N-Heterocyclic Carbene Organocatalytic Transformations in One-Pot Sequential and Domino Reactions

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades einer Doktorin der Naturwissenschaften genehmigte Dissertation

vorgelegt von

Master of Engineering

Xiaoxiao Song

aus Hebei, China

Berichter: Universitätsprofessor Dr. rer. nat. Dieter Enders
Universitätsprofessor Dr. rer. nat. Markus Albrecht

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The work presented in this thesis was carried out at the Institute of Organic Chemistry of RWTH Aachen University between September 2012 until July 2015 under the supervision of Prof. Dr. Dieter Enders.

Parts of this work have already been published:

1. “*Asymmetric N-Heterocyclic Carbene Catalyzed Annulation of 2-Alkenylbenzothiazoles with α-Chloro Aldehydes*”

   Xiaoxiao Song, Qijian Ni, Chen Zhu, Gerhard Raabe, and Dieter Enders*, *Synthesis*, **2015**, *47*, 421-428.

2. “*N-Heterocyclic Carbene-Catalyzed One-Pot Synthesis of Hydroxamic Esters*”

   Xiaoxiao Song, Qijian Ni, André Grossmann, and Dieter Enders*, *Chem. Asian J.*, **2013**, *8*, 2965-2969.

Contributions to other group projects:

3. “*N-Heterocyclic Carbene-Catalyzed Enantioselective Annulation of Indolin-3-ones with Bromoenals*”

   Qijian Ni, Xiaoxiao Song, Gerhard Raabe, and Dieter Enders*, *Chem. Asian J.*, **2014**, *9*, 1535-1538.

4. “*Regio- and stereoselective synthesis of benzothiazolo-pyrimidinones via an NHC-catalyzed Mannich/lactamization domino reaction*”

   Qijian Ni, Xiaoxiao Song, Jiawen Xiong, Gerhard Raabe, and Dieter Enders*, *Chem. Commun.*, **2015,** *51*, 1263-1266.

Table of Contents

1. Introduction

1.1 Introduction to carbenes

Carbenes are defined as neutral compounds, which consist of two valence bonds and two non-bonding electrons. The unshared electrons on the carbene carbon atom are classified into two categories based on the hybrid structures: singlet state carbene with a pair of electrons in the same orbital behaves as an ambiphile and triplet state with the two unpaired electrons in different orbitals can be seen as highly active diradical. Methylene was considered as the most classical and simplest carbene. As shown in Figure 1, the bent geometry is based on the two non-bonding electrons on the sp^2-hybridized carbene carbon atom, which can occupy the δ orbital in antiparallel spin orientation ($\sigma^2p_\pi^0$) or the two empty orbitals ($\sigma^1p_\pi^1$) with a parallel spin orientation. Alternatively, an linear triplet state is generated *via* sp-hybridization with two degenerated orbitals (p_x, p_y).[1]

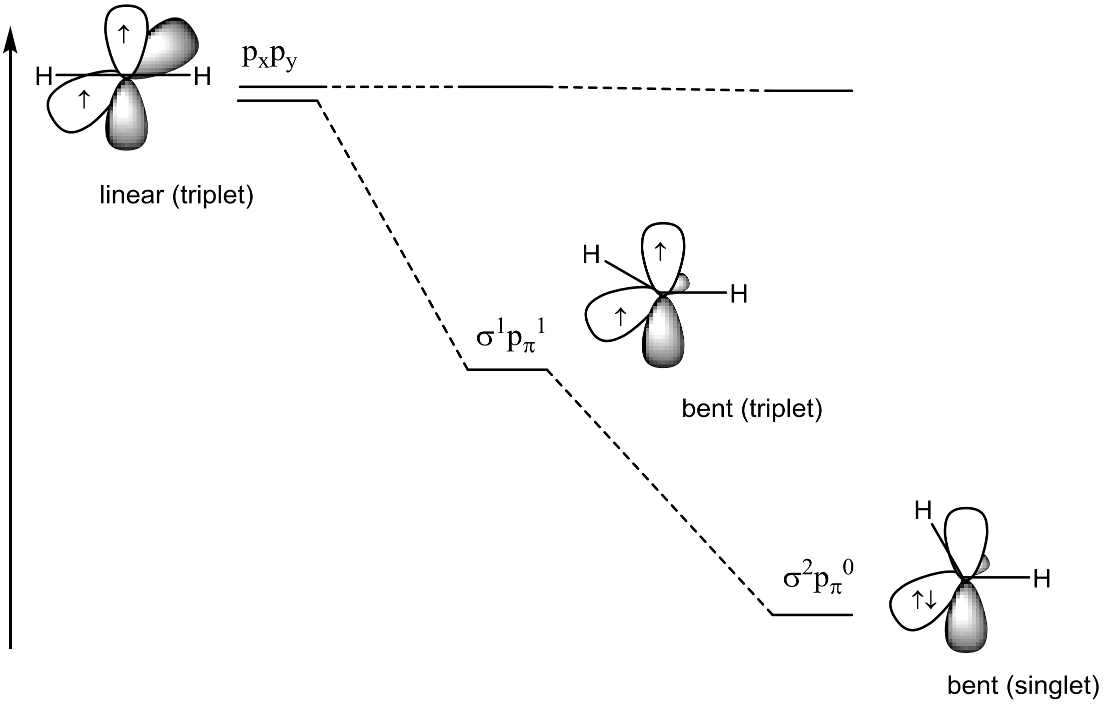


Figure 1 *Electronic configurations of carbenes.*

In general, electronic and mesomeric effects of the α-substituents at the carbene carbon atom play a crucial role. σ-Electron-withdrawing substituents or π-electron-donating group such as F, Cl, Br, NR_2, PR_2, OR, SR increase the energy gap of σ and p_π orbitals, thus favors the singlet ground state. Whereas, triplet ground state is stabilized by σ-electron-donating subtituents and π-electron-aceptors such as -COR, -SOR, $-SO_2R$ or -CN.[2] In addition, steric effects can also influence the spin multiplicity. The steric bulk of carbene substituents broadens the bond angle, thus favoring the triplet state.[3]

1.1.1 History of N-heterocyclic carbenes

Five-membered N-heterocyclic carbenes (NHCs) are the most important singlet carbenes stabilized by two α-bonding heteroatoms. σ-Electron-withdrawing groups and two π-electron-donating groups increase the σ-p_π energy gap. Moreover, the formation of four-electron three-centre π system could further increase the stability of NHCs (Figure 2).

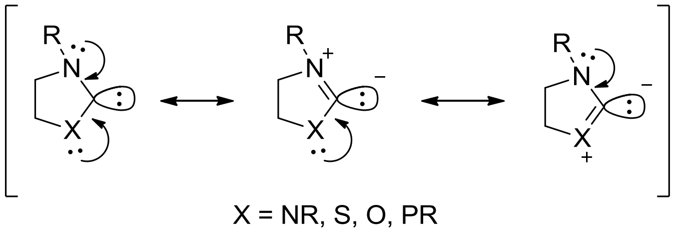
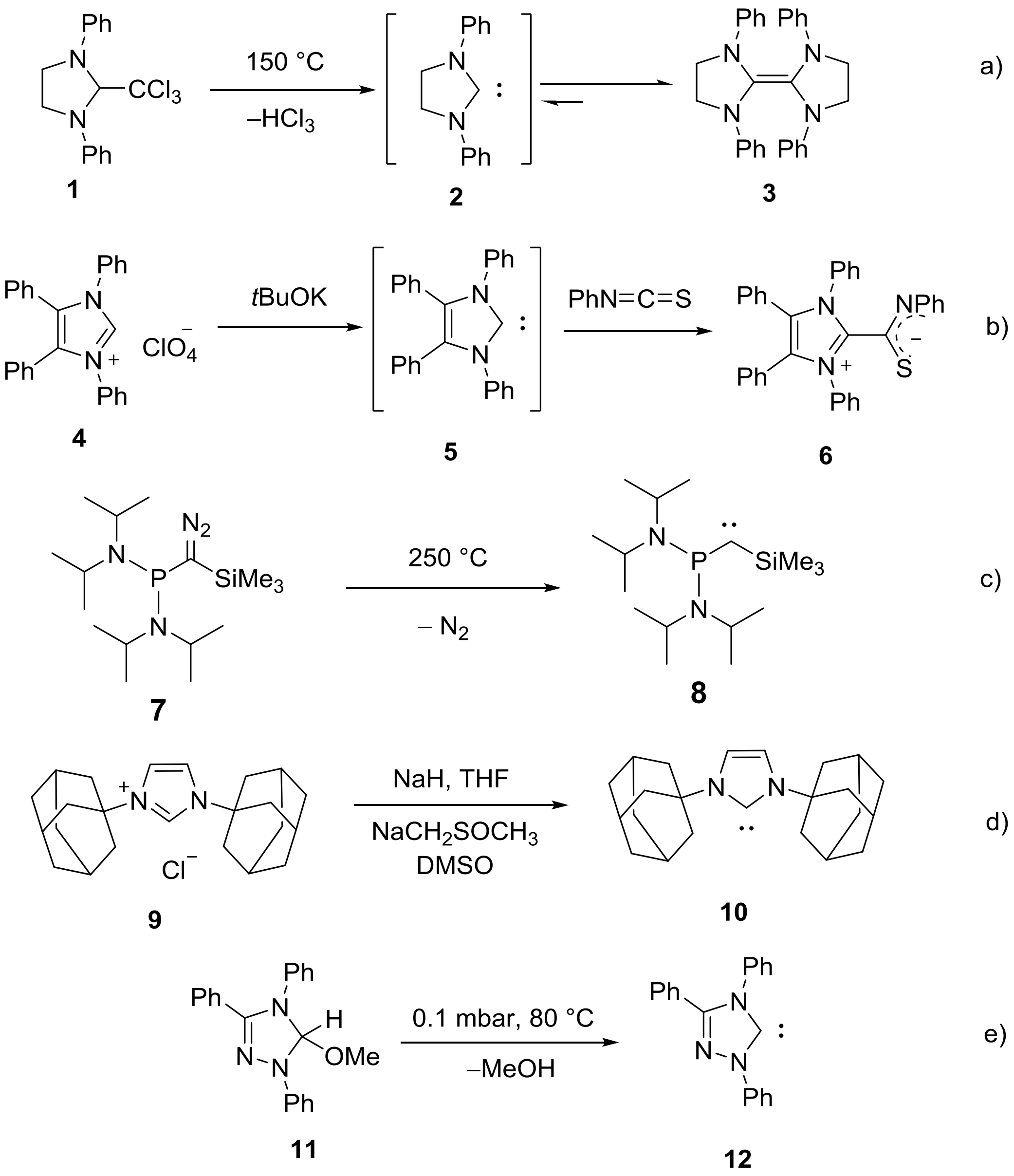


Figure 2 *Resonance structures of N-heterocyclic carbenes.*

However, the discovery and isolation of the N-heterocyclic carbenes is a lengthy history. In the early 1960s, Wanzlick *et al.* first investigated the reactivity and stability of N-heterocyclic carbenes. They discovered that amino substituents on the α-position could dramatically enhance the stability of carbenes. Moreover, they successfully synthesized dimeric electron-rich olefin **3** by thermal elimination of chloroform from **1** (Scheme 1a).[4] Denk's report supported the equilibrium between **3** and the two carbene units **2**.[5] Shortly thereafter, Wanzlick and co-workers demonstrated that imidazolium salts **4** could be deprotonated by *t*-BuOK to afford the more stable



***Scheme 1** Discovery and preparation of stable NHCs.*

2-ylidene **5**, which did not dimerize. However, this free carbene could not be isolated, but trapped with isothiocyanate to give **6** (Scheme 1b).[6] In 1988, Bertrand and co-workers first realized the synthesis of isolable phosphinocarbene **8** stabilized by the phosphorus lone pair and the bulky group (Scheme 1c).[7] Three years later, Arduengo *et al.* obtained the crystalline carbene 1,3-adamantyl imidazole-2-ylidene **10**, which was stablilized by two N atoms, aromaticity and two adamantyl groups as N-substituents.[8] As shown in Scheme 1d, the deprotonation of

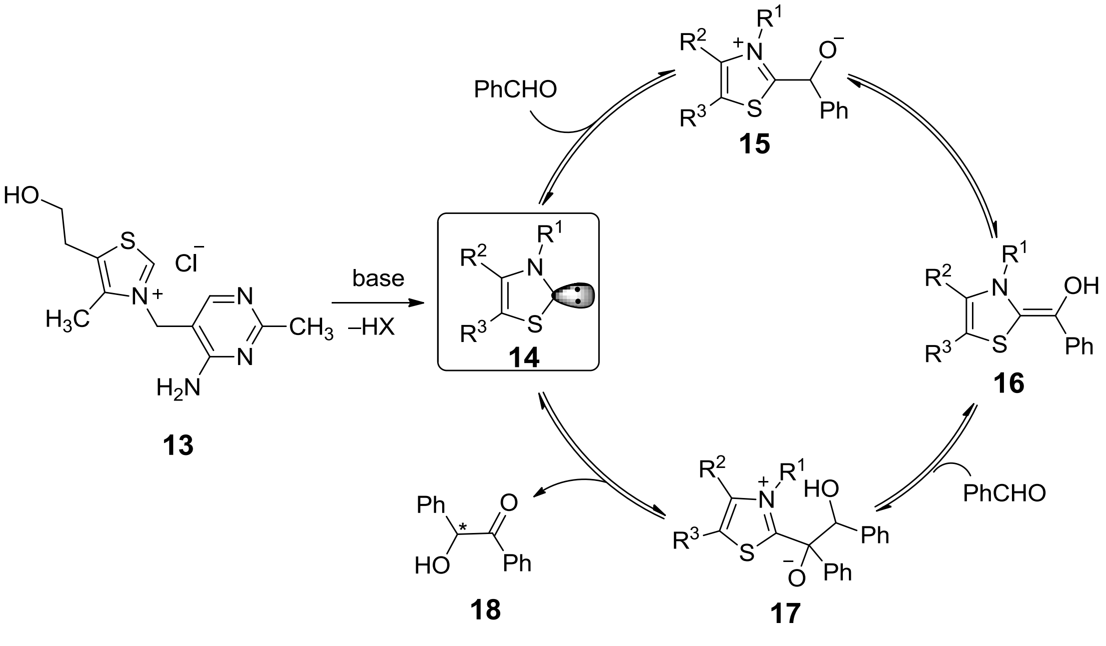
1,3-di-1-adamantylimidazolium chloride **9** in dry THF at room temperature with NaH in the presence of catalytic NaDMSO afforded free carbene **10**. This successful isolation opened a new view of the nature and reactivity of the NHCs. Followed by this work, in 1995 our workgroup realized the quantitative preparation of 1,2,4-triazol-5-ylidene **12** from the corresponding triazole **11** by thermal elimination of methanol under 80 ℃ and 0.1 mbar (Scheme 1e).[9] This extraordinarily stable carbene was the first commercially available carbene (Acros, Nr. 10682613; 262.50 €/g). Afterwards, numerous of researchers moved attention to the investigation of NHCs. The σ-electron-donating properties of NHCs allow them the role as excellent ligands in transition-metal catalyzed reactions instead of phosphines.[10] NHCs are comparably or more reactive than phosphines, easily removable and there is no need for an excess of the NHC ligand. The salts of the NHCs are stable, which make them easy to preserve. Besides the role of ligands, the past decades have witnessed extraordinary progress in NHC-organocatalysis, which is more economical and environmentally friendly.[11]

1.2.2 NHC organocatalysis

The lone pair on NHCs leading to a strong Lewis base[12] and excellent nucleophilic character, therefore the NHCs act as organocatalyst enabling the Michael additions[13] with nitroalkenes,[14] allenoates[15] and alkynes,[16] as well as Morita-Baylis-Hillman reactions,[17] transesterifications[18] and ring-opening polymerizations.[19] Besides this, the most important application was devoted to NHCs-catalyzed reactions of aldehydes. The umpolung of aldehyde reversed the polarity of the carbonyl carbon, so the adduct can be considered as an acyl anion equivalent, which could undergo nucleophilic addition with another equivalent of aldehyde *via* the benzoin reaction or with an enone *via* the Stetter reaction. Beyond the classic NHC-catalyzed umpolung of aldehydes, the conjugate umpolung of α,β-unsaturated aldehydes and the extended generation of azolium enolates opened a new strategy to the formation of C-C bonds. The detailed applications of NHC-promoted acyl anion equivalents, the conjugate umpolung and azolium enolate chemistry are introduced in the following parts.

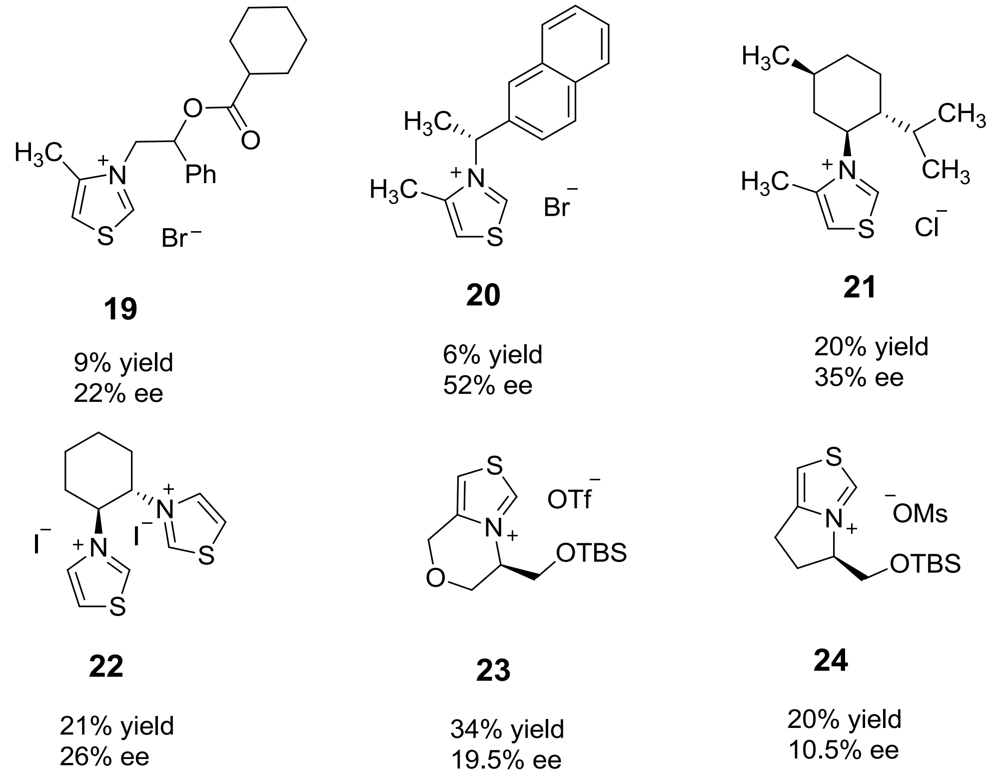
1.2 Acyl anion equivalent

The studies of NHC organocatalysis dates back to 1943 when Ukai and co-workers discovered that thiamine (**13**, Vitamin B_1) could replace cyanide in benzoin condensations. In 1958 Breslow *et al.* presented a mechanism based on the previous work. As shown in Scheme 2, deprotonation of the thiazolium salt formed the active NHC thiazol-2-ylidene **14**. Initial nucleophilic attack of **14** on benzaldehyde generated thiazolium salt adduct **15**. The subsequent proton transfer then leads to the enamine analog Breslow intermediate **16**, which shows nucleophilic character at carbon. The reaction with a second electrophilic benzaldehyde molecule produces benzoin **18** and returns carbene catalyst.[20]



Scheme 2 *Proposed mechanism of the NHC-catalyzed Benzoin reaction by Breslow et al.*

In 1966 Sheehan *et al.* reported the first asymmetric benzoin condensation of benzaldehyde forming the benzion product in 22% ee with the use of chiral thiazolium salt **19** as precatalyst.[21] Later, they improved the ee up to 52% by utilizing the modified thiazolium salt **20**.[22] Takagi *et al.* synthesized the chiral menthyl-substituted thiazolium salt **21**, which could undergo the benzoin reaction in a micellar two-phase system with 35% ee and 20% yield.[23] In 1993, López-Calahorra *et al.* designed a bisthiazolium salt catalyst **22** for the asymmetric benzoin condensation, providing the benzoin in up to 26% ee and 21% yield.[24] In 1997 Leeper and co-workers introduced novel bicyclic thiazolium salts **23, 24** for the asymmetric benzoin condensations. However, there was no improvement on stereocontrol and yield.[25]


19
9% yield
22% ee

20
6% yield
52% ee

21
20% yield
35% ee

22
21% yield
26% ee

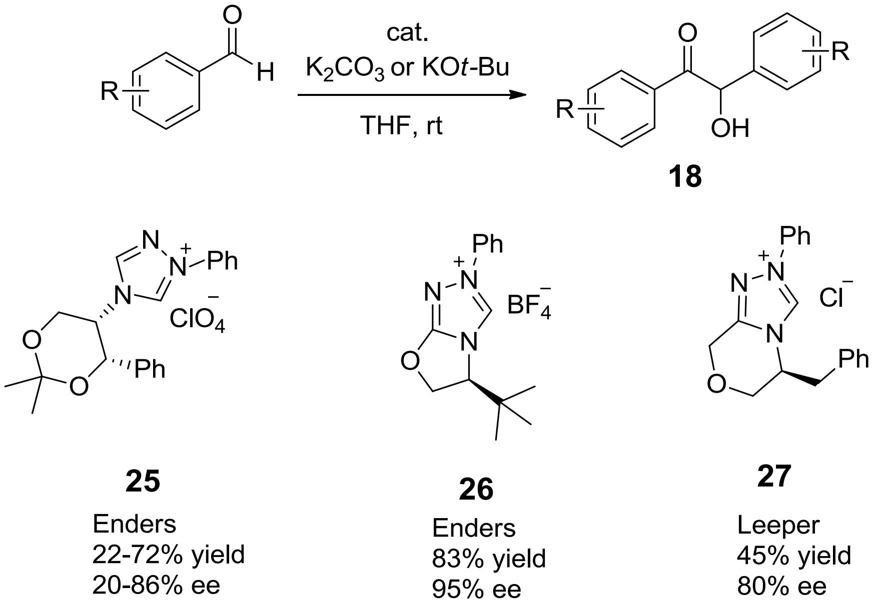
23
34% yield
19.5% ee

24
20% yield
10.5% ee

Figure 3 *Chiral thiazolium salts for the asymmetric benzoin condensations.*

At the same time, our research group identified triazolium salt **25** as a catalytic core, which showed efficient activity and provided the benzoins in good yields with a range of 20-86% ee.[26] Another bicyclic triazolium salt **26** was reported in 2002 which could lead to a highly enantioselective benzoin condensation in up to 83% yield and 95% ee.[27] In addition, Leeper *et al.* also introduced a bicyclic skeleton as chiral triazolium salt **27**, which afforded the benzoin products in 19.5-82.5% ee

(Scheme 3).[28]



18

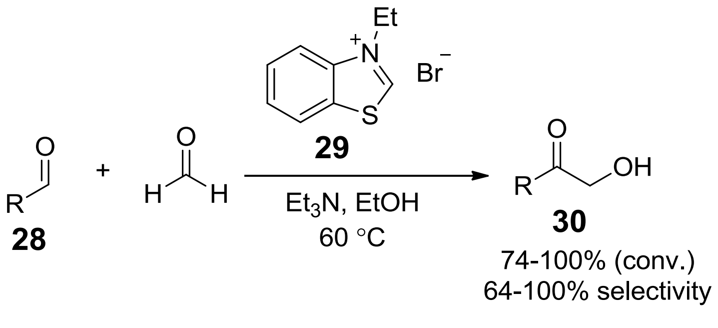
25
Enders
22-72% yield
20-86% ee

26
Enders
83% yield
95% ee

27
Leeper
45% yield
80% ee

Scheme 3 *Asymmetric benzoin condensation by triazolium salts.*

In addition, attempts to use two distinct aldehydes as substrates for the NHC-catalyzed benzoin condensation were initially reported by Stetter *et al.* in 1977.[29] Later, Inoue and co-workers described a selective cross-acyloin condensation of formaldehyde and another aldehyde catalyzed by 3-ethylbenzothiazolium bromide **29** to give exclusively 1-hydroxy-2-ones **30** (Scheme 4).[30]



29

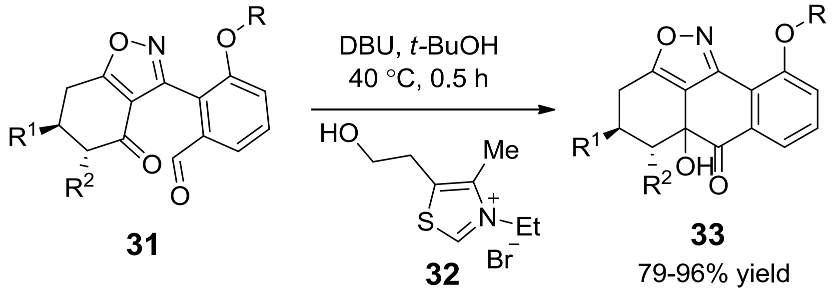
28

30
74-100% (conv.)
64-100% selectivity

Scheme 4 *Selective cross-benzoin condensation by Inoue et al.*

In 2003, Suzuki and co-workers described the first intramolecular cross-benzoin condensation of ketone-alehdye **31** catalyzed by thiazolium salt **32**. The aldehyde reacts intramolecularly with a ketone motif to provide the desired α-hydroxy-ketone

