.1, 131.4, 130.8, 129.2, 128.7, 128.6, 128.5, 128.2, 127.8, 125.6, 118.8, 85.8, 84.0, 73.6, 41.7. IR (KBr) 2210, 1622, 1556, 1156, 776, 696; HRMS (ESI) calcd for $C_{24}H_{18}ClN_2O_3$ $[M+H]^+$ 417.10005, found 417.10039.



2.4m

(2S*,3S*,4R*)-4-(4-chlorophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 73 mg, 87%; **2.4 m/2.3 m** = 3/1; yellow solid. A small amount of **2.4 m** was obtained by carful chromatograph. Analytical data for **2.4 m**: mp 176–178 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.93 (m, 2H), 7.53–7.46 (m, 5H), 7.39–7.37 (m, 5H), 7.25–7.23 (m, 2H), 5.35 (d, *J* = 2.3 Hz, 1H), 5.01 (t, *J* = 2.2 Hz, 1H), 4.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 136.4, 135.4, 133.3, 131.9, 131.8, 130.2, 129.9, 129.7, 129.2, 128.8, 128.5, 125.7, 118.5, 87.2, 83.4, 74.0, 43.6; IR (KBr) 2210, 1624, 1555, 1298, 1159, 828, 697; HRMS (ESI) calcd for $C_{24}H_{18}ClN_2O_3$ $[M+H]^+$ 417.10005, found 417.09975.

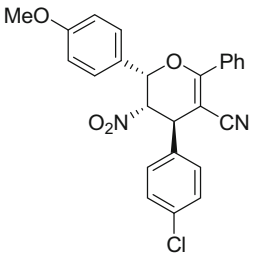


2.4n

(2S*,3S*,4R*)-4-(4-chlorophenyl)-3-nitro-6-phenyl-2-(p-tolyl)-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 78 mg, 91%; **2.4n/2.3n** = 3/1; yellow solid. A small amount of **2.4n** was obtained by carful chromatograph. Analytical data for **2.4n**: mp 159–161 °C;

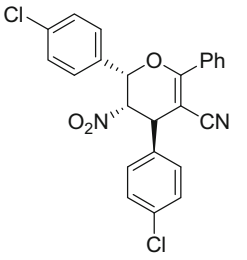
R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.52–7.45 (m, 5H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.14 (dd, *J* = 19.6, 8.2 Hz, 4H), 5.33 (d, *J* = 2.3 Hz, 1H), 4.98 (t, *J* = 2.4 Hz, 1H), 4.36 (d, *J* = 1.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 139.7, 136.4, 135.3, 131.9, 131.8, 130.3, 130.1, 129.9, 129.8, 128.8, 128.5, 125.6, 118.6, 87.3, 83.4, 74.1, 43.5, 21.3; IR (KBr) 2210, 1624, 1555, 1298, 1159, 830, 696; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_3$ $[M+H]^+$ 431.11570, found 431.11618.



2.4o

(2S*,3S*,4R*)-4-(4-chlorophenyl)-2-(4-methoxyphenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 75 mg, 85%; **2.4o/2.3o** = 2/1; yellow solid. A small amount of **2.4o** was obtained by carful chromatograph. Analytical data for **2.4o**: mp 179–181 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94–7.91 (m, 2H), 7.55–7.45 (m, 5H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.31 (d, *J* = 2.5 Hz, 1H), 4.97 (t, *J* = 2.3 Hz, 1H), 4.36 (d, *J* = 1.6 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 160.6, 136.4, 135.3, 131.9, 131.8, 130.1, 129.9, 128.8, 128.5, 127.1, 125.2, 118.6, 114.6, 87.3, 83.4, 74.0, 55.5, 43.5; IR (KBr) 2210, 1615, 1555, 1254, 1159, 826, 772, 696; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_4$ $[M+H]^+$ 447.11061, found 447.11062.

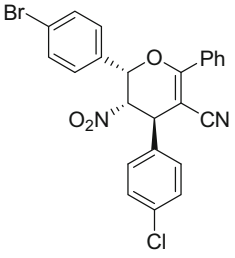


2.4p

(2S*,3S*,4R*)-2,4-bis(4-chlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 83 mg, 92%; **2.4p/2.3p** = 2/1; yellow solid. A small amount of **2.4p** was obtained by carful chromatograph. Analytical data for **2.4p**: mp 174–176 °C;

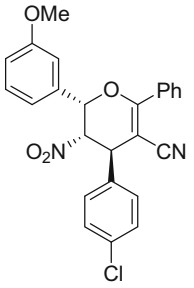
R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.91 (m, 2H), 7.57–7.46 (m, 5H), 7.39–7.34 (m, 4H), 7.18 (d, *J* = 8.5 Hz, 2H), 5.31 (d, *J* = 2.2 Hz, 1H), 4.97 (t, *J* = 2.1 Hz, 1H), 4.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 136.2, 135.7, 135.5, 132.0, 131.9, 131.6, 130.3, 129.8, 129.4, 128.9, 128.4, 127.1, 118.3, 87.0, 83.5, 73.4, 43.5; IR (KBr) 2210, 1624, 1555, 1298, 1159, 830, 696; HRMS (ESI) calcd for $C_{24}H_{17}Cl_2N_2O_3$ $[M+H]^+$ 451.06107, found 451.06127.



2.4q

(2S*,3S*,4R*)-2-(4-bromophenyl)-4-(4-chlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

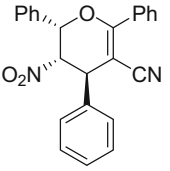
Total yield: 82 mg, 83%; **2.4q/2.3q** = 2/1; yellow solid. A small amount of **2.4q** was obtained by carful chromatograph. Analytical data for **2.4q**: mp 186–188 °C; R_f = 0.42 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.90 (m, 2H), 7.56–7.46 (m, 7H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.29 (d, *J* = 1.8 Hz, 1H), 4.97 (d, *J* = 1.8 Hz, 1H), 4.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 136.2, 135.5, 132.4, 132.4, 132.0, 131.6, 130.2, 129.8, 128.9, 128.4, 127.3, 123.9, 118.3, 86.9, 83.5, 73.4, 43.5; IR (KBr) 2210, 1620, 1555, 1297, 1158, 826, 695; HRMS (ESI) calcd for $C_{24}H_{17}BrClN_2O_3$ $[M+H]^+$ 495.01056, found 495.01076.



2.4r

(2S*,3S*,4R*)-4-(4-chlorophenyl)-2-(3-methoxyphenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

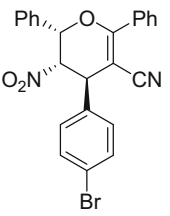
Total yield: 80 mg, 90%; **2.4r/2.3r** = 4/1; yellow solid. A small amount of **2.4r** was obtained by carful chromatograph. Analytical data for **2.4r**: mp 154–156 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.55–7.45 (m, 5H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.28–7.25 (m, 1H), 6.91–6.88 (m, 1H), 6.80–6.78 (m, 2H), 5.30 (d, *J* = 2.2 Hz, 1H), 5.00 (t, *J* = 2.1 Hz, 1H), 4.37 (d, *J* = 0.9 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.1, 136.4, 135.4, 134.8, 131.9, 130.3, 130.2, 129.9, 128.8, 128.5, 118.5, 117.8, 114.6, 111.8, 87.2, 83.4, 73.8, 55.5, 43.5; IR (KBr) 2210, 1613, 1555, 1293, 1151, 772, 694; HRMS (ESI) calcd for $C_{25}H_{20}ClN_2O_4$ $[M+H]^+$ 447.11061, found 447.11061.



2.4s

(2S*,3S*,4R*)-3-nitro-2,4,6-triphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 68 mg, 89%; **2.4s/2.3s** = 5/1; yellow solid. A small amount of **2.4s** was obtained by carful recrystallization. Analytical data for **2.4s**: R_f = 0.5 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.53–7.35 (m, 11H), 7.25 (s, 2H), 5.38 (d, *J* = 2.1 Hz, 1H), 5.10 (t, *J* = 2.1 Hz, 1H), 4.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 138.0, 133.6, 132.0, 131.7, 129.9, 129.6, 129.4, 129.2, 129.1, 128.8, 128.5, 125.7, 118.8, 87.5, 83.7, 73.8, 44.3; IR (KBr) 2210, 1623, 1556, 1290, 1152, 769, 698. HRMS (ESI) calcd for $C_{24}H_{19}N_2O_3$ $[M+H]^+$ 383.13902, found 383.13918.

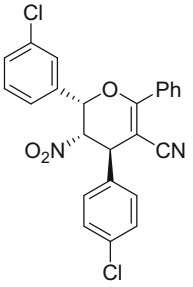


2.4t

(2S*,3S*,4R*)-4-(4-bromophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 85 mg, 93%; **2.4t/2.3t** = 4/1; yellow solid. A small amount of **2.4t** was obtained by carful chromatograph. Analytical data for **2.4t**: mp 170–172 °C; R_f = 0.35 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 6.6 Hz, 2H), 7.63–7.05 (m, 5H), 7.38–7.22 (m, 7H), 5.35 (d, *J* = 1.9 Hz, 1H), 5.01 (d, *J* = 1.8 Hz, 1H), 4.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$)

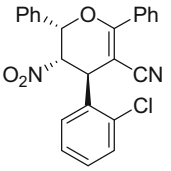
δ 166.5, 136.9, 133.3, 133.1, 131.9, 131.8, 130.2, 129.7, 129.1, 128.8, 128.5, 125.6, 123.5, 118.5, 87.1, 83.3, 74.0, 43.6; IR (KBr) 2210, 1624, 1555, 1298, 1159, 824, 696; HRMS (ESI) calcd for $C_{24}H_{18}BrN_2O_3$ $[M+H]^+$ 461.04953, found 461.04928.



2.4v

(2S*,3S*,4R*)-2-(3-chlorophenyl)-4-(4-chlorophenyl)-3-nitro-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Total yield: 79 mg, 88%; **2.4v**/**2.3v** = 2/1; yellow solid. A small amount of **2.4v** was obtained by carful chromatograph. Analytical data for **2.4v**: mp 100–102 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.57–7.47 (m, 5H), 7.39–7.23 (m, 5H), 7.13 (d, *J* = 7.3 Hz, 1H), 5.29 (s, 1H), 4.99 (dd, *J* = 2.3, 1.6 Hz, 1H), 4.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 136.1, 135.5, 135.4, 135.2, 132.0, 131.6, 130.5, 130.3, 129.8, 128.9, 128.5, 125.9, 123.8, 118.3, 86.9, 83.6, 73.1, 43.6; IR (KBr) 2210, 1556, 1298, 1151, 831, 694; HRMS (ESI) calcd for $C_{24}H_{17}Cl_2N_2O_3$ $[M+H]^+$ 451.06107, found 451.06113.

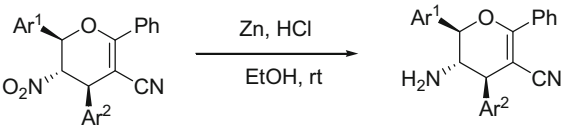


2.4w

(2S*,3S*,4R*)-4-(2-chlorophenyl)-3-nitro-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

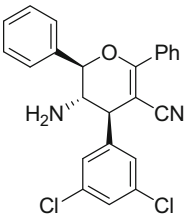
Yield: 37 mg, 44%; white solid; mp 158–160 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.94 (m, 2H), 7.57–7.47 (m, 5H), 7.43–7.35 (m, 5H), 7.24–7.21 (m, 2H), 5.26 (d, *J* = 1.8 Hz, 1H), 5.04 (dd, *J* = 2.4, 1.1 Hz, 1H), 4.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 134.8, 134.2, 133.4, 131.9, 131.8, 131.0, 130.6, 130.3, 129.6, 129.1, 128.8, 128.5, 128.1, 125.7, 118.6, 85.5, 83.0, 74.1, 41.8; IR (KBr) 2359, 2210, 1622, 1555, 1295, 1156, 856, 695; HRMS (ESI) calcd for $C_{24}H_{18}ClN_2O_3$ $[M+H]^+$ 417.10005, found 417.10029.

2.8.4 Reduction of the Nitro Group of 2.3



2.3 **2.5**

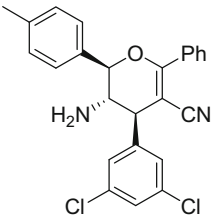
Typical procedure: To a stirred solution of **2.3c** (128 mg, 0.28 mmol) in EtOH (4 mL) was added zinc powder (330 mg, 18.0 eq.) and 1.5 mL of 6 M HCl (aq.). The resulting reaction mixture was stirred at room temperature for 1.0 h. followed by the filtration through Celite with washing by ether. The solvent was removed in vacuo. NaOH (15%) was added to the above mixture until pH 10. The aqueous layer was extracted with ether, the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the products **2.5c**.



2.5b

(2R*,3S*,4R*)-3-amino-4-(3,5-dichlorophenyl)-2,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile

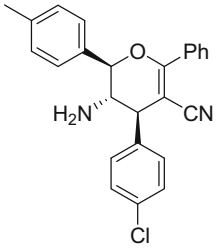
Yield: 79%; yellow solid; mp 181–183 °C; R_f = 0.5 (petroleum ether/ethyl acetate = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.47–7.35 (m, 9H), 7.28 (d, *J* = 1.8 Hz, 2H), 4.86 (d, *J* = 9.5 Hz, 1H), 3.60 (d, *J* = 9.5 Hz, 1H), 3.23 (t, *J* = 9.5 Hz, 1H), 0.93 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 143.0, 135.9, 132.1, 131.6, 129.7, 129.2, 128.8, 128.6, 128.5, 127.8, 127.1, 118.9, 86.7, 84.6, 56.3, 49.9; IR (KBr) 2359, 2207, 1613, 1587, 1270, 1156, 801, 698; HRMS (ESI) calcd for $C_{24}H_{19}Cl_2N_2O$ $[M+H]^+$ 421.08690, found 421.08717.



2.5c

(2R*,3S*,4R*)-3-amino-4-(3,5-dichlorophenyl)-6-phenyl-2-(p-tolyl)-3,4-dihydro-2H-pyran-5-carbonitrile

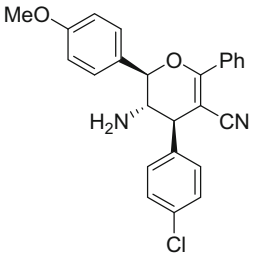
Yield: 86%; yellow solid; mp 100–102 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.45–7.20 (m, 10H), 4.82 (d, *J* = 9.5 Hz, 1H), 3.57 (d, *J* = 9.5 Hz, 1H), 3.22 (t, *J* = 9.5 Hz, 1H), 2.37 (s, 3H), 0.98 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 143.1, 139.6, 135.8, 132.9, 132.1, 131.4, 129.7, 128.6, 128.5, 128.5, 127.7, 127.1, 118.9, 86.5, 84.6, 56.1, 50.0, 21.3; IR (KBr) 2360, 2207, 1613, 1567, 1269, 1156, 803, 696; HRMS (ESI) calcd for $C_{25}H_{21}Cl_2N_2O$ $[M+H]^+$ 435.10255, found 435.10376.



2.5n

(2R*,3S*,4R*)-3-amino-4-(4-chlorophenyl)-6-phenyl-2-(p-tolyl)-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 90%; yellow solid; mp 169–171 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.45–7.31 (m, 9H), 7.24 (d, *J* = 7.8 Hz, 2H), 4.85 (d, *J* = 9.5 Hz, 1H), 3.62 (d, *J* = 9.5 Hz, 1H), 3.23 (t, *J* = 9.5 Hz, 1H), 2.37 (s, 3H), 0.96 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 139.6, 137.9, 134.2, 133.3, 132.4, 131.3, 129.9, 129.8, 129.6, 128.8, 128.5, 127.7, 119.2, 87.4, 84.6, 56.3, 49.8, 21.4; IR (KBr) 2359, 2206, 1613, 1516, 1274, 1154, 816, 697; HRMS (ESI) calcd for $C_{25}H_{22}ClN_2O$ $[M+H]^+$ 401.14152, found 401.14203.

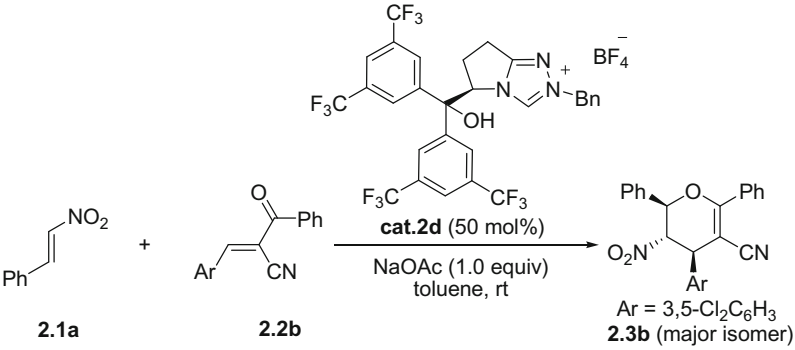


2.5o

(2R*,3S*,4R*)-3-amino-4-(4-chlorophenyl)-2-(4-methoxyphenyl)-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile

Yield: 70%; yellow solid; mp 180–182 °C; R_f = 0.5 (petroleum ether/ethyl acetate = 1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.38-7.25 (m, 9H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.77 (d, *J* = 9.5 Hz, 1H), 3.75 (s, 3H), 3.55 (d, *J* = 9.5 Hz, 1H), 3.16 (t, *J* = 9.5 Hz, 1H), 1.18 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 160.6, 138.0, 134.2, 132.5, 131.3, 129.9, 129.6, 129.1, 128.5, 128.5, 128.2, 119.2, 114.5, 87.4, 84.4, 56.3, 55.5, 49.8; IR (KBr) 23580, 2206, 1613, 1515, 1277, 1153, 829, 698; HRMS (ESI) calcd for $C_{25}H_{22}ClN_2O_2$ $[M+H]^+$ 417.13643, found 417.13700.

2.8.5 Recation Catalyzed by Chiral NHC-Precursor Cat.2d



The reaction was carried out as the same procedure in Table 2.1: Yield: 24%; HPLC analysis: 29% ee. [Daicel CHIRALPAK AD-H column; 20 °C; 0.8 mL/min; solvent system: isopropanol/hexanes = 8:92; retention times: 13.5 min (minor), 14.9 min (major)].

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Chapter 3
NHC-Catalyzed Enantioselective Annulations of Enals

3.1 Introduction

The combination of N-heterocyclic carbene (NHC) catalysts with enals has emerged as one of the most powerful methods for annulation reactions. In recent years, inspired by the pioneering studies of Bode et al. [1] and Glorius et al. [2], many research groups have shown that [3+n] annulation of enals through an a^3–d^3 umpolung are able to construct a range of hetero- and carbocyclic compounds [3–8]. Enals via α-addition for [2+4] annulation under the catalyst of NHC were also established [9]. In sharp contrast to these well-developed annulations, the corresponding [4+2] annulations of enals via γ-addition were hardly reported. In 2011, Ye and coworkers reported an NHC-catalyzed [4+2] annulation of α,β-unsaturated acyl chlorides with activated ketones (Fig. 3.1) [10].

In 2012, Chi and co-workers reported a pioneering oxidative NHC-catalyzed [4+2] annulation of enals with trifluoromethyl ketones via γ-addition (Fig. 3.2) [11].

γ-Amino acids and their derivatives play an important role in the central nervous system (CNS) [12–14]. Especially, chiral derivatives of γ-amino acids with branch-chains have shown useful pharmacological properties for the treatment of several nervous system disorders as important pharmaceuticals. Therefore, great efforts have been devoted to this field. However, the development of stereoselective process for synthesis of γ-amino acid derivatives from simple starting materials is still an unmet challenge [15, 16]. The catalytic asymmetric amination provide efficient and useful access to *N*-containing compounds. However, to the best of our knowledge, only sporadic applications were reported to afford γ-amino acid derivatives by this methodology [17, 18].

Recently, we reported a cinchona alkaloids-catalyzed [4+2] annulation of α,β-unsaturated acyl chlorides and azodicarboxylates. The reaction worked well for the synthesis of various γ-amino acids but not for γ-aryl ones due to the difficulty in preparation of γ-aryl-α,β-unsaturated acyl chlorides (Fig. 3.3) [19].