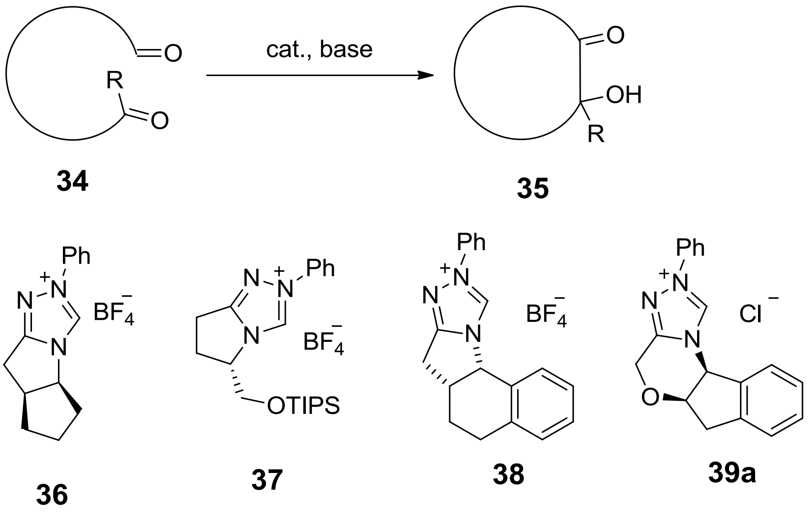
33 in 79-96% yield (Scheme 5).[31]



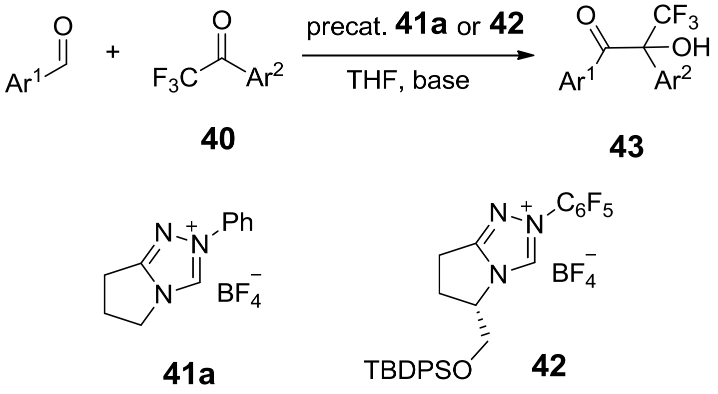
***Scheme 5** Intramolecular crossed aldehyde-ketone benzoin reactions by Suzuki et al.*

Our research group also reported an intramolecular crossed aldehyde-ketone benzoin reaction to construct five- and six-membered cyclic acyloins in the presence of thiazolium salt **32**. Notably, the reactions between aliphatic aldehydes and aromatic ketones proceeded well, albeit with relatively low yields.[32] In order to develop an enantioselective variant, our group synthesized the novel polycyclic triazolium salts **36-38** for the asymmetric intramolecular benzoin reactions. As shown in Scheme 6, the precatalyst **36** gave rise to the desired acyloins in good yields. However, only moderate ee values were achieved, even at 5 ℃. The TIPS-substituted triazolium salt **37** derived from *L*-pyroglutamic acid turned out to be more active and gave a higher stereocontrol. Promising results were achieved when introducing tetracyclic triazolium salt **38** as precatalyst for the intramolecular crossed benzoin condensation of aldehyde-ketones.[33] Later, Suzuki *et al.* published their results utilizing Rovis' aminoindanol-derived chiral triazolium salt **39a** as precatalyst for the enantioselective intramolecular crossed bezoin condensation of a wide range of substrates in up to 99% ee.[34]

Our group further realized direct intermolecular cross-benzoin-type condensations of aldehydes with ketones. Precatalyst **41a** was efficient to catalyze the cross-couplings of aromatic aldehydes and trifluoromethyl ketones **40** with high levels of chemoselectivity.[35] A subsequent asymmetric intermolecular cross-coupling of heteroaromatic aldehydes and trifluoromethyl ketones **40** was carried out in the presence of triazolium salt **42** (Scheme 7).[36]



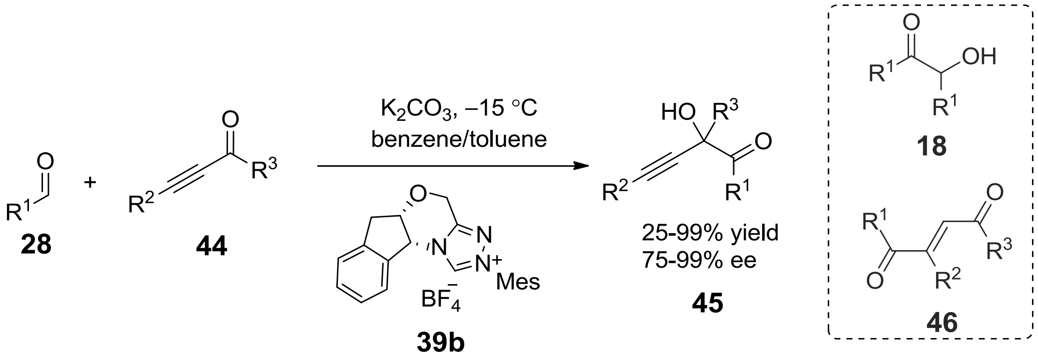
Scheme 6 *Asymmetric intramolecular crossed benzoin condensations.*



Scheme 7 *NHC-catalyzed direct intermolecular cross-benzoin reactions by Enders et al.*

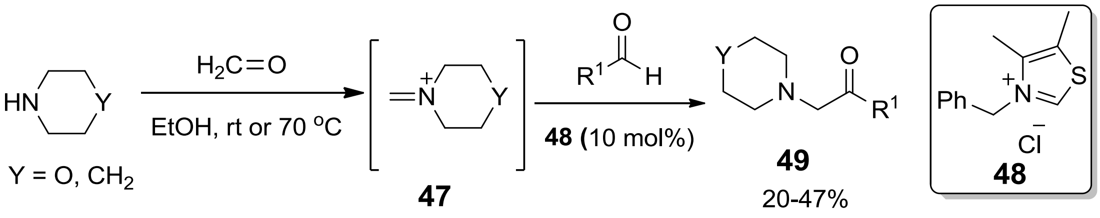
Later, Connon and co-workers found that N-C_6F_5 substituted triazolium precatalysts promoted highly chemoselective crossed acyloin reactions between aliphatic aldehydes and 2-substituted benzaldehydes.[37] Recently, Gravel and co-workers reported a highly chemoselective cross-benzoin reaction between aliphatic and aromatic aldehydes catalyzed by morpholinone- and piperidinone-derived triazolium salts.[38] Comparison of the rates and transition states of the nucleophilic addition of the triazolium catalysts to aldehydes suggested that steric interactions and kinetic control played key roles in chemoselectivity.[39]

Very recently, the groups of Reyes and Vicario presented an NHC-catalyzed enantioselective cross-benzoin reaction of aldehydes **28** with alkynones **44**. Under the optimized conditions, the reaction occured with high yield, enantioselectivity and complete chemoselectivity without the formation of any self-benzoins **18** or Stetter by-products **46** (Scheme 8).[40]

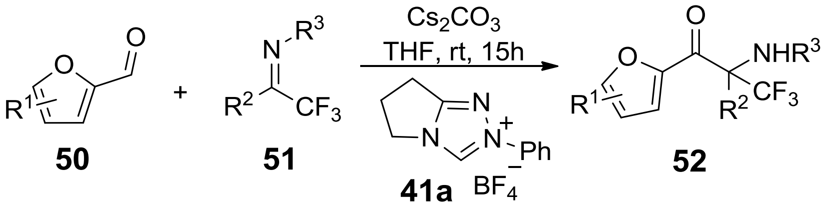


Scheme 8 *Asymmetric cross-benzoin reaction of aldehydes with alkynones.*

In addition, the cross-benzoin condensation could be extended to the reactions of aldehydes and imines. In 1988, López-Calahrra *et al.* published the first NHC-catalyzed cross-aza-benzoin reaction of aldehydes with the *in situ* generated iminium salts **47** in the presence of thiazolium salt **48**, which produced the α-aminoketones **49** (Scheme 9).[41] Our research group also presented an NHC-catalyzed nucleophilic acylation of trifluoromethyl ketimines. The cross-couplings of N-aryl trifluoromethyl ketimines with furan-2-carbaldehydes chemoselectively produced the corresponding α-amino-α-trifluoromethyl ketones in moderate to very good yields (32-87%) (Scheme 10).[42]

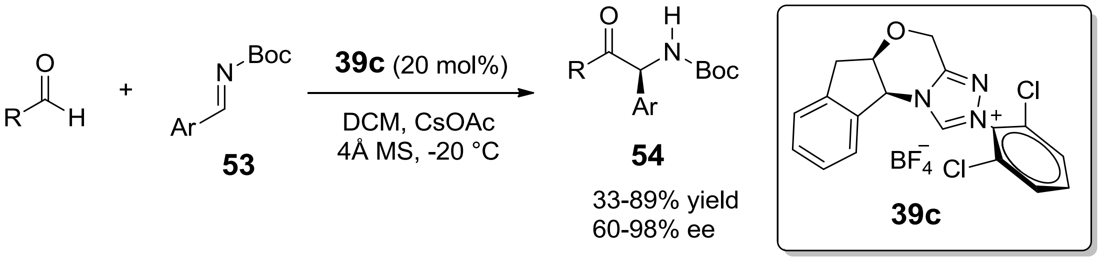


Scheme 9 *The first cross-aza-benzoin reaction by López-Calahrra et al.*



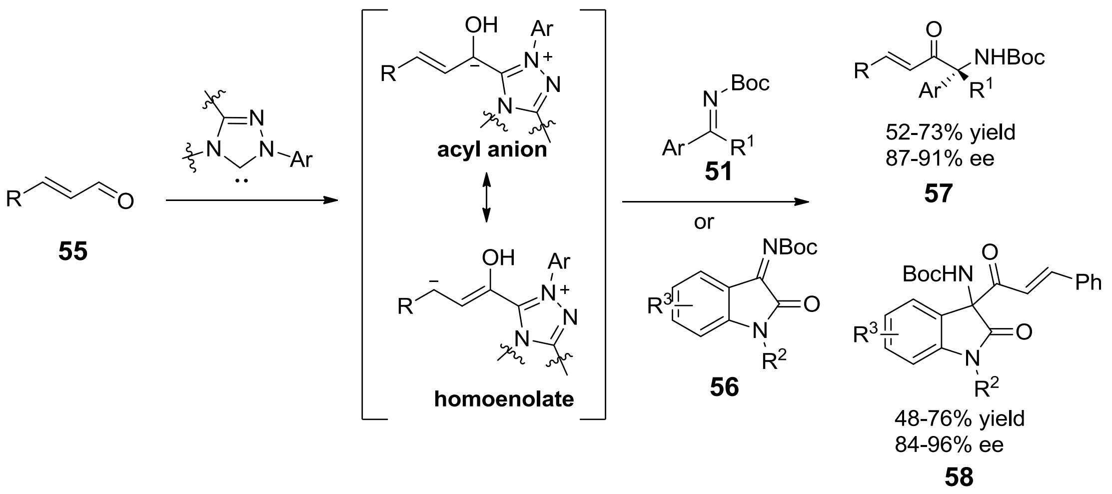
Scheme 10 NHC-catalyzed furan-2-carbaldehydes/trifluoromethyl ketimine cross-couplings by Enders et al.

In 2012 Rovis *et al.* realized a highly enantioselective cross-aza-benzoin reaction of aliphatic aldehydes and N-Boc-protected imines **53**, providing the α-amido ketones **54** in good yields (33-89%) and excellent enantioselectivities (60-98%) (Scheme 11).[43] It was found that catalytic amount of acetate acid could reverse the aza-Breslow intermediates and regeneration of the active carbene.[44]



Scheme 11 Asymmetric cross-aza-benzoin reactions by Rovis et al.

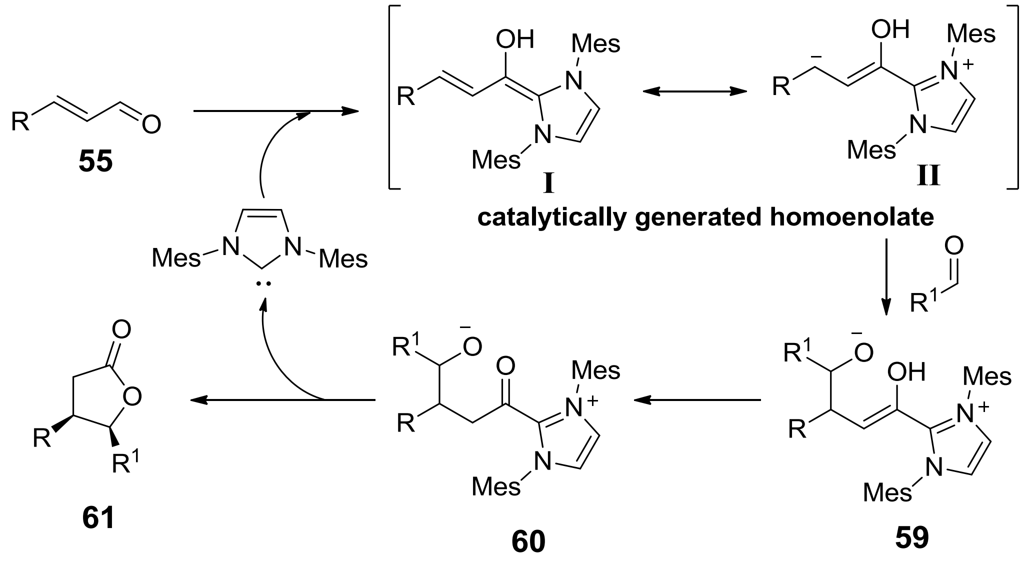
Notably, the enal carbonyl carbon as a reactive nucleophilic carbon (acyl anion intermediate) could undergo benzoin or Stetter reactions. An interesting report on the asymmetric cross-aza-benzoin reactions of enals **55** with activated ketimines **51** involving the nucleophilic C1 addition of enals was presented by Ye *et al.*[45] Very recently, Chi *et al.* also reported a chemo- and enantioselective cross-aza-benzoin reaction of enals with isatin-derived ketamines **56**. This methodology afforded the produced 3-aminooxindoles **58** bearing a quaternary stereogenic center with high ee values (84-96%) (Scheme 12).[46]



Scheme 12 *NHC-catalyzed cross-aza-benzoin reactions of enals with ketimines.*

1.3 Homoenolate

In contrast to the acyl anion intermediate as the normal d^1 synthon, the umpolung of α,β-unsaturated aldehydes formed conjugated acyl anion equivalents (also known as “homoenolate”) and acted as nucleophiles at the β-position. The pioneering synthetic utility of this homoenolate equivalents was independently reported by the groups of Bode [47] and Glorius.[48]

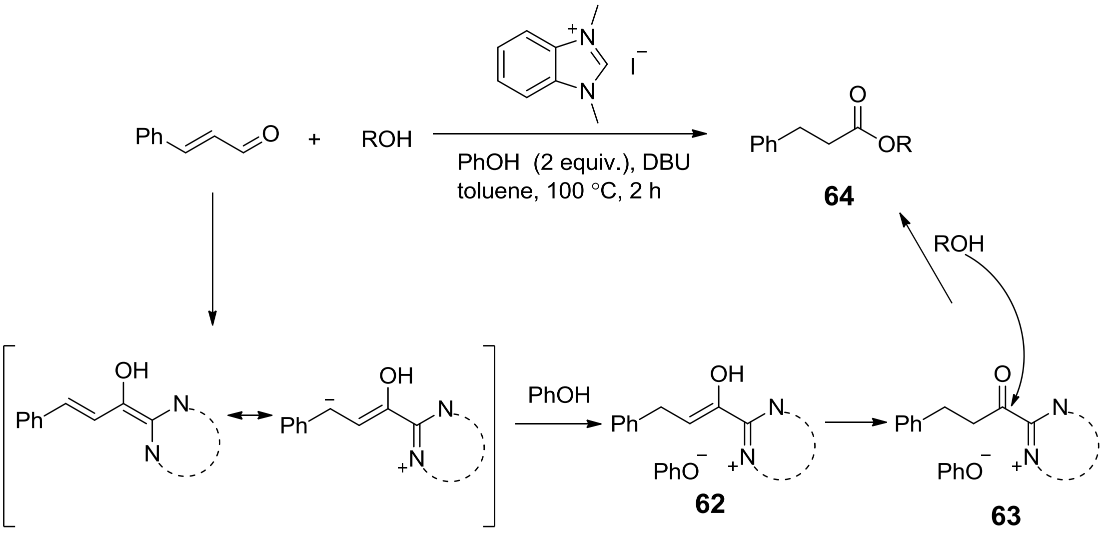


Scheme 13 *NHC-catalyzed generation of homoenolates.*

As shown in Scheme 13, nucleophilic addition of the NHC to the α,β-unsaturated aldehyde **55** generated a conjugated acyl anion equivalent **I**, which can be drawn as a zwitterionic homoenolate mesomer **II**. The nucleophilic attack of homoenolate to the aromatic aldehyde gave rise to alcoholate **59**. Tautomerization led to the acyl azolium **60**, which subsequently underwent intramolecular lactonization to result in the formation of γ-butyrolactone **61** and the regeneration of the nucleophilic catalyst.

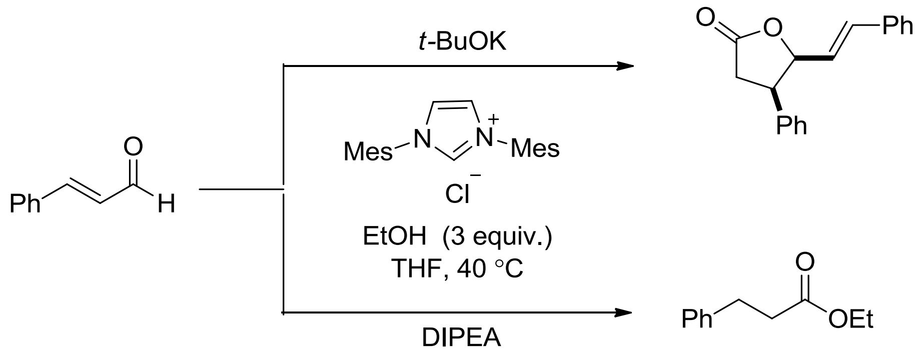
1.3.1 Protonation of homoenolates

The unique homoenolate nucleophiles were significantly utilized in organic synthesis with various electrophiles. When employing the simplest electrophile—proton, a protonation of the homoenolate would be established. Scheidt and Chan showed that enals in combination of NHCs generated homoenolate equivalents, which subsequently trapped by a proton from phenol at the β-position to give **62**. After tautomerization, the activated carboxyl surrogate **63** was trapped by the nucleophilic alcohol. This methodology provided a strategy to the synthesis of saturated esters **64** (Scheme 14).[49] Notably, a kinetic resolution of racemic 1-phenylethanol can be achieved with the use of chiral imidazoylidene catalysts, resulting in an *s* factor of 4.8.[50]



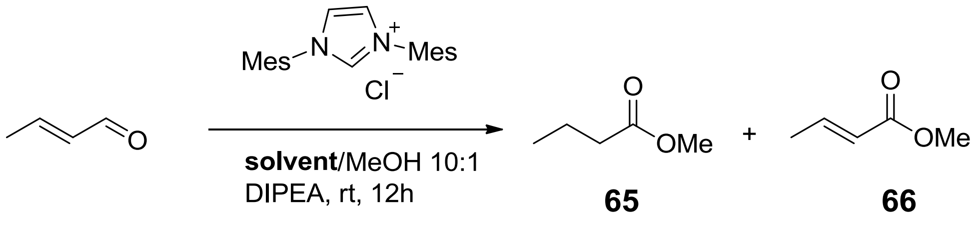
Scheme 14 *Preparation of saturated esters via homoenolate.*

Similar works were reported by Bode and Sohn. Interestingly, the base played a product-determining role in this reaction. The combination of a strong base such as *t*-BuOK prefered the formation of a C-C bond, whereas a weak base such as DIPEA led to the protonation of the homoenolate and subsequent formation of the ester (Scheme 15).[51]



***Scheme 15** Base dominated generation of ester.*

In 2009 Scheidt and co-workers demonstrated that homoenolate and redox acyl azolium intermediates were competitive under the same reaction conditions. Fortunately, the ratio could be controlled by the choice of the solvent. As shown in Scheme 16, MeOH favored the formation of the redox ester **66** due to the solvation of α,β-unsaturated acylazolium, while nonprotic solvent THF and toluene dominated the protonation of homoenolate to give ester **65**.[52]



solvent		ratio	
MeOH	1	:	11.8
THF	2.2	:	1
toluene	3.0	:	1

***Scheme 16** Solvation effects on the NHC-catalyzed pathways.*

1.3.2 NHC-catalyzed homoenolate reactions

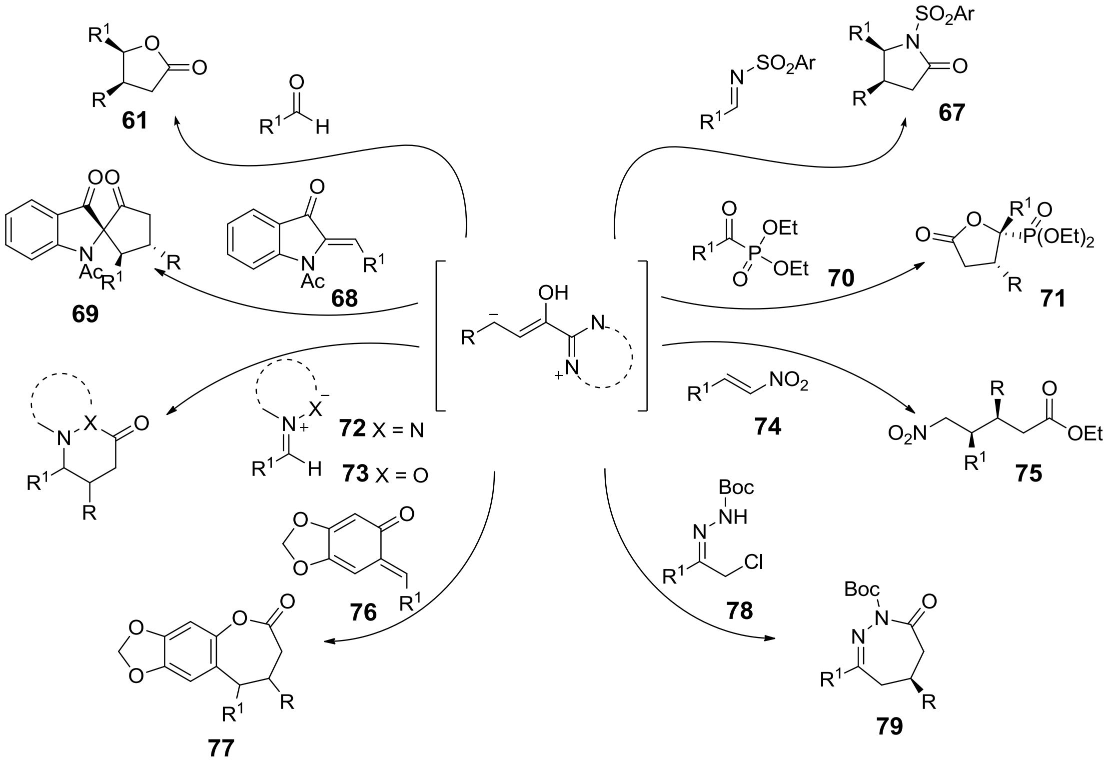
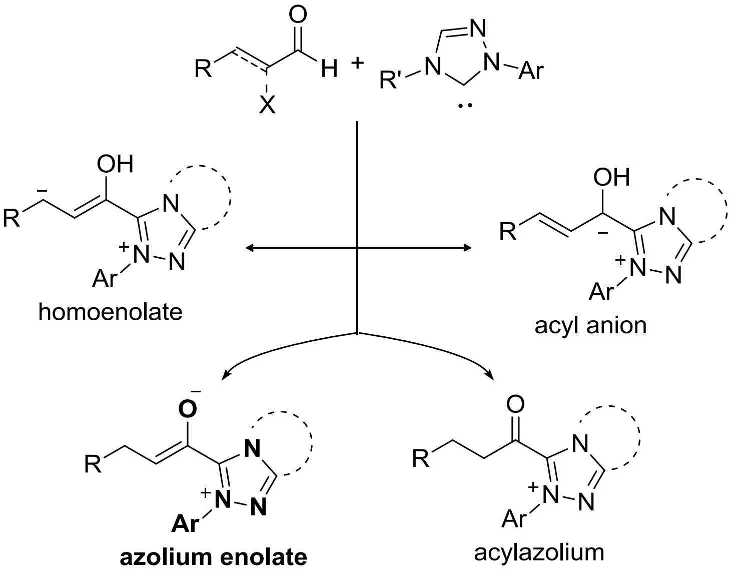


Figure 4 *NHC-catalyzed homoenolate additions.*

Besides the protonation reactions, the NHC-based homoenolates can also undergo a series of reactions with various types of reactive electrophiles at the β-position, resulting in the formation of a variety of annulated as well as acyclic products (Figure 4). Bode *et al.* and Glorius *et al.* first realized the cycloadditions of homoenolate equivalents with aldehydes to conduct γ-butyrolactones **61**.[47-48] Subsequently, Bode and co-workers extended this methodology to the synthesis of γ-butyrolactams **67** *via* formal [3+2] cycloadditions of enals and N-sulfonylimines.[53] Very recently, Glorius *et al.* developed an NHC-catalyzed formal [3+2] annulation of azaaurones or aurones **68**, which provided an efficient asymmetric access to spiro-heterocycles **69**.[54] Scheidt and co-workers also reported asymmetric [3+2] homoenolate additions to acyl phosphonates **70**.[55] In addition to [3+2] cycloadditions, they also realized the enantioselective [3+3] cycloadditions of homoenolate equivalents to azomethine imines **72**[56] and nitrones **73**.[57] Amongst Michael acceptors, nitroalkenes **74** proved to be promising electophiles for the homoenolate in the formations of δ-nitroesters **75**.[58] Furthermore, Ye *et al.*[59] and Glorius *et al.*[60] reported NHC-catalyzed [3+4] homoenolate annulations with *o*-quinone methides **76** and azoalkenes **78** for the synthesis of benzo-ε-lactones **77** and 1,2-diazepine derivatives **79**.