X. Chen, *New Strategies for N-Heterocyclic Carbenes Catalyzed Annulations*,
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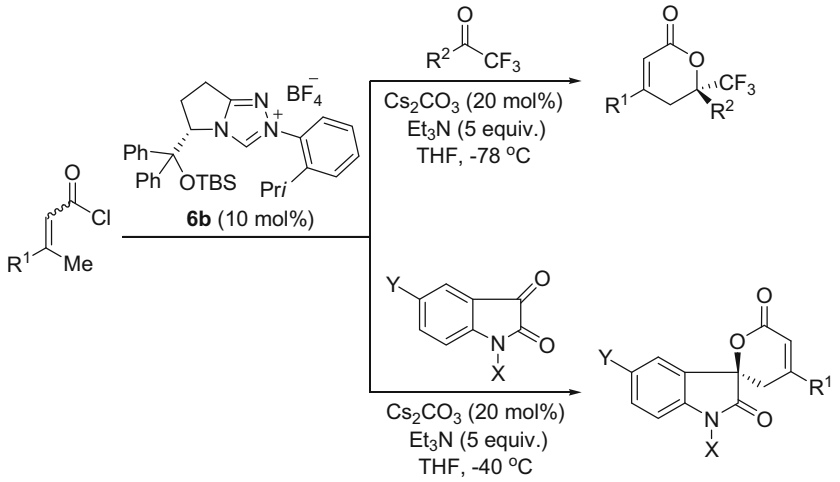


Fig. 3.1 NHC-catalyzed [4+2] annulation of α,β-unsaturated acyl chlorides

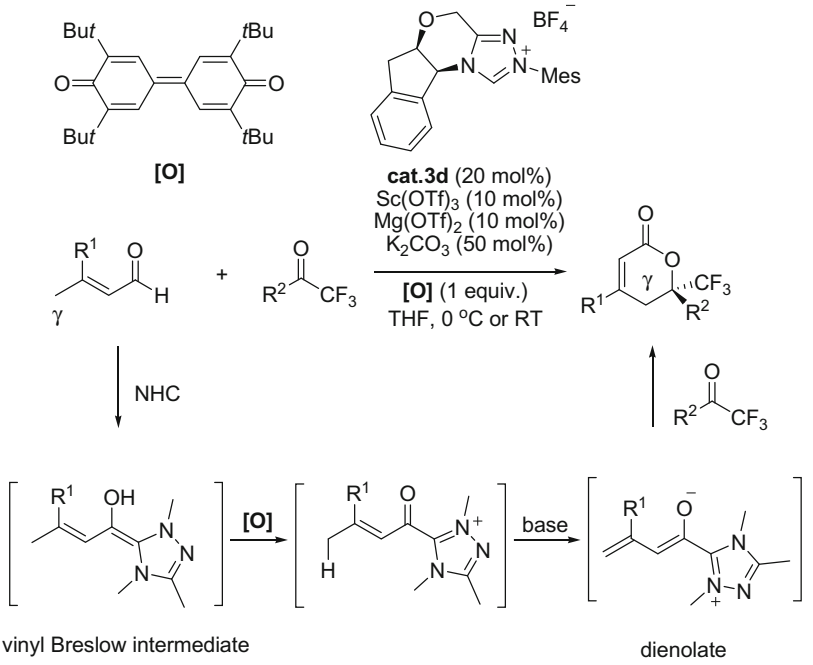


Fig. 3.2 NHC-catalyzed oxidative [4+2] annulation of enals

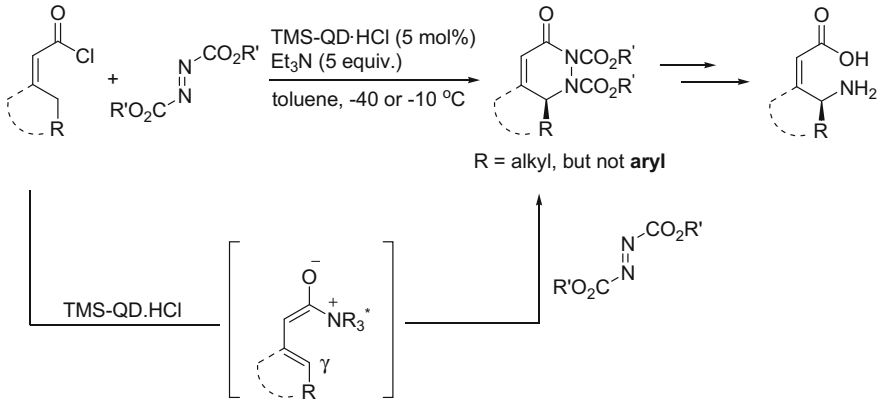


Fig. 3.3 Alkaloids-catalyzed [4+2] annulation of α,β-unsaturated acyl chlorides

We envisioned that if a leaving group was introduced to the γ position of enals, the dienolate intermediate would be formed to react with azodicarboxylates. And the γ-amino acid derivatives could be prepared by subsequent transformations of the resulting dihydropyridazinones (Fig. 3.4).

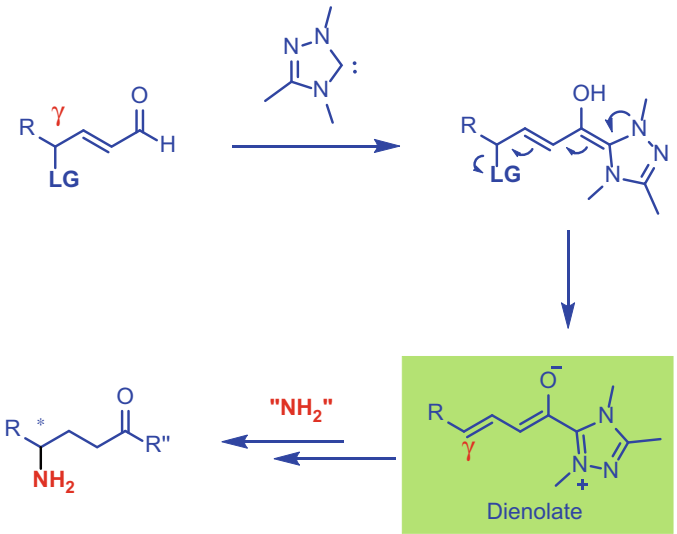
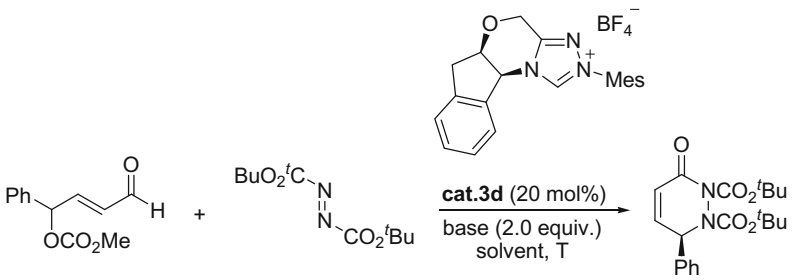


Fig. 3.4 Reaction design

3.2 Optimization of Conditions

Initially, the model reaction of enal **3.1a** and *di-tert*-butyl azodicarboxylate (DTBAD) **3.2a** was investigated under various reaction conditions (Table 3.1). We were pleased to find that catalyst **cat.3d** furnished the desired product **3.3a** in 33% yield and 99% ee in the presence of sodium acetate as the base (entry 1). Attempts to increase the yield by tuning the reaction temperature proved unsatisfactory (entries 2–3). Solvent screening revealed that reaction in THF gave the better yield and high enantioselectivity (entries 3–6). Further investigations showed that an excess of DTBAD instead of an excess of aldehyde has limited effect for the reaction (entries 7–9). The yield was improved when potassium carbonate was used as the base (entries 10–12), and satisfactory yield (82%) with 99% ee was obtained when 1.1 equiv of DTBAD was employed (entry 11).

Table 3.1 Reaction optimization



3.1a **3.2a** **3.3a**

Entry	**3.1a/3.2a**	Solvent	Base	Yield (%)[a]	Ee (%)[b]
1	1.5/1	DCM	AcONa	33	99
2	1.5/1	DCM	AcONa	44[c]	99
3	1.5/1	DCM	AcONa	41[d]	99
4	1.5/1	CH_3CN	AcONa	Trace	/
5	1.5/1	Toluene	AcONa	41	96
6	1.5/1	THF	AcONa	60	99
7	1.2/1	THF	AcONa	57	99
8	1/1.2	THF	AcONa	60	99
9	1/1.5	THF	AcONa	53	99
10	1/1.5	THF	K_2CO_3	81	99
11	*1/1.1*	*THF*	*K_2CO_3*	82	*99*
12	1/1.0	THF	K_2CO_3	79	99

[a]Isolated yield
[b]Determined by HPLC using a chiral stationary phase
[c]The reaction was carried out at 30 °C
[d]The reaction was carried out under reflux

3.3 Substrate Scope

With these optimized conditions in hand, we tested a broad scope of different enals (Table 3.2). Both electron-donating (4-MeC_6H_4) and electron-withdrawing group (4-F, 4-Cl, 4-BrC_6H_4) in aromatic enals were tolerable to give the cycloadducts **3.3a–3.3e** in good yields with good enantioselectivities. Aromatic enals with *meta*-substituents (3-Br, 3-Me, 3-OMeC_6H_4) also went well (cycloadducts **3.3f**, **3.3g**, and **3.3h**). Substituent(s) at *ortho*-position (2-MeC_6H_4) or *di-meta*-positions (3,5-Me_2-C_6H_3) had no negative effect on the reaction and good yield and high enantioselectivity were obtained (**3.3i** and **3.3j**). The reaction of 1-naphthyl enals and 2-naphthyl enals gave the corresponding dihydropyridazinone in 73% yield with 98% ee, and 61% yield with 98% ee, respectively (**3.3k** and **3.3l**). It was worth noting that aliphatic enals were also tested for the reaction, affording the desired cycloadducts **3.3m–3.3n** in good yield with excellent enantioselectivity. In addition, the substrate with a vinyl group (**3.3o**) gave the product in 54% yield with 94% ee.

The scope of the general organocatalytic system was further investigated by the reaction of different azodicarboxylates under the optimized conditions (Table 3.3). Various alkyl group R′ at azodicarboxylates **3.2** were successfully employed, and the desired cycloadducts were obtained in 49–65% yield with excellent enantioselectivity (**3.3p–3.3s**).

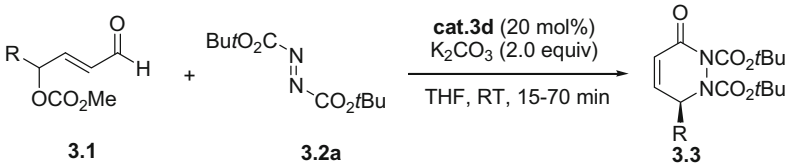
The *R* configuration of **3.3d** having a γ-aryl group was determined by the X-ray analysis of its crystal (Fig. 3.5).

3.4 Applications

Dihydropyridazinones are structurally interesting in their own right; they could be also rapidly transformed to the corresponding tetrahydropyridazin-3-ones, which have been widely used as orally active, selective, potent 5-lipoxygenase inhibitors [20–25]. When the *N*-Boc protected dihydropyridazinone **3.3c** was employed, the corresponding product **3.4c** could be easily afforded by a process of hydrogenation and deprotection (Fig. 3.6a). The *N*-Cbz protected dihydropyridazinone **3.3s** could be converted to the desired product **3.4s** in quantitative yield and high enantioselectivety by hydrogenation with Pd/C (Fig. 3.6b).

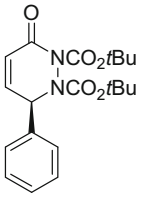
Our utmost interest is to gain access to optically active γ-amino acid derivatives through this method. We were happy to find that a series of different aryl γ-amino acid derivatives (**3.5b** and **3.5c**) was successfully afforded in good yield without loss of optical purity via hydrogenation of the dihydropyridazinones **3.3**, followed by hydrolysis, esterification, deprotection, and finally N–N bond cleavage (Fig. 3.7).

Table 3.2 Scope of enals

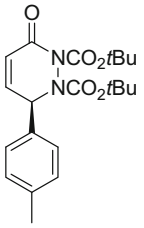


3.1 **3.2a** **3.3**

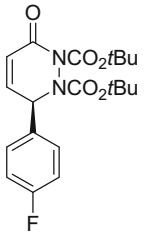
Isolated yield and ee of **3.3**



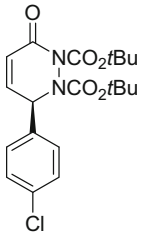
3.3a 82%, 99% ee



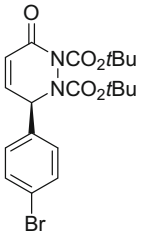
3.3b 81%, 99% ee



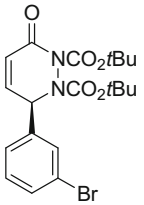
3.3c 80%, 98% ee



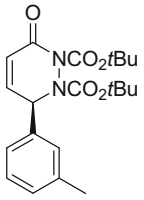
3.3d 71%, 98% ee



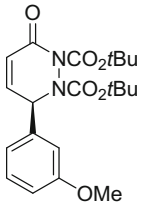
3.3e 79%, 97% ee



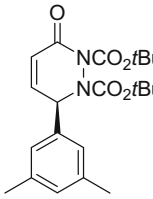
3.3f 64%, 99% ee



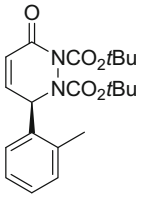
3.3g 86%, 99% ee



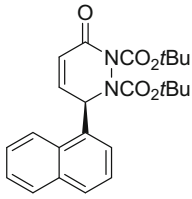
3.3h 58%, 95% ee



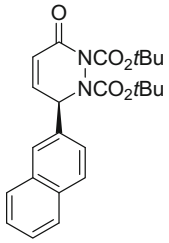
3.3i 79%, 97% ee



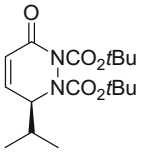
3.3j 74%, 99% ee



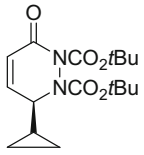
3.3k 73%, 98% ee



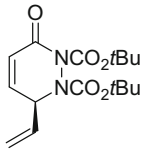
3.3l 61%, 98% ee



3.3m 52%, 98% ee

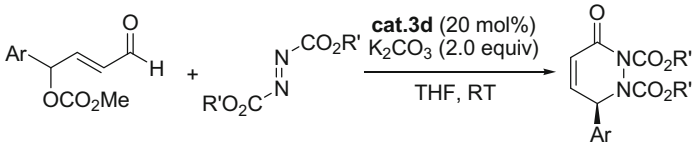


3.3n 62%, 96% ee



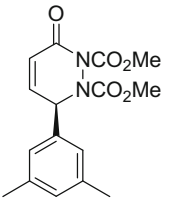
3.3o 54%, 94% ee

Table 3.3 Scope of azodicarboxylates

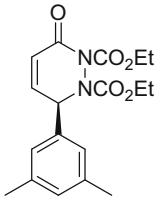


3.1 **3.2** **3.3**

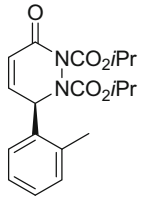
Isolated yield and ee of **3.3**



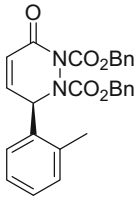
3.3p 49%, 98% ee



3.3q 58%, 98% ee

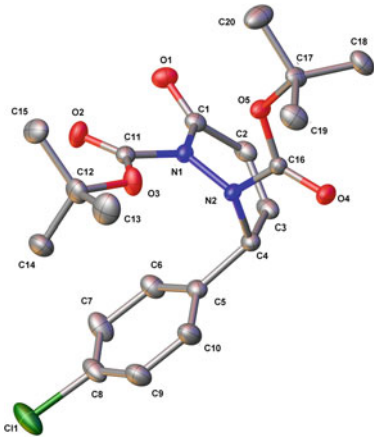


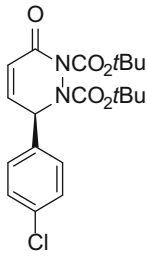
3.3r 65%, 98% ee



3.3s 57%, 99% ee

Fig. 3.5 X-ray structure of **3.3d**





3.3d

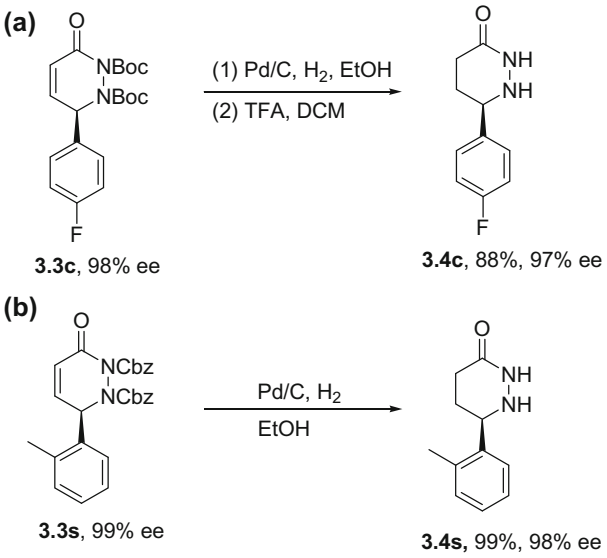


Fig. 3.6 Synthesis of tetrahydropyridazinones. Reproduced from Ref. [26] by permission of John Wiley & Sons Ltd.

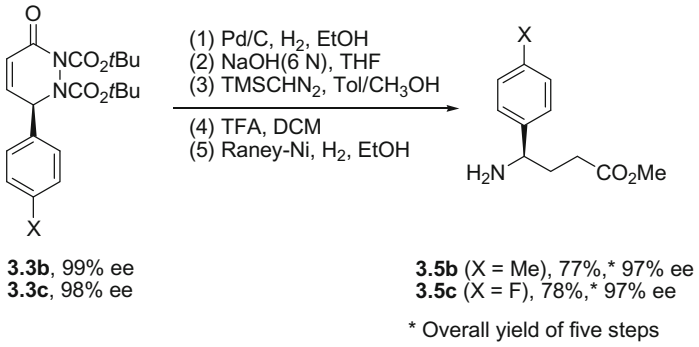


Fig. 3.7 Synthesis of γ-amino esters. Reproduced from Ref. [26] by permission of John Wiley & Sons Ltd.

3.5 Mechanistic Studies

A plausible catalytic cycle is depicted in Fig. 3.8. Firstly, the addition of NHC to enals affords the vinyl Breslow intermediate **I**. Then the azolium dienol **II** is formed by removal of the γ leaving group. The γ addition of the dienol to the

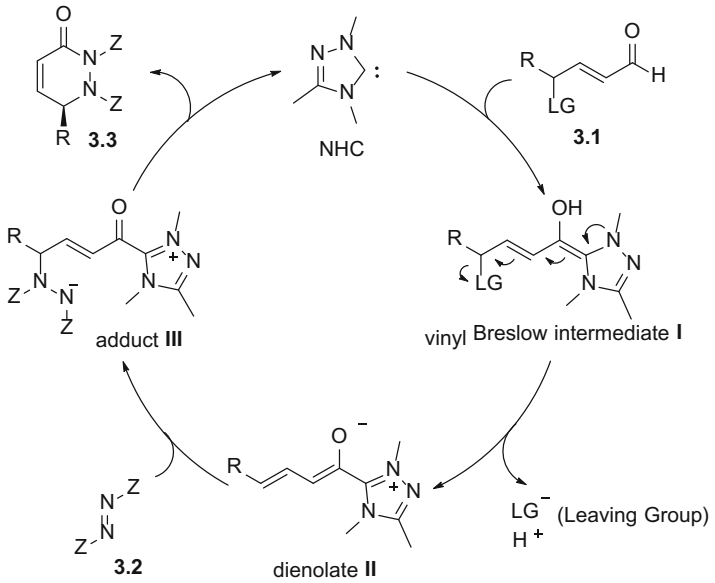


Fig. 3.8 Plausible catalytic cycle. Reproduced from Ref. [26] by permission of John Wiley & Sons Ltd.