1.4 NHC-catalyzed reactions *via* azolium enolates

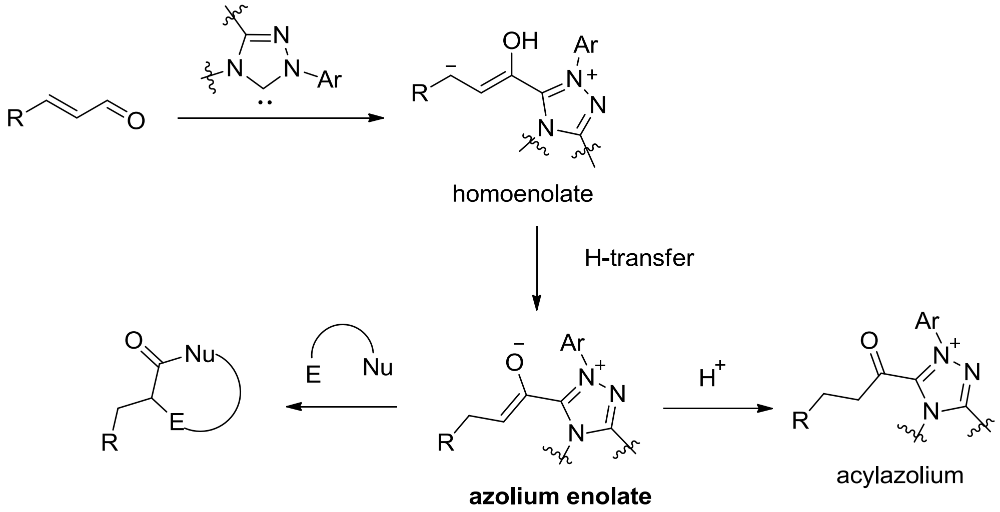
Beyond acyl anion and homoenolate equivalents, a third NHC-mediated reactive nucleophilic intermediate was assigned to azolium enolate equivalents (Scheme 17), which provided a 2C synthon in the synthesis of various important heterocyclic scaffolds *via* formal [2+2]-, [2+4]- and very few [2+3]-cycloadditions. Another major reactions involved electrophilic acylazolium intermediates, which could be attacked by alcohols or amines to form esters or amides and regenerate active NHCs. As to the azolium enolate generations, six distinct approaches have been widely employed to date – *via* enals, α-functionalized aldehydes, ketenes, stoichiometric oxidation of acyl anion equivalents, activated esters and recent report concerning the use of saturated carboxylic acids as azolium enolate precursors, which serve as subclasses for the detail introductions.



Scheme 17 *Major NHC-mediated reactive intermediates.*

1.4.1 Azolium enolate generation *via* enals

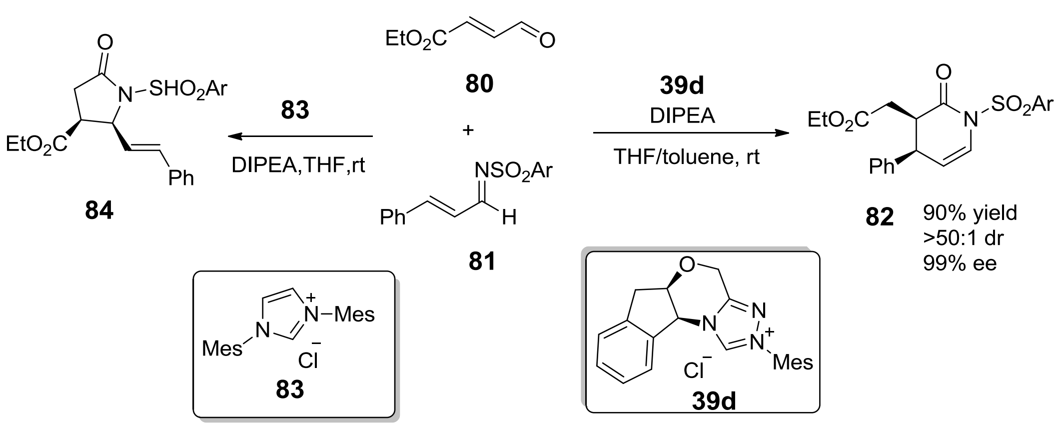
The addition of NHC to enal allows the generation of nucleophilic homoenolate. Proton transfer of the homoenolate equivalent leads to the azolium enolate, which could either trap a proton to form acylazolium species or react with an electrophilic partner (Scheme 18).



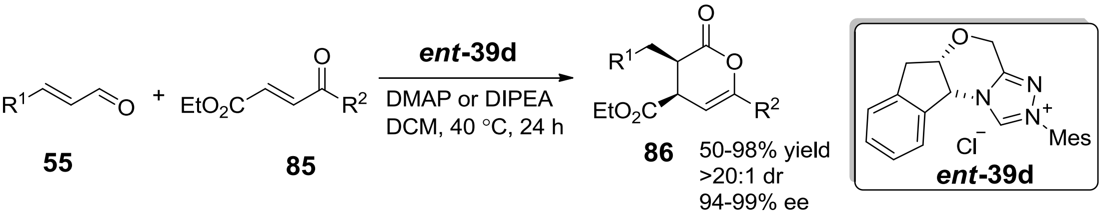
Scheme 18 *Generation of azolium enolates from enals.*

In 2006, Bode and co-workers first demonstrated the role of enal **80** as competent precursor for the generation of enolate and underwent an inverse electron demand-Diels–Alder reaction with α,β-unsaturated imine **81** for the synthesis of [2+4] cycloaddition product. Notably, triazolium precatalyst **39d** led to the formation of dihydropyridinone in 90% yield, >50:1 dr and 99% ee, while imidazolium-derived carbene **83** favored the construction of γ-lactam **84** (Scheme 19).[61]

Later, they further expanded the application of NHC-bound enolates from enals to the synthesis of dihydropyran-2-ones **86** through asymmetric oxa-Diels–Alder reactions with electron-deficient enones **85**. They disclosed that the key to control the enolate generation was the strength of the catalytic base used. Strong amine base, such as DBU favored homoenolate pathway, while the promotion of the enolate formation was the use of weak amine bases such as NMM or DMAP (Scheme 20).[62]

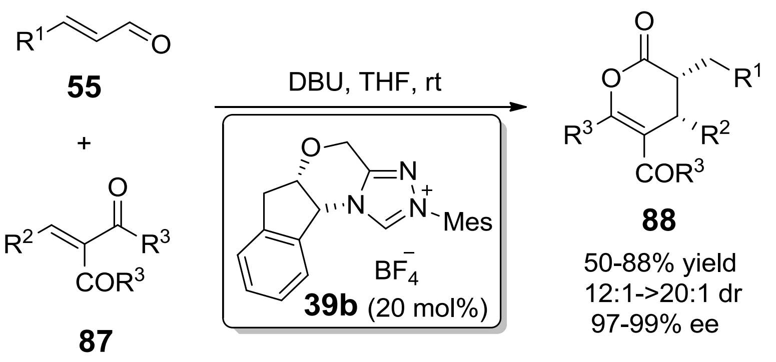


Scheme 19 *NHC-catalyzed cyclizations of enals with α,β-unsaturated imines by Bode et al.*



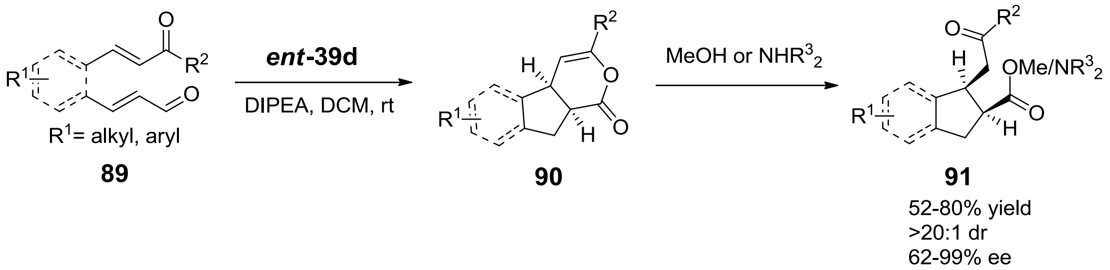
Scheme 20 *NHC-catalyzed oxa-Diels–Alder reactions by Bode et al.*

Chi and co-workers have also accessed the enolate species from enals to furnish dihydropyranones. The NHC-catalyzed [2+4] cycloadditions of β-aryl enals and enones **87** generated dihydropyranones **88** in 50-88% yields with high stereoselectivities (12:1 to >20:1 dr, 97-99% ee). With β-alkyl enals, only Stetter-type products were obtained when using catalyst **39b** (Scheme 21).[63]



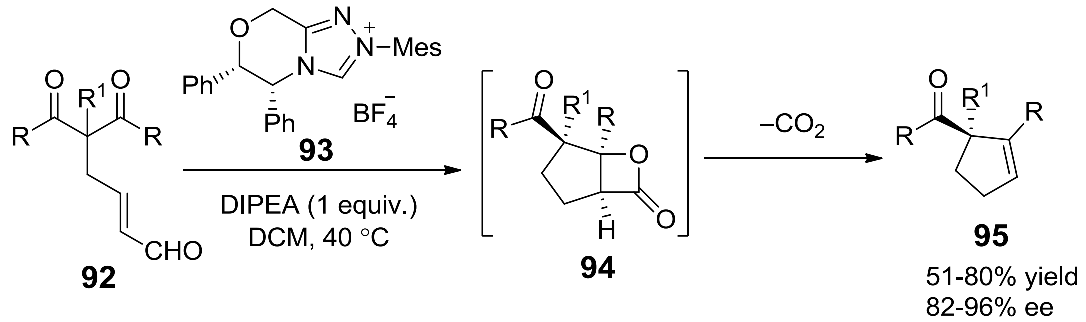
Scheme 21 *NHC-derived hetero-D–A reaction by Chi et al.*

In 2007, Scheidt and co-workers developed an intramolecular Michael/lactonization reaction of enals **89** initiating through catalytic enolate in the presence of precatalyst ***ent*-39d**. The afforded tricyclic acylated enols **90** subsequently underwent hydrolysis by MeOH or amines to generate the corresponding esters or amides **91** in good yields (52-80%) and excellent enantiocontrol (>20:1 dr, 62-99% ee). The reaction was tolerated to both aryl and aliphatic enals (Scheme 22).[64]



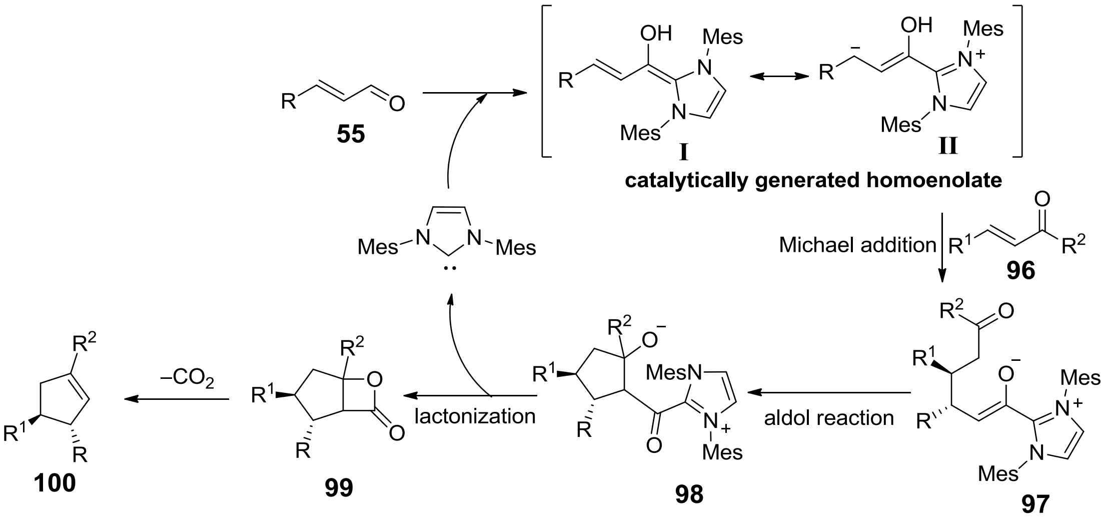
Scheme 22 Intramolecular Michael/lactonization reaction.

Almost at the same time they demonstrated the ability of enals **92** and precatalyst **93** to generate enolate equivalents with a subsequent intramolecular desymmetrizing aldol reaction, followed by the loss of carbondioxide to afford functionalized cyclopentenes **95** in good yields (51-80%) and excellent enantioselectivities (82-96% ee).[65]



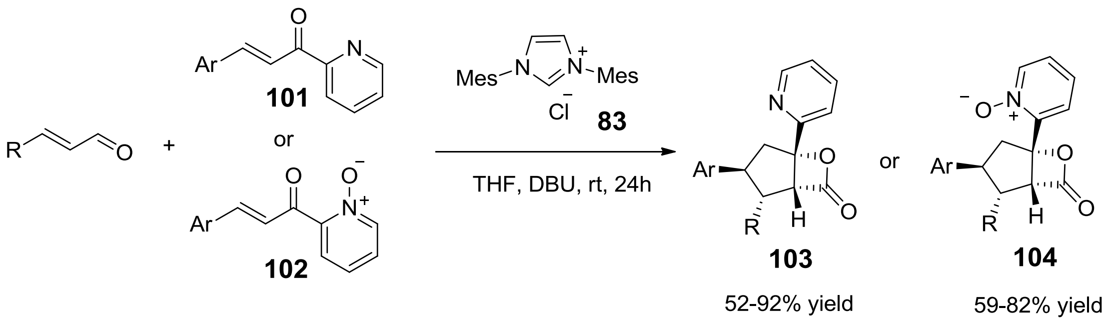
Scheme 23 NHC-catalyzed desymmetrization of 1,3-diketones.

In addition, enals allow homoenolate/enolate cascade reactions in the presence of an NHC precatalyst. In 2006 Nair *et al.* reported the first example of such a cascade process *via* a Michael/aldol/lactonization/decarboxylation sequence, leading to the formation of cyclopentenes in moderate to good yields (55-88%). The homoenolate derived from the enal and generated *via* imidazolium carbene catalysis led to a Michael addition with chalcone **96**. Then the adduct **97** subsequently underwent an intramolecular aldol reaction *via* the enolate species to give the carboxyl surrogate **98**. β-Lactonization of **98** regenerated the free carbene and yielded the bicyclic β-lactone **99**. The ring strain of **99** forced the loss of carbondioxide and formed the stable cyclopentene **100** (Scheme 24).[66]



***Scheme 24** NHC-based Michael/aldol/lactonization/decarboxylation reaction.*

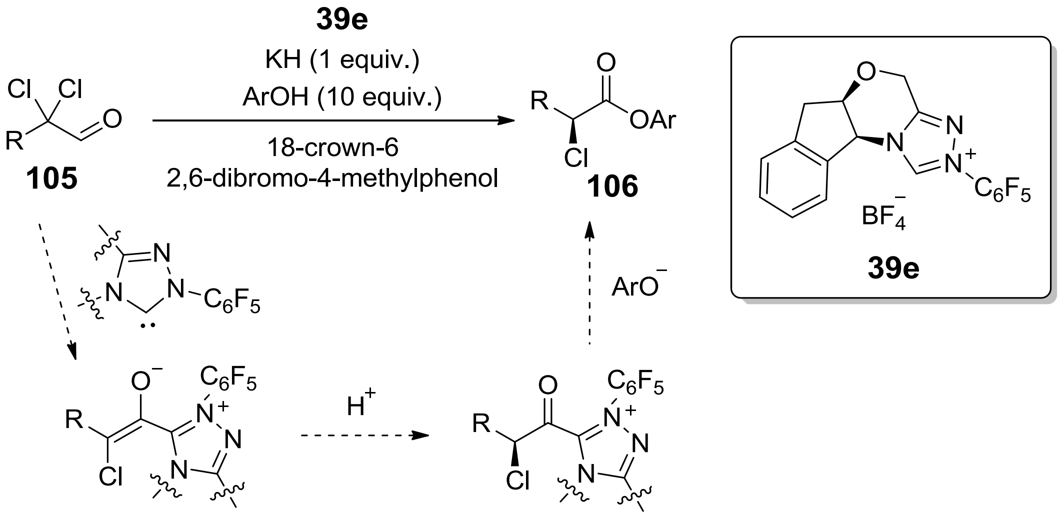
Later, the enantioselective version of this reaction was developed by the group of Bode with the use of precatalyst **39a**, giving the *cis*-products in 96-99% ee and 4:1-20:1 dr.[67] Very recently Biju and co-workers demonstrated the synthesis of β-lactone-fused cyclopentanes through the NHC-derived homoenolate/enolate cyclization with 2-enoylpyridines or 2-enoylpyridine N-oxides. Notably, the 2-pyridine moiety on the enone significantly stabilized the β-lactone product, inhibiting the further decarboxylation. However, the 3-enoylpyridine and 4-enoylpyridine only yielded cyclopentene derivatives after the loss of CO_2 (Scheme 25).[68]



Scheme 25 *The homoenolate/enolate domino reaction by Biju et al.*

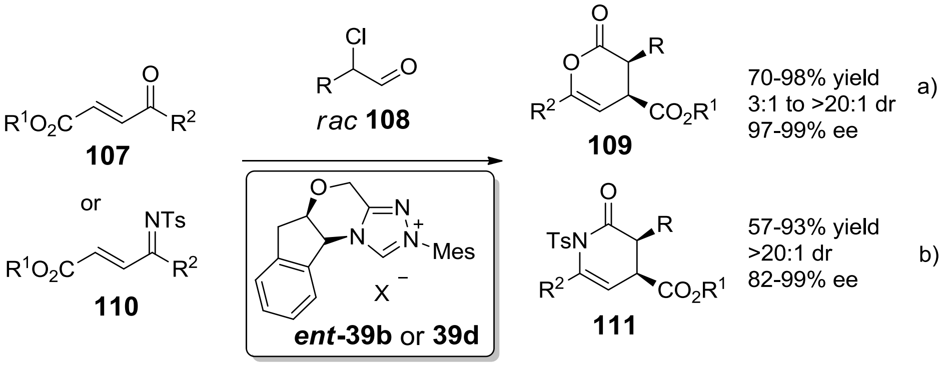
1.4.2 Azolium enolate generation *via* α-functionalized aldehydes

Another widely used strategy to access the enolate species is to use α-functionalized aldehydes *via* a sequential elimination of a leaving group in the presence of base. This process also allowed the generation of acylazolium species. For example, Rovis *et al.* disclosed that α,α-dichloroaldehydes **105** produced the azolium enolate species through elimination of hydrogen chloride in the presence of chiral triazolium carbene **39e** and base. After enantioselective protonation and subsequent esterification, α-chloroesters **106** were generated in good yields (65-79%) and excellent ee values (84-93%).[69]



Scheme 26 *Synthesis of α-chloroesters by Rovis et al.*

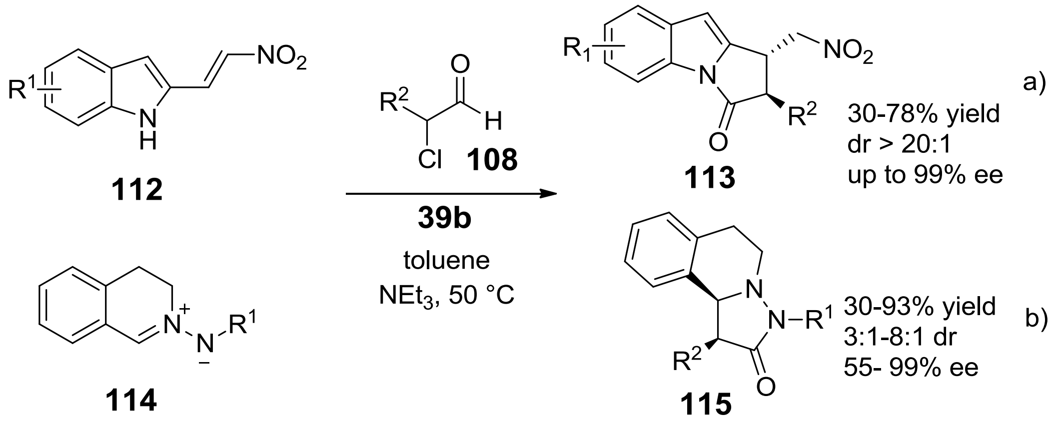
In 2006 Bode and co-workers realized the use of racemic α-chloroaldehydes **108** as enolate precursors, which proved to be reactive in the [2+4] oxa-Diels-Alder reaction with enones **107** with 0.5 mol% of triazolium salt **39d**. The dihydropyran-2-one adducts **109** were afforded in excellent yields (70-98%), high diastereo- and enantioselectivities (3:1->20:1 dr, 97-99% ee) (Scheme 27a).[70] An extention of this reaction was presented by Ye and co-workers, who realized the NHC-catalyzed [2+4] annulation of α-chloroaldehydes **108** and 1-azadienes **110**, affording a range of dihydropyridinones **111** in good yields (57-93%) with good to excellent enantioselectivities (>20:1 dr, 82-99% ee) (Scheme 27b).[71]



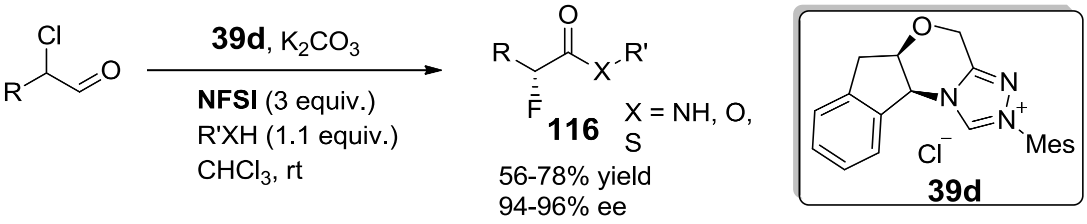
Scheme 27 *NHC-catalyzed [2+4] cyclization with α-chloroaldehydes.*

Recently, our work group described an asymmetric NHC-catalyzed [2+3] annulation of *in situ* generated azolium enolates from α-chloroaldehydes **108** with nitrovinylindoles **112** to access pyrroloindolones **113** *via* a Michael/lactamization domino reaction (Scheme 28a).[72] Very recently Ye *et al.* developed an NHC-catalyzed enantioselective [2+3] cycloaddition of α-chloroaldehydes with azomethine imines **114**, providing the corresponding pyrazolidinones **115** in good yields (30-93%), moderate to good diastereoselectivities (3:1-8:1 dr) and excellent enantioselectivities (up to 99% ee) (Scheme 28b).[73]

Very recently, an interesting asymmetric fluorination of azolium enolates derived from α-chloroaldehydes was described by Sun *et al.* This process provided a facile access to various α-fluoro esters, amides, and thioesters with excellent enantioselectivities (Scheme 29).[74]



***Scheme 28** NHC-catalyzed [2+3] cyclization with α-chloroaldehydes.*



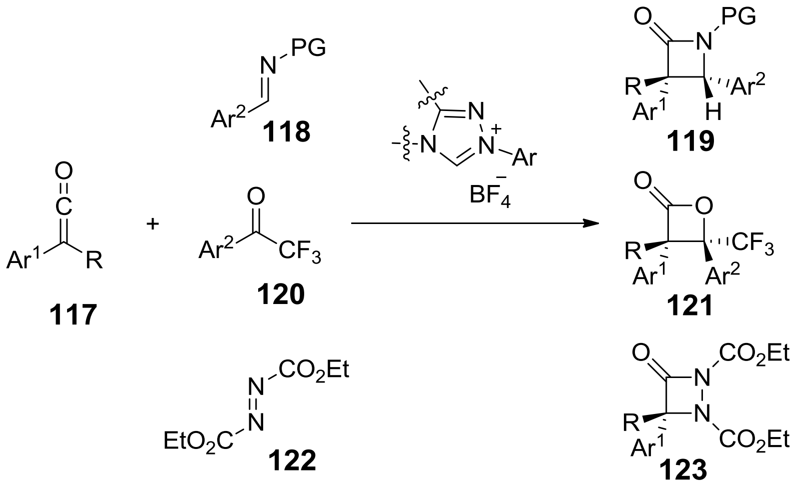
***Scheme 29** NHC-derived enantioselective α-fluorination of α-chloroaldehydes.*

1.4.3 Azolium enolate generation *via* ketenes

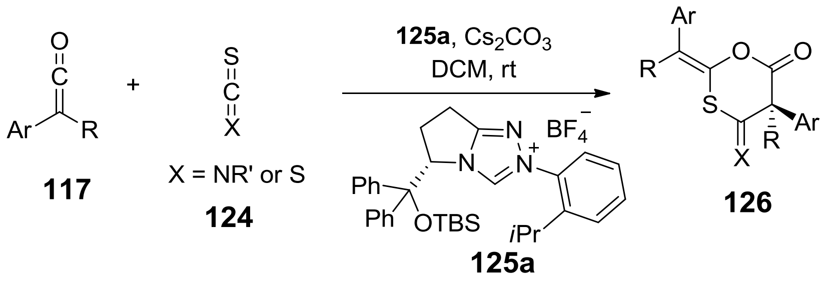
The facil and direct access to the generation of azolium enolate intermediates was the addition of a chiral NHC to ketenes **117**. The groups of Ye and Smith indenpendly described an interesting NHC-catalyzed enantioselective Staudinger-type [2+2] cycloaddition between ketenes and N-protected imines.[75] Ye and co-workers further explored other electrophiles, such as trifluoromethyl ketones **120**[76] or diazenedicarboxylates **122**,[77] which could react with the *in situ* generated azolium enolates from ketenes in formal [2+2] cycloadditions (Scheme 30).