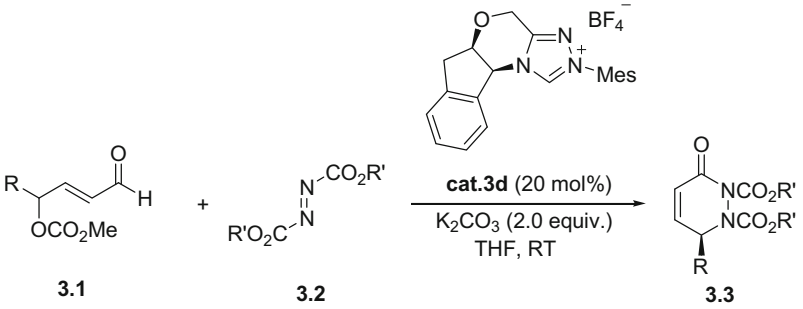
azodicarboxylate gives the acyl azolium adduct **III**, the following subsequent cyclization provides the final annulation product **3.3** and regenerates the NHC catalyst.

3.6 Conclusion

In conclusion, a quite general strategy has been developed for the preparation of a wide scope of γ-amino acid derivatives and tetrahydropyridazin-3-ones, which were afforded in good yields with excellent enantioselectivities [26]. In this strategy, enals were employed as four-carbon synthons for the NHC-catalyzed [4+2] annulations with azodicarboxylates. The reaction worked well for γ-aryl, alkyl and alkenyl enal derivatives.

3.7 Experimental Section

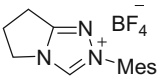
3.7.1 NHC-Catalyzed [4+2] Annulation of Enals and Azodicarboxylates



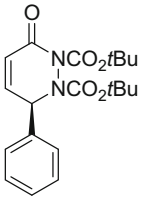
3.1 **3.2** **3.3**

To a solution of γ-oxidized enals **3.1** (0.2 mmol, 1.0 equiv.) in THF (2 ml), was added azodicarboxylates **3.2** (0.22 mmol, 1.1 equiv.), NHC precursor **cat.3d** (0.04 mmol, 16.7 mg, 0.2 equiv.) and K_2CO_3 (0.4 mmol, 55 mg, 2.0 equiv.). The reaction mixture was stirred at room temperature until the full consumption of the enals (typically, 15–70 min). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleumether/EtOAc as the eluent, typically 20:1-2:1) to furnish the corresponding products.

Racemic samples for the chiral phase HPLC analysis were prepared using triazolium **cat.5b** as the NHC pre-catalyst under the same conditions.



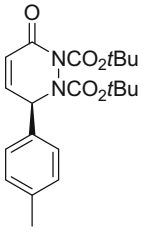
cat.5b



3.3a

(*R*)-di-*tert*-butyl 3-oxo-6-phenylpyridazine-1,2(*3H*,*6H*)-dicarboxylate

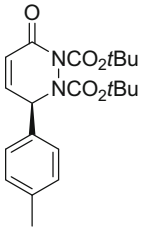
Yield 82%; yellow solid, mp 65–67 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 158.2 (*c* 1.0, CH_2Cl_2), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 10.9 min (major), 14.4 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.14 (dd, *J* = 9.6, 5.0 Hz, 1H), 6.25 (d, *J* = 9.8 Hz, 1H), 6.15 (br, 1H), 1.49 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 154.1, 148.8, 145.4, 134.0, 128.8, 128.7, 128.5, 125.0, 83.1, 83.0, 55.8, 28.1, 27.5; IR (KBr) 2979, 1778, 1720, 1369, 1293, 1253, 1155, 850, 762, 700; HRMS (ESI) calcd for $C_{20}H_{26}N_2O_5Na$ $[M+Na]^+$ 397.17339, found 397.17285.



3.3b

(*R*)-di-*tert*-butyl 3-oxo-6-(p-tolyl)pyridazine-1,2(*3H*,*6H*)-dicarboxylate

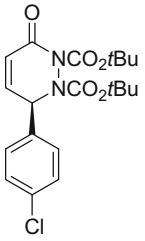
Yield 81%; yellow solid, mp 76–78 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 175.5 (*c* 1.0, CH_2Cl_2), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 11.8 min (major), 14.6 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.08 (m, 5H), 6.22 (d, *J* = 9.8 Hz, 1H), 6.11 (br, 1H), 2.34 (s, 3H), 1.49 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 154.2, 149.0, 145.7, 138.7, 131.0, 129.4, 128.5, 124.9, 83.1, 83.0, 55.7, 28.2, 27.6, 21.2; IR (KBr) 2979, 1776, 1720, 1369, 1266, 1155, 807, 741; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_5Na$ $[M+Na]^+$ 411.18904, found 411.18869.



3.3b

(*R*)-di-*tert*-butyl 3-(4-fluorophenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

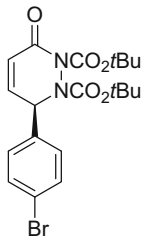
Yield 80%; yellow solid, mp 102–104 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 146.4 (*c* 1.0, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 9.7 min (major), 12.6 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.29 (m, 2H), 7.14–7.02 (m, 3H), 6.25 (d, *J* = 9.8 Hz, 1H), 6.13 (br, 1H), 1.49 (s, 9H), 1.27 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0 (d, *J* = 248.4 Hz), 160.7, 154.1, 148.8, 145.1, 130.4 (d, *J* = 8.0 Hz), 130.0, 125.3, 115.69 (d, *J* = 21.7 Hz), 83.4, 83.3, 55.1, 28.2, 27.6; IR (KBr) 2980, 1778, 1717, 1510, 1393, 1369, 1293, 1253, 1156, 872, 812, 744; HRMS (ESI) calcd for $C_{20}H_{25}FN_2O_5Na$ $[M+Na]^+$ 415.16397, found 415.16354.



3.3d

(*R*)-di-*tert*-butyl 3-(4-chlorophenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

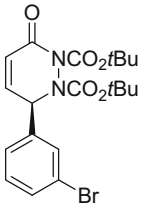
Yield 71%; yellow solid, mp 114–116 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 191.4 (*c* 1.0, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 10.4 min (major), 13.5 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.11 (dd, *J* = 9.6, 5.0 Hz, 1H), 6.25 (d, *J* = 9.8 Hz, 1H), 6.12 (br, 1H), 1.49 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 153.9, 148.7, 144.7, 134.7, 132.7, 129.7, 128.7, 125.2, 83.3, 83.2, 55.1, 28.0, 27.5; IR (KBr) 2979, 1778, 1720, 1394, 1369, 1292, 1252, 1154, 871, 811, 745; HRMS (ESI) calcd for $C_{20}H_{25}ClN_2O_5Na$ $[M+Na]^+$ 431.13442, found 431.13420.



3.3e

(*R*)-di-*tert*-butyl 3-(4-bromophenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

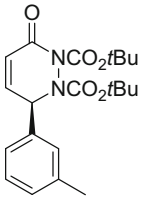
Yield 79%; yellow solid, mp 105–107 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 197.2 (*c* 1.0, CH_2Cl_2), HPLC analysis: 97% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 11.3 min (major), 13.8 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.1 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.11 (dd, *J* = 9.6, 5.0 Hz, 1H), 6.24 (d, *J* = 9.8 Hz, 1H), 6.10 (br, 1H), 1.49 (s, 9H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 154.0, 148.7, 144.7, 133.3, 131.8, 130.1, 125.4, 123.0, 83.4, 83.3, 55.2, 28.1, 27.6; IR (KBr) 2979, 1777, 1717, 1394, 1369, 1291, 1251, 1154, 871, 849, 810; HRMS (ESI) calcd for $C_{20}H_{25}BrN_2O_5Na$ $[M+Na]^+$ 475.08391, found 475.08375.



3.3f

(*R*)-di-*tert*-butyl 3-(3-bromophenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

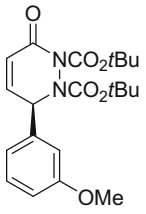
Yield 64%; yellow solid, mp 119–120 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 123.1 (*c* 1.0, CH_2Cl_2), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 12.1 min (major), 14.2 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55–7.47 (m, 2H), 7.35–7.22 (m, 2H), 7.15 (dd, *J* = 9.6, 5.0 Hz, 1H), 6.25 (d, *J* = 9.8 Hz, 1H), 6.12 (br, 1H), 1.50 (s, 9H), 1.32 (s, 9); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 154.1, 148.7, 144.5, 136.8, 131.8, 131.4, 130.2, 126.8, 125.5, 122.8, 83.5, 83.4, 55.2, 28.1, 27.6; IR (KBr) 2979, 1777, 1720, 1394, 1369, 1291, 1252, 1154, 883, 848, 816; HRMS (ESI) calcd for $C_{20}H_{25}BrN_2O_5Na$ $[M+Na]^+$ 475.08391, found 475.08350.



3.3g

(*R*)-di-*tert*-butyl 3-oxo-6-(m-tolyl)pyridazine-1,2(3*H*,6*H*)-dicarboxylate

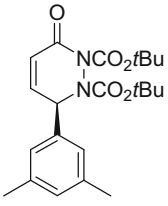
Yield 86%; yellow solid, mp 85–87 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 167.7 (*c* 1.0, CH_2Cl_2), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 9.9 min (major), 12.2 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.09 (m, 5H), 6.24 (d, *J* = 9.8 Hz, 1H), 6.11 (br, 1H), 2.34 (s, 3H), 1.49 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 154.2, 148.9, 145.6, 138.5, 134.0, 129.5, 129.2, 128.6, 125.6, 125.0, 83.1, 83.0, 55.9, 28.2, 27.6, 21.4; IR (KBr) 2979, 1778, 1717, 1394, 1369, 1293, 1255, 1157, 851, 828, 742; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_5Na$ $[M+Na]^+$ 411.18904, found 411.18869.



3.3h

(*R*)-di-*tert*-butyl 3-(3-methoxyphenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

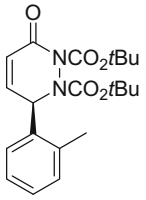
Yield 58%; yellow solid, mp 107–109 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 223.7 (*c* 1.0, CH_2Cl_2), HPLC analysis: 95% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 14.0 min (major), 18.5 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.23 (m, 1H), 7.12 (dd, *J* = 9.6, 5.0 Hz, 1H), 6.91–6.87 (m, 3H), 6.23 (d, *J* = 9.8 Hz, 1H), 6.11 (br, 1H), 3.79 (s, 3H), 1.49 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 159.9, 154.2, 148.9, 145.3, 135.6, 129.7, 125.0, 120.6, 114.3, 114.2, 83.2, 83.1, 55.8, 55.4, 28.2, 27.6; IR (KBr) 2979, 1776, 1717, 1394, 1369, 1292, 1267, 1155, 850, 743, 700; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_6Na$ $[M+Na]^+$ 427.18396, found 427.18359.



3.3i

(*R*)-di-*tert*-butyl 3-(3,5-dimethylphenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

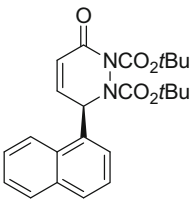
Yield 79%; yellow solid, mp 107–109 °C; R_f = 0.3 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 157.8 (*c* 1.0, CH_2Cl_2), HPLC analysis: 97% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 8.6 min (major), 10.3 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 9.6, 5.0 Hz, 1H), 6.97–6.93 (m, 3H), 6.22 (d, *J* = 9.8 Hz, 1H), 6.07 (br, 1H), 2.29 (s, 6H), 1.49 (s, 9H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1, 154.2, 148.9, 145.8, 138.3, 133.9, 130.3, 126.2, 124.8, 82.9, 55.9, 28.2, 27.5, 21.2; IR (KBr) 2979, 1778, 1717, 1393, 1369, 1296, 1254, 1156, 874, 851, 761; HRMS (ESI) calcd for $C_{22}H_{30}N_2O_5Na$ $[M+Na]^+$ 425.20469, found 425.20444.



3.3j

(*R*)-di-*tert*-butyl 3-oxo-6-(o-tolyl)pyridazine-1,2(3*H*,6*H*)-dicarboxylate

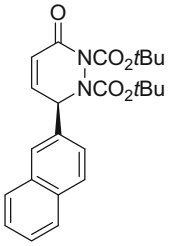
Yield 74%; yellow solid, mp 134–136 °C; R_f = 0.33 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 122.5 (*c* 1.0, CH_2Cl_2), HPLC analysis: 99% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 7.6 min (major), 9.4 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.13–7.04 (m, 3H), 6.31–6.28 (m, 1H), 6.23 (br, 1H), 2.51 (s, 3H), 1.49 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 154.3, 148.8, 146.2, 138.7, 131.1, 131.0, 129.2, 128.2, 126.0, 125.6, 83.1, 82.9, 53.8, 28.2, 27.5, 19.6; IR (KBr) 2979, 1777, 1716, 1368, 1292, 1255, 1155, 871, 850, 821; HRMS (ESI) calcd for $C_{21}H_{28}N_2O_5Na$ $[M+Na]^+$ 411.18904, found 411.18873.



3.3k

(*R*)-di-*tert*-butyl 3-(naphthalen-1-yl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

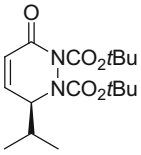
Yield 73%; yellow solid, mp 122–123 °C; R_f = 0.25 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ −22.0 (*c* 1.0, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 14.2 min (major), 18.7 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 8.4 Hz, 1H), 7.87 (t, *J* = 8.9 Hz, 2H), 7.64–7.51 (m, 2H), 7.37–7.17 (m, 3H), 6.82 (d, *J* = 4.1 Hz, 1H), 6.39 (d, *J* = 9.7 Hz, 1H), 1.50 (s, 9H), 0.68 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 154.1, 148.7, 146.0, 134.2, 132.1, 130.1, 129.1, 128.7, 127.1, 126.8, 126.3, 126.0, 124.8, 124.3, 83.2, 82.6, 53.2, 28.2, 27.0; IR (KBr) 2980, 1776, 1709, 1393, 1370, 1294, 1268, 1155, 820, 747; HRMS (ESI) calcd for $C_{24}H_{28}N_2O_5Na$ $[M+Na]^+$ 447.18904, found 447.18880.



3.3l

(*R*)-di-*tert*-butyl 3-(naphthalen-2-yl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

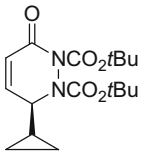
Yield 61%; yellow solid, mp 120–122 °C; R_f = 0.4 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 221.2 (*c* 1.0, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 14.1 min (major), 18.5 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86–7.76 (m, 3H), 7.66 (s, 1H), 7.55–7.48 (m, 3H), 7.23 (dd, *J* = 9.6, 5.1 Hz, 1H), 6.33–6.30 (m, 2H), 1.51 (s, 9H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0, 154.3, 148.9, 145.4, 133.3, 133.0, 131.6, 128.7, 128.1, 127.6, 127.4, 126.8, 126.6, 126.5, 125.4, 83.2, 56.0, 28.2, 27.5; IR (KBr) 2979, 1777, 1717, 1394, 1369, 1293, 1254, 1154, 851, 812, 750; HRMS (ESI) calcd for $C_{24}H_{28}N_2O_5Na$ $[M+Na]^+$ 447.18904, found 447.18899.



3.3m

(*S*)-di-*tert*-butyl 3-isopropyl-6-oxopyridazine-1,2(3*H*,6*H*)-dicarboxylate

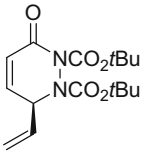
Yield 52%; yellow oil; R_f = 0.4 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 89.8 (*c* 1.0, $CHCl_3$) (Ref. [4] $[\alpha]_D^{25}$ 123.5 (*c* 1.0, $CHCl_3$)); HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 10.7 min (major), 12.3 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (br, 1H), 5.97 (d, *J* = 9.8 Hz, 1H), 4.56 (br, 1H), 1.94–1.86 (m, 1H), 1.55 (s, 9H), 1.47 (s, 9H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7, 155.2, 149.4, 147.5, 123.4, 83.6, 82.9, 60.3, 30.4, 28.2, 28.1, 20.2, 19.1; IR (KBr) 2979, 1778, 1720, 1393, 1369, 1294, 1253, 1159; HRMS (ESI) calcd for $C_{17}H_{28}N_2O_5Na$ $[M+Na]^+$ 363.18904, found 363.18895.



3.3n

(*S*)-di-*tert*-butyl 3-cyclopropyl-6-oxopyridazine-1,2(3*H*,6*H*)-dicarboxylate

Yield 62%; yellow oil; R_f = 0.25 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 100.5 (*c* 2.2, CH_2Cl_2), HPLC analysis: 96% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 0.5 mL/min, 254 nm, 12.0 min (major), 14.3 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (br, 1H), 5.97 (d, *J* = 9.8 Hz, 1H), 4.40 (br, 1H), 1.55 (s, 9H), 1.46 (s, 9H), 0.88–0.86 (m, 2H), 0.63–0.56 (m, 2H), 0.43 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 154.3, 149.5, 146.2, 123.7, 83.2, 82.6, 57.2, 28.1, 27.9, 11.1, 2.8, 2.7; IR (KBr) 2979, 1777, 1717, 1394, 1369, 1294, 1274, 1155; HRMS (ESI) calcd for $C_{17}H_{26}N_2O_5Na$ $[M+Na]^+$ 361.17339, found 361.17319.

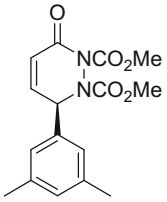


3.3o

(*S*)-di-*tert*-butyl 3-oxo-6-vinylpyridazine-1,2(3*H*,6*H*)-dicarboxylate

Yield 54%; yellow oil; R_f = 0.4 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 218.5 (*c* 1.9, CH_2Cl_2), HPLC analysis: 94% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 95:5, 1.0 mL/min, 254 nm, 6.4 min (major), 7.8 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, *J* = 9.4, 4.8 Hz,

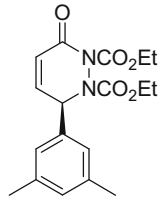
1H), 6.07 (d, *J* = 9.8 Hz, 1H), 5.93–5.82 (m, 1H), 5.52 (br, 1H), 5.30 (dd, *J* = 21.8, 13.9 Hz, 2H), 1.52 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 154.3, 149.4, 145.3, 130.8, 124.6, 120.3, 83.4, 83.0, 54.5, 28.0, 27.9; IR (KBr) 2980, 1775, 1724, 1394, 1370, 1292, 1254, 1155; HRMS (ESI) calcd for $C_{16}H_{24}N_2O_5Na$ $[M+Na]^+$ 347.15774, found 347.15756.



3.3p

(*R*)-dimethyl 3-(3,5-dimethylphenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-di-carboxylate

Yield 49%; yellow oil; R_f = 0.1 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 303.0 (*c* 1.0, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK OD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 80:20, 1.0 mL/min, 254 nm, 8.9 min (major), 17.1 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 9.7, 5.1 Hz, 1H), 6.97–6.93 (m, 3H), 6.22 (dd, *J* = 9.8, 1.2 Hz, 1H), 6.11 (br, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.29 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 156.3, 151.5, 146.3, 138.5, 133.2, 130.6, 126.0, 124.3, 57.0, 54.4, 54.1, 21.3; IR (KBr) 2957, 1743, 1724, 1440, 1291, 1260, 1077, 822, 759, 692; HRMS (ESI) calcd for $C_{16}H_{18}N_2O_5Na$ $[M+Na]^+$ 341.11079, found 341.11035.

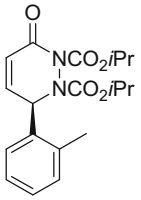


3.3q

(*R*)-diethyl 3-(3,5-dimethylphenyl)-6-oxopyridazine-1,2(3*H*,6*H*)-dicarboxylate

Yield 58%; yellow oil; R_f = 0.1 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 184.4 (*c* 0.7, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK IB-H column, 20 °C, 254 nm hexane/*i*-PrOH = 92:8, 1.0 mL/min, 254 nm, 12.2 min (major), 22.3 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 9.8, 5.1 Hz, 1H), 6.96-6.94 (m, 3H), 6.23 (dd, *J* = 9.8, 1.3 Hz, 1H), 6.11 (br, 1H), 4.34–4.23 (m, 2H), 4.07 (q, *J* = 7.0 Hz, 2H), 2.29 (s, 6H), 1.28 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR

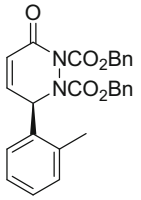
(75 MHz, $CDCl_3$) δ 160.6, 155.6, 150.7, 146.0, 138.4, 133.4, 130.5, 126.0, 124.4, 63.6, 63.1, 56.8, 21.2, 14.4, 13.9; IR (KBr) 2982, 1779, 1723, 1368, 1281, 1257, 1073, 819, 757; HRMS (ESI) calcd for $C_{18}H_{22}N_2O_5Na$ $[M+Na]^+$ 369.14209, found 369.14157.



3.3r

(*R*)-diisopropyl 3-oxo-6-(o-tolyl)pyridazine-1,2(3*H*,6*H*)-dicarboxylate

Yield 65%; yellow oil; R_f = 0.2 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 129.1 (*c* 1.0, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK IB-H column, 20 °C, 254 nm hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, 12.3 min (minor), 17.0 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.03 (m, 5H), 6.32–6.26 (m, 2H), 5.05–5.00 (m, 1H), 4.76–4.68 (m, 1H), 2.51 (s, 3H), 1.26 (d, *J* = 3.3 Hz, 6H), 1.11 (d, *J* = 6.2 Hz, 3H), 0.78 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 155.3, 149.8, 146.5, 138.8, 131.2, 130.8, 129.3, 128.1, 126.0, 125.4, 71.7, 70.9, 54.7, 22.0, 21.9, 21.6, 21.0, 19.4; IR (KBr) 2982, 1777, 1722, 1376, 1281, 1225, 1105, 870, 755, 726; HRMS (ESI) calcd for $C_{19}H_{24}N_2O_5Na$ $[M+Na]^+$ 383.15774, found 383.15707.



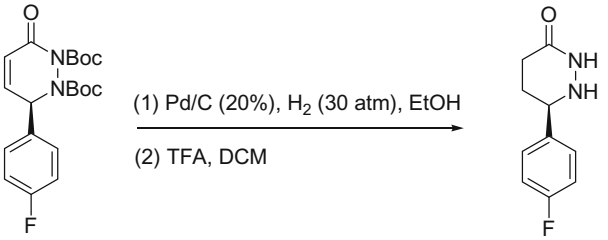
3.3s

(*R*)-dibenzyl 3-oxo-6-(o-tolyl)pyridazine-1,2(3*H*,6*H*)-dicarboxylate

Yield 57%; yellow oil; R_f = 0.2 (petroleum ether/ethyl acetate = 5/1); $[\alpha]_D^{25}$ 98.6 (*c* 1.0, CH_2Cl_2), HPLC analysis: 99% ee [Daicel CHIRALPAK OJ-H column, 20 °C, 254 nm hexane/*i*-PrOH = 70:30, 1.2 mL/min, 254 nm, 31.1 min (minor), 42.6 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–6.92 (m, 16H), 6.31–6.27 (m, 1H), 5.26–4.77 (m, 4H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 155.5, 150.4, 146.6, 138.8, 135.3, 134.8, 131.4, 130.4, 129.4, 128.7, 128.5, 128.3,

128.1, 127.9, 127.7, 126.0, 125.2, 69.0, 68.5, 55.0, 19.30; IR (KBr) 2962, 1779, 1724, 1392, 1282, 1262, 1070, 751, 697; HRMS (ESI) calcd for $C_{27}H_{24}N_2O_5Na$ $[M+Na]^+$ 479.15774, found 479.15723.

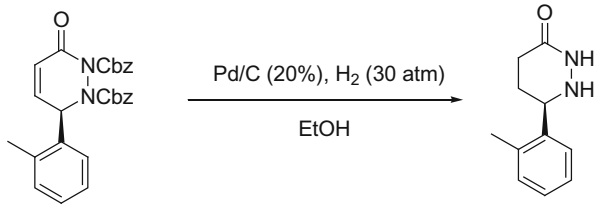
3.7.2 Synthesis of Tetrahydropyridazinones



3.3c, 98% ee

3.4c, 88%, 97% ee

To a solution of cycloadduct **3.3c** (50 mg, 0.13 mmol) in EtOH (2 mL) was added 20% Pd/C (7 mg) at room temperature, then the mixture was stirred at room temperature under 30 atm of hydrogen for overnight. The reaction mixture was diluted with ethyl acetate, and passed through a short Celite pad. After evaporation of the solvent, the residue was dissolved in TFA/DCM (1:3, 4 mL) and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the excess trifluoroacetic acid was neutralize by saturated Na_2CO_3 solution, then extracted with ethyl acetate, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford a residue, which was purified by chromatography on silica gel to give **3.4c** (22 mg, 88% yield). Yellow foam; R_f = 0.5 (DCM/MeOH = 10/1); $[\alpha]_D^{25}$ −2.3 (*c* 1.0, CH_2Cl_2), HPLC analysis: 97% ee [Daicel CHIRALPAK OJ-H column, 20°C, 210 nm hexane/*i*-PrOH = 90:10, 1.0 mL/min, 210 nm, 29.6 min (minor), 34.9 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.06 (dd, *J* = 11.9, 5.3 Hz, 2H), 4.16 (dd, *J* = 9.9, 4.1 Hz, 1H), 2.65–2.60 (m, 2H), 2.42–2.36 (m, 1H), 2.23–2.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 162.45 (d, *J* = 246.7 Hz), 135.15 (d, *J* = 3.4 Hz), 128.59 (d, *J* = 8.1 Hz), 115.69 (d, *J* = 21.4 Hz), 57.1, 29.1, 28.9; IR (KBr) 2919, 1688, 1682, 1510, 1417, 1224, 1251, 839; HRMS (ESI) calcd for $C_{10}H_{12}FN_2O$ $[M+H]^+$ 195.09282, found 195.09282.

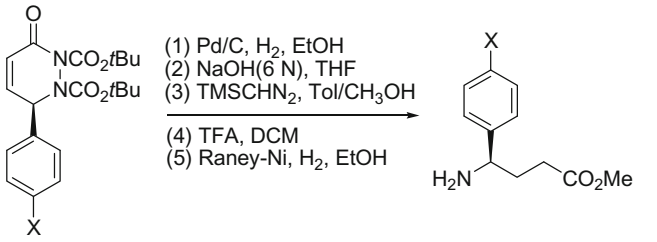


3.3s, 99% ee

3.4s, 99%, 98% ee

To the solution of cycloadduct **3.3s** (43 mg, 0.094 mmol) in EtOH (2 mL) was added 20% Pd/C (5 mg) at room temperature, then the mixture was stirred at room temperature under 30 atm of hydrogen for overnight. The reaction mixture was diluted with ethyl acetate, and passed through a short Celite pad. The solvent was removed under reduced pressure to give the corresponding products **3.4 s** in quantitative yield. Yellow foam; $R_f = 0.5$ (DCM/MeOH = 10/1); $[\alpha]_D^{25}$ −24.2 (*c* 0.5, CH_2Cl_2), HPLC analysis: 98% ee [Daicel CHIRALPAK AD-H column, 20 °C, 254 nm hexane/*i*-PrOH = 90:10, 1.0 mL/min, 254 nm, 16.5 min (minor), 21.4 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (br, 1H), 7.23–7.21 (m, 4H), 4.32–4.28 (m, 1H), 3.87 (br, 1H), 2.68–2.62 (m, 2H), 2.42 (s, 3H), 2.30–2.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 137.5, 137.2, 131.0, 128.1, 126.3, 124.8, 55.3, 29.9, 28.4, 19.3; IR (KBr) 2910, 1639, 1464, 1400, 929, 754, 727; HRMS (ESI) calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$ 191.11789, found 191.11780.

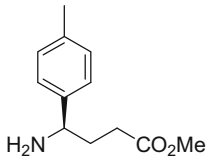
3.7.3 Synthesis of γ-Amino Esters



3.3b, 99% ee
3.3c, 98% ee

3.5b (X = Me), 77%,* 97% ee
3.5c (X = F), 78%,* 97% ee

* Overall yield of five steps

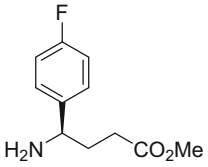


3.5b

(*R*)-methyl 4-amino-4-(p-tolyl)butanoate

Yield 77%; yellow oil; $R_f = 0.33$ (DMC/MeOH = 10/1); $[\alpha]_D^{25}$ −10.1 (*c* 1.0, CH_2Cl_2), HPLC analysis: 97% ee [Daicel CHIRALPAK OD-H column, 20 °C, 210 nm hexane/*i*-PrOH = 90:10, 1.0 mL/min, 210 nm, 12.3 min (major), 16.6 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (br, 2H), 7.18 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 7.9$ Hz, 2H), 4.15 (br, 1H), 3.54 (s, 3H), 2.28–2.14 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 139.3, 132.6, 129.9, 127.3, 55.0, 51.9, 30.0, 29.2, 21.2;

IR (KBr) 2954, 1679, 1519, 1439, 1137, 837, 799, 722; HRMS (ESI) calcd for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.13321, found 208.13312.



3.5c

(*R*)-methyl 4-amino-4-(4-fluorophenyl)butanoate

Yield 78%; yellow oil; R_f = 0.33 (DCM/MeOH = 10/1); $[\alpha]_D^{25}$ −8.1 (*c* 1.0, CH_2Cl_2), HPLC analysis: 97% ee [Daicel CHIRALPAK OB-H column, 20°C, 210 nm hexane/*i*-PrOH = 92:8, 0.8 mL/min, 210 nm, 23.3 min (major), 27.5 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (br, 2H), 7.33 (dd, *J* = 8.2, 5.2 Hz, 2H), 7.04 (t, *J* = 8.4 Hz, 2H), 4.25–4.22 (m, 1H), 3.60 (s, 3H), 2.34–2.12 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 163.20 (d, *J* = 248.6 Hz), 131.8, 129.37 (d, *J* = 8.5 Hz), 116.33 (d, *J* = 21.5 Hz), 54.6, 52.0, 29.9, 29.4; IR (KBr) 2928, 1732, 1681, 1515, 1227, 1202, 1138, 838, 800, 722; HRMS (ESI) calcd for $C_{11}H_{15}FNO_2$ $[M+H]^+$ 212.10813, found 212.10783.

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Chapter 4
NHC-Catalyzed Cyclocondensation of α,β-Unsaturated Carboxylic Acids

4.1 Introduction

Catalytic enantioselective reactions employing α,β-unsaturated acyl azolium intermediate have attracted great attention and have been intensively explored in these years. A variety of α,β-unsaturated carbonyl compounds have been developed for these reactions (Fig. 4.1). In this area, the α,β-unsaturated acyl azolium is usually generated from ynals, enals, α-bromoenals, α,β-unsaturated acyl fluorides and esters by (oxidative) N-heterocyclic carbene (NHC) catalysis. For example, Lupton and co-workers have shown that α,β-unsaturated acyl azolium could be generated from α,β-unsaturated acyl fluorides [1, 2]. Studer and coworkers have reported that oxidative NHC-catalyzed Michael-proton transfer-lactonization process with enals and 1,3-dicarbonyl compounds by oxidation of the initially generated Breslow intermediate [3–6]. While Bode and coworkers have employed ynals as α,β-unsaturated acyl azolium precursors for highly enantioselective Claisen rearrangements [7, 8]. Ye and coworkers have successfully introduced α-bromoenals for the synthesis of dihydropyranones [9–12]. While Chi and coworkers have fulfilled Michael-proton transfer-lactamization process under NHC catalysis using α,β-unsaturated esters and enamides [13].

The α,β-unsaturated acyl ammonium is typically generated from anhydrides with isothiourea, or α,β-unsaturated acyl chlorides with cinchona alkaloid, or using thiourea from α,β-unsaturated acyl cyanides. For example, Smith and coworkers have reported isothiourea promoted Michael-proton transfer-lactonization of anhydrides [14]. Very recently acyl chlorides have been successfully used as α,β-unsaturated acyl ammonium precursors for Michael-proton transfer-lactamization process with cinchona alkaloid as catalyst [15], while Bonne and Rodriguez et al. have employed similar processes using α,β-unsaturated acyl

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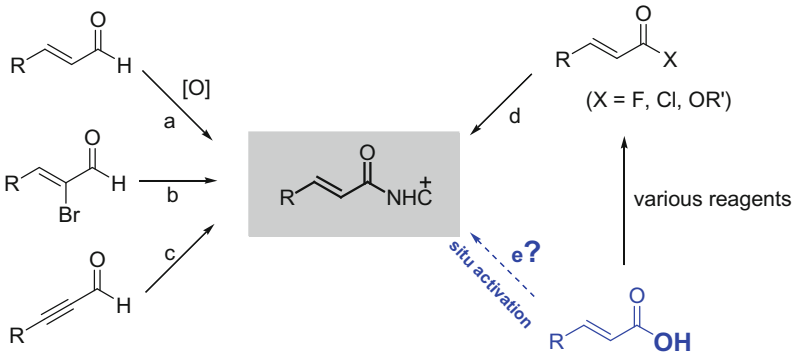


Fig. 4.1 Generation of α,β-unsaturated acyl azolium via NHC

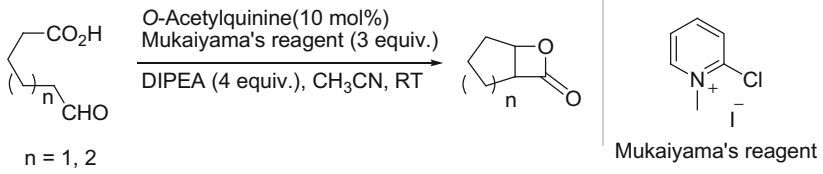


Fig. 4.2 Cinchona alkaloids-catalyzed aldol-lactonization of aldehyde acids

cyanides as starting materials under the catalyst of thiourea [16]. Although these elegant methods play an important role in the enantioselective Michael-proton transfer-cyclisation processes, expensive organic oxidants must be needed for the oxidative NHC catalysis when enals were used as substrates. When ynals were employed as substrates, the starting materials were expensive and substitution scope was limited. Other carbonyl compounds (e.g., anhydride, acyl fluorides, acyl chlorides and acyl cyanides) all must be prepared from corresponding carboxylic acids.

To date, an alternative but highly desirable strategy to generate α,β-unsaturated acyl azolium directly from carboxylic acids for enantioselective Michael-proton transfer-cyclisation events has received too little attention (Fig. 4.1e). For the organocatalytic functionalization of carboxylic acids, Romo and coworkers reported the pioneering cinchona alkaloids-catalyzed aldol-lactonization process of aldehyde acids via enolate intermediate (Fig. 4.2) [17–23].

Recently, Smith and coworkers have elegantly utilized isothioureas to generate this intermediate from carboxylic acids for enantioselective Michael-cyclisation processes (Fig. 4.3) [24–31].

Given these reasons and based on our own interest in NHC catalysis [32–35], we envisaged a more convenient and direct access to achieve α,β-unsaturated acyl azolium from carboxylic acids themselves via in situ generated mixed anhydrides for enantioselective Michael-proton transfer-lactamization processes catalyzed by NHC (Fig. 4.4).

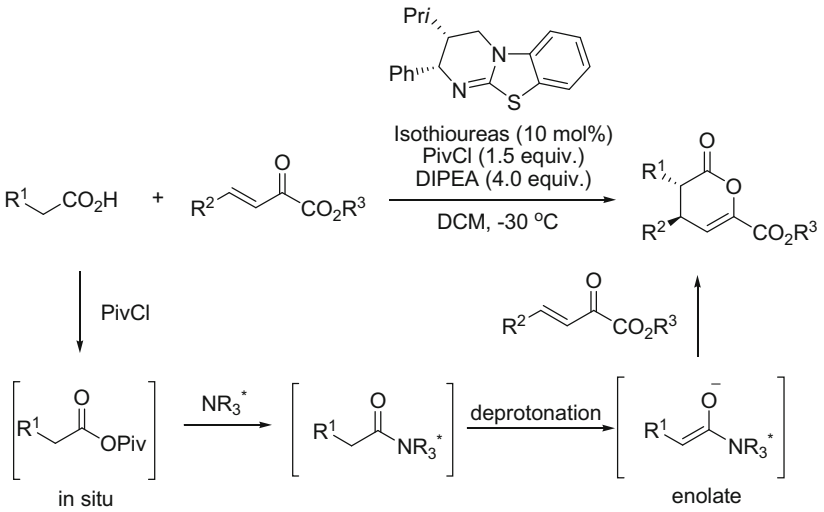


Fig. 4.3 Generation of enolate intermediate via isothioureas

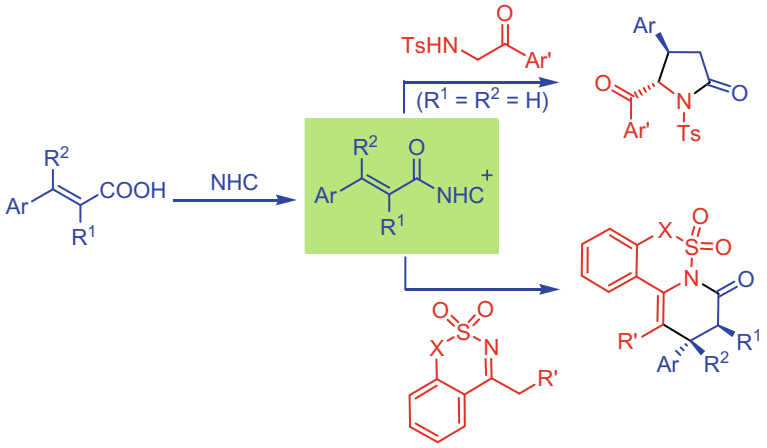


Fig. 4.4 Reaction design

4.2 Optimization of Conditions

Initially, the model reaction of the α-amino ketone **4.2a** with cinnamic acid **4.1a** in the presence of pivaloyl chloride as the reagent to generate the mixed anhydride was investigated under isothiourea DHPB (Fig. 4.5). It was interesting that the isothiourea catalyst, which has been powerful catalyst to generate enolate from carboxylic acids, only gave amidation product **4.3a** in 89% yield, no Michael-proton transfer-lactamization product was observed. Interestingly, when

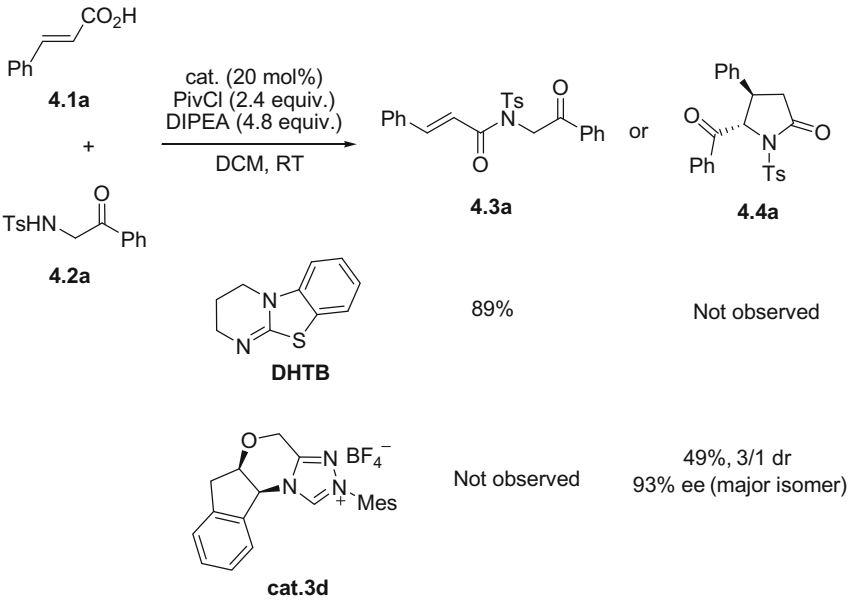


Fig. 4.5 Initial studies. Reproduced from Ref. [41] by permission of John Wiley & Sons Ltd.

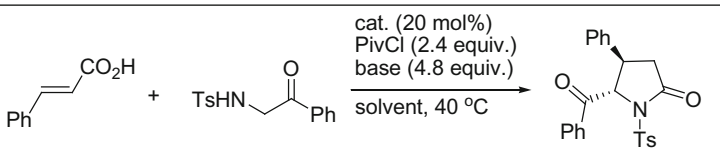
the NHC catalyst **cat.3d** was employed for the same reaction, we were pleased to find that the desired Michael-proton transfer-lactamization product **4.4a** was achieved in 49% yield with 93% ee. We proposed that compared to the α,β-unsaturated acyl ammonium, the unfavored amidation of α,β-unsaturated acyl azolium makes the Michael-proton transfer-lactamization feasible [36, 37].