In addition to the [2+2] cycloaddition, a formal [2+2+2] NHC-catalyzed cycloaddition was presented by Ye *et al.*, who carried out the reactions of ketenes with isothiocyanates or carbon disulfide to yield heterocycles **126** (Scheme 31).[78]

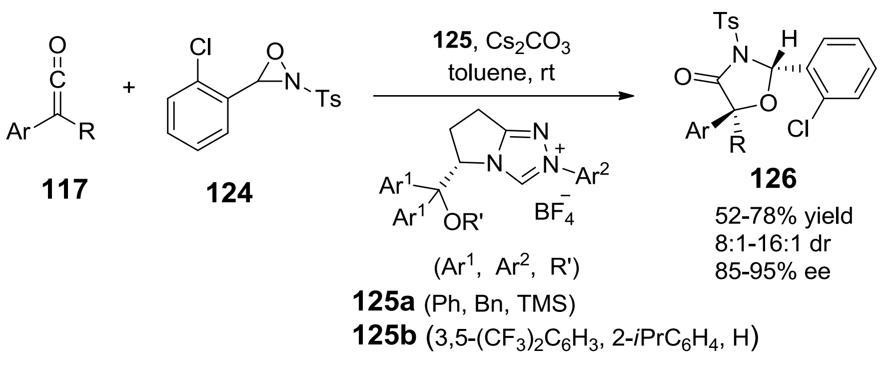
In 2010, Ye and co-workers realized an enantioselective formal [2+3] cycloaddition of ketenes **117** to racemic oxaziridines **124** for the synthesis of oxazolin-4-ones. Interestingly, NHC **125a** and bifunctional precatalyst **125b** bearing a free hydroxyl group provided the two enantiomers of oxazolin-4-ones **126** in moderate to good yields (52-78%) with good diastereo- and enantioselectivities (Scheme 32).[79]



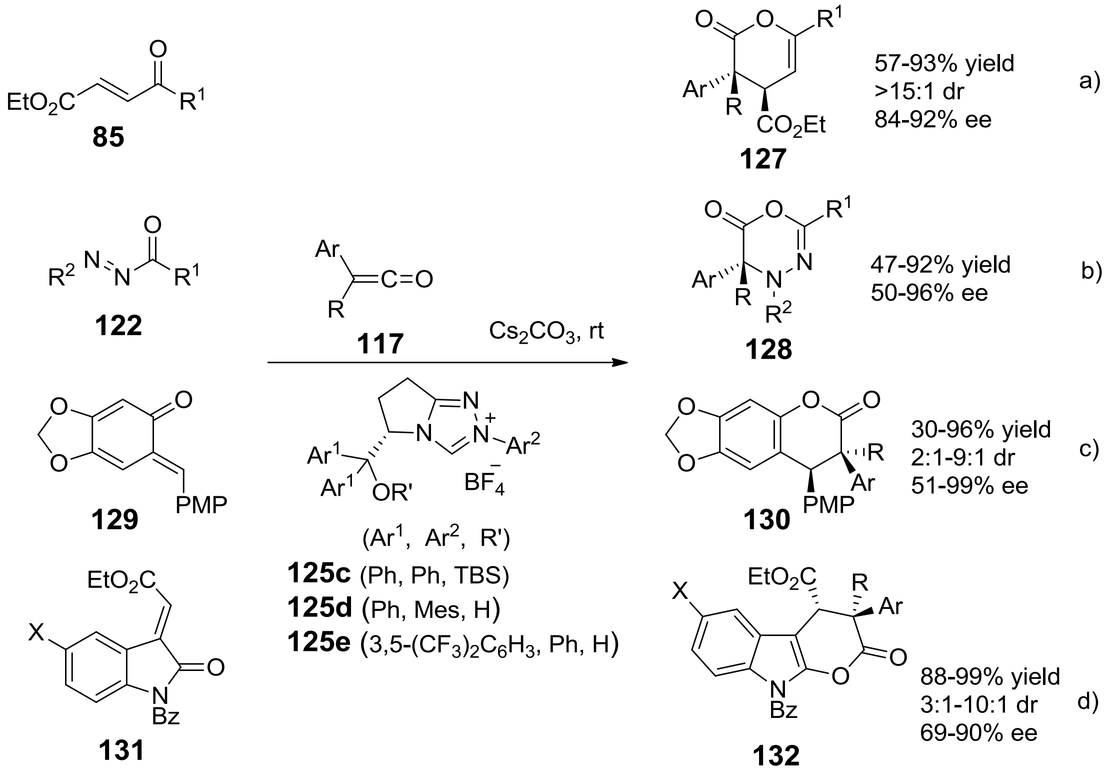
Scheme 30 *NHC-catalyzed [2+2] cycloadditions of ketenes.*



Scheme 31 *NHC-catalyzed [2+2+2] cycloaddition.*



Scheme 32 *NHC-derived [2+3] cycloaddition of ketenes and oxaziridines by Ye et al.*

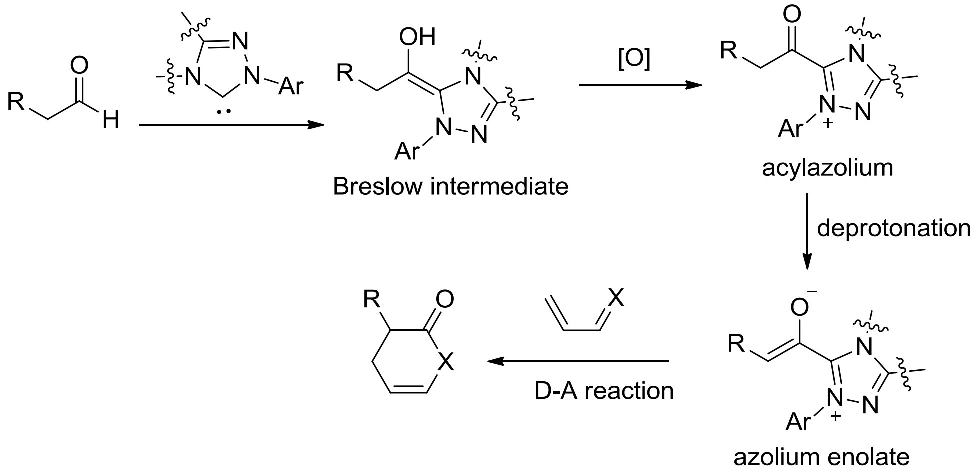


Scheme 33 *NHC-catalyzed formal [2+4] cycloadditions of ketene-derived azolium enolates.*

The ketene-derived azolium enolates also allowed formal [2+4] cycloadditions with electrophilic components, such as enones **85**. δ-Lactones **127** bearing a quaternary stereocenter were obtained in good yields with high stereocontrol catalyzed *via* the precatalyst **125c**. Notably, this process dominated *trans*-δ-lactones under thermodynamically controlled conditions, while kinetically controlled conditions led to the formation of the *cis*-isomer (Scheme 33a).[80] N-benzoyldiazenes **122** as alternative electrophiles were employed by Ye *et al.*, who developed the catalytic enantioselective [2+4] cycloaddition with ketenes by chiral NHCs to give 1,3,4-oxadiazin-6-ones **128**. Interestingly, both of the two enantiomers could be obtained by the use of precatalysts **125c** and **125d** (Scheme 33b).[81] An analogous work was reported by the same group *via* the [2+4] cycloaddition of alkylarylketenes **117** and *o*-quinone methides **129** to give the dihydrocoumarins **130** in good yields (30-96%) with good diastereoselectivities (up to 9:1 *cis:trans*) and excellent enantioselectivities (51-99% ee) (Scheme 33c).[82] Later, they further developed a facil access to the synthesis of indole-fused dihydropyranones **132** *via* the annulations of ketenes with 3-alkenyloxindoles **131** in the presence of precatalyst **125e** (Scheme 33d).[83]

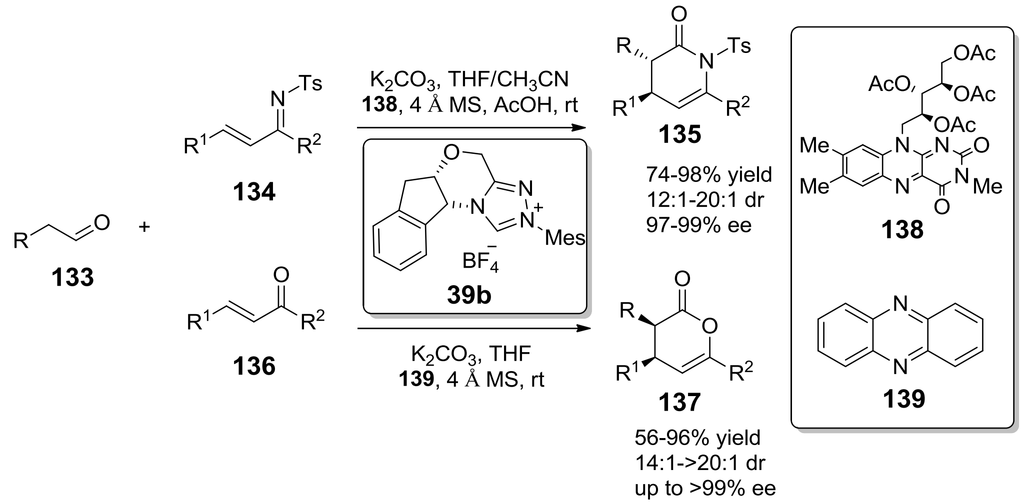
1.4.4 Azolium enolate generation *via* aliphatic aldehydes in the presence of an oxidant

As shown in Scheme 34, an NHC nucleophilic addition to aliphatic aldehydes would give the Breslow intermediate, followed by oxidation and deprotonation in a basic environment to generate *in situ* the corresponding azolium enolate.



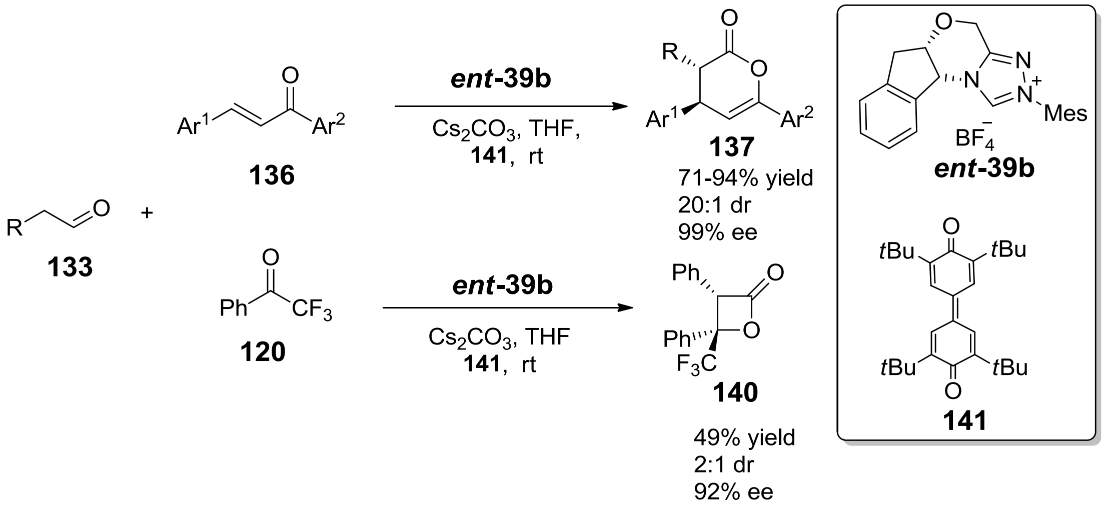
Scheme 34 *Generation of azolium enolate from aliphatic aldehydes.*

In 2012, Rovis *et al.* successfully realized this methodology to conduct an enantioselective hetero-Diels–Alder reaction of simple aliphatic aldehydes **133** with α,β-unsaturated ketimines **134**, providing *trans*-lactams in high yields with excellent diastereo- and enantiocontrol with the use of triazolium salt **39b** and the stoichiometric oxidant **138**. Interestingly, when enones **136** served as the electrophiles, *cis*-lactones **137** were obtained employing **139** as the oxidant instead of **138** (Scheme 35).[84]



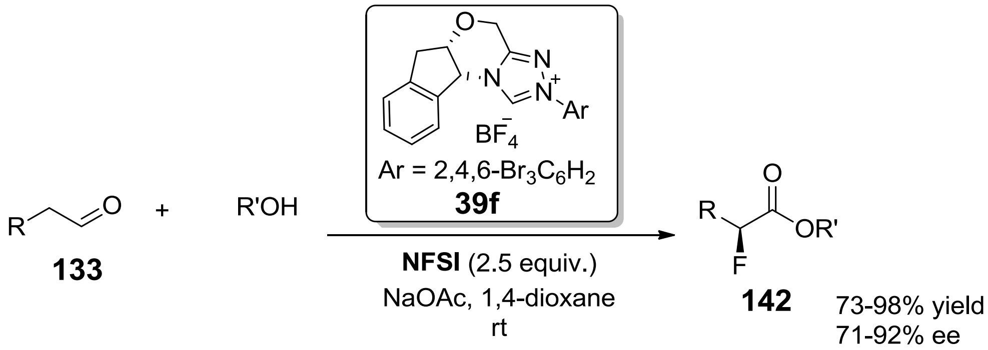
***Scheme 35** NHC-catalyzed hetero-Diels–Alder reaction with aliphatic aldehydes.*

Almost at the same time, Chi *et al.* also disclosed the direct generation of ester enolate equivalents from aliphatic aldehydes and the applications in the reactions with enones and trifluoromethyl ketones. They found that a catalytic amount of quinone **141** in combination of a stoichiometric amount of MnO_2 showed comparable reactivity and stereoselectivity (Scheme 36).[85]



***Scheme 36** NHC-derived enolates from simple aliphatic aldehydes by Chi et al.*

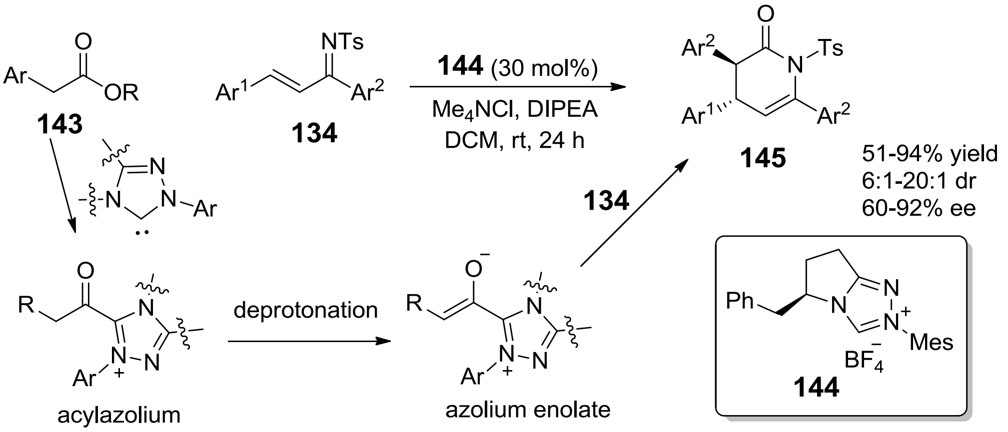
Very recently Wang and co-workers presented an interesting oxidative enantioselective α-fluorination of simple aliphatic aldehydes for the C-F bond formation in good to excellent enantioselectivities. In this process NFSI played a role as both electrophilic fluorinating source and oxidant.[86] Similar work was also reported by Sun *et al.*[74]



Scheme 37 *α-Fluorination of simple aliphatic aldehydes by Wang et al.*

1.4.5 Azolium enolate generation *via* activated esters

The group of Chi realized an alternative synthetic route for obtaining azolium enolates from stable carboxylic esters bearing a good leaving group. As shown in Scheme 38, the free carbene nucleophilic substitution on carboxylic esters generated acylazolium intermediates, which increased the acidity of the α C-H bonds. The subsequent deprotonation gave the nucleophilic azolium enolate, generating dihydropyridones **145** in good to excellent yields (51-94%) and high stereocontrol (up to >20:1 dr and 92% ee) in a formal asymmetric [2+4] process with α,β-unsaturated ketimines **134** by the use of precatalyst **144**.[87]

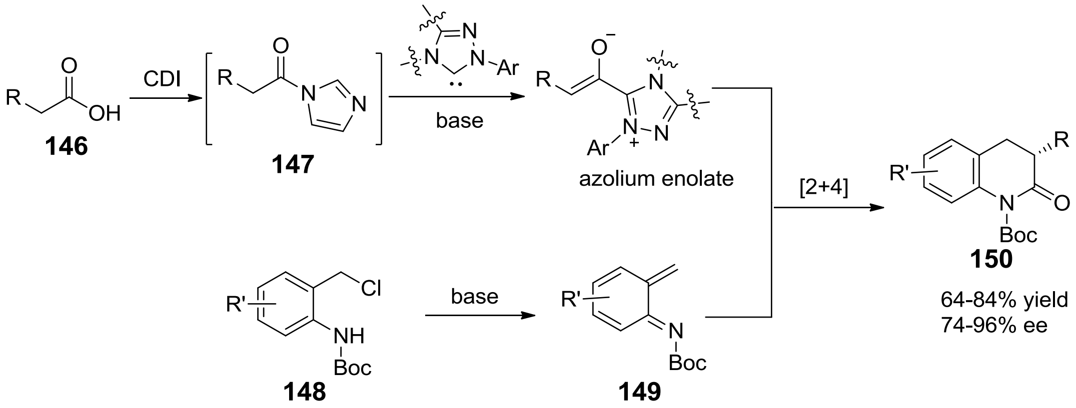


Scheme 38 *Chi's [2+4] cyclization with activated esters.*

Later, they further employed an acetic ester as suitable precursor for a two-carbon enolate intermediate. This simplest azolium enolate underwent enantioselective reactions with various electrophiles, such as enone **136** and α,β-unsaturated imine **134**.[88]

1.4.6 Azolium enolate generation *via* saturated carboxylic acids

Saturated carboxylic acids, as stable, cheap and easily available substrates could be employed as precursors to azolium enolates *via in situ* activation strategies. In 2014, Scheidt and co-workers disclosed an asymmetric formal [2+4] annulation for the synthesis of dihydroquinolones. The NHC-promoted generation of enolate formed by the addition of NHC to acyl imidazole **147** generated *in situ* from the carboxylic acid **146** and carbonyldiimidazole (CDI). This *in situ* generated enolate could react with the *in situ* formed electrophilic aza-*o*-quinone methide **149** from 2-aminobenzyl chloride **148**, afording the dihydroquinolones **150** in good to high yields (64-84%) and good to excellent ee values (74-96%) (Scheme 39).[89] Subsequently, the same group directly used the acyl imidazole **147** as precursor and successfully conducted the same reaction with good yields and enantioselectivities.[90]



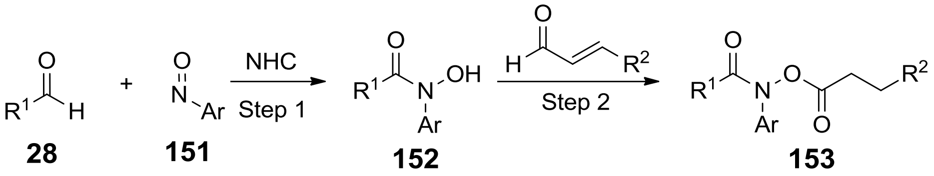
Scheme 39 *Scheidt's [2+4] cyclization with carboxylic acids.*

1.5 Research plan

Inspired by the recent progress on the applications of NHC-organocatalysis, my doctoral studies were focused on the exploration of facile and direct reactions of NHC-derived acyl anion, homoenolate or azolium enolate equivalents with various electrophiles.

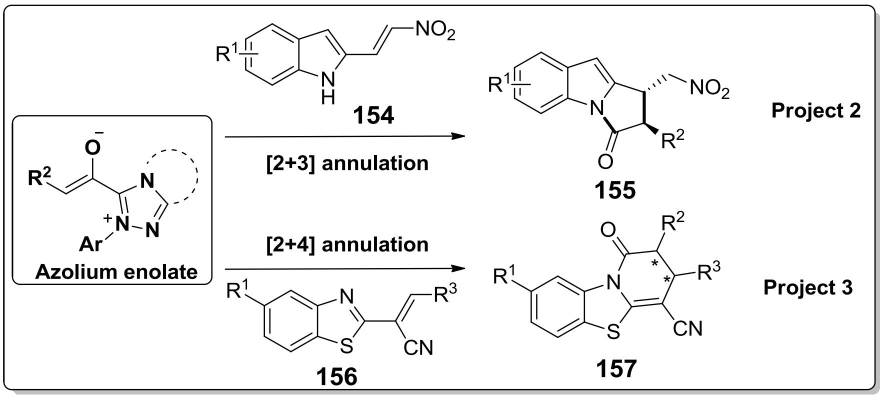
The research plan for this thesis was composed of three projects:

The first project involved an NHC-catalyzed one-pot synthesis of hydroxamic esters **153** *via* the combination of an aza-benzoin-type reaction of nitrosobenzenes **151** with various aldehydes and the subsequent protonation of the homoenolate under the same reaction conditions and a single catalyst (Scheme 40).



***Scheme 40** NHC-catalyzed one-pot reaction.*

The other two projects were concerned with the development of an NHC-derived access to the generation of azolium enolate equivalents and their applications in the reaction with suitable electrophiles (Scheme 41). The former project presented the generation of the azolium enolate *via* oxidation of the Breslow intermediate for the [2+3] annulation with nitrovinylindoles **154**. The desired pyrroloindolones **155** were obtained through a Michael/lactamization domino reaction. In the latter project, an enantioselective [2+4] annulation of styrylbenzo[*d*]thiazoles **156** with α-chloroaldehydes was disclosed. This reaction provided an efficient approach to the synthesis of tricyclic dihydrobenzothiazolopyridin-1-ones **157**.



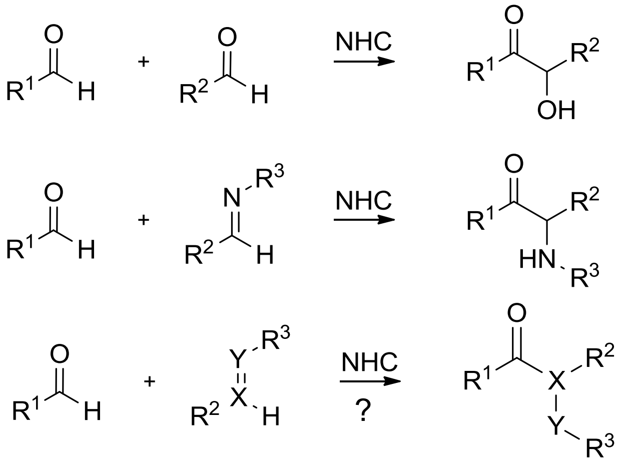
Scheme 41 *NHC-derived annulations via azolium enolates.*

2. Results and Discussion

2.1 NHC-catalyzed one-pot synthesis of hydroxamic esters

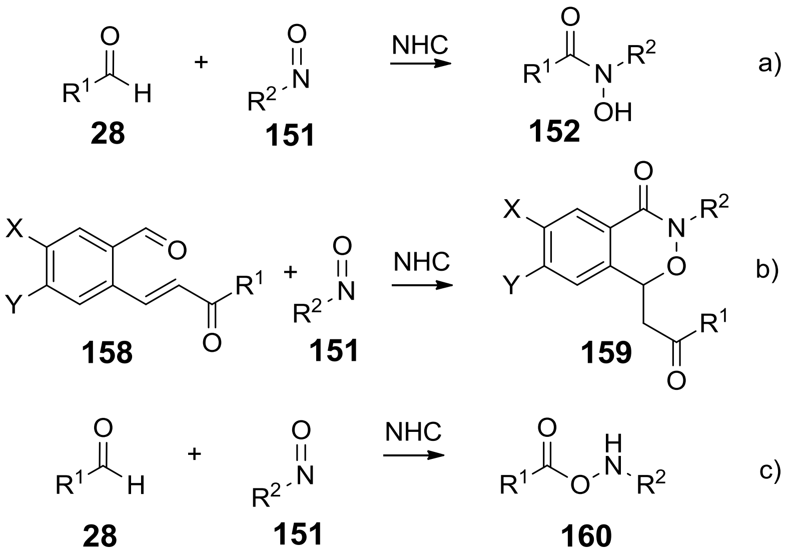
2.1.1 Background

The benzoin reaction is one of the most important NHC-organocatalytic transformations for the formation of a new C-C bond and stereogenic center. In addition to the self-condensation, the cross-benzoin reaction of aldehydes with other aldehydes or ketones, as well as the intermolecular transformations, attracted much attention. On-going exploration of NHC-catalyzed benzoin condensations was devoted to cross-aza-benzoin reactions. The imines were employed as electrophiles instead of aldehydes or ketones to give α-amino ketone products. However, the above mentioned benzoin reactions mainly focused on the construction of C-C bonds. The reports concerning the formations of carbon-heteroatom bonds were relatively rare (Scheme 42).