Further optimization showed that other bases gave no or poor results (Table 4.1, entries 1–2). A screen of solvent revealed that the reaction gave the best results in toluene (entries 3–6). Furthermore, a series of NHC-catalysts was investigated and showed chiral azolium salt-bearing *N*-phenyl group gave a trace of product (entry 7), chiral azolium salts bearing other *N*-groups (e.g., Bn, 2-*i*PrC_6H_4 and 2,6-$Et_2C_6H_3$) gave very poor yields even the reaction time was prolonged several days (entries 8–10). Other amino alcohol-derived catalyst **cat.4d** and chiral azolium salts **cat.2a** and **cat.6a** derived from pyroglutamic acid had no catalytic effects on the reaction under current conditions (entries 11–13).

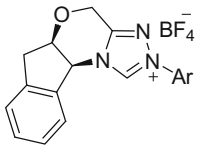
4.3 Substrate Scope

With these optimized conditions in hand, the scope of α,β-unsaturated carboxylic acids was briefly investigated (Table 4.2). The reaction proceeded smoothly when the aryl group was substituted with electron-withdrawing (4-Cl, 4-Br) or electron-donating

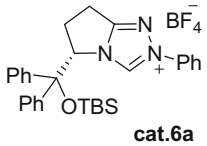
Table 4.1 Optimization of reaction conditions



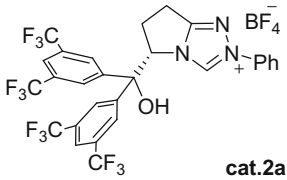
4.1a (2.0 equiv.) **4.2a** **4.4a**



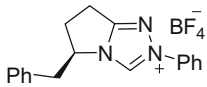
cat.3a, Ar = 2,6-$(Et)_2C_6H_3$
cat.3c, Ar = Ph
cat.3d, Ar = Mes
cat.3e, Ar = Bn
cat.3f, Ar = 2-*i*PrC_6H_4



cat.6a



cat.2a



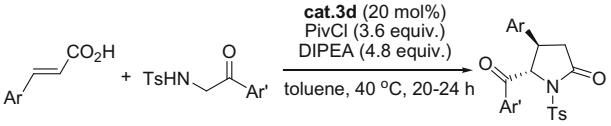
cat.4d

Entry	Cat.	Base	Solvent	Yield (%)[a]	D.r.[b]	Ee (%)[c]
1	**Cat.3d**	K_2CO_3	DCM	NR	/	/
2	**Cat.3d**	Et_3N	DCM	38	4/1	88
3	**Cat.3d**	DIPEA	DCM	60	3/1	93
4	**Cat.3d**	DIPEA	$CHCl_3$	Trace	/	/
5[d]	**Cat.3d**	DIPEA	THF	31	3/1	93
6	***Cat.3d***	*DIPEA*	*Toluene*	*64*	*5/1*	*96*
7	**Cat.3c**	DIPEA	Toluene	Trace	/	/
8	**Cat.3e**	DIPEA	Toluene	9	n.d.	n.d.
9	**Cat.3f**	DIPEA	Toluene	7	n.d.	n.d.
10[e]	**Cat.3a**	DIPEA	Toluene	20	3/1	79
11	**Cat.6a**	DIPEA	Toluene	Trace	/	/
12	**Cat.2a**	DIPEA	Toluene	Trace	/	/
13	**Cat.4d**	DIPEA	Toluene	Trace	/	/

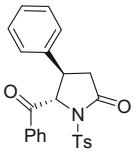
[a]Isolated yield of the mixture of stereoisomers
[b]Determined by ^{1}H NMR spectroscopy (300 MHz) of the raw product
[c]Determined by HPLC using a chiral stationary phase
[d]The reaction was carried out for 2 days
[e]The reaction was carried out for 3 days. *Mes* 2,4,6-trimethylphenyl, *THF* tetrahydrofuran, *TBS* tert-butyldimethylsilyl, *Ts* 4-toluenesulfonyl

(4-Me) groups, affording the desired products **4.4b**–**4.4d** in good yields with high enantioselectivities. Substrates with *meta*-substituents (3-OMe, 3-Br and 3-ClC_6H_4) also worked well (**4e**–**4g**). The disubstituted cinnamic acid derivative (3,4-$Cl_2C_6H_3$)

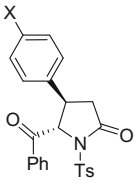
Table 4.2 Enantioselective [3+2] cyclocondensation



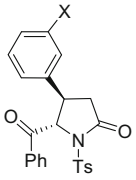
4.1 (3.0 equiv.) **4.2** **4.4**



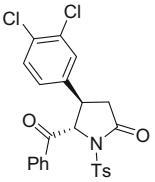
4.4a[a] d.r. = 5/1, 64%, 96% ee



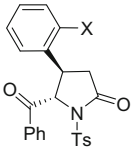
4.4b X = Me, d.r. = 3/1, 60%, 92% ee
4.4c[a] X = Cl, d.r. = 6/1, 63%, 92% ee
4.4d[a] X = Br, d.r. = 5/1, 68%, 92% ee



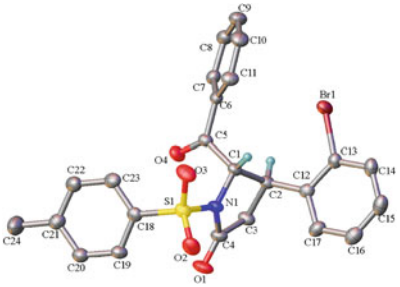
4.4e X = OMe, d.r. = 4/1, 69%, 94% ee
4.4f[a] X = Br, d.r. = 4/1, 69%, 90% ee
4.4g[a] X = Cl, d.r. = 4/1, 63%, 90% ee



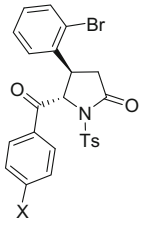
4.4h d.r. = 5/1, 67%, 95% ee



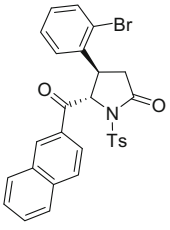
4.4i X = OMe, d.r. = 4/1, 54%, 90% ee
4.4j X = Me, d.r. = 4/1, 73%, 88% ee
4.4k X = Br, d.r. = 7/1, 70%, 95% ee
4.4l X = Cl, d.r. = 6/1, 63%, 98% ee



4.4k



4.4m X = Me, d.r. = 5/1, 73%, 96% ee
4.4n X = Cl, d.r. = 7/1, 65%, 97% ee
4.4o X = Br, d.r. = 6/1, 55%, 95% ee



4.4p d.r. = 12/1, 52%, 95% ee

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[a]Used **1** (2.0 equiv) and PivCl (2.4 equiv)

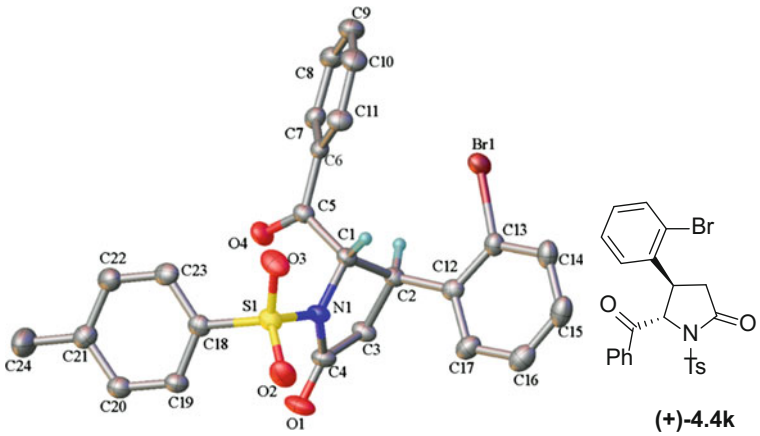


Fig. 4.6 X-ray structure of **4.4k**

gave the desired pyrrolidinone **4.4 h** in 67% yield with 95% ee. It should be noted that the reaction with the challenge *ortho*-substituted substrates (2-OMe, 2-Me, 2-Br and 2-ClC_6H_4) were also successful (**4.4i**–**4.4**l). Then the scope of amino ketones was studied. Amino ketones with electron-withdrawing or electron-donating substituents (4-MeC_6H_4, 4-ClC_6H_4, and 4-BrC_6H_4) worked well, affording the desired pyrrolidinones **4.4m**–**4.4o** in good yields with excellent enantioselectivities. Amino ketone with 2-naphthyl also worked well and gave the corresponding pyrrolidinone (**4.4p**) in moderate yield with excellent diastereoselectivity and enantioselectivity.

The 4*R*,5*S* configuration of the cycloadduct **4.4k** was determined by the X-ray analysis of a single crystal (Fig. 4.6).

4.4 Mechanistic Studies

A plausible catalytic cycle is depicted in Fig. 4.7. At first, the transient mixed anhydride is formed in situ from the corresponding acid **4.1**. Then, the addition of in situ generated NHC to mixed anhydride gives α,β-unsaturated acyl azolium intermediate **I**. In the presence of base, the Michael addition of **4.2** gives adduct **II**, followed by proton transfer to afford **III**, which undergoes intramolecular lactamization to afford the final product **4.4** and regenerate the NHC catalyst.

4.5 Optimization of Conditions

In order to extend the breadth of this strategy for the synthesis of *N*-heterocycles, we turned our focus on sulfamate-derived cyclic imines as bis-nucleophiles to give sulfamate-fused dihydropyridinones. Sulfamate moiety has many biological

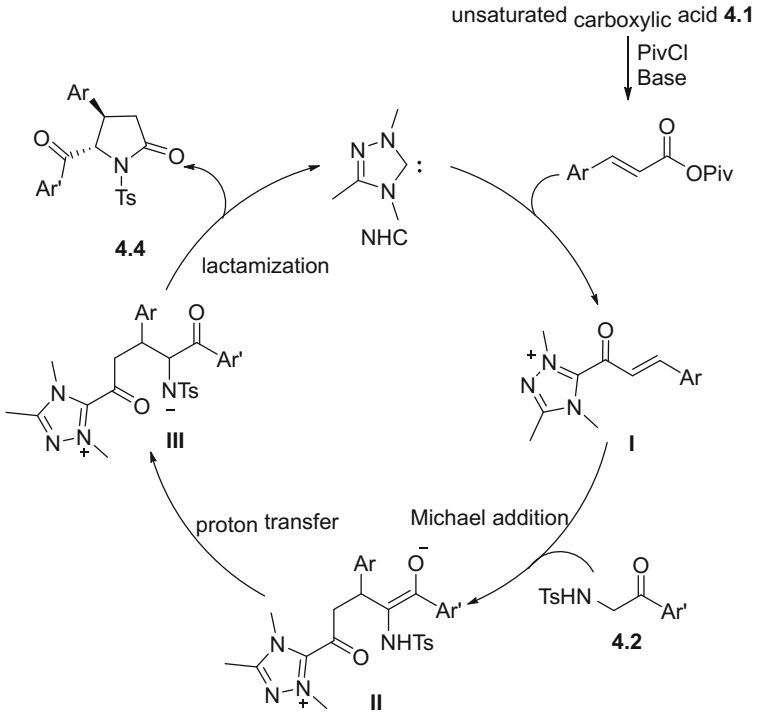


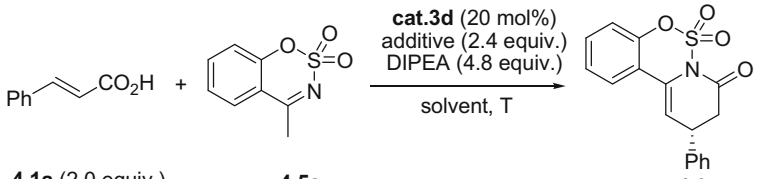
Fig. 4.7 Plausible catalytic cycle. Reproduced from Ref. [41] by permission of John Wiley & Sons Ltd.

activities, such as inhibiting hyperlipidemia, anticancer, antiobesity, and antiarthritis activity [38–40]. After a simple optimization using chiral azolium salt **cat.3d** as catalyst (Table 4.3), we were happy to find that the conditions in our previous Michael-proton transfer-lactamization procedure was also the most effective for this process (entry 10). Other additives gave no or dramatically reduced yields (entries 1–6). Solvent screening showed that THF gave a trace of product (entry 7) and DCM afforded slightly reduced yield (entry 8).

4.6 Substrate Scope

Under the optimized conditions, the generality of this Michael-proton transfer-lactamization process was next tested (Table 4.4). The reactions were tolerant of a wide range of α,β-unsaturated carboxylic acids with electron-donating group (4-MeC_6H_4) and electron-withdrawing group (4-ClC_6H_4) to gave the

Table 4.3 Optimization of reaction conditions



4.1a (2.0 equiv.) **4.5a** **4.6a**

Entry	Additive	T (°C)	Solvent	Yield (%)[a]	Ee (%)[b]
1	/	RT	DCM	NR	/
2	$ClCO_2Me$	RT	DCM	NR	/
3	DCC	RT	DCM	Trace	/
4	TFAA	RT	DCM	11	97
5	MTsCl	RT	DCM	31	99
6	PNBC	RT	DCM	Trace	/
7	PivCl	RT	DCM	70	98
8	PivCl	RT	THF	Trace	/
9	PivCl	RT	Toluene	68	98
10	*PivCl*	*40*	*Toluene*	*72*	*98*

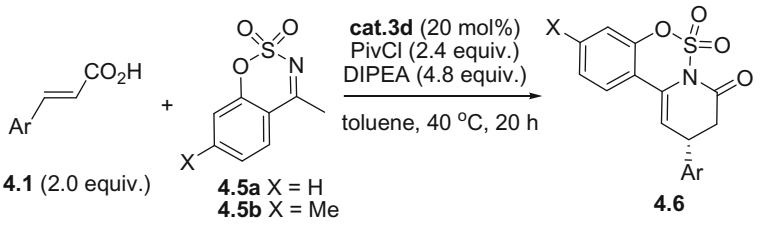
[a]Isolated yield
[b]Determined by HPLC using a chiral stationary phase
[c]*DCC* dicyclohexylcarbodiimide, *TFAA* trifluoroacetic anhydride, *MTsCl* 2-mesitylenesulfonyl chloride, *PNBC* *p*-Nitrobenzoyl chloride

corresponding sulfamate-fused dihydropyridazinones (**4.6b** and **4.6c**) in good yields with excellent enantioselectivities. *Ortho* substituted (2-Me and 2-BrC_6H_4) or *meta*-substituted substrates (3-Me, 3-OMe and 3-BrC_6H_4) also worked well (**4.6d**–**4.6h**). The substituted cyclic imine worked as well to give the desired product in 58% yield with 95% ee (**4.6i**).

The *S* configuration of **4.6c** was determined by the X-ray analysis of a single crystal (Fig. 4.8).

Different sultam-derived cyclic imines were also investigated under the optimized conditions (Table 4.5). Similarly, a wide range of α,β-unsaturated carboxylic acids were proved to be suitable reaction substrates (**4.8a**–**4.8e**). More sterically hindered and electron-donating carboxylic acid led to slightly diminished enantioselectivity (**4.8f**). It was worth noting that the reaction with β,β-disubstituted unsaturated carboxylic acids was also successful to create chiral quaternary carbon center (**4.8g** and **4.8h**). In addition, the α,β-disubstituted unsaturated carboxylic acid also worked well to give **4.8i** in better enantioselectivity than other methods. Sultam-derived cyclic imine with *n*-butyl group was also examined (**4.8j**). We found that the reaction was very slow under the standard reaction conditions in

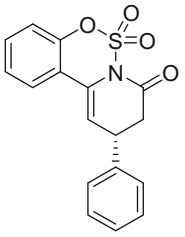
Table 4.4 Enantioselective [3+3] cyclocondensation with sulfamate-derived cyclic imines



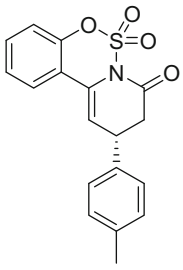
4.1 (2.0 equiv.)

4.5a X = H
4.5b X = Me

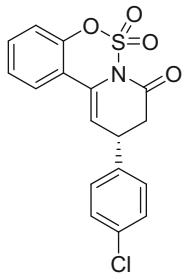
4.6



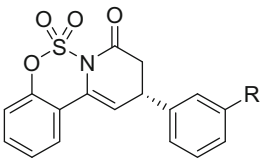
4.6a 72%, 98% ee



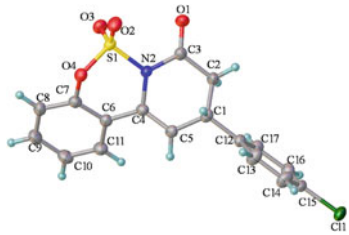
4.6b 75%, 98% ee

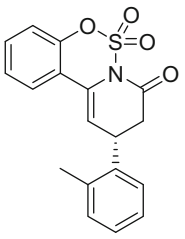


4.6c 58%, 99% ee

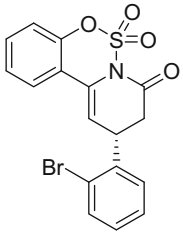


4.6d R = Me, 86%, 97% ee
4.6e R = OMe, 62%, 97% ee
4.6f R = Br, 57%, 97% ee

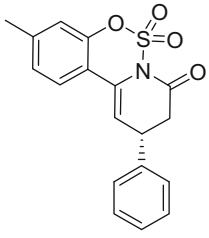




4.6g 85%, 96% ee



4.6h 65%, 97% ee



4.6i 58%, 95% ee

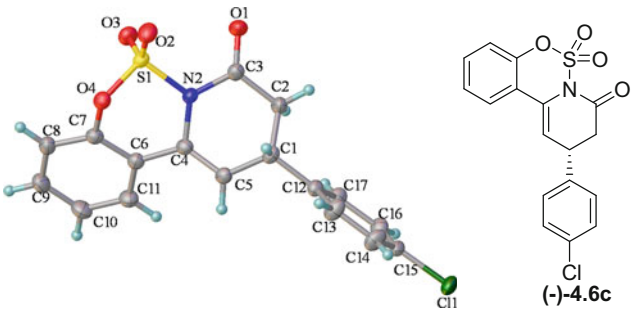
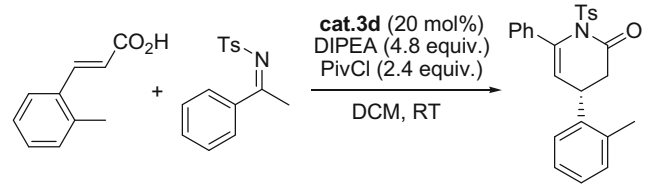


Fig. 4.8 X-ray structure of **4.6c**

toluene, only trace of **4.8j** was obtained after several days. The use of DCM as solvent let **4.8j** in 68% yield with 85% ee.

Toward further expanding the generality of this strategy, acyclic imine **4.9** was then tested under current reaction conditions, the desired product **4.10** was obtained in good yield with excellent enantioselectivity (Eq. 4.1. Reproduced from Ref. [41] by permission of John Wiley & Sons Ltd.).

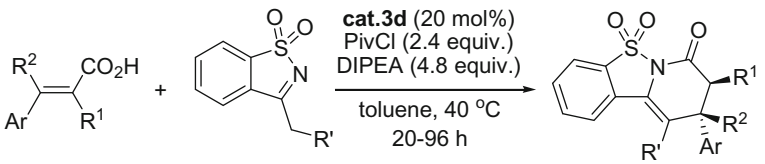


(4.1) (4.1)

4.7 Summary

In summary, the NHC-catalyzed enantioselective Michael-proton transfer-lactamization process of α,β-unsaturated carboxylic acids through α,β-unsaturated acyl azolium intermediate is developed, giving the corresponding *N*-heterocycles in good yields with high to excellent enantioselectivities [41]. The readily available, and easy to handle α,β-unsaturated carboxylic acid is successfully used as suitable starting materiel for NHC catalysis, which has explored new possibilities of NHC. The described strategy is quite convenient with mild reaction conditions. We believe this new strategy may find more applications in organic synthesis.

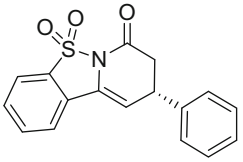
Table 4.5 Enantioselective [3+3] cyclocondensation with sultam-derived cyclic imines



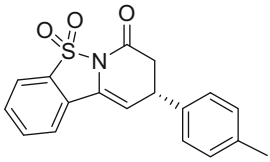
4.1 (2.0 equiv.)