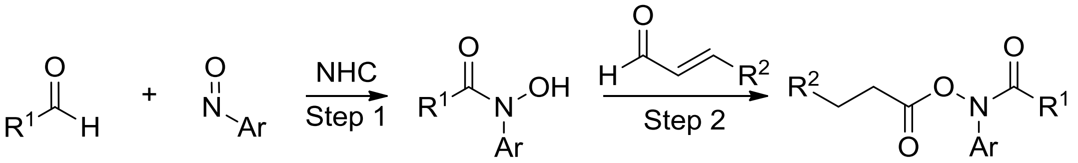
***Scheme 42** NHC-based Benzoin-type condensations.*

Nitroso compounds are versatile reagents utilized as nitrogen and/or oxygen sources in organic synthesis. The polarization of the N-O bond and specific structure enabls a highly electrophilic character of the nitroso group. In 2008 Zhang and co-workers developed a direct NHC-catalyzed amidation of aldehydes with nitroso compounds for the synthesis of N-arylhydroxamic acids **152** (Scheme 43a).[91] Later, Cheng *et al.* demonstrated a facile access to 2,3-benzoxazin-4-ones **159** *via* NHC-catalyzed cascade aza-benzoin reactions between *o*-vinylarylaldehydes **158** and nitrosoarenes followed by an intramolecular oxo-Michael addition (Scheme 43b).[92] Then they realized an NHC-catalyzed three-component reaction of enals, nitrosoarenes and enones in one-step to produce N-hydroxylacrylamides in moderate to good yields.[93] Recently, Ma *et al.* described an NHC-catalyzed O-selective benzoin-type condensation of nitrosoarenes with aldehydes to generate various O-acyl hydroxylamines **160** (Scheme 43c).[94]



Scheme 43 *NHC-catalyzed benzoin-type condensations of nitrosoarenes.*

As stated in "*chapter 1.3*", the generation of homoenolate equivalents was first pioneered by the groups of Bode and Glorius. This reactive nucleophilic intermediate enabled various transformations with different electrophiles. The protonation of homoenolate equivalents accomplish an internal redox esterification or amidation. In Zhang's report,[91] the resulted N-arylhydroxamic acids **152** may provide the proton for the protonation of the homoenolate. Hence, we envision a new combination of an aza-benzoin-type reaction of nitrosobenzenes with various aldehydes and the subsequent redox esterification of the resulting hydroxamic acids with enals in a one-pot process (Scheme 44).



Scheme 44 *NHC-catalyzed one-pot reaction of hydroxamic esters.*

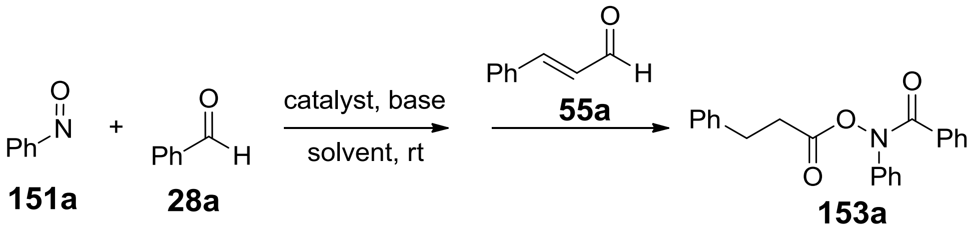
2.1.2 Optimization of conditions

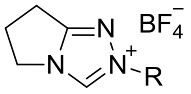
We started our studies with the optimization of the reaction conditions. As a model reaction we treated nitrosobenzene (**151a**) with benzaldehyde (**28a**) in the presence of a triazolium salt **41b** and DABCO in toluene. Indeed, the desired hydroxamic acid product was generated rapidly *via* a cross-aza-benzoin reaction after just 1.5 hour. Fortunately, after directly adding cinnamaldehyde (**55a**) to the reaction mixture, the final product hydroxamic ester **153a** was afforded in 87% yield after 24 hours (Table 1, entry 1). Encouraged by this result, we tested several different azolium salts on this model reaction. However, precatalysts **41a**, **41c**, **161** and **83** showed no activity under the same reaction conditions (Table 1, entries 2, 3, 5, and 6) and only 27% yield was obtained using the precatalyst **41d** (Table 1, entry 4).

Since no satisfying increase of the reactivity was obtained by changing the catalysts, we continued to investigate the optimization of the solvent and base. In this context toluene, THF and DCM led to similar yields (85-87%), and hence, we could not observe significant difference between polar and unpolar solvents (Table 1, entries 1, 7, 8). On the other hand, much stronger effects were exhibited on this one-pot process by changing the bases. The amino-bases DABCO, TIPEA, TEA, DBU and TMEDA gave all high reactivities affording the desired product in 74-88% yields (Table 1, entries 8-11, 13). As opposed to this, sodium acetate as a typical inorganic base showed a relatively low reactivity with only 25% yield after a strongly prolonged reaction time (Table 1, entry 12). In conclusion, TMEDA was identified superior to all other tested bases generating the final product hydroxamic ester **153a** in 87% yield in

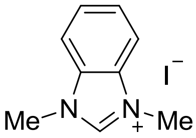
DCM as solvent after a short overall reaction time of approximately one hour (Table 1, entry 13).

Table 1 *Optimization of the reaction conditions.*[a]

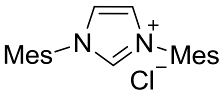




41a R = C_6H_5
41b R = C_6F_5
41c R = 4-$MeOC_6H_4$
41d R = 4-$CF_3C_6H_4$



161



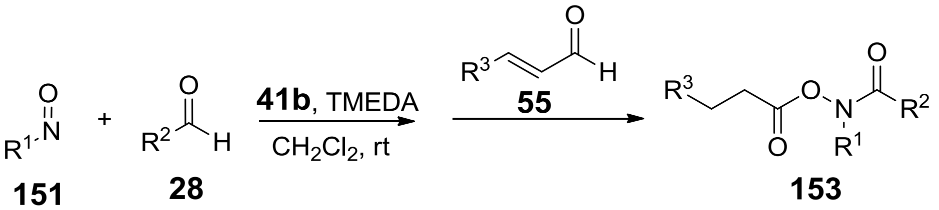
83

Entry	Cat.	Solvent	Base	Time 1	Time 2	Yield [%][b]
1	**41a**	toluene	DABCO	25.5 h	--	NR
2	**41b**	toluene	DABCO	1.5 h	24 h	87
3	**41c**	toluene	DABCO	25.5 h	--	NR
4	**41d**	toluene	DABCO	4 h	21.5 h	27
5	**161**	toluene	DABCO	25.5 h	--	NR
6	**83**	toluene	DABCO	25.5 h	--	NR
7	**41b**	THF	DABCO	1.5 h	24 h	85
8	**41b**	DCM	DABCO	1.5 h	24 h	87
9	**41b**	DCM	DIPEA	15 min	1 h	85
10	**41b**	DCM	TEA	15 min	5 h	88
11	**41b**	DCM	DBU	15 min	25 h	74
12	**41b**	DCM	NaOAc	6 h	19.5 h	25
13	**41b**	DCM	TMEDA	15 min	40 min	87

[a] Reaction conditions: base (0.04 mmol) was added to a solution of nitrosobenzene **151a** (0.2 mmol), benzaldehyde **28a** (0.2 mmol), catalyst (0.02 mmol) in solvent (2 mL) at rt under argon. After **151a** was converted completely (monitored by TLC), cinnamaldehyde **55a** (0.4 mmol) was added. [b] Yields of isolated product **153a** after flash chromatography.

2.1.3 Determination of substrate scope

Table 2 *Substrate scope of the NHC-catalyzed one-pot reaction.*[a]



153	R^1	R^2	R^3	Time [min][b]	Yield [%]
a	Ph	Ph	Ph	15+40	87
b	Ph	4-Me-C_6H_4	Ph	15+45	88
c	Ph	4-Cl-C_6H_4	Ph	15+30	77
d	Ph	4-Br-C_6H_4	Ph	15+25	76
e	Ph	Ph	4-Me-C_6H_4	15+210	89
f	Ph	4-Me-C_6H_4	4-Me-C_6H_4	15+180	88
g	Ph	4-Cl-C_6H_4	4-Me-C_6H_4	15+60	81
h	Ph	Ph	4-Cl-C_6H_4	15+20	82
i	Ph	4-Me-C_6H_4	4-Cl-C_6H_4	15+30	80
j	Ph	4-Cl-C_6H_4	4-Cl-C_6H_4	15+30	62
k	Ph	Ph	4-NO_2-C_6H_4	15+210	79
l	Ph	4-Me-C_6H_4	4-NO_2-C_6H_4	15+60	74
m	Ph	4-Br-C_6H_4	4-NO_2-C_6H_4	15+60	70
n	4-Me-C_6H_4	Ph	Ph	15+20	57
o	3- NO_2-C_6H_4	Ph	Ph	30+180	69
p	Ph	Ph-C_2H_4	Ph	40+150	83

q	Ph	*n*-Pent	Ph	40+60	78
r	Ph	Et	Ph	40+60	84
s	Ph	3-MeO-C_6H_4	Ph	15+30	92
t	Ph	Ph	Me	15+60	81
u	Ph	Ph	2-MeO-C_6H_4	15+35	75
v[c]	Ph	Ph-CH=CH	Ph	30	80

[a] Reaction conditions: TMEDA (0.1 mmol) was added to a solution of nitrosoarene **151** (0.5 mmol), aldehyde **28** (0.5 mmol), precatalyst **41b** (0.05 mmol) in DCM (5 mL) at rt under argon. After **151** was converted completely (monitored by TLC), enal **55** (1.0 mmol) was added. All yields are based on the isolated products. [b] Time for Step 1 + time for Step 2. [c] TMEDA (0.1 mmol) was added to solution of nitrosobenzene (0.5 mmol), cinnamaldehyde (1.5 mmol), precatalyst **41b** (0.05 mmol) in DCM (5 mL) at rt under argon.

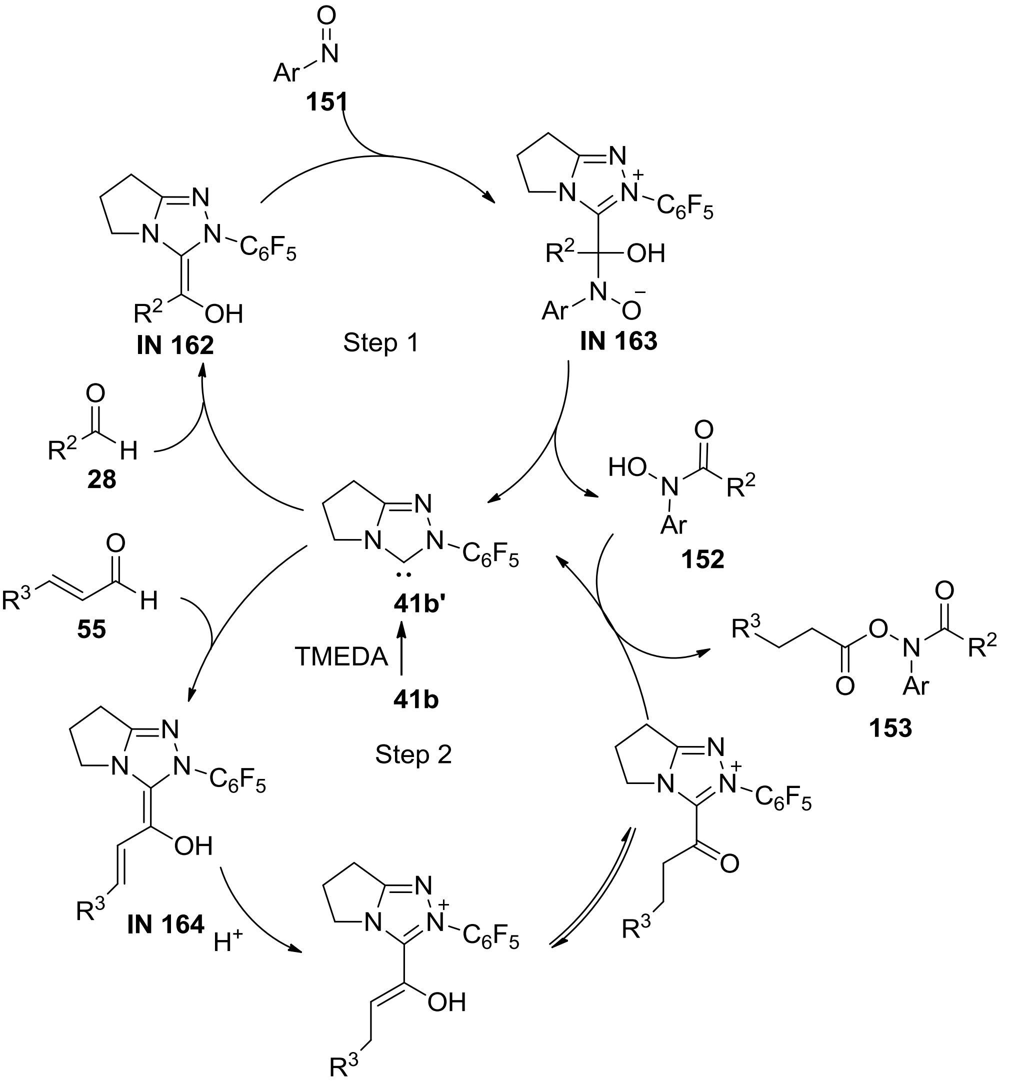
We then evaluated the scope and limitations of the whole one-pot process under the optimized reaction conditions. First, we studies the reactions of nitrosobenzene **151a** with a series of aldehydes **28** followed by the addition of cinnamaldehyde **55a** (Table 2, **153a-d**). The results showed that a small effect on the reaction was detected when an electron-rich group was a substituent on the benzaldehyde derivatives. In comparison, benzaldehyde **28a** and 4-methylbenzaldehyde **28b** afforded the desired products **153a** and **153b** in 87% and 88%, respectively. Similar effects were observed for the pairs **153e**/**f**, **h**/**i** and **k**/**l**. On the contrary, electron-deficient groups on the benzaldehyde derivatives such as 4-chlorobenzaldehyde **28c** and 4-bromobenzaldehyde **28d** gave lower yields (**153c**, **d**, **g**, **j** and **m**). Interestingly, the reaction time for the electron-deficient substrates was the same as for the electron-rich ones demonstrating that the loss of yield was likely because of the electronically controlled side reaction. For example, a homo-benzoin reaction could take place, which is known to prefer electron-deficient substrates due to the more stable Breslow intermediates. We then changed the aromatic aldehydes to aliphatic ones for the *aza*-benzoin-type reaction. We were pleased to find that enolizable substrates such as alkyl-substituted aldehydes were also tolerated and yielded the products **153p**, **q** and **r** in 83%, 78% and 84% yields, respectively, albeit the necessary reaction time was increased in these cases. It's worth mentioning that the reaction with 3-methoxybenzaldehyde was carried out with an excellent yield of 92% (**153s**). 2-Chlorobenzaldehyde was also investigated, but unfortunately no product was observed (TLC).

Our second part of the substrate scope focused on the different enal components **153** in the subsequent redox esterification. Interestingly, we observed that the reactivity was in line with the observation of the preliminary *aza*-benzoin-type reaction. In comparison, the enals with an electron-rich 4-tolyl group generated the final products in similar yields as the unsubstituted cinnamaldehyde (Table 2, entries **153a**/**e**, **b**/**f**, **c**/**g**). However, the time needed to finish the reaction was much longer. On the other hand, electron-deficient enals such as 4-chloro- or 4-nitrocinnamaldehyde occured with lower yields and in shorter reaction times (Table 2, **153h-m**). As for the aza-benzoin-type reaction, a possible explanation for this fact is an electronically controlled side reaction, such as the homo-benzoin reaction. In order to further expand the scope of enals, we tested crotonaldehyde bearing an aliphatic group (R^3 = Me) as a substrate, too. In this case, we were pleased to find that **153t** was afforded in a yield of 81%. In addition, we also studied the effect of steric hindrance by using *ortho*-methoxycinnamaldehyde and 75% yield of **153u** was observed.

The last part of our scope investigation was carried out to investigate the influences of nitrosobenzenes **151**. Therefore, we tested nitrosobenzene (**151a**), electron-rich 4-methylnitrosobenzene and electron-deficient 3-nitronitrosobenzene under the optimized reaction conditions. In these three control experiments, 87%, 57% and 69% yields were obtained for the corresponding products **153a**, **n** and **o**. This demonstrated that the unsubstituted nitrosobenzene **151a** was more active than substituted ones whether an electron-rich or an electron-deficient group was present.

At last, we envisaged a domino reaction, cinnamaldehyde **55a** as sole aldehyde-component utilized for both reaction steps. To our delight, after a short reaction time of 30 min, a very good yield of 80% was obtained for the desired domino product **153v**. A similar reaction was reported by Ying in 2008.[91]

2.1.4 Proposed mechanism for the NHC-catalyzed one-pot reactions



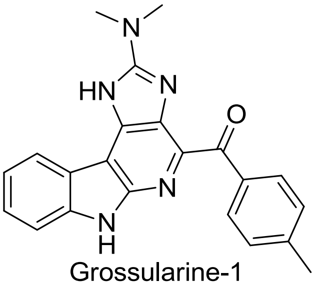
Scheme 45 *Possible mechanism for the NHC-catalyzed one-pot reaction.*

The proposed pathway for the NHC-catalyzed one-pot reaction is shown in Scheme 45. The first cycle constructs the C-N bond in the N-arylhydroxamic acid 152 by the aza-benzoin-type reaction of aldehyde **28** and nitrosobenzene **151**. Secondly, the generated N-arylhydroxamic acid **152** is employed as substrate for the subsequent protonation of homoenolate to the corresponding the saturated ester **153**. In this protocol, both cycles are operated with the same catalyst **41b** and hence, involve Breslow intermediate **IN162** and homoenolate **IN164**. The comparable, electronic properties of these intermediates are responsible for the observed trends in the corresponding substrate scope as mentioned above.

2.2 NHC-catalyzed [2+3]-annulation of nitrovinylindoles with aliphatic aldehydes

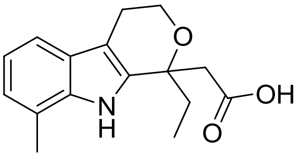
2.2.1 Background

The annulated indole skeleton is found in many natural products and biologically active molecules. Especially, tricyclic [2,3]-fused indole derivatives received much attention and these prevail in various alkaloids. For example, grossularine-1 (**165**) was isolated from α-carboline derivatives and showed antitumor properties. Etodolac (**166**) was used as non-steroidal anti-inflammatory drug, as well as yohimbine (**167**), a veterinary drug used to reverse sedation in dogs and deer. Interestingly, another family of annulated indoles, such as [1,2]-fused indole derivatives, exist in numerous natural products and pharmaceuticals, such as flinderole C (**168**), greenwayodendrin-3a-ol (**169**), as well as the tetracyclic indole derivatives **170** and **171**.



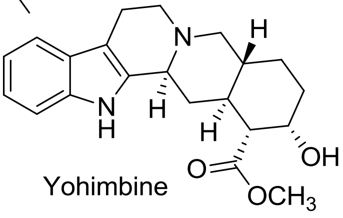
Grossularine-1

165



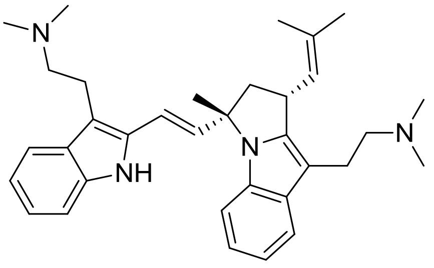
Etodolac

166



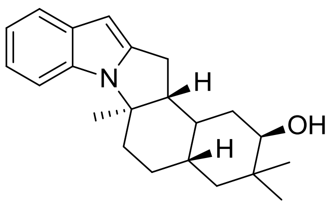
Yohimbine

167



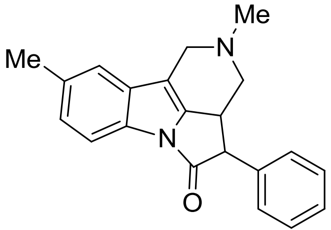
Flinderole C

168



Greenwayodendrin-3α-ol

169



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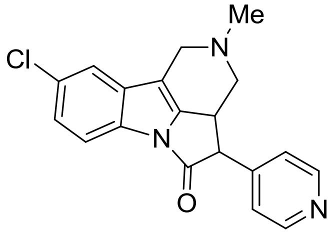
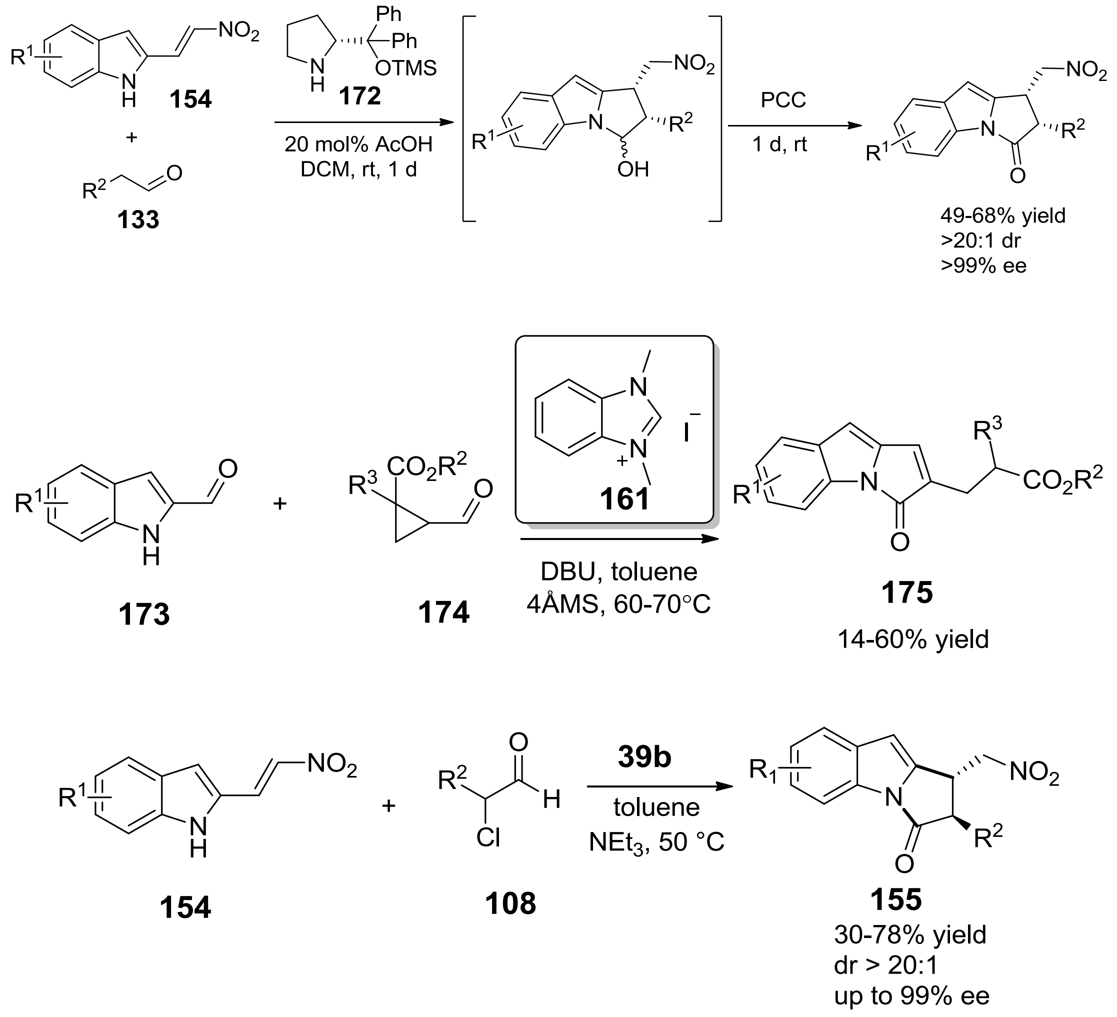


171

***Figure 5** Annulated indole derivatives.*

However, organocatalytic methods to access the [1,2]-fused indoles are rarely developed. In 2011, our workgroup reported a one-pot asymmetric reaction of (*E*)-2-(2-nitrovinyl)-1*H*-indoles with aldehydes for the synthesis of *cis*-1H-pyrrolo[1,2a]indol-3(2H)-ones *via* a Michael–hemiaminalization-oxidation sequence catalyzed by (*R*)-diphenylprolinol TMS-ether **172** and subsequent oxidation by PCC.[95] In addition, the NHC-catalyzed synthesis of [1,2]-fused indoles was realized by Wang *et al.*, who conducted a formal hetero-[3+2] annulation of 1*H*-indole-2-carbaldehydes **173** with formylcyclopropane 1,1-diesters **174** for the construction of tricyclic pyrrolo[1,2-a]indole skeletons **175**.[96] Recently, an interesting NHC-catalyzed [2+3] annulation towards to the synthesis of *trans*-disubstituted pyrroloindolones **155** was developed by our group through the Michael addition of the *in situ* generated enolate species from α-chloroaldehydes **108** to electrophilic nitroalkenes **165** and followed by a lactamization. This process tolerated a range of substrates and gave the corresponding products in good yields and excellent stereocontrol.[72] However, as the substrate α-chloroaldehyde is unstable, an alternative approach for the generation of the azolium enolate from aliphatic aldehydes was envisaged, which are stable and easily available. So we envisioned the NHC-catalyzed annulation of (*E*)-2-(2-nitrovinyl)-1*H*-indoles with aliphatic aldehydes in combination with a stoichiometric amount of an oxidant.

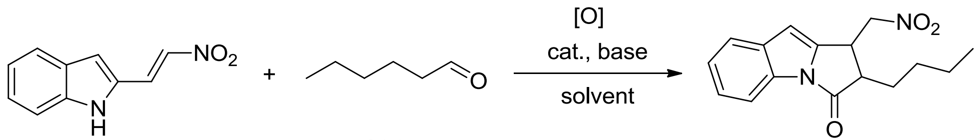


Scheme 46 *Organocatalytic synthesis of [1,2]-fused indoles.*

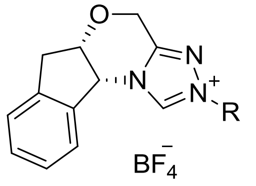
2.2.2 Optimization of conditions

To test our hypothesis, we initially evaluted several triazolium precatalysts on the model reaction of (*E*)-2-(2-nitrovinyl)-1*H*-indole **154a** with hexanal **133a** at 50 ℃ employing bisquinone **141** as oxidant. We were pleased to find that the use of chiral triazolium salt **39b** showed excellent stereoselective of **155a** (98% ee, >20:1 dr) with a yield of 40% (Table 3, entry 2). In order to improve the the yield of **155a**, we next tested a series of bases. When TMEDA was employed as the base, the yield was increased to 43%, remaining the excellent stereoselectivity (Table 3, entry 6). The studies of solvent optimization revealed no improvement in yield (Table 3, entries 15-18). After base and solvent screening, we further tested different oxidant. Unfortunately, the use of phenazine **141** and inorganic oxidant MnO_2 showed very low reactivity. Another strategy was the combination of bisquinone **141** with MnO_2, which was inspired by Chi's report. However, only 8% yield was obtained (Table 3, entry 21). When we added 4 Å MS as additive, a dramatically improved yield (61%) was received with a slightly decrease of enantioselectivity (96% ee) (Table 3, entry 22).

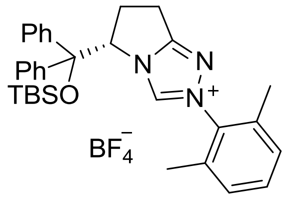
Table 3 *Optimization of the reaction conditions.*[a]



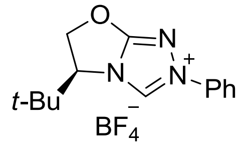
154a **133a** **155a**



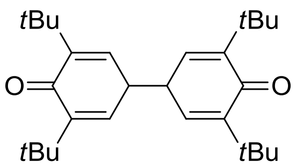
39b R = Mes
ent-39e R = C_6F_5
39g R = 2,6-diMePh



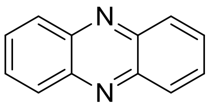
125f



26



141



139

Entry	cat.	Base	[O]	Solvent	Yield (%)[b]	dr [c]	ee (%)[d]
1	**39b**	Et_3N	**141**	toluene	40	>20:1	98

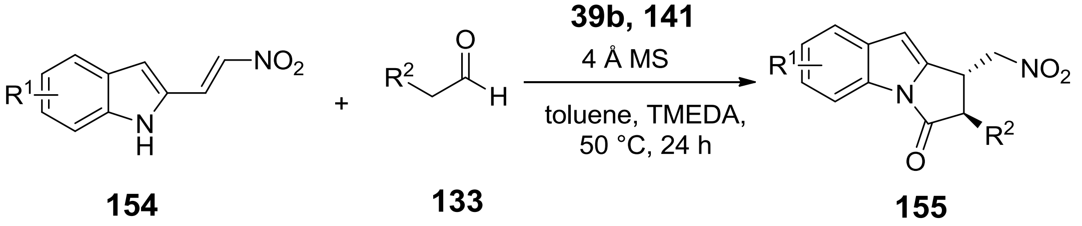
2	**ent-39e**	Et_3N	**141**	toluene	n.r.	--	--
3	**39g**	Et_3N	**141**	toluene	15	>20:1	96
4	**125f**	Et_3N	**141**	toluene	n.r.	--	--
5	**26**	Et_3N	**141**	toluene	n.r.	--	--
6	**39b**	TMEDA	**141**	toluene	43	>20:1	98
7	**39b**	DABCO	**141**	toluene	36	>20:1	94
8	**39b**	DMAP	**141**	toluene	24	>20:1	97
9	**39b**	DIPEA	**141**	toluene	27	>20:1	99
10	**39b**	DBU	**141**	toluene	n.r.	--	--
11	**39b**	NaOAc	**141**	toluene	17	>20:1	99
12	**39b**	K_2CO_3	**141**	toluene	12	>20:1	98
13	**39b**	K_3PO_4	**141**	toluene	trace	--	--
14	**39b**	*t*-BuOK	**141**	toluene	n.r.	--	--
15	**39b**	TMEDA	**141**	THF	18	>20:1	98
16	**39b**	TMEDA	**141**	$CHCl_3$	n.r.	--	--
17	**39b**	TMEDA	**141**	CH_3CN	11	>20:1	90
18	**39b**	TMEDA	**141**	mesitylene	41	>20:1	97
19	**39b**	TMEDA	**139**	toluene	6	>20:1	98
20	**39b**	TMEDA	MnO_2	toluene	n.r.	--	--
21	**39b**	TMEDA	MnO_2+**141**	toluene	8	>20:1	98
22[e]	**39b**	TMEDA	**141**	toluene	61	>20:1	96

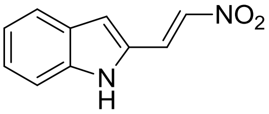
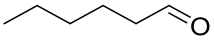
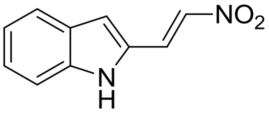
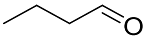
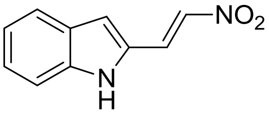
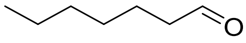
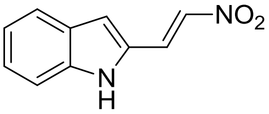
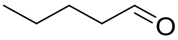
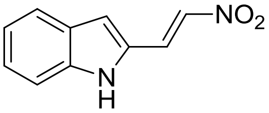
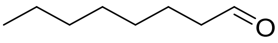
[a] Reaction conditions : **154a** (0.2 mmol), **133a** (0.4 mmol), precat. (10 mol%), [O] (1.0 equiv.), base (1.1 equiv.), solvent (2 mL), at 50 ℃ for 24 h. [b] Isolated yield after purification by column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] The ee value was determined by HPLC on a chiral stationary phase. [e] 4 Å MS (100 mg) was added.

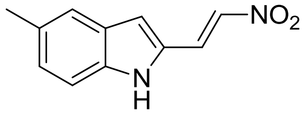
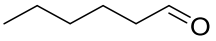
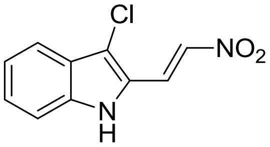
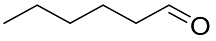
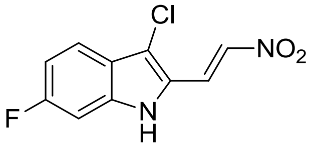
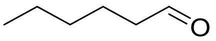
2.2.3 Determination of substrate scope

With the optimized reaction conditions in hand, the scope and limitations of the annulations were evaluated. First, we tested the tolerance of this reaction with various aliphatic aldehydes. A variety of pyrroloindolones **155a-e** could be obtained in excellent diastereoselectivities and enantioselectivities with the yields of 31-61%. Some other aliphatic aldehydes, such as hydrocinnamaldehyde was also examined, however no product was obtained. Next, we also investigated the variation on the 2-nitrovinylindole moiety. Different substituents on the aryl ring, such as 5-CH_3, 3-Cl or 3-Cl, 6-F, gave the desired products **155f-h** in excellent stereocontrol with acceptable yields. Moreover, the absolute configuration of **155a** was unambiguously comfirmed to have the (1*S*,2*R*)-configuration by comparing the optimal rotation data with similar compounds reported in previous work.[72]

Table 4 *Scope of 2-nitrovinylindoles with aliphatic aldehydes[a]*



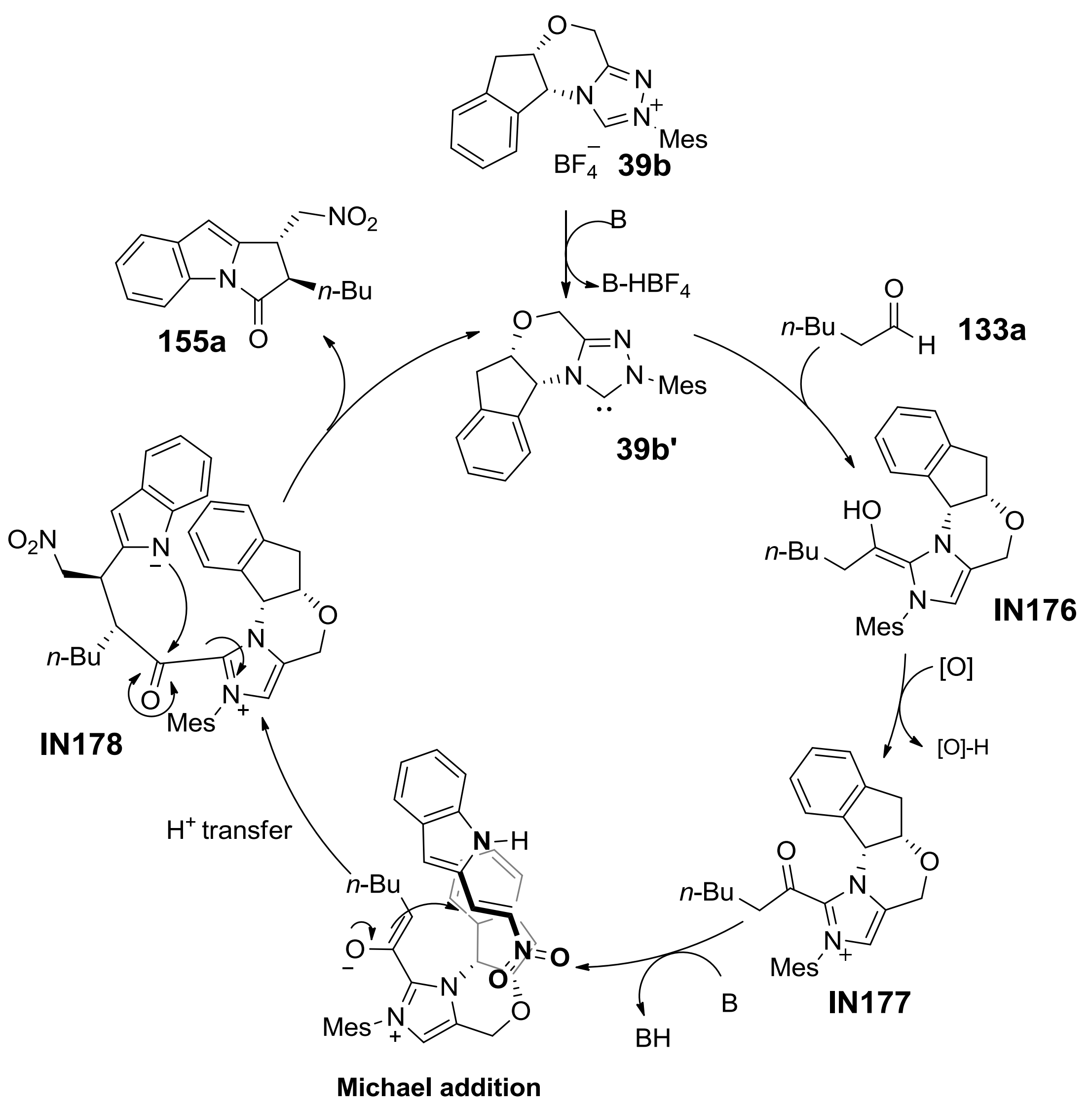
155	154	133	Yield (%)[b]	dr	ee (%)[c]
a			61	>20:1	96
b			57	>20:1	98
c			31	>20:1	97
d			39	>20:1	96
e			49	>20:1	96

f			44	>20:1	97
g			38	>20:1	97
h			33	>20:1	96

[a] Reaction conditions: **154** (0.2 mmol), **133** (0.4 mmol), **39b** (10 mol%), **141** (1.0 equiv.), TMEDA (1.1 equiv.), toluene (2 mL), 4 Å MS (100 mg), at 50 ℃ for 24 h. [b] Yield of product isolated after purification by column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] The ee value was determined by HPLC on a chiral stationary phase.

2.2.4 Mechanistic studies

A plausible mechanism for this NHC-catalyzed annulation reaction is shown in Scheme 47. Initially, the free NHC **39b’**, generated by deprotonation of the precatalyst salt **39b**, reacts with the aliphatic aldehyde **133a** to give the Breslow intermediate **IN176**, which is subsequently oxidized by **141** to form the acylazolium ion **IN177**. Deprotonation of **IN177** in the presence of base generates the nucleophilic azolium enolate, which subsequently undergoes a Michael reaction with 2-nitrovinylindole **154a**. This key step forms two stereogenic centers in a *trans*-configuration. The following proton transfer and intramolecular lactamization of **IN178** affords the final cycloadduct **155** and releases the NHC catalyst.

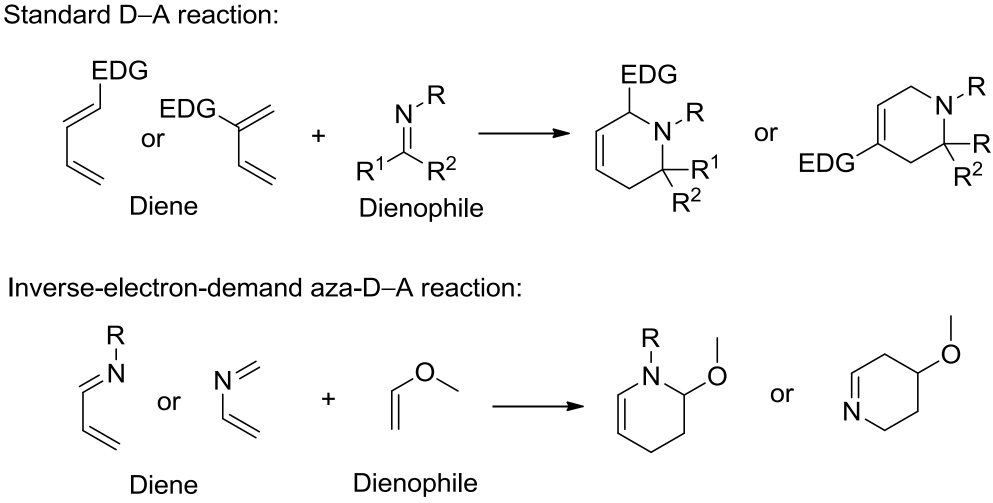


*Scheme 47 Proposed pathway for the formation of pyrroloindolones **155.***

2.3 Asymmetric NHC-catalyzed [2+4]-annulation of 2-alkenyl-benzothiazoles with α-chloroaldehydes

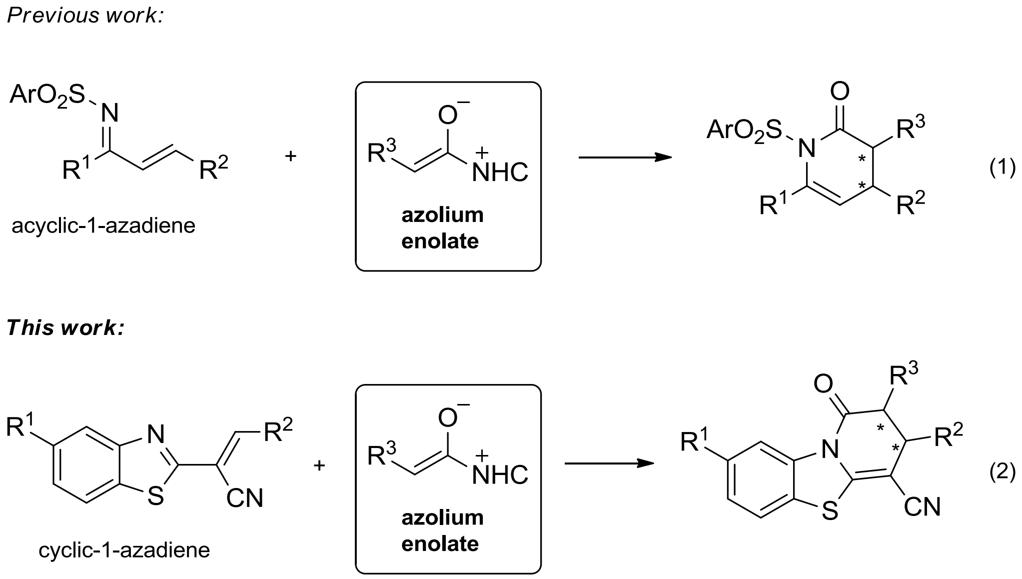
2.3.1 Background

Since the discovery of the Diels–Alder (D–A) reaction in 1928,[97] the aza-D–A reaction is one of the most powerful and convergent synthetic approaches to form six-membered heterocycle containing a nitrogen atom. This bimolecular [4+2] reaction of an electron-rich diene, such as Danishefsky's diene, with an electron-deficient dienophile such as an imine shows excellent regio- and stereoselectivity. Another possible combination is an electron-deficient diene with the electron-rich dienophile, which is known as inverse-electron-demand aza-D–A (IEDADA) reaction (Scheme 48). Various organocatalytic enantioselective aza-DA reactions catalyzed by amines[98] or chiral phosphoric acids[99] have been intensively investigated.



Scheme 48 *Formal pathway in [2+4] cycloadditions.*

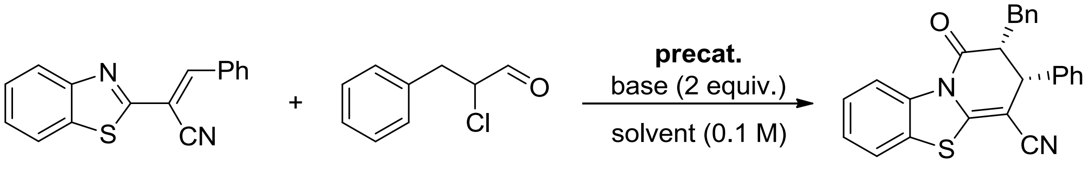
The NHC-mediated *in situ* generated azolium enolates acted as reactive 2C nucleophiles and paved the way to various important heterocyclic manifolds *via* [2+2], [2+3] cycloadditions, as well as the [2+4] IEDADA reactions. In 2006, Bode and co-workers first reported a highly enantioselective NHC-catalyzed aza-DA reaction of N-sulfonyl-1-aza-butadienes with β-activated enals.[61] Later, Ye and co-workers developed the generation of azolium enolates from ketenes[100] and α-chloroaldehydes[71] for the [2+4] IEDADA reactions with α,β-unsaturated ketimines in the presence of NHC catalysts. Then Rovis and co-workers realized the construction of *trans*-lactams through the IEDADA reaction of simple aliphatic aldehydes with α,β-unsaturated ketimines.[84] Recently, the group of Chi demonstrated an NHC-catalyzed [2+4] cycloaddition of α-aryl esters with α,β-unsaturated ketimines.[87] However, in these reports only acyclic-1-azadienes were utilized as reaction partners (Scheme 49, eq 1). Few reports disclosed the IEDADA reaction of cyclic-1-azadienes with *in situ* generated azolium enolate species. Herein we report an enantioselective NHC-catalyzed annulation of (*E*)-2-styrylbenzo[*d*]thiazoles with *in situ* formed azolium enolates from α-chloroaldehydes to afford highly functionalized dihydro-1*H*-benzothiazolopyridines bearing two contiguous tertiary stereogenic centers with excellent diastereoselectivities and enantioselectivities (Scheme 49, eq 2). The resulting tricyclic skeletons can be found in various biologically active products and numerous pharmaceuticals, such as antitumor and antibacterial drugs.



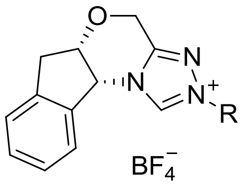
Scheme 49 *NHC-catalyzed aza-Diels–Alder reactions.*

2.3.2 Catalyst screening and optimization of conditions

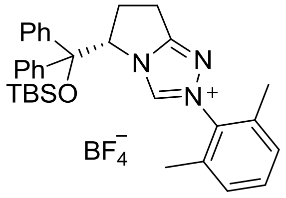
Table 5 *Optimization of the reaction conditions.*[a]



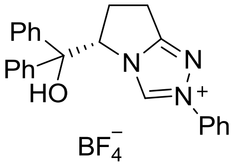
156a **108a** **157a**



39b R = Mes
***ent*-39e** R = C_6F_5



125f



125g

Entry	Precat.	Base	Solvent	Yield[%][b]	dr[c] cis:trans	*ee*[%][d] (*cis*)
1	**39b**	Et_3N	toluene	29	6:1	95
2	**ent-39e**	Et_3N	toluene	trace	--	--
3	**125f**	Et_3N	toluene	n.r.	--	--
4	**125g**	Et_3N	toluene	trace	--	--
5[e]	**39b**	Et_3N	toluene	29	6:1	93
6	**39b**	TMEDA	toluene	40	5:1	95
7	**39b**	DIPEA	toluene	37	7:1	94
8	**39b**	DABCO	toluene	30	3:1	94
9	**39b**	NaOAc	toluene	trace	--	--
10	**39b**	K_2CO_3	toluene	NR	--	--
11	**39b**	TMEDA	THF	41	3:1	94
12	**39b**	TMEDA	mesitylene	29	3.5:1	94
13	**39b**	TMEDA	CH_2Cl_2	46	3:1	97
14	**39b**	TMEDA	CH_3CN	96	1:2.5	96
15	**39b**	DABCO	CH_3CN	58	1:13	87
16	**39b**	DIPEA	CH_3CN	99	3.5:1	97
17	**39b**	DIPEA	toluene: CH_3CN = 4:1	76	7.5:1	97
18	**39b**	DIPEA	toluene: CH_3CN = 1:4	97	5:1	97
19	**39b**	DIPEA	toluene: CH_3CN = 2:1	94	7:1	97
20	**39b**	**DIPEA**	**toluene: CH_3CN = 1:2**	**95**	**7:1**	**98**

[a] Reaction conditions: **156a** (0.2 mmol), **108a** (0.3 mmol), precatalyst (0.02 mmol), base (0.4

mmol), solvent (V/V, 2 mL in total), rt, under argon, reaction time: 16 h. [b] Yield of isolated product **157a** after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] The ee value was determined by HPLC on a chiral stationary phase. [e] Performed at 40 °C.

We initiated our investigation on the reaction of (*E*)-2-(benzo[*d*]thiazol-2-yl)-3-phenylacrylonitrile (**156a**) with 2-chloro-3-phenylpropanal (**108a**) at room temperature in toluene in the presence of Et_3N and triazolium precatalyst **39b**. The reaction gave 29% yield of the aza-DA adduct **157a** in a good *cis*/*trans*-diastereoselectivity (dr = 6:1) and an excellent ee value (95%) of the major *cis*-diastereomer (Table 5, entry 1). The other triazolium precatalysts **ent-39e, 125f**, as well as the bifunctional triazolium precatalyst bearing a hydroxyl group gave only trace amounts of the product (Table 5, entries 2 and 4) or even no product at all (Table 5, entry 3).

In order to improve the yield of the desired **157a**, we elevated the reaction temperature to 40 °C. However, this strategy did not lead to the desired result (Table 5, entry 5).