4.7a R' = H
4.7b R' = *n*-Pr

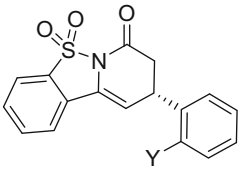
4.8



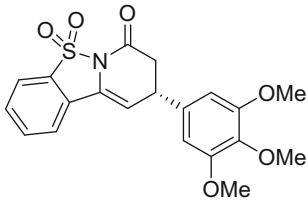
4.8a 69%, 95% ee



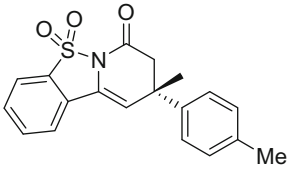
4.8b 78%, 92% ee



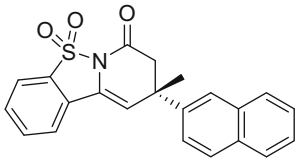
4.8c Y = Me, 90%, 98% ee
4.8d Y = OMe, 72%, 96% ee
4.8e Y = Br, 83%, 94% ee



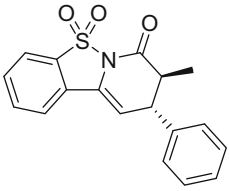
4.8f 60%, 87% ee



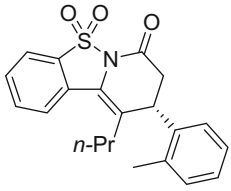
4.8g 61%, 96% ee



4.8h 75%, 96% ee



4.8i[a] d.r. > 20/1[b]
52%, 77% ee



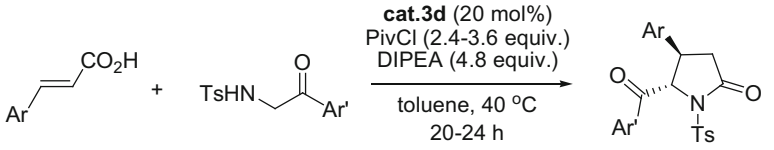
4.8j[a] 68%, 85% ee

[a]The reaction was carried in DCM at RT

[b]Determined by ^{1}H NMR spectroscopy (300 MHz) of the unpurified reaction mixture

4.8 Experimental Part

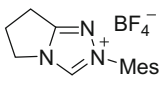
4.8.1 Enantioselective [3+2] Annulation with Amino Ketones



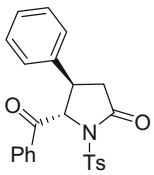
4.1 **4.2** **4.4**

To a solution of amino ketone **4.2** (0.2 mmol, 58 mg) and α,β-unsaturated carboxylic acid **4.1** (0.4–0.6 mmol, 2.0–3.0 equiv.) in toluene (2.0 ml) was added DIPEA (0.96 mmol, 124 mg, 4.8 equiv.) and pivaloyl chloride (0.48–0.72 mmol, 58–87 mg, 2.4–3.6 equiv.) at room temperature. The reaction mixture was stirred at room temperature for 15 min, then NHC precursor **cat.3d** (0.04 mmol, 17 mg, 0.2 equiv.) was added. The reaction mixture was stirred at 40 °C until the full consumption of the amino ketone (typically, 20–24 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleumether/EtOAc as the eluent, typically 20:1–1:1) to furnish the corresponding cycloadduct.

Racemic samples for the chiral phase HPLC analysis were prepared using NHC precursor **cat.5b** under the same conditions.



cat.5b

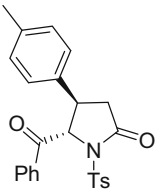


4.4a

(4*R*,5*S*)-5-benzoyl-4-phenyl-1-tosylpyrrolidin-2-one

Total yield: 54 mg, 64%, d.r. = 5/1. Yellow solid; mp 143–144 °C; $[\alpha]_D^{25}$ +23.2 (*c* 1.0, CH_2Cl_2); 96% ee as determined by HPLC (AD, 90:10 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 54.7 min, $t_{r\ min}$ = 87.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 10.1, 8.1 Hz, 4H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.40–7.33 (m, 5H), 7.17 (dd, *J* = 6.5, 2.8 Hz, 2H), 5.87 (d, *J* = 1.9 Hz, 1H), 3.39

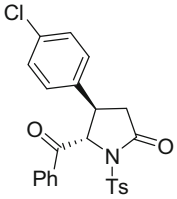
(d, J = 9.1 Hz, 1H), 2.99 (dd, J = 17.6, 9.2 Hz, 1H), 2.53 (dd, J = 17.6, 2.2 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 172.4, 145.6, 141.8, 134.8, 134.6, 133.7, 129.7, 129.5, 129.4, 129.3, 128.9, 128.4, 126.4, 69.0, 40.9, 38.6, 21.9; IR (KBr) 1743, 1696, 1359, 1219, 1168, 760, 674, 608; HRMS (ESI) calcd for $C_{24}H_{21}NO_4SNa$ $[M+Na]^+$ 442.10835, found 442.10809.



4.4b

(4*R*,5*S*)-5-benzoyl-4-(p-tolyl)-1-tosylpyrrolidin-2-one

Total yield: 52 mg, 60%, d.r. = 3/1. Yellow solid; mp 127–128 °C; $[\alpha]_D^{25}$ +36.8 (*c* 1.0, CH_2Cl_2); 92% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 15.8 min, $t_{r\ min}$ = 24.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.91 (m, 4H), 7.65 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.7 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 5.84 (d, J = 1.7 Hz, 1H), 3.36 (d, J = 9.0 Hz, 1H), 2.97 (dd, J = 17.6, 9.2 Hz, 1H), 2.53–2.47 (m, 4H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 172.5, 145.5, 138.9, 138.1, 134.9, 134.5, 133.7, 130.3, 129.4, 129.4, 129.2, 128.9, 126.2, 69.2, 40.5, 38.7, 21.9, 21.2; IR (KBr) 1743, 1695, 1586, 1359, 1220, 1168, 1137, 748, 674, 606; HRMS (ESI) calcd for $C_{25}H_{23}NO_4SNa$ $[M+Na]^+$ 456.12400, found 456.12396.

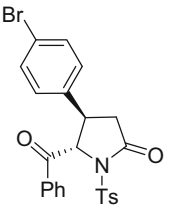


4.4c

(4*R*,5*S*)-5-benzoyl-4-(4-chlorophenyl)-1-tosylpyrrolidin-2-one

Total yield: 57 mg, 63%, d.r. = 6/1. Yellow solid; mp 85–86 °C; $[\alpha]_D^{25}$ +57.6 (*c* 1.0, CH_2Cl_2); 92% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.2 min, $t_{r\ min}$ = 23.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.90 (m, 4H), 7.66 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.34 (dd, J = 12.1, 8.4 Hz, 4H), 7.11 (d, J = 8.4 Hz, 2H), 5.81 (d, J = 1.8 Hz, 1H), 3.38 (dd, J = 8.1, 2.9 Hz, 1H), 2.99 (dd, J = 17.7, 9.2 Hz, 1H), 2.48 (d, J = 15.60, 2.1 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 172.0, 145.7, 140.2, 134.7,

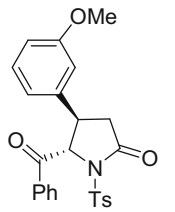
134.2, 133.6, 129.8, 129.4, 129.4, 129.3, 128.8, 127.7, 68.7, 40.3, 38.5, 21.9; IR (KBr) 1744, 1697, 1493, 1361, 1168, 1138, 752, 672, 603; HRMS (ESI) calcd for $C_{24}H_{20}ClNO_4SNa$ $[M+Na]^+$ 476.06938, found 476.06921.



4.4d

(4*R*,5*S*)-5-benzoyl-4-(4-bromophenyl)-1-tosylpyrrolidin-2-one

Total yield: 68 mg, 68%, d.r. = 5/1. Yellow solid; mp 91–92 °C; $[\alpha]_D^{25}$ +40.0 (*c* 1.0, CH_2Cl_2); 92% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.3 min, $t_{r\ min}$ = 23.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.89 (m, 4H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.54–7.47 (m, 4H), 7.37 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 5.81 (d, *J* = 1.8 Hz, 1H), 3.34 (d, *J* = 1.9 Hz, 1H), 2.99 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.50–2.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5, 172.0, 145.7, 140.8, 134.7, 133.7, 132.8, 129.5, 129.4, 129.4, 128.9, 128.0, 122.3, 68.6, 40.4, 38.4, 21.9; IR (KBr) 1743, 1689, 1596, 1489, 1361, 1218, 1168, 1133, 1088, 699, 591, 564; HRMS (ESI) calcd for $C_{24}H_{20}BrNO_4SNa$ $[M+Na]^+$ 520.01886, found 520.01839.

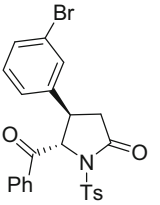


4.4e

(4*R*,5*S*)-5-benzoyl-4-(3-methoxyphenyl)-1-tosylpyrrolidin-2-one

Total yield: 62 mg, 69%, d.r. = 4/1. Yellow wax; $[\alpha]_D^{25}$ +20.0 (*c* 1.0, CH_2Cl_2); 94% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 23.1 min, $t_{r\ min}$ = 29.3 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (t, *J* = 7.4 Hz, 4H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.27 (dd, *J* = 9.2, 6.6 Hz, 1H), 6.87 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 5.87 (d, *J* = 1.7 Hz, 1H), 3.77 (s, 3H), 3.38–3.35 (m, 1H), 2.98 (dd, *J* = 17.6, 9.2 Hz, 1H), 2.55–2.47 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 172.4, 160.5, 145.5, 143.3, 134.9, 134.6, 133.7, 130.8, 129.4, 129.3, 128.9, 118.4, 113.8, 111.8, 68.9, 55.4, 40.9, 38.6, 21.9;

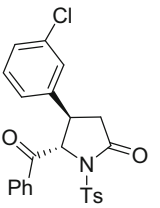
IR (KBr) 1743, 1697, 1597, 1360, 1215, 1169, 1134, 1087, 780, 676, 586, 555; HRMS (ESI) calcd for $C_{25}H_{23}NO_5SNa$ $[M+Na]^+$ 472.11891, found 472.11826.



4.4f

(4*R*,5*S*)-5-benzoyl-4-(3-bromophenyl)-1-tosylpyrrolidin-2-one

Total yield: 69 mg, 69%, d.r. = 4/1. Yellow solid; mp 126–127 °C; $[\alpha]_D^{25}$ +31.6 (*c* 1.0, CH_2Cl_2); 90% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.3 min, $t_{r\ min}$ = 21.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97–7.91 (m, 4H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.55–7.46 (m, 3H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.27–7.22 (m, 2H), 7.14 (d, *J* = 7.8 Hz, 1H), 5.83 (d, *J* = 1.8 Hz, 1H), 3.35 (d, *J* = 9.2 Hz, 1H), 3.00 (dd, *J* = 17.7, 9.2 Hz, 1H), 2.52–2.45 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 171.8, 145.7, 143.9, 134.7, 133.5, 131.6, 131.3, 129.5, 129.5, 129.3, 129.2, 128.9, 124.9, 123.6, 68.5, 40.4, 38.4, 21.9; IR (KBr) 1742, 1698, 1596, 1362, 1186, 1169, 1138, 1082, 694, 671, 608; HRMS (ESI) calcd for $C_{24}H_{20}BrNO_4SNa$ $[M+Na]^+$ 520.01886, found 520.01825.

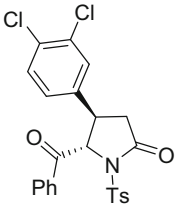


4.4g

(4*R*,5*S*)-5-benzoyl-4-(3-chlorophenyl)-1-tosylpyrrolidin-2-one

Total yield: 57 mg, 63%, d.r. = 4/1. Yellow solid; mp 144–145 °C; $[\alpha]_D^{25}$ +22.0 (*c* 1.0, CH_2Cl_2); 90% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 17.6 min, $t_{r\ min}$ = 21.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (t, *J* = 8.5 Hz, 4H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.38–7.26 (m, 4H), 7.10–7.07 (m, 2H), 5.83 (d, *J* = 1.8 Hz, 1H), 3.36 (d, *J* = 9.2 Hz, 1H), 3.00 (dd, *J* = 17.7, 9.2 Hz, 1H), 2.52–2.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 171.9, 145.7, 143.7, 135.5, 134.7, 133.6, 131.1, 129.5, 129.4, 129.3, 128.9, 128.6, 126.6, 124.4, 68.5, 40.5, 38.4, 21.9; IR (KBr) 1743, 1698,

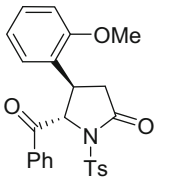
1597, 1362, 1218, 1169, 1139, 1088, 730, 673, 609; HRMS (ESI) calcd for $C_{24}H_{20}ClNO_4SNa$ $[M+Na]^+$ 476.06938, found 476.06938.



4.4h

(4*R*,5*S*)-5-benzoyl-4-(3,4-dichlorophenyl)-1-tosylpyrrolidin-2-one

Total yield: 65 mg, 67%, d.r. = 5/1. Yellow wax; $[\alpha]_D^{25}$ +34.4 (*c* 1.0, CH_2Cl_2); 95% ee as determined by HPLC (AD, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 26.2 min, $t_{r\ min}$ = 29.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (t, *J* = 7.8 Hz, 4H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.80 (d, *J* = 1.8 Hz, 1H), 3.34 (d, *J* = 9.1 Hz, 1H), 3.01 (dd, *J* = 17.7, 9.2 Hz, 1H), 2.49–2.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 171.6, 145.8, 141.8, 134.8, 134.7, 133.8, 133.6, 132.7, 131.8, 129.6, 129.4, 129.3, 128.8, 128.5, 125.6, 68.2, 40.0, 38.3, 21.9; IR (KBr) 1744, 1698, 1596, 1362, 1219, 1169, 1132, 1087, 724, 672, 604, 552; HRMS (ESI) calcd for $C_{24}H_{19}Cl_2NO_4SNa$ $[M+Na]^+$ 510.03041, found 510.02983.

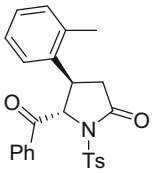


4.4i

(4*R*,5*S*)-5-benzoyl-4-(2-methoxyphenyl)-1-tosylpyrrolidin-2-one

Total yield: 48 mg, 54%, d.r. = 4/1. Yellow wax; $[\alpha]_D^{25}$ -3.6 (*c* 1.0, CH_2Cl_2); 90% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 15.3 min, $t_{r\ min}$ = 18.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.90–7.87 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.37–7.26 (m, 3H), 7.00–6.86 (m, 3H), 5.83 (d, *J* = 2.7 Hz, 1H), 3.72 (s, 3H), 3.51 (dt, *J* = 10.0, 2.6 Hz, 1H), 2.95 (dd, *J* = 17.7, 10.1 Hz, 1H), 2.57 (dd, *J* = 17.7, 2.7 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 173.2, 157.0, 145.2, 135.3, 134.2, 134.1, 129.5, 129.5, 129.3, 129.3, 129.1, 128.9, 128.5, 120.9, 111.2, 67.7, 55.1, 37.4, 37.1, 21.9; IR (KBr) 1743, 1693, 1597, 1359,

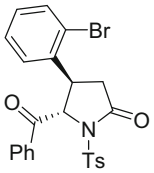
1249, 1219, 1169, 1145, 1088, 750, 675, 550; HRMS (ESI) calcd for $C_{25}H_{23}NO_5SNa$ $[M+Na]^+$ 472.11891, found 472.11839.



4.4j

(4*R*,5*S*)-5-benzoyl-4-(o-tolyl)-1-tosylpyrrolidin-2-one

Total yield: 63 mg, 73%, d.r. = 4/1. Yellow solid; mp 151–152 °C; $[\alpha]_D^{25}$ +28.0 (*c* 1.0, CH_2Cl_2); 88% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 11.9 min, $t_{r\ min}$ = 21.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.32–7.30 (m, 1H), 7.26–7.21 (m, 2H), 7.15–7.12 (m, 1H), 5.93 (d, *J* = 2.3 Hz, 1H), 3.61 (dt, *J* = 9.4, 2.4 Hz, 1H), 3.03 (dd, *J* = 17.6, 9.5 Hz, 1H), 2.47–2.39 (m, 4H), 2.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 172.4, 145.6, 139.9, 135.0, 134.8, 134.5, 133.9, 131.1, 129.4, 129.4, 129.2, 128.8, 128.0, 127.7, 124.8, 68.1, 38.8, 36.2, 21.9, 19.6; IR (KBr) 1744, 1698, 1644, 1597, 1448, 1362, 1216, 1169, 760, 677, 594; HRMS (ESI) calcd for $C_{25}H_{23}NO_4SNa$ $[M+Na]^+$ 456.12400, found 456.12358.

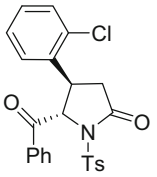


4.4k

(4*R*,5*S*)-5-benzoyl-4-(2-bromophenyl)-1-tosylpyrrolidin-2-one

Total yield: 70 mg, 70%, d.r. = 7/1. Yellow solid; mp 133–134 °C; $[\alpha]_D^{25}$ +14.0 (*c* 1.0, CH_2Cl_2); 95% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 12.7 min, $t_{r\ min}$ = 32.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (t, *J* = 7.3 Hz, 4H), 7.66–7.57 (m, 2H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.38–7.34 (m, 4H), 7.26–7.18 (m, 1H), 5.93 (d, *J* = 1.6 Hz, 1H), 3.93 (d, *J* = 9.3 Hz, 1H), 3.08 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.52–2.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 172.1, 145.6, 140.4, 134.6, 134.6, 133.8, 133.7, 129.7, 129.4, 129.2, 129.1, 129.0, 126.9, 123.8, 67.1, 39.6, 38.3, 21.9; IR (KBr) 1744, 1698, 1597, 1472, 1449,

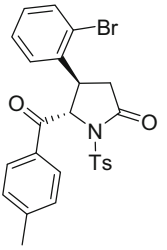
1362, 1218, 1168, 1087, 758, 671, 585; HRMS (ESI) calcd for $C_{24}H_{20}BrNO_4SNa$ $[M+Na]^+$ 520.01886, found 520.01844.



4.4l

(4*R*,5*S*)-5-benzoyl-4-(2-chlorophenyl)-1-tosylpyrrolidin-2-one

Total yield: 57 mg, 63%, d.r. = 6/1. Yellow solid; mp 144–145 °C; $[\alpha]_D^{25}$ +13.6 (*c* 1.8, CH_2Cl_2); 98% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 12.8 min, $t_{r\ min}$ = 31.6 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (t, *J* = 7.4 Hz, 4H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.41–7.26 (m, 6H), 5.93 (d, *J* = 2.0 Hz, 1H), 3.92 (dt, *J* = 9.3, 2.0 Hz, 1H), 3.07 (dd, *J* = 17.7, 9.4 Hz, 1H), 2.53–2.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 172.1, 145.6, 138.7, 134.7, 134.5, 133.8, 133.2, 130.4, 129.5, 129.4, 129.1, 129.0, 128.3, 127.0, 67.0, 38.0, 37.1, 21.9; IR (KBr) 1743, 1693, 1596, 1361, 1218, 1169, 1088, 760, 673, 608; HRMS (ESI) calcd for $C_{24}H_{20}ClNO_4SNa$ $[M+Na]^+$ 476.06938, found 476.06879.

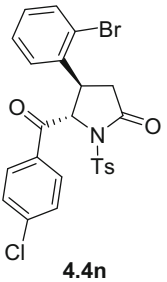


4.4m

(4*R*,5*S*)-4-(2-bromophenyl)-5-(4-methylbenzoyl)-1-tosylpyrrolidin-2-one

Total yield: 75 mg, 73%, d.r. = 5/1. Yellow wax; $[\alpha]_D^{25}$ +20.2 (*c* 1.9, CH_2Cl_2); 96% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 13.3 min, $t_{r\ min}$ = 35.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.40–7.29 (m, 4H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.22–7.17 (m, 1H), 5.91 (d, *J* = 1.8 Hz, 1H), 3.92 (dd, *J* = 7.5, 1.8 Hz, 1H), 3.08 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.50–2.42 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 172.2, 145.7, 145.6, 140.6, 134.7, 133.7, 131.3, 129.8, 129.7, 129.4, 129.4, 129.2, 129.0, 126.9, 123.8, 66.9, 39.7, 38.3, 21.9, 21.9;

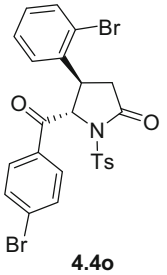
IR (KBr) 1744, 1688, 1606, 1362, 1211, 1168, 1135, 1088, 664, 566, 554; HRMS (ESI) calcd for $C_{25}H_{23}BrNO_4S$ $[M+H]^+$ 512.05257, found 512.05200.