Next, a series of bases such as TMEDA, DIPEA or DABCO, NaOAc and K_2CO_3 were examined. The result revealed that organic bases were much more effective than inorganic bases (Table 5, entries 6-10), and the organic base TMEDA gave the highest yield as well as excellent stereoselectivity (Table 5, entry 6).

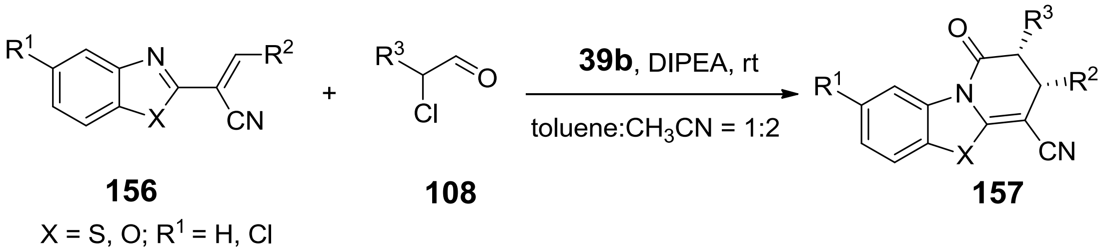
After the catalyst and base screening, we then tested a series of the reaction solvents in the presence of precatalyst **39b** and TMEDA at room temperature (Table 5, entries 11-14). We found that an excellent yield (96%) and enantioselectivity (96% ee) could be obtained when employing CH_3CN as solvent (Table 5, entry 14). However, the dr (*cis:trans*) dropped down to 1:2.5. In order to improve the diastereoselectivity, several organic bases were tested again in CH_3CN and a better dr (3.5:1) was received using DIPEA as base (Table 5, entry 16). Furthermore, we noticed that toluene gave a better dr value than CH_3CN, even though with lower yield. So, we tried to mix the solvent of toluene and CH_3CN and examined the solvent ratio. Excitingly, when the solvent ratio of toluene and CH_3CN reached 1:2, excellent yield and ee, as well as good dr (7:1) were obtained (Table 5, entry 20). Based on the above results, we could conclude that the combination of precatalyst **39b** and DIPEA in a mixed solvent of toluene/CH_3CN (1:2) at room temperature proved to be the optimized conditions.

2.3.3 Determination of substrate scope of 2-alkenyl-benzothiazoles with α-chloroaldehydes

With the optimized conditions in hand, we initially emplified the scope of the model reaction to a 0.5 mmol scale (Table 6). Indeed, the reactivity and stereoselectivity were remained to be best without obvious loss (Table 6, **157a**). Subsequently, the variation on the benzo[*d*]thiazole moiety was examined. The electron-donating effect lowered the reaction reactivity and decreased yields of the desired products, even though good dr and excellent ee values were observed when 4-Me or 4-OMe groups as R^2 were used (Table 6, **157b** and **157c**). As for the benzo[*d*]thiazole with electron-withdrawing groups, such as 3-OMe, 4-Cl, 3-Cl or 4-F, the reactions underwent smoothly within 16 h and afforded the desired lactams in good to excellent yields, good diastereoselectivities and excellent enantioselectivities (Table 6, **157d-g**). Moreover, due to the electron-donating effect of the furan ring, the 2-furyl group as R^2 reduced the reactivity and produced only 68% of desired **157h** in 40 h (Table 6, **157h**). The tolerance of this reaction with the variation of R^1 on the benzothiazole motif **156** has been tested. A chloro substituent on R^1 produced the product **157i** in 97% yield and excellent steroselectivity (9:1 dr, 98% ee). Gratifyingly, benzo[*d*]oxazol substrate **156j** afforded the expected cycloaddition adduct **157j** in 97% yield, 4:1 dr and 95% ee.

In addition, the α-chloroaldehydes **108** with unbranched alkyl chains were also tolerated, affording to the corresponding adducts **157k** and **157l** in 44-71% yields and excellent steroselectivities.

Table 6 *Scope of 2-alkenyl-benzothiazoles with α-chloroaldehydes*



157	R^2	R^3	Yield (%)[b]	dr[c]	ee (%)[d]
a	Ph	Bn	93	7:1	96
b	4-MePh	Bn	74	9:1	96
c[e]	4-MeOPh	Bn	72	8:1	94
d	3-MeOPh	Bn	94	6:1	98
e	4-ClPh	Bn	84	6:1	97
f	3-ClPh	Bn	97	4:1	98
g	4-FPh	Bn	97	4:1	97
h[f]	2-furyl	Bn	68	6:1	92
i[g]	Ph	Bn	97	9:1	98
j[h]	Ph	Bn	97	4:1	95
k	Ph	n-Bu	71	8:1	98
l	Ph	n-Hex	44	5:1	96

[a] Reaction conditions: **156** (0.5 mmol), **108** (0.75 mmol), precatalyst **39b** (0.05 mmol), DIPEA (1.0 mmol), toluene/CH_3CN (V/V = 1:2, 5 mL in total), rt, under argon, 16 h, R^1 = H, X = S. [b] Yield of isolated product **157** as a mixture of diasteromers after column chromatography. [c] Determined by ^{1}H NMR spectroscopy. [d] The ee value was determined by HPLC on a chiral stationary phase. [e] Reaction time is 43 h. [f] Reaction time is 40 h. [g] R^1 = Cl, reaction time is 18 h. [h] X = O.

2.3.4 Determination of the absolute configuration and molecular constitution

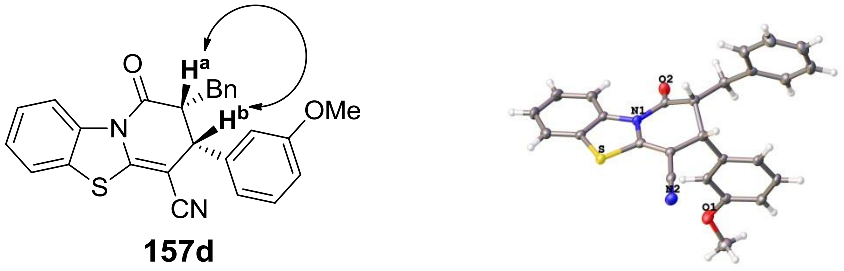
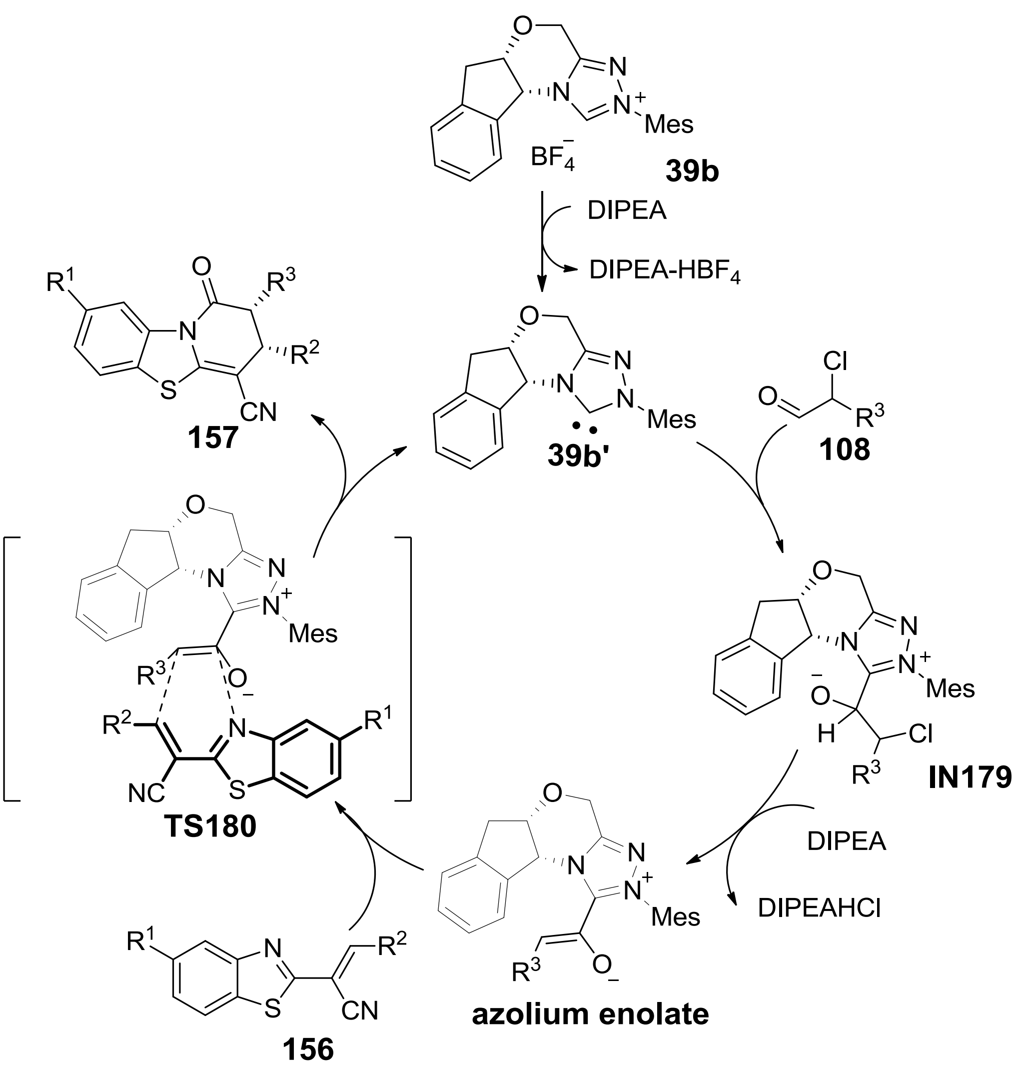


***Figure 6** The relative (NOE) and absolute configuration of **157d**.*

The relative configuration of the major diasteromer **157** was determined by NOE measurements for compound **157d**. It is obvious that H^a and H^b are in a *cis* relationship, which is in accordance with the absolute configuration of compound **157d** assigned by X-ray crystal-structure analysis (Figure 6).

2.3.5 Proposed mechanism of 2-Alkenyl-Benzothiazoles with α-Chloroaldehydes

A plausible catalytic cycle explaining the *cis*-configuration of the major diastereomer is illustrated in Scheme 50. Initially, the nucleophilic addition of the free carbene **39b'** to the α-chloroaldehyde **108** generates the zwitterionic species **IN179**, followed by the elimination of hydrogen chloride to form the enolate species. The chiral backbone of the NHC blocked the *Si*-face of the azolium enolate, so it forces the subsequent aza-DA reaction on its *Re*-face with the (*E*)-2-styrylbenzo[*d*]thiazole **156** *via* the favored *endo* transition state **TS180**. Subsequent acylation constructs the final product **157** and liberates the NHC catalyst for further cycles.

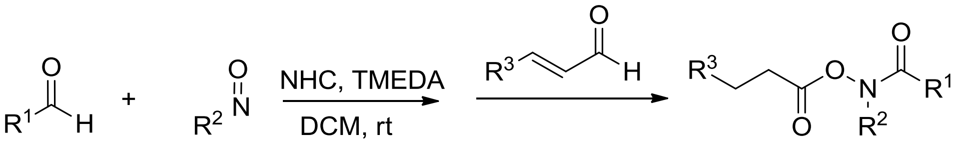


Scheme 50 *Plausible catalytic cycle.*

3. Research Summary and Outlook

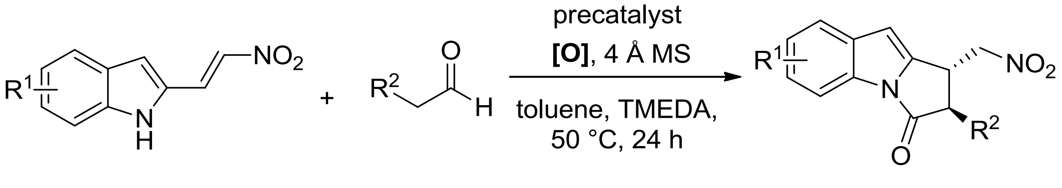
The aim of this thesis was to develop efficient and enantioselective NHC-catalyzed reactions. The three kinds of NHC-mediated nucleophilic intermediates, the acyl anion, the homoenolate and the azolium enolate were all employed in my three projects.

3.1 NHC-catalyzed one-pot synthesis of hydroxamic esters



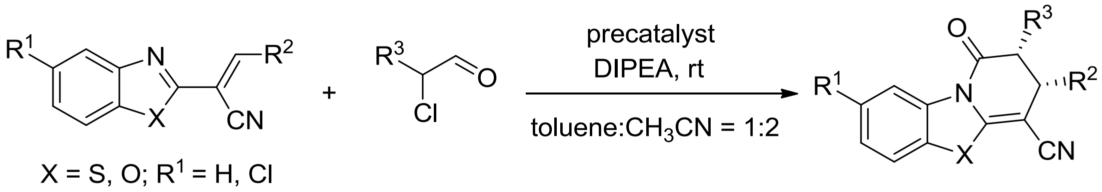
In this work, a novel NHC-catalyzed one-pot reaction of nitrosobenzenes, aldehydes and enals for the synthesis of hydroxamic esters was developed. This one-pot reaction involved two steps under the same conditions and in the presence of a single precatalyst. First the aza-benzoin-type condensation of nitrosobenzenes with aldehydes *via* the Breslow intermediate occured. Subsequently, the resulting N-arylhydroxamic acids reacted with enals through protonation of the homoenolate intermediate under the same conditions without addition of any other reagents. This protocol tolerated a broad range of aliphatic and aromatic substrates and afforded the desired hydroxamic esters, which are known to exhibit potential anti-inflammatory and anti-cancer activities.

3.2 NHC-catalyzed [2+3]-annulation of nitrovinylindoles with aliphatic aldehydes



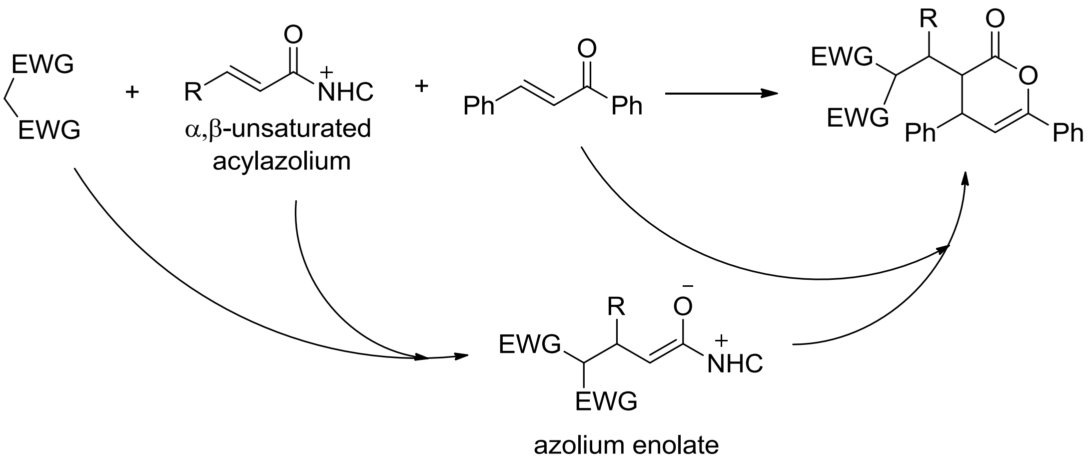
Inspired by our previous report in the NHC-catalyzed [2+3]-annulation *via* azolium enolates from α-chloroaldehydes, the alternative generation of enolates from aliphatic aldehydes was investigated. In this work we conducted an asymmetric NHC-catalyzed [2+3] annulation reaction of nitrovinylindoles with aliphatic aldehydes in the presence of an oxidant *via* a Michael/lactamization sequence. Various *trans*-disubstituted pyrroloindolones could be obtained in acceptable yields with excellent stereoselectivities.

3.3 Asymmetric NHC-catalyzed annulation of 2-alkenyl-benzothiazoles with α-chloroaldehydes



This project presented an efficient NHC-catalyzed asymmetric inverse-electron-demand aza-Diels–Alder reaction of (*E*)-2-styrylbenzo[*d*]thiazoles with α-chloroaldehydes, affording the *cis*-dihydrobenzothiazolopyridin-1-ones in good to excellent yields, good dr and excellent ee values. This [2+4]-annulation protocol tolerated a wide range of substrates leading to medicinally interesting tricyclic dihydrobenzothiazolopyridins. In addition, an explanation for the *cis*-configuration was given.

Asymmetric NHC-organocatalysis is a powerful and versatile tool for the formation of various carbon-carbon bonds. Over the past decades, we have witnessed the significant progress on the application of NHC-derived acyl anion, homoenolate, azolium enolate intermediates, as well as the electrophilic α,β-unsaturated acylazoliums. For example, various annulations, activation of stable carboxylic esters, even activation of stable carboxylic acids were all realized. There is still room for improvement with NHC-organocatalysis, such as the multicomponent domino reaction (Scheme 51) or in combination with metal catalysis.



Scheme 51 *Proposed NHC-catalyzed three-component domino reaction.*

4. Experimental Part

General Information on the Preparative Work

General Information

All reactions were carried out under argon using standard Schlenk techniques and PTFE-coated magnetic stirrers.

All solvents were distilled, purified and dried according to standard procedures prior to use. Absolute THF pre-dried over basic alumina and distillation, followed by further distillation over sodium-lead (Solvona®) alloy/benzophenone under argon. Toluene and mestylene were distilled over sodium-lead (Solvona®) alloy/benzophenone under argon. Absolute CH_2Cl_2 and $CHCl_3$ were distilled over calcium hydride under argon. Absolute CH_3CN was distilled over calcium oxide under argon.

Reaction Control

All reactions were monitored by thin layer chromatography using pre-coated aluminum sheets silica TLC plates with fluorescent indicator UV_{254} from MACHERY-NAGEL. Visualization of the developed TLC plates was performed either with ultraviolet irradiation (λ = 254 nm) or by staining with potassium permanganate, following by heating with a heat gun.

Flash Column Chromatography

Chromatographic purification of the products was performed on Merck -Schuchardt silica gel 60 as the stationary phase, particle size range 0.040-0.063 mm (230-240 mesh, flash). Varying diameters and lengths glass columns were used for different purifications. During the flash, generally low air over-pressure was used to push the eluting solvent.

Commercially available reagents

All commercially available reagents purchased from Sigma-Aldrich, Acros, ABCR, Alfa Aesar, Apollo Chemicals, Carbolution, Fluorochem, Strem and TCI Europe, were used without further purification. Air or moisture sensitive compounds were kept under argon and stored in a freezer.

General Information on the Analytical Methods

Analytical HPLC

Apparatus: Hewlett-Packard 1050 Series or Agilent 1100 instrument with chiral stationary phases.

Column (chiral):	Chiralpak AD (10 µm) (250 mm x 4.6 mm)
	Chiralpak IA (5 µm) (250 mm x 4.6 mm)
	Chiralpak IC (5 µm) (150 mm x 4.6 mm)
	Chiralpak OD (10 µm) (250 mm x 4.6 mm)

Polarimetry (Optical Rotation)

Optical rotation values were measured on a Perkin-Elmer P241 polarimeter. Microanalyses were performed with a Vario EL element analyzer.

Melting points

Melting points were determined using a Büchi 510 apparatus and were uncorrected. The units were reported in °C.

IR Spectroscopy

IR spectra were taken on a Perkin-Elmer FT-IR Spectrum 100 using a Diamant/KRS5 ATR. Evaluation was done using the supplementary software. The absorption bands are given in wave numbers (cm^{-1}).

NMR spectroscopy

^{1}H- spectra were recorded at ambient temperature on Varian Gemini 300 (300 MHz), Mercury 300 (300 MHz), Varian Inova 400 (400 MHz) or Varian Innova 600 (600 MHz) instruments. ^{13}C- spectra were recorded at ambient temperature on Varian Inova 400 (100 MHz) or Varian Innova 600 (150 MHz) instruments. The chemical shifts are reported in ppm downfield of tetramethylsilane (TMS) and referenced to residual solvent peaks resonance as internal standard. The order of citation in parentheses is [a] multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, td = triplet of doublet, m = multiplet), [b] coupling constants, [c] number of protons, and [d] assignment. Coupling constants (*J*) are reported in Hertz (Hz).

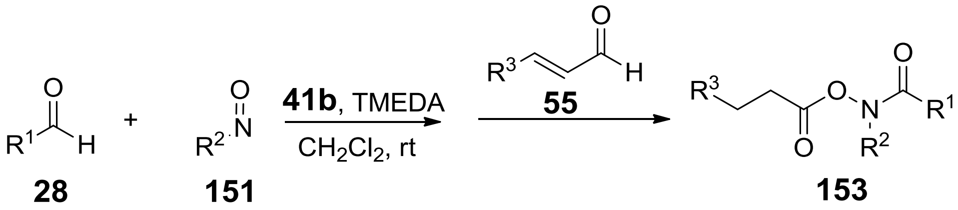
Mass Spectrometry

Mass spectra and high resolution mass spectra were acquired on a Finnigan MAT 95 (EI/CI) or on a ThermoFisher Scientific LTQOrbitrap XL (ESI). The results are given by presenting the mass of the fragments (m/z) as a proportion of intensity compared to the base peak (100%) in percentage. Only signals presenting high intensity (>10%) or characteristic signals (generally M^+, $[M+H]^+$, $[M+Na]^+$, $[M+K]^+$ or $[M-H]^-$) are reported.

Elemental Analysis

Microanalyses were performed with a Vario EL element analyzer.

General Procedure and Analytical Data of Synthesized Compounds for Project 1



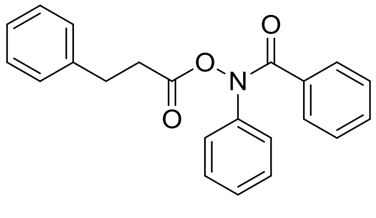
General Procedure 1 (GP1)

Base (0.1 mmol) was added under argon to the solution of nitroso compound **151** (0.5 mmol), aldehyde **28** (0.5 mmol), and triazolium salt **41b** (0.05 mmol) in DCM (5 mL). The mixture was stirred at room temperature for 15-40 min. Then enal **55** (1.0 mmol) was added under argon to the resulted mixture which was stirred for additional 20 min - 3.5 h. The product was isolated by chromatography on a short silica gel column.

For **153v**, TMEDA (0.1 mmol) was added to the solution of nitrosobenzene **151a** (0.5 mmol), cinnamaldehyde **55a** (1.5 mmol), triazolium salt **41b** (0.05 mmol) in DCM (5 mL) at rt under argon. The mixture was stirred for 30 min. The product was isolated by chromatography on a short silica gel column.

Analytical Data of Synthesized Compounds

N-Phenyl-1-phenylformamido 3-phenylpropanoate (153a)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 150.2 mg, 87%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

Melting point: 75.5-76.0 °C.

IR (ATR): 3842, 3647, 3347, 3023, 2933, 2689, 2485, 2276, 2158, 2062, 1943, 1741, 1678, 1593, 1489, 1450, 1348, 1218, 1087, 991, 908, 764, 694 cm^{-1}.

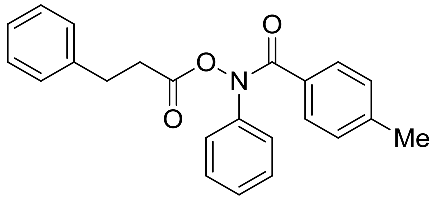
^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.53 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.36 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.29-7.19 (m, 10H, Ar-*H*), 7.15 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 2.98 (t, *J* = 7.8 Hz, 2H, ArC*H*$_2$), 2.76 (t, *J* = 7.8 Hz, 2H, C*H*$_2$CO) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 170.1 (CH$_2$*C*O), 166.8 (*C*OAr), 140.5 (Ar-*C*), 139.6 (Ar-*C*), 133.3 (Ar-*C*), 131.1 (Ar-*C*), 129.1 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.3 (Ar-*C*), 128.2 (2C, Ar-*C*), 128.1 (2C, Ar-*C*), 126.7 (Ar-*C*), 126.5 (2C, Ar-*C*), 33.3 (*C*H$_2$CO), 30.5 (Ar*C*H$_2$) ppm.

MS (EI, 70 eV): m/z (%) = 344.9 (51) [M$^+$], 213.7 (21), 196.9 (27), 104.6 (100), 91.6 (19), 77.7 (26).

Elemental Analysis: calcd. for $C_{22}H_{19}NO_3$ (345.14) C, 76.50; H, 5.54; N, 4.06 found: C, 76.55; H, 5.60; N, 3.97.

N-Phenyl-1-(4-methylphenyl)formamido 3-phenylpropanoate (153b)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 10:1). The product was obtained as a light yellow solid.

Yield: 158.8 mg, 88%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

Melting point: 65.5-66.0 °C.

IR (ATR): 3849, 3339, 3032, 2928, 2673, 2325, 2103, 1891, 1784, 1674, 1603, 1491, 1451, 1336, 1187, 1089, 1033, 914, 829, 743, 695 cm^{-1}.