4.4n

(4*R*,5*S*)-4-(2-bromophenyl)-5-(4-chlorobenzoyl)-1-tosylpyrrolidin-2-one

Total yield: 69 mg, 65%, d.r. = 7/1. Yellow solid; mp 146–147 °C; $[\alpha]_D^{25}$ +18.7 (*c* 2.4, CH_2Cl_2); 97% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 17.0 min, $t_{r\ min}$ = 26.3 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.83 (m, 4H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.0 Hz, 2H), 7.34 (dd, *J* = 7.8, 5.0 Hz, 4H), 7.23–7.18 (m, 1H), 5.84 (d, *J* = 2.1 Hz, 1H), 3.91 (dt, *J* = 9.3, 2.3 Hz, 1H), 3.08 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.54–2.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 172.0, 145.7, 141.2, 140.2, 134.6, 133.8, 132.3, 130.5, 129.9, 129.5, 129.5, 129.4, 129.0, 127.0, 123.7, 67.0, 39.6, 38.2, 21.9; IR (KBr) 1745, 1693, 1589, 1361, 1215, 1168, 1090, 785, 669, 610; HRMS (ESI) calcd for $C_{24}H_{19}BrClNO_4SNa$ $[M+Na]^+$ 553.97989, found 553.97928.

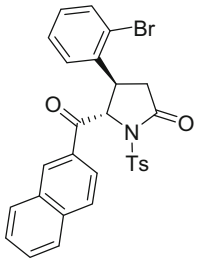


4.4o

(4*R*,5*S*)-5-(4-bromobenzoyl)-4-(2-bromophenyl)-1-tosylpyrrolidin-2-one

Total yield: 63 mg, 55%, d.r. = 6/1. Yellow solid; mp 139–140 °C; $[\alpha]_D^{25}$ +24.6 (*c* 1.9, CH_2Cl_2); 95% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.1 min, $t_{r\ min}$ = 27.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.6 Hz, 2H), 7.60 (dd, *J* = 11.4, 8.4 Hz, 3H), 7.35 (d, *J* = 8.2 Hz, 4H), 7.22–7.18 (m, 1H), 5.83 (d, *J* = 2.1 Hz, 1H), 3.91 (dt, *J* = 9.2, 2.1 Hz, 1H), 3.08 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.54–2.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.6, 172.0, 145.7, 140.2, 134.6, 133.8, 132.7, 132.5,

130.5, 130.0, 129.9, 129.5, 129.4, 129.0, 127.0, 123.8, 67.0, 39.6, 38.2, 21.9; IR (KBr) 1743, 1693, 1585, 1361, 1216, 1167, 1134, 1088, 756, 608, 588; HRMS (ESI) calcd for $C_{24}H_{19}Br_2NO_4SNa$ $[M+Na]^+$ 597.92938, found 597.92858.

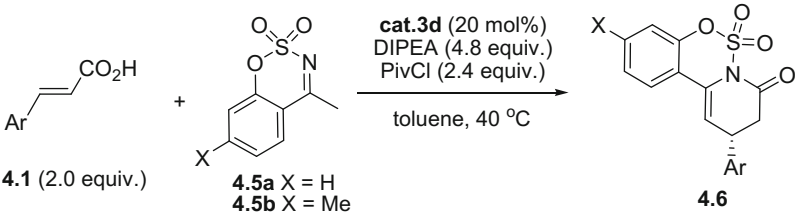


4.4p

(4*R*,5*S*)-5-(2-naphthoyl)-4-(2-bromophenyl)-1-tosylpyrrolidin-2-one

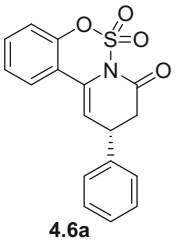
Total yield: 57 mg, 52%, d.r. = 12/1. Yellow wax; $[\alpha]_D^{25}$ −9.3 (*c* 1.5, CH_2Cl_2); 95% ee as determined by HPLC (AD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.3 min, $t_{r\ min}$ = 39.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.00–7.87 (m, 6H), 7.66–7.53 (m, 3H), 7.43–7.34 (m, 4H), 7.26–7.19 (m, 1H), 6.07 (d, *J* = 2.0 Hz, 1H), 4.03–3.99 (m, 1H), 3.13 (dd, *J* = 17.8, 9.4 Hz, 1H), 2.54 (dd, *J* = 17.8, 2.3 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ195.1, 172.3, 145.6, 140.6, 136.3, 134.7, 133.7, 132.4, 131.5, 131.1, 130.0, 129.8, 129.4, 129.4, 129.1, 129.0, 128.0, 127.3, 127.2, 124.1, 123.8, 67.3, 39.8, 38.3, 21.9; IR (KBr) 1744, 1688, 1626, 1596, 1361, 1168, 1142, 1088, 664, 565, 553; HRMS (ESI) calcd for $C_{28}H_{22}BrNO_4SNa$ $[M+Na]^+$ 570.03451, found 570.03386.

4.8.2 Enantioselective [3+3] Annulation with Sulfamate-Derived Cyclic Imines



To a solution of imines **4.5** (0.2 mmol, 1.0 equiv.) and α,β-unsaturated carboxylic acid **4.1** (0.4 mmol, 2.0 equiv.) in toluene (2.0 ml) was added DIPEA (0.96 mmol, 124 mg, 4.8 equiv.) at room temperature, then pivaloyl chloride (0.48 mmol, 58 mg, 2.4 equiv.) was added at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then **cat.3d** (0.04 mmol, 17 mg, 0.2 equiv.) was added.

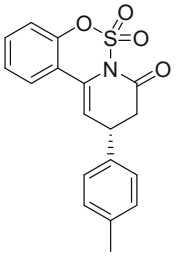
The reaction mixture was stirred at 40 °C until the full consumption of the imines (typically, 20–96 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleumether/EtOAc as the eluent, typically 20:1–1:1) to furnish the corresponding products.



4.6a

(*S*)-10-phenyl-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide[7]

Yield: 47 mg, 72%; yellow solid; mp 162–163 °C; $[\alpha]_D^{25}$ −18.4 (*c* 1.0, CH_2Cl_2); 98% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 16.9 min, $t_{r\ min}$ = 15.3 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.49–7.43 (m, 1H), 7.42–7.31 (m, 4H), 7.29–7.21 (m, 3H), 6.08 (d, *J* = 4.2 Hz, 1H), 4.06–3.99 (m, 1H), 3.04 (dd, *J* = 16.3, 6.3 Hz, 1H), 2.87 (dd, *J* = 16.3, 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 147.4, 140.4, 133.2, 131.6, 129.4, 127.9, 127.7, 127.1, 125.7, 120.4, 119.5, 112.1, 40.1, 37.7; IR (KBr) 1727, 1595, 1491, 1457, 1408, 1174, 870, 761, 662; HRMS (ESI) calcd for $C_{17}H_{13}NO_4SNa$ $[M+Na]^+$ 350.04575, found 350.04559.

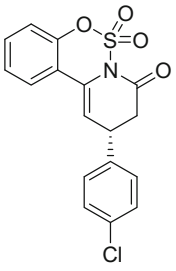


4.6b

(*S*)-10-(p-tolyl)-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide

Yield: 51 mg, 75%; yellow solid; mp 170–171 °C; $[\alpha]_D^{25}$ −28.8 (*c* 1.0, CH_2Cl_2); 98% ee as determined by HPLC (OD, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.5 min, $t_{r\ min}$ = 13.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.45 (td, *J* = 7.9, 1.5 Hz, 1H), 7.33 (td, *J* = 7.7, 1.2 Hz, 1H),

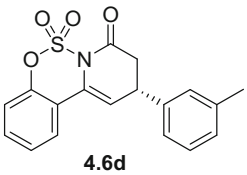
7.22–7.13 (m, 5H), 6.06 (d, J = 4.3 Hz, 1H), 4.01–3.94 (m, 1H), 3.01 (dd, J = 16.3, 6.1 Hz, 1H), 2.84 (dd, J = 16.2, 10.0 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.4, 137.7, 137.3, 133.1, 131.5, 130.0, 127.7, 127.0, 125.7, 120.4, 119.5, 112.4, 40.2, 37.3, 21.1; IR (KBr) 1732, 1514, 1485, 1457, 1409, 1175, 871, 795, 652; HRMS (ESI) calcd for $C_{18}H_{15}NO_4SNa$ $[M+Na]^+$ 364.06140, found 364.06104.



4.6c

(*S*)-10-(4-chlorophenyl)-9,10-dihydro-8H-benzoepyrido[1,2-c] [1,2,3] oxathiazin-8-one 6,6-dioxide

Yield: 42 mg, 58%; yellow solid; mp 170–171 °C; $[\alpha]_D^{25}$ −18.8 (c 1.0, CH_2Cl_2); 99% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 21.6 min, $t_{r\ min}$ = 20.3 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 7.8 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.38–7.34 (m, 3H), 7.26–7.20 (m, 3H), 6.04 (d, J = 4.4 Hz, 1H), 4.04–3.97 (m, 1H), 3.03 (dd, J = 16.2, 6.3 Hz, 1H), 2.84 (dd, J = 16.2, 9.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 147.4, 138.8, 133.8, 133.6, 131.7, 129.6, 128.5, 127.7, 125.7, 120.2, 119.6, 111.3, 40.0, 37.1; IR (KBr) 1730, 1515, 1488, 1458, 1409, 1175, 871, 760, 651; HRMS (ESI) calcd for $C_{17}H_{12}ClNO_4SNa$ $[M+Na]^+$ 384.00678, found 384.00657.

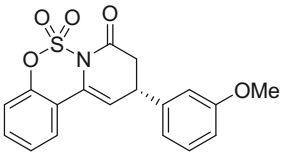


4.6d

(*S*)-10-(m-tolyl)-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide

Yield: 58 mg, 86%; yellow solid; mp 90–91 °C; $[\alpha]_D^{25}$ −26.0 (c 1.0, CH_2Cl_2); 97% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 13.7 min, $t_{r\ min}$ = 12.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.8, 1.4 Hz, 1H), 7.46 (td, J = 8.0, 1.5 Hz, 1H), 7.37–7.21 (m, 3H), 7.13 (d, J = 7.6 Hz, 1H), 7.07–7.05 (m, 2H), 6.07 (d, J = 4.2 Hz, 1H), 4.02–3.95 (m, 1H),

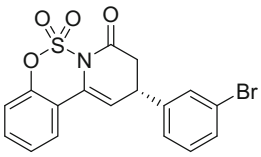
3.03 (dd, J = 16.3, 6.2 Hz, 1H), 2.87 (dd, J = 16.2, 10.4 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 147.4, 140.4, 139.2, 133.1, 131.5, 129.3, 128.7, 127.9, 127.7, 125.7, 124.1, 120.4, 119.5, 112.3, 40.1, 37.7, 21.6; IR (KBr) 1723, 1486, 1457, 1409, 1175, 851, 794, 759; HRMS (ESI) calcd for $C_{18}H_{15}NO_4SNa$ [M +Na]$^+$ 364.06140, found 364.06116.



4.6e

(*S*)-10-(3-methoxyphenyl)-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3] oxathiazin-8-one 6,6-dioxide

Yield: 44 mg, 62%; yellow solid; mp 108–109 °C; $[\alpha]_D^{25}$ −22.0 (c 1.0, CH_2Cl_2); 97% ee as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 27.9 min, $t_{r\ min}$ = 24.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.8, 1.4 Hz, 1H), 7.46 (td, J = 8.0, 1.5 Hz, 1H), 7.37–7.21 (m, 3H), 6.87–6.81 (m, 3H), 6.07 (d, J = 4.3 Hz, 1H), 4.02–3.97 (m, 1H), 3.81 (s, 3H), 3.04 (dd, J = 16.2, 6.3 Hz, 1H), 2.87 (dd, J = 16.2, 10.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 160.4, 147.4, 141.9, 133.3, 131.6, 130.5, 127.7, 125.7, 120.4, 119.5, 119.3, 113.1, 113.0, 112.0, 55.4, 40.1, 37.7; IR (KBr) 1728, 1600, 1488, 1457, 1408, 1175, 851, 795, 759; HRMS (ESI) calcd for $C_{18}H_{15}NO_5SNa$ [M+Na]$^+$ 380.05631, found 380.05607.

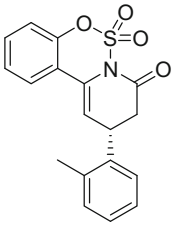


4.6f

(*S*)-10-(3-bromophenyl)-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3] oxathiazin-8-one 6,6-dioxide

Yield: 46 mg, 57%; yellow solid; mp 172–173 °C; $[\alpha]_D^{25}$ +2.0 (c 1.0, CH_2Cl_2); 97% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 19.7 min, $t_{r\ min}$ = 16.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 7.8, 1.3 Hz, 1H), 7.50–7.42 (m, 3H), 7.36 (td, J = 7.7, 1.0 Hz, 1H), 7.29–7.20 (m, 3H), 6.03 (d, J = 4.2 Hz, 1H), 4.03–3.96 (m, 1H), 3.03 (dd, J = 16.3, 6.2 Hz, 1H), 2.84 (dd, J = 16.3, 10.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 147.4, 142.7, 133.8, 131.8, 131.2, 131.1, 130.4, 127.7, 125.8, 125.8, 123.4, 120.2, 119.6, 111.0,

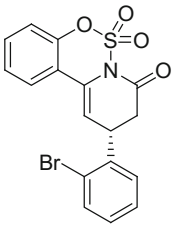
40.0, 37.4; IR (KBr) 1728, 1597, 1457, 1409, 1176, 881, 792, 760; HRMS (ESI) calcd for $C_{17}H_{12}BrNO_4SNa$ $[M+Na]^+$ 427.95626, found 427.95612.



4.6g

(*S*)-10-(o-tolyl)-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3]oxathiazin-8-one 6,6-dioxide

Yield: 58 mg, 85%; yellow solid; mp 150–151 °C; $[\alpha]_D^{25}$ −4.4 (*c* 1.0, CH_2Cl_2); 96% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 13.0 min, $t_{r\ min}$ = 11.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.48–7.43 (m, 1H), 7.35 (dd, *J* = 7.5, 6.9 Hz, 1H), 7.25–7.21 (m, 5H), 6.04 (d, *J* = 3.9 Hz, 1H), 4.29–4.22 (m, 1H), 2.99 (dd, *J* = 16.3, 6.1 Hz, 1H), 2.81 (dd, *J* = 16.3, 10.8 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 147.3, 138.4, 135.5, 133.5, 131.5, 131.2, 127.8, 127.7, 127.2, 126.3, 125.7, 120.5, 119.5, 112.4, 39.0, 33.9, 19.5; IR (KBr) 1728, 1602, 1457, 1409, 1175, 874, 789, 759; HRMS (ESI) calcd for $C_{18}H_{15}NO_4SNa$ $[M+Na]^+$ 364.06140, found 364.06097.

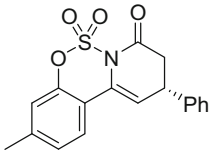


4.6h

(*S*)-10-(2-bromophenyl)-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3] oxathiazin-8-one 6,6-dioxide

Yield: 53 mg, 65%; yellow solid; mp 159–160 °C; $[\alpha]_D^{25}$ −1.2 (*c* 1.0, CH_2Cl_2); 97% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 15.9 min, $t_{r\ min}$ = 13.1 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.9, 1.0 Hz, 2H), 7.48 (td, *J* = 7.9, 1.5 Hz, 1H), 7.39–7.32 (m, 3H), 7.26–7.16 (m, 2H), 6.08 (d, *J* = 4.7 Hz, 1H), 4.52–4.45 (m, 1H), 3.10 (dd, *J* = 16.4, 6.6 Hz, 1H), 2.90 (dd, *J* = 16.4, 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 147.4, 139.0, 133.9, 133.8, 131.7, 129.6, 128.6, 128.2, 127.7, 125.8, 124.0, 120.3, 119.6, 110.6,

38.4, 37.1; IR (KBr) 1727, 1457, 1409, 1175, 871, 794, 757; HRMS (ESI) calcd for $C_{17}H_{12}BrNO_4SNa$ $[M+Na]^+$ 427.95626, found 427.95596.

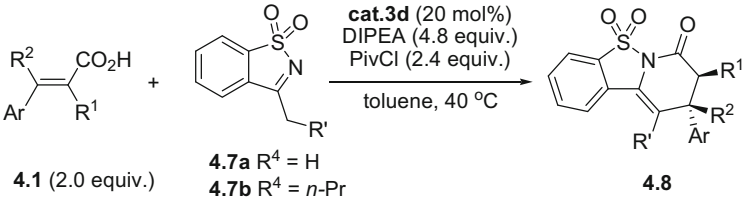


4.6i

(*S*)-3-methyl-10-phenyl-9,10-dihydro-8H-benzoepyrido[1,2-c][1,2,3] oxathiazin-8-one 6,6-dioxide

Yield: 40 mg, 58%; yellow solid; mp 168–169 °C; $[\alpha]_D^{25}$ −1.2 (*c* 1.0, CH_2Cl_2); 95% ee as determined by HPLC (IA, 90:10 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 25.1 min, $t_{r\ min}$ = 23.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.23 (m, 7H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.04 (d, *J* = 4.1 Hz, 1H), 4.0–3.98 (m, 1H), 3.04 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.87 (dd, *J* = 16.2, 10.4 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 145.4, 140.5, 137.7, 133.4, 132.3, 129.4, 128.0, 127.2, 125.9, 120.0, 119.2, 111.7, 40.2, 37.8, 21.2; IR (KBr) 1728, 1454, 1489, 1409, 1173, 878, 765, 701; HRMS (ESI) calcd for $C_{18}H_{15}NO_4SNa$ $[M+Na]^+$ 364.06140, found 364.06082.

4.8.3 *Enantioselective [3+3] Annulation with Sultam-Derived Cyclic Imines*

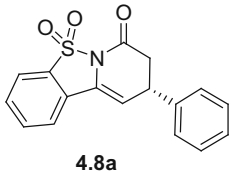


4.1 (2.0 equiv.)

4.7a R^4 = H
4.7b R^4 = *n*-Pr

4.8

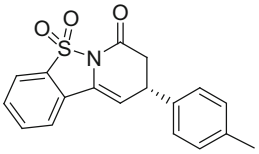
The same experimental procedure as in Table 4.4 was employed except using sultam-derived cyclic imines **4.7** as the 1,3-bisnucelophiles.



4.8a

(*S*)-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide[7]

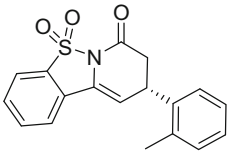
Yield: 43 mg, 69%; yellow solid; mp 232–233 °C; $[\alpha]_D^{25}$ −168.4 (*c* 1.0, CH_2Cl_2); 95% ee as determined by HPLC (IA, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 20.5 min, $t_{r\ min}$ = 16.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.74–7.73 (m, 2H), 7.67–7.62 (m, 1H), 7.40−7.31 (m, 3H), 7.27 −7.24 (m, 2H), 6.08 (d, *J* = 4.1 Hz, 1H), 4.13−4.06 (m, 1H), 3.08 (dd, *J* = 16.6, 7.2 Hz, 1H), 2.88 (dd, *J* = 16.6, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 141.3, 134.2, 132.6, 131.2, 130.0, 129.4, 127.9, 127.1, 126.8, 121.8, 121.8, 106.3, 39.9, 39.1; IR (KBr) 1714, 1339, 1278, 1177, 761, 694; HRMS (ESI) calcd for $C_{17}H_{13}NO_3SNa$ $[M+Na]^+$ 334.05084, found 334.05065.



4.8b

(*S*)-9-(p-tolyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide

Yield: 51 mg, 78%; yellow solid; mp 198–199 °C; $[\alpha]_D^{25}$ −138.4 (*c* 1.0, CH_2Cl_2); 92% ee as determined by HPLC (OD, 60:40 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 23.8 min, $t_{r\ min}$ = 16.4 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.74–7.72 (m, 2H), 7.66–7.63 (m, 1H), 7.19–7.12 (m, 4H), 6.08 (d, *J* = 4.1 Hz, 1H), 4.08–4.02 (m, 1H), 3.05 (dd, *J* = 16.6, 7.2 Hz, 1H), 2.84 (dd, *J* = 16.6, 8.9 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 138.2, 137.6, 134.2, 132.5, 131.1, 130.0, 129.8, 127.0, 126.8, 121.8, 121.7, 106.6, 40.0, 38.7, 21.1; IR (KBr) 1714, 1471, 1341, 1277, 1178, 762, 630; HRMS (ESI) calcd for $C_{18}H_{15}NO_3SNa$ $[M+Na]^+$ 348.06649, found 348.06638.

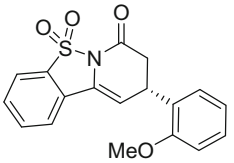


4.8c

(*S*)-9-(o-tolyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a]pyridin-7-one 5,5-dioxide

Yield: 59 mg, 90%; yellow solid; mp 224–225 °C; $[\alpha]_D^{25}$ −76.0 (*c* 1.0, CH_2Cl_2); 98% ee as determined by HPLC (IA, 75:25 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 18.1 min, $t_{r\ min}$ = 15.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84

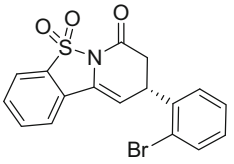
(d, J = 7.8 Hz, 1H), 7.77–7.70 (m, 2H), 7.66–7.61 (m, 1H), 7.22–7.18 (m, 4H), 6.07 (d, J = 3.8 Hz, 1H), 4.37–4.31 (m, 1H), 3.03 (dd, J = 16.6, 7.1 Hz, 1H), 2.77 (dd, J = 16.6, 9.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 139.4, 135.2, 134.2, 132.4, 131.1, 130.2, 127.7, 127.2, 126.7, 126.6, 121.8, 121.7, 106.5, 38.8, 35.2, 19.4; IR (KBr) 1713, 1472, 1343, 1281, 1180, 764, 658; HRMS (ESI) calcd for $C_{18}H_{15}NO_3SNa$ $[M+Na]^+$ 348.06649, found 348.06606.



4.8d

(*S*)-9-(2-methoxyphenyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a] pyridin-7-one 5,5-dioxide

Yield: 49 mg, 72%; yellow solid; mp 226–227 °C; $[\alpha]_D^{25}$ −216.4 (*c* 1.0, CH_2Cl_2); 96% ee as determined by HPLC (IA, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 24.7 min, $t_{r\ min}$ = 17.1 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 3.8 Hz, 2H), 7.63–7.59 (m, 1H), 7.30–7.24 (m, 1H), 7.16 (dd, J = 7.5, 1.5 Hz, 1H), 6.91 (dd, J = 14.3, 7.8 Hz, 2H), 5.98 (d, J = 4.9 Hz, 1H), 4.28–4.23 (m, 1H), 3.82 (s, 3H), 3.09 (dd, J = 16.8, 8.6 Hz, 1H), 2.85 (dd, J = 16.8, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 157.3, 134.0, 132.4, 130.8, 129.3, 129.1, 128.4, 127.1, 121.7, 121.6, 121.0, 111.0, 105.0, 55.1, 37.5, 35.4; IR (KBr) 1713, 1493, 1470, 1340, 1278, 1178, 757, 658; HRMS (ESI) calcd for $C_{18}H_{15}NO_4SNa$ $[M+Na]^+$ 364.06140, found 364.06116.

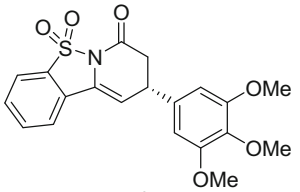


4.8e

(*S*)-9-(2-bromophenyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a] pyridin-7-one 5,5-dioxide

Yield: 65 mg, 83%; yellow solid; mp 235–236 °C; $[\alpha]_D^{25}$ −35.2 (*c* 1.0, CH_2Cl_2); 94% ee as determined by HPLC (IA, 75:25 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 20.8 min, $t_{r\ min}$ = 19.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 7.8 Hz, 1H), 7.80–7.72 (m, 2H), 7.68–7.59 (m, 2H), 7.35–7.25 (m, 2H), 7.20–7.14 (m, 1H), 6.10 (d, J = 4.3 Hz, 1H), 4.62–4.55 (m, 1H), 3.15 (dd, J = 16.7, 7.5 Hz, 1H), 2.83 (dd, J = 16.7, 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 140.1, 134.3, 133.6, 132.5, 131.3, 130.6, 129.5, 128.7,

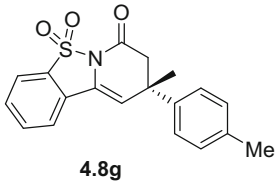
128.2, 126.6, 123.8, 121.9, 121.8, 104.8, 38.4, 38.2; IR (KBr) 1716, 1470, 1345, 1279, 1182, 761, 650, 559; HRMS (ESI) calcd for $C_{17}H_{12}BrNO_3SNa$ $[M+Na]^+$ 411.96135, found 411.96115.



4.8f

(*S*)-9-(3,4,5-trimethoxyphenyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a] pyridin-7-one 5,5-dioxide

Yield: 48 mg, 60%; yellow solid; mp 270–271 °C; $[\alpha]_D^{25}$ −105.2 (*c* 1.0, CH_2Cl_2); 87% ee as determined by HPLC (IA, 70:30 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 25.3 min, $t_{r\ min}$ = 20.8 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 1H), 7.75–7.66 (m, 3H), 6.45 (s, 2H), 6.08 (d, *J* = 4.1 Hz, 1H), 4.04–3.97 (m, 1H), 3.84–3.81 (m, 9H), 3.09 (dd, *J* = 16.5, 7.2 Hz, 1H), 2.89 (dd, *J* = 16.5, 8.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 154.0, 137.7, 136.9, 134.2, 132.8, 131.3, 130.0, 126.8, 121.9, 121.8, 106.3, 104.0, 61.0, 56.4, 40.0, 39.6; IR (KBr) 1716, 1591, 1508, 1468, 1340, 1278, 1181, 767, 558; HRMS (ESI) calcd for $C_{20}H_{19}NO_6SNa$ $[M+Na]^+$ 424.08253, found 424.08246.

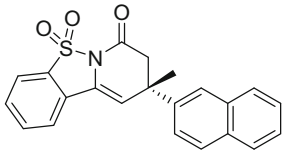


4.8g

(*S*)-9-methyl-9-(p-tolyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a] pyridin-7-one 5,5-dioxide

Yield: 41 mg, 61%; yellow solid; mp 197–198 °C; $[\alpha]_D^{25}$ −27.6 (*c* 1.0, CH_2Cl_2); 96% ee as determined by HPLC (IA, 85:15 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 31.0 min, $t_{r\ min}$ = 27.7 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 1H), 7.77–7.70 (m, 2H), 7.65–7.60 (m, 1H), 7.25 (d, *J* = 7.1 Hz, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.11 (s, 1H), 3.07 (d, *J* = 16.2 Hz, 1H), 2.83 (d, *J* = 16.2 Hz, 1H), 2.33 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 141.9, 137.3, 134.2, 132.8, 131.1, 129.8, 128.6, 126.9, 125.4, 121.9, 121.7, 112.2,

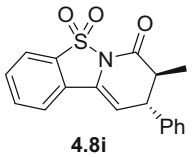
47.0, 40.4, 27.7, 21.0; IR (KBr) 1716, 1513, 1469, 1341, 1278, 1179, 763, 611; HRMS (ESI) calcd for $C_{19}H_{17}NO_3SNa$ [M+Na]$^+$ 362.08213, found 362.08155.



4.8h

(*S*)-9-methyl-9-(naphthalen-2-yl)-8,9-dihydro-7H-benzo[4,5]I sothiazolo [2,3-a] pyridin-7-one 5,5-dioxide

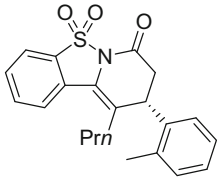
Yield: 56 mg, 75%; yellow solid; mp 249–250 °C; $[\alpha]_D^{25}$ −17.8 (*c* 1.3, CH_2Cl_2); 96% ee as determined by HPLC (IA, 75:25 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 21.3 min, $t_{r\ min}$ = 19.2 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.71 (m, 7H), 7.67–7.61 (m, 1H), 7.51–7.46 (m, 3H), 6.20 (s, 1H), 3.22 (d, *J* = 16.3 Hz, 1H), 2.92 (d, *J* = 16.3 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 142.1, 134.2, 133.4, 132.9, 132.5, 131.2, 129.2, 128.9, 128.2, 127.6, 126.9, 126.8, 126.5, 124.0, 123.9, 121.9, 121.8, 111.8, 46.8, 40.9, 27.6; IR (KBr) 1715, 1559, 1469, 1337, 1277, 1175, 761, 596; HRMS (ESI) calcd for $C_{22}H_{17}NO_3SNa$ [M +Na]$^+$ 398.08214, found 398.08174.



4.8i

(8*S*,9*R*)-8-methyl-9-phenyl-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a] pyridin-7-one 5,5-dioxide[7]

Yield: 34 mg, 52%, d.r. > 20/1; yellow solid; mp 173–174 °C; $[\alpha]_D^{25}$ −64.8 (*c* 1.0, CH_2Cl_2); 77% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 30.7 min, $t_{r\ min}$ = 20.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 1H), 7.72–7.61 (m, 3H), 7.42–7.30 (m, 3H), 7.26–7.23 (m, 2H), 5.98 (d, *J* = 3.3 Hz, 1H), 3.68 (dd, *J* = 10.7, 3.3 Hz, 1H), 2.94–2.84 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 141.3, 134.2, 132.7, 131.1, 129.3, 129.2, 127.9, 127.9, 126.7, 121.8, 121.7, 106.7, 46.8, 43.9, 14.0; IR (KBr) 1713, 1471, 1453, 1341, 1260, 1210, 1177, 1162, 763, 631; HRMS (ESI) calcd for $C_{18}H_{15}NO_3SNa$ [M+Na]$^+$ 348.06649, found 348.06625.

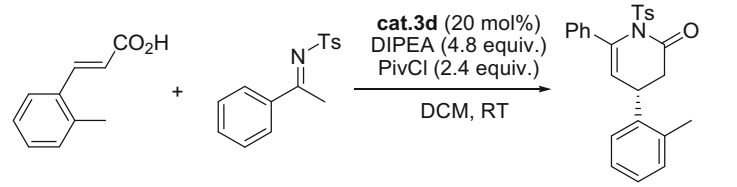


4.8j

(*R*)-10-propyl-9-(o-tolyl)-8,9-dihydro-7H-benzo[4,5]isothiazolo[2,3-a] pyridin-7-one 5,5-dioxide

Yield: 50 mg, 68%; yellow solid; mp 225–226 °C; $[\alpha]_D^{25}$ −196.4 (*c* 1.0, CH_2Cl_2); 85% ee as determined by HPLC (OD, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 19.8 min, $t_{r\ min}$ = 13.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.83–7.75 (m, 2H), 7.67–7.61 (m, 1H), 7.2–7.08 (m, 3H), 7.03–7.00 (m, 1H), 4.15–4.11 (m, 1H), 3.08 (dd, *J* = 15.9, 8.0 Hz, 1H), 2.76–2.64 (m, 2H), 2.40 (s, 3H), 2.14–2.04 (m, 1H), 1.72–1.56 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 137.4, 135.4, 134.2, 133.2, 131.3, 130.0, 127.9, 127.4, 127.3, 126.3, 125.9, 125.8, 124.7, 122.2, 40.8, 38.3, 33.4, 22.0, 19.6, 14.3; IR (KBr) 1715, 1556, 1483, 1337, 1277, 1174, 765, 597; HRMS (ESI) calcd for $C_{21}H_{21}NO_3SNa$ $[M+Na]^+$ 390.11344, found 390.11286.

4.8.4 Reaction with Acyclic Imine 4.9



The same procedure as in Table 4.4, except acyclic imine **4.9** was used as the 1,3-bisnucelophile and the reaction was carried out in DCM at room temperature. Yield: 64 mg, 77%; yellow solid; mp 175–176 °C; $[\alpha]_D^{25}$ −20.0 (*c* 1.5, CH_2Cl_2); 96% ee as determined by HPLC (IA, 80:20 hexanes/*i*-PrOH, 1.0 ml/min), $t_{r\ maj}$ = 15.3 min, $t_{r\ min}$ = 12.5 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.39–7.32 (m, 5H), 7.29–7.24 (m, 2H), 7.17–7.10 (m, 4H), 5.89 (d, *J* = 4.1 Hz, 1H), 4.06–4.00 (m, 1H), 2.86–2.72 (m, 2H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 145.2, 141.2, 138.4, 137.3, 136.7, 135.6, 130.9, 129.3, 129.2, 128.5, 127.4, 126.8, 126.1, 123.7, 42.1, 33.6, 21.8, 19.6; IR (KBr) 1719, 1603, 1492, 1365, 1172, 1162, 763, 592; HRMS (ESI) calcd for $C_{25}H_{23}NO_3SNa$ $[M+Na]^+$ 440.12909, found 440.12879.

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Chapter 5
Summary

More applications of *N*-heterocyclic carbenes for annulations were developed via designing suitable substrates (Fig. 5.1). These reactions added synthetically interesting examples for *N*-heterocyclic carbene catalysis. We believe the new strategies for *N*-heterocyclic carbenes catalyzed annulations will find more valuable applications in organic synthesis.

The Rauhut–Currier (RC) reaction of activated alkenes is one of the most useful organic reactions. However, compared to the well-developed Morita–Baylis–Hillman reaction, it developed slowly, especially, for β-substituted activated alkenes due to lack of selectivity and low reactivity of Lewis bases (e.g., amine, phosphine) for this type of reaction. In addition, *N*-heterocyclic carbenes are typically used for reaction of C–X (X=O, S, N) unsaturated bonds. In this work, *N*-heterocyclic carbenes were found to be efficient catalysts for the RC reaction of β-substituted nitroalkenes and oxodienes, followed by cyclization, giving the corresponding dihydropyrans in good yield with good diastereoselectivity [1]. Subsequent transformations offered the corresponding 3-amino dihydropyrans in good yield. The reaction worked well for various β-aryl and alkyl substituted nitroalkenes (Fig. 5.2).

Enals are typically employed for [3+n] and [2+n] annulations by α- and β-addition via *N*-heterocyclic carbene catalysis. In this work, enals were successfully used for [4+2] annulations with azodicarboxylates by γ-addition via dienolate intermediate when a leaving group was introduced to enals [2]. The corresponding dihydropyridazinones were afforded in good yields with excellent enantioselectivities. The reaction worked well for γ-aryl, alkyl, and alkenyl enal derivatives. Highly enantiopure tetrahydropyridazinones and γ-amino acid derivatives could be easily prepared by subsequent transformations of the resulting dihydropyridazinones. The readily available substrates, broad reaction scope, excellent

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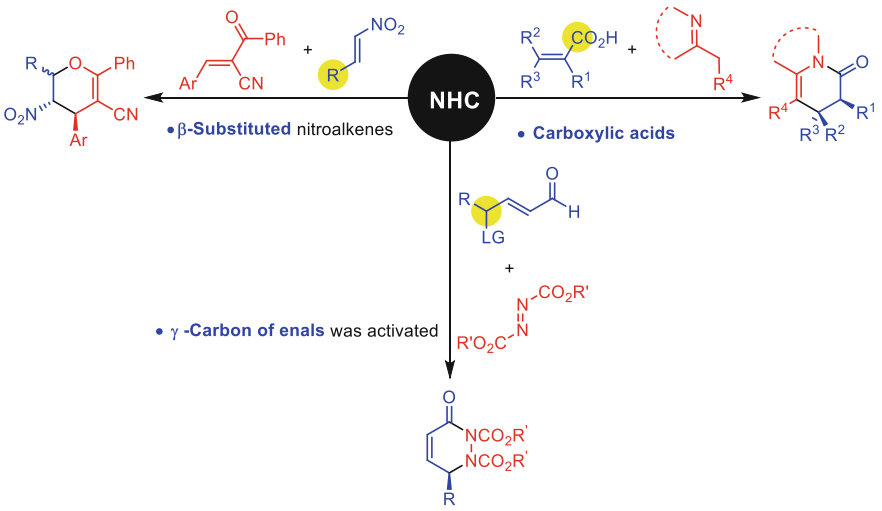

Fig. 5.1 Summary of the thesis

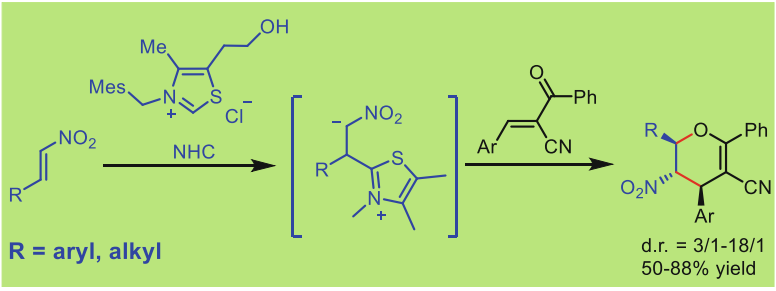

Fig. 5.2 NHC-catalyzed annulations of nitroalkenes

enantioselectivity, and mild reaction conditions make this γ-amination process potentially useful for the synthesis of γ-amino acids and their derivatives (Fig. 5.3).

α,β-Unsaturated acyl azolium, which is an important 1,3-biselectrophile intermediate, is typically generated from carboxylate derivatives (such as enals, ynals, α-bromoenals, α,β-unsaturated acyl fluorides, and α,β-unsaturated esters) using *N*-heterocyclic carbene as catalyst. In this work, the readily available α,β-unsaturated carboxylic acids were successfully employed to generate the α,β-unsaturated acyl azolium intermediates via in situ generated mixed anhydrides for the enantioselective [3+2] and [3+3] cyclocondensation with α-amino ketones and alkyl(aryl) imines, respectively [3]. The corresponding pyrrolidinones and dihydropyridinones were isolated in good yields with high to excellent enantioselectivities (Fig. 5.4).

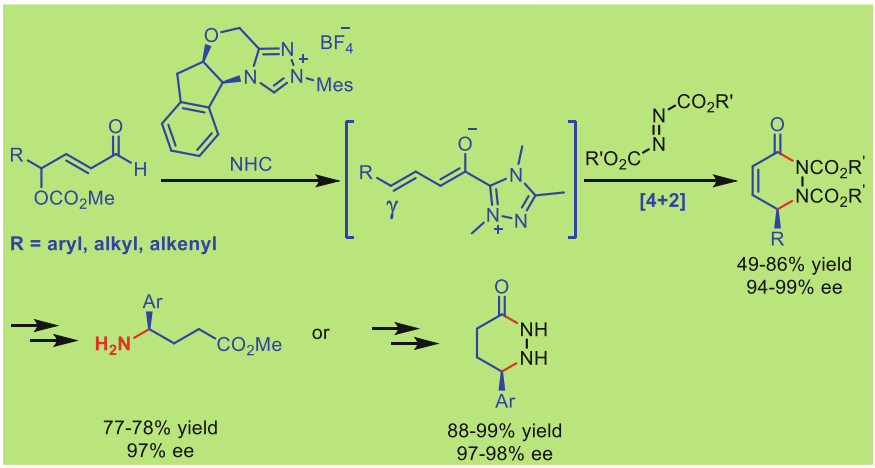

Fig. 5.3 NHC-catalyzed enantioselective annulations of enals

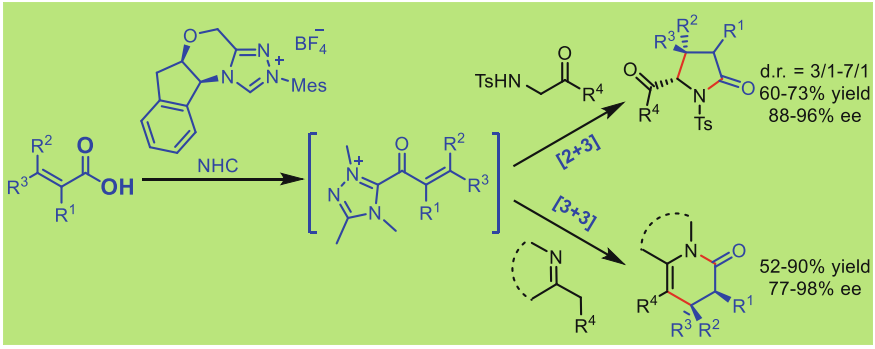

Fig. 5.4 NHC-catalyzed cyclocondensation of α,β-unsaturated carboxylic acids

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