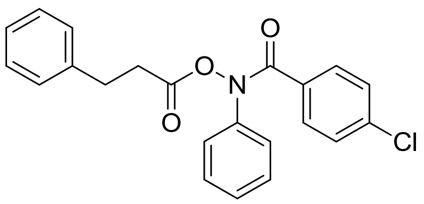
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.30-7.16 (m, 10H, Ar-*H*), 7.06 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 3.00 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.78 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.31(s, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (CH_2*C*O), 166.9 (*C*OAr), 141.6 (Ar-*C*), 140.8 (Ar-*C*), 139.6 (Ar-*C*), 130.3 (Ar-*C*), 129.1 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 128. 8 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.3 (2C, Ar-*C*), 128.2 (Ar-*C*), 126.7 (Ar-*C*), 126.5 (2C, Ar-*C*), 33.4 (*C*H_2CO), 30.6 (Ar*C*H_2), 21.5 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 359.3 (18) [M^+], 210.8 (100), 119.4 (56), 91.5 (26).

Elemental Analysis: calcd. for $C_{23}H_{21}NO_3$ (359.15) C, 76.86; H, 5.89; N, 3.90 found: C, 76.58; H, 5.65; N, 4.16.

N-Phenyl-1-(4-chlorophenyl)formamido 3-phenylpropanoate (153c)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 145.3 mg, 77%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 76.5-77.0 °C.

IR (ATR): 3842, 3339, 3086, 3030, 2943, 2693, 2322, 2193, 2106, 1971, 1773, 1675, 1590, 1488, 1403, 1352, 1282, 1166, 1091, 1032, 983, 907, 836, 746, 694 cm^{-1}.

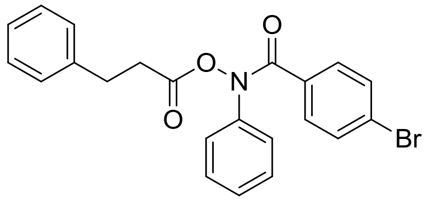
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.46 (td, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 2H, Ar-*H*), 7.32-7.19 (m, 10H, Ar-*H*), 7.15 (d, *J* = 6.6 Hz, 2H, Ar-*H*), 2.99 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.77 (t, *J* = 7.8 Hz, 2H, CH_2CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0 (CH_2*C*O), 165.7 (*C*OAr), 140.2 (Ar-*C*), 139.5 (Ar-*C*), 137.3 (Ar-*C*), 131.6 (Ar-*C*), 130.2 (2C, Ar-*C*), 129.3 (2C, Ar-*C*), 128.59 (2C, Ar-*C*), 128.57 (Ar-*C*), 128.4 (2C, Ar-*C*), 128.2 (2C, Ar-*C*), 126.8 (Ar-*C*), 126.5 (2C, Ar-*C*), 33.3 (*C*H_2CO), 30.5 (Ar*C*H_2) ppm.

MS (EI, 70 eV): m/z (%) = 379.1 (3) [M^+], 139.1 (100), 111.1 (27), 105.6 (36), 104.5 (51), 91.2 (34), 77.6 (15).

Elemental Analysis: calcd. for $C_{22}H_{18}ClNO_3$ (379.10) C, 69.57; H, 4.78; N, 3.69 found: C, 69.72; H, 4.79; N, 3.62.

N-Phenyl-1-(4-bromophenyl)formamido 3-phenylpropanoate (153d)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 161.8 mg, 76%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 88.0-89.0 °C.

IR (ATR): 3843, 3637, 3450, 3347, 3067, 3020, 2956, 2700, 2075, 1940, 1779, 1679, 1586, 1486, 1332, 1257, 1077, 1012, 906, 824, 779, 737, 696 cm^{-1}.

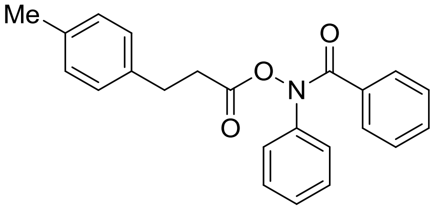
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.40-7.37 (m, 4H, Ar-*H*), 7.31-7.19 (m, 8H, Ar-*H*), 7.15 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 2.99 (t, *J* = 7.8 Hz, 2H, $ArCH_2$), 2.77 (t, *J* = 7.8 Hz, 2H, CH_2CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0 (CH_2CO), 165.8 (*C*OAr), 140.2 (Ar-*C*), 139.5 (Ar-*C*), 132.1 (Ar-*C*), 131.4 (2C, Ar-*C*), 130.4 (2C, Ar-*C*), 129.3 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.2 (2C, Ar-*C*), 126.8 (2C, Ar-*C*), 126.5 (2C, Ar-*C*), 125.8 (Ar-*C*), 33.3 (CH_2CO), 30.5 ($ArCH_2$) ppm.

MS (EI, 70 eV): m/z (%) = 423.5 (14) [M^+], 291.6 (14), 274.6 (32), 183.5 (100), 155.5 (16), 133.2 (11), 104.7 (47), 91.6 (15), 77.7 (17).

Elemental Analysis: calcd. for $C_{22}H_{18}BrNO_3$ (423.05) C, 62.28; H, 4.28; N, 3.30 found: C, 62.01; H, 4.35; N, 3.17.

N-Phenyl-1-phenylformamido 3-(4-methylphenyl)propanoate (153e)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a light yellow solid.

Yield: 159.7 mg, 89%.

TLC: $R_f = 0.4$ (*n*-pentane: Et_2O = 2:1).

Melting point: 66.0-67.5 °C.

IR (ATR): 3337, 3056, 2919, 2649, 2320, 2168, 2084, 1904, 1771, 1673, 1591, 1490, 1448, 1338, 1250, 1178, 1082, 1022, 906, 782, 696 cm^{-1}.

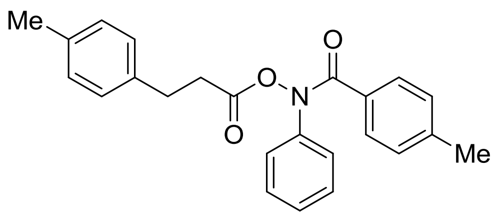
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 6.6 Hz, 2H, Ar-*H*), 7.37 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.29-7.23 (m, 7H, Ar-*H*), 7.07 (q, *J* = 8.4 Hz, 4H, Ar-*H*), 2.95 (t, *J* = 7.8 Hz, 2H, ArC*H*$_2$), 2.75 (t, *J* = 7.8 Hz, 2H, C*H*$_2$CO), 2.32 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.2 (CH$_2$*C*O), 166.9 (*C*OAr), 140.5 (Ar-*C*), 136.5 (Ar-*C*), 136.0 (Ar-*C*), 133.3 (Ar-*C*), 131.1 (2C, Ar-*C*), 129.3 (2C, Ar-*C*), 129.1 (2C, Ar-*C*), 128.8 (Ar-*C*), 128.3 (2C, Ar-*C*), 128.13 (2C, Ar-*C*), 128.11 (Ar-*C*), 126.7 (2C, Ar-*C*), 33.5 (*C*H$_2$CO), 30.1 (Ar*C*H$_2$), 21.0 (*C*H$_3$) ppm.

MS (EI, 70 eV): m/z (%) = 358.8 (6) [M^+], 196.1 (100), 105.6 (77), 91.6 (25), 77.6 (23).

HRMS (ESI): calcd for $C_{23}H_{21}NO_3$ $[M+H]^+$: 360.1594; found: 360.1583.

N-Phenyl-1-(4-methylphenyl)formamido 3-(4-methylphenyl)propanoate (153f)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a light yellow solid.

Yield: 164.1 mg, 88%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

Melting point: 78.5-79.5 °C.

IR (ATR): 3844, 3320, 3028, 2923, 2732, 2310, 2163, 2109, 1978, 1904, 1779, 1665, 1607, 1490, 1441, 1335, 1262, 1181, 1081, 983, 906, 817, 774, 737, 696 cm^{-1}.

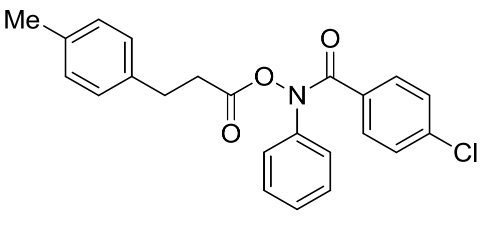
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.29-7.22 (m, 5H, Ar-*H*), 7.08-7.04 (m, 6H, Ar-*H*), 2.95 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.74 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.312 (s, 3H, COPhCH_3), 2.307 (s, 3H, CH_3PhCH$_2$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.2 (CH$_2$*C*O), 166.9 (*C*OAr), 141.5 (Ar-*C*), 140.8 (Ar-*C*), 136.6 (Ar-*C*), 135.9 (2C, Ar-*C*), 130.3 (Ar-*C*), 129.2 (2C, Ar-*C*), 129.1 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.1 (2C, Ar-*C*), 126.7 (2C, Ar-*C*), 33.5 (*C*H$_2$CO), 30.2 (Ar*C*H$_2$), 21.5 (COPh*C*H$_3$), 21.0 (*C*H$_3$PhCH$_2$) ppm.

MS (EI, 70 eV): m/z (%) = 372.8 (7) [M^+], 210.7 (65), 118.6 (100), 104.6 (13), 91.6 (21).

Elemental Analysis: calcd. for $C_{24}H_{23}NO_3$ (373.17) C, 77.19; H, 6.21; N, 3.75 found: C, 77.19; H, 6.06; N, 3.57.

N-Phenyl-1-(4-chlorophenyl)formamido 3-(4-methylphenyl)propanoate (153g)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a light yellow solid.

Yield: 159.3 mg, 81%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 75.5-77.0 °C.

IR (ATR): 3837, 3352, 3061, 2920, 2667, 2317, 2158, 2088, 1898, 1776, 1676, 1590, 1487, 1437, 1333, 1266, 1080, 1016, 988, 907, 816, 740, 689 cm^{-1}.

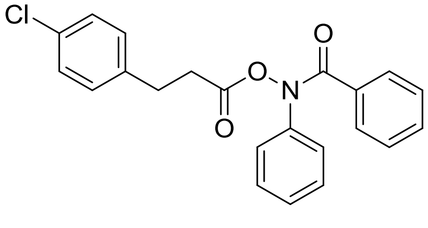
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.31-7.22 (m, 7H, Ar-*H*), 7.05 (dd, J_1 = 18.6 Hz, J_2 = 7.8 Hz, 4H, Ar-*H*), 2.95 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.74 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.31 (s, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (CH_2*C*O), 165.8 (*C*OAr), 140.2 (Ar-*C*), 137.3 (Ar-*C*), 136.4 (Ar-*C*), 136.0 (2C, Ar-*C*), 131.6 (2C, Ar-*C*), 130.2 (2C, Ar-*C*), 129.3 (2C, Ar-*C*), 128.5 (2C, Ar-*C*), 128.4 (2C, Ar-*C*), 128.1 (2C, Ar-*C*), 126.7 (Ar-*C*), 33.4 (*C*H_2CO), 30.1 (Ar*C*H_2), 21.0 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 393.8 (6) [M^+], 247.6 (12), 231.8 (100), 147.7 (15), 138.6 (88), 105.6 (26), 91.6 (16).

Elemental Analysis: calcd. for $C_{23}H_{20}ClNO_3$ (393.11) C, 70.14; H, 5.12; N, 3.56 found: C, 69.06; H, 5.19; N, 3.38.

N-Phenyl-1-phenylformamido 3-(4-chlorophenyl)propanoate (153h)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 155.4 mg, 82%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 91.0-92.5 °C.

IR (ATR): 3846, 3333, 3057, 2931, 2688, 2473, 2314, 2100, 1904, 1765, 1670, 1589, 1488, 1345, 1263, 1169, 1084, 908, 817, 693 cm^{-1}.

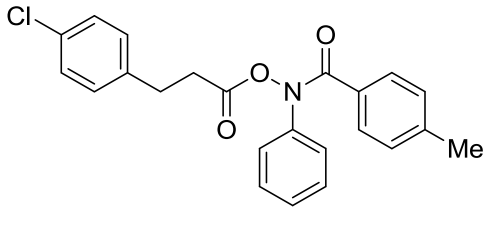
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51-7.50 (m, 2H, Ar-*H*), 7.37-7.35 (m, 1H, Ar-*H*), 7.29-7.23 (m, 5H, Ar-*H*), 7.20 (d, *J* = 8.4 Hz, 4H, Ar-*H*), 7.07 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 2.95 (t, *J* = 7.8 Hz, 2H, ArC*H*$_2$), 2.74 (t, *J* = 7.8 Hz, 2H, C*H*$_2$CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8 (CH_2*C*O), 166.8 (*C*OAr), 140.4 (Ar-*C*), 137.9 (Ar-*C*), 133.1 (Ar-*C*), 132.3 (Ar-*C*), 131.1 (Ar-*C*), 129.6 (2C, Ar-*C*), 129.1 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.4 (Ar-*C*), 128.1 (2C, Ar-*C*), 126.8 (2C, Ar-*C*), 33.2 (*C*H_2CO), 29.9 (Ar*C*H_2) ppm.

MS (EI, 70 eV): m/z (%) = 378.8 (100) [M^+], 213.0 (47), 196.8 (87), 167.5 (17), 139.6 (13), 105.1 (14).

Elemental Analysis: calcd. for $C_{22}H_{18}ClNO_3$ (379.10) C, 69.57; H, 4.78; N, 3.69 found: C, 69.24; H, 4.62; N, 3.53.

N-Phenyl-1-(4-methylphenyl)formamido 3-(4-chlorophenyl)propanoate (153i)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 157.7 mg, 80%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 107.0-108.0 °C.

IR (ATR): 3845, 3321, 3034, 2932, 2681, 2317, 2106, 1986, 1906, 1773, 1666, 1607, 1489, 1447, 1342, 1261, 1173, 1086, 1017, 980, 910, 822, 781, 736, 697 cm^{-1}.

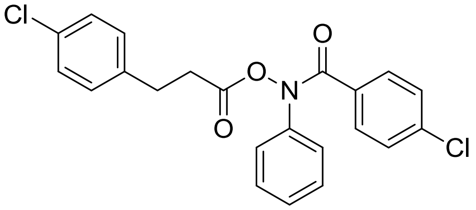
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41-7.39 (m, 2H, Ar-*H*), 7.29-7.23 (m, 3H, Ar-*H*), 7.21-7.18 (m, 4H, Ar-*H*), 7.08 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.05 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 2.96 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.75 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.30 (s, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.9 (CH_2*C*O), 166.8 (*C*OAr), 141.6 (Ar-*C*), 140.8 (Ar-*C*), 138.0 (Ar-*C*), 132.2 (Ar-*C*), 130.1 (Ar-*C*), 129.7 (2C, Ar-*C*), 129.1 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.3 (Ar-*C*), 126.8 (2C, Ar-*C*), 33.2 (*C*H_2CO), 29.9 (Ar*C*H_2), 21.4 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 393.4 (47) [M^+], 210.3 (68), 119.6 (100).

Elemental Analysis: calcd. for $C_{23}H_{20}ClNO_3$ (393.11) C, 70.14; H, 5.12; N, 3.56 found: C, 70.41; H, 4.98; N, 3.43.

N-Phenyl-1-(4-chlorophenyl)formamido 3-(4-chlorophenyl)propanoate (153j)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 128.1 mg, 62%.

TLC: $R_f = 0.4$ (*n*-pentane: Et_2O = 2:1).

Melting point: 112.0-113.5 °C.

IR (ATR): 3845, 3341, 3067, 2928, 2691, 2303, 2051, 1983, 1906, 1777, 1677, 1589, 1486, 1401, 1337, 1259, 1081, 1014, 909, 823, 738, 690 cm^{-1}.

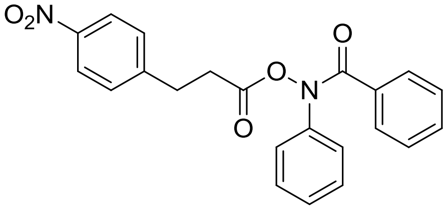
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.4 Hz 2H, Ar-*H*), 7.31-7.27 (m, 3H, Ar-*H*), 7.24-7.18 (m, 6H, Ar-*H*), 7.07 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 2.96 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.75 (t, *J* = 7.8 Hz, 2H, CH_2CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8 (CH_2*C*O), 165.7 (*C*OAr), 140.2 (Ar-*C*), 137.8 (Ar-*C*), 137.4 (2C, Ar-*C*), 132.3 (Ar-*C*), 131.5 (Ar-*C*), 130.2 (2C, Ar-*C*), 129.6 (2C, Ar-*C*), 129.3 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.4 (2C, Ar-*C*), 126.9 (2C, Ar-*C*), 33.1 (*C*H_2CO), 29.9 (Ar*C*H_2) ppm.

MS (EI, 70 eV): m/z (%) = 413.0 (21) [M^+], 247.5 (30), 230.8 (72), 139.7 (100).

Elemental Analysis: calcd. for $C_{22}H_{17}Cl_2NO_3$ (413.06) C, 63.78; H, 4.14; N, 3.38 found: C, 63.92; H, 4.07; N, 3.24.

N-Phenyl-1-phenylformamido 3-(4-nitrophenyl)propanoate (153k)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as colourless oil.

Yield: 154.3 mg, 79%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

IR (ATR): 3069, 2983, 2454, 2302, 1960, 1785, 1674, 1597, 1513, 1448, 1339, 1185, 1089, 1029, 917, 851, 697 cm^{-1}.

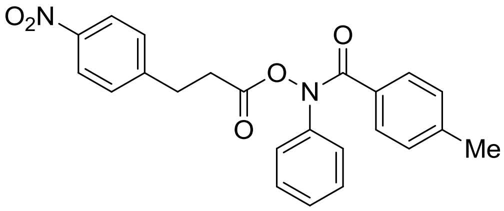
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.49-7.47 (m, 2H, Ar-*H*), 7.34 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.31 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.28-7.20 (m, 7H, Ar-*H*), 3.09 (t, *J* = 7.2 Hz, 2H, ArCH_2), 2.82 (t, *J* = 7.2 Hz, 2H, CH_2CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5 (CH_2*C*O), 166.7 (*C*OAr), 147.1 (Ar-*C*), 146.7 (Ar-*C*), 140.4 (Ar-*C*), 133.0 (Ar-*C*), 131.2 (2C, Ar-*C*), 129.2 (4C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.6 (Ar-*C*, Ar-*C*), 128.1 (2C, Ar-*C*), 127.1 (Ar-*C*), 123.8 (2C, Ar-*C*), 32.6 (*C*H_2CO), 30.3 (Ar*C*H_2) ppm.

MS (EI, 70 eV): m/z (%) = 390.0 (12) [M^+], 196.9 (15), 105.2 (100), 91.5 (12), 77.0 (16).

HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_5$ $[M+Na]^+$: 413.1108; found: 413.1096.

N-Phenyl-1-(4-methylphenyl)formamido 3-(4-nitrophenyl)propanoate (153l)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a light yellow solid.

Yield: 149.8 mg, 74%.

TLC: $R_f = 0.3$ (*n*-pentane: Et_2O = 2:1).

Melting point: 90.0-91.5 °C.

IR (ATR): 3557, 3073, 2877, 2452, 2302, 2094, 1925, 1782, 1661, 1601, 1505, 1329, 1092, 1031, 916, 840, 739, 690 cm^{-1}.

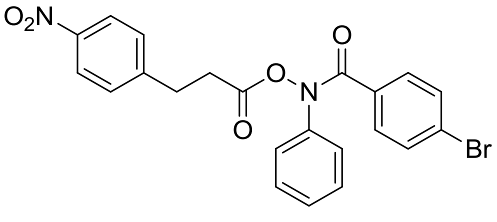
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.38 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.31 (d, J = 9.0 Hz, 2H, Ar-*H*), 7.27-7.19 (m, 5H, Ar-*H*), 7.03 (d, J = 7.8 Hz, 2H, Ar-*H*), 3.10 (t, J = 7.8 Hz, 2H, ArCH_2), 2.82 (t, J = 7.8 Hz, 2H, CH_2CO), 2.28 (s, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5 (CH_2*C*O), 166.7 (*C*OAr), 147.2 (Ar-*C*), 146.7 (Ar-*C*), 141.8 (Ar-*C*), 140.7 (Ar-*C*), 129.9 (Ar-*C*), 129.22 (2C, Ar-*C*), 129.20 (2C, Ar-*C*), 129.0 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.5 (2C, Ar-*C*), 127.1 (Ar-*C*), 123.8 (2C, Ar-*C*), 32.6 (*C*H_2CO), 30.3 (Ar*C*H_2), 21.4 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 403.5 (11) [M^+], 359.4 (16), 211.0 (100).

HRMS (ESI): calcd. for $C_{23}H_{20}N_2O_5$ $[M+H]^+$: 405.1445; found: 405.1429.

N-Phenyl-1-(4-bromophenyl)formamido 3-(4-nitrophenyl)propanoate (153m)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a light yellow solid.

Yield: 163.1 mg, 70%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 96.5-98.0 ^{o}C.

IR (ATR): 3332, 3077, 2934, 2856, 2644, 2299, 2089, 1923, 1786, 1671, 1591, 1500, 1329, 1178, 1088, 1010, 916, 841, 738, 687 cm^{-1}.

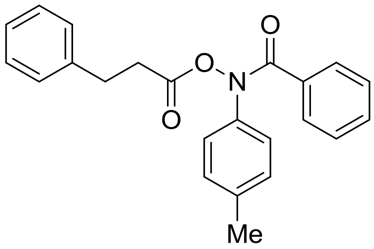
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.39-7.34 (m, 4H, Ar-*H*), 7.31 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.29-7.27(m, 3H, Ar-*H*), 7.20-7.19 (m, 2H, Ar-*H*), 3.10 (t, *J* = 7.8 Hz, 2H, ArC*H*$_2$), 2.82 (t, *J* = 7.8 Hz, 2H, C*H*$_2$CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4 (CH_2*C*O), 165.6 (*C*OAr), 147.0 (Ar-*C*), 146.7 (Ar-*C*), 140.1 (Ar-*C*), 131.8 (Ar-*C*), 131.4 (2C, Ar-*C*), 130.4 (2C, Ar-*C*), 129.4 (2C, Ar-*C*), 129.2 (2C, Ar-*C*), 129.0 (Ar-*C*), 127.2 (2C, Ar-*C*), 125.9 (Ar-*C*), 123.8 (2C, Ar-*C*), 32.5 (*C*H_2CO), 30.3 (Ar*C*H_2) ppm.

MS (EI, 70 eV): m/z (%) = 468.9 (13) [M^+], 287.4 (20), 275.7 (100), 183.8 (59).

HRMS (ESI): calcd for $C_{22}H_{17}BrN_2O_5$ $[M+K]^+$: 506.9952; found: 506.9945.

N-(4-Mthylphenyl)-1-phenylformamido 3-phenylpropanoate (153n)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as light yellow oil.

Yield: 101.8 mg, 57%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

IR (ATR): 3479, 3344, 3033, 2927, 2311, 1964, 1903, 1785, 1678, 1597, 1506, 1449, 1341, 1188, 1093, 1032, 990, 913, 822, 785, 704, 594, 557, 507 cm^{-1}.

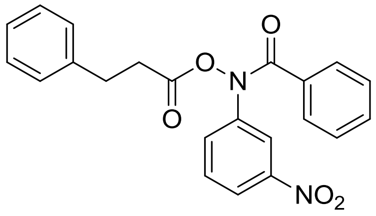
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.36 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.28-7.25 (m, 4H, Ar-*H*), 7.21 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.17-7.11 (m, 4H, Ar-*H*), 7.08 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 2.99 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.76 (t, *J* = 7.8 Hz, 2H, CH_2CO), 2.31 (s, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (CH_2*C*O), 166.9 (*C*OAr), 139.7 (Ar-*C*), 138.7 (Ar-*C*), 138.0 (Ar-*C*), 133.4 (Ar-*C*), 131.0 (Ar-*C*), 129.8 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.2 (2C, Ar-*C*), 128.1 (2C, Ar-*C*), 127.1 (Ar-*C*), 126.4 (2C, Ar-*C*), 33.4 (*C*H_2CO), 30.6 (Ar*C*H_2), 21.2 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 359.5 (12) [M^+], 104.5 (100), 91.5 (17), 77.3 (74).

Elemental Analysis: calcd. for $C_{23}H_{21}NO_3$ (359.15) C, 76.86; H, 5.89; N, 3.90 found: C, 76.67; H, 5.91; N, 4.25.

N-(3-Nitrophenyl)-1-phenylformamido 3-phenylpropanoate (153o)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a light yellow solid.

Yield: 135.0 mg, 69%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

Melting point: 100.5-101.0 °C.

IR (ATR): 3563, 3078, 2934, 2328, 1781, 1688, 1549, 1519, 1333, 1270, 1188, 1077, 1016, 923, 856, 694 cm^{-1}.

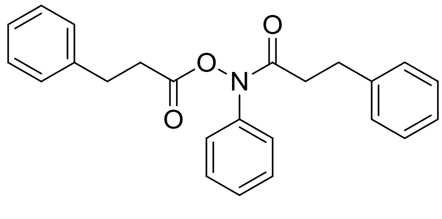
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.17 (s, 1H, Ar-*H*), 8.07-7.99 (m, 1H, Ar-*H*,) 7.59-7.55 (m, 3H, Ar-*H*), 7.49 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 7.35 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 7.24 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 7.19 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.10 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 2.88 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.70 (t, *J* = 7.8 Hz, 2H, CH_2CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (CH_2*C*O), 167.6 (*C*OAr), 148.4 (Ar-*C*), 141.2 (Ar-*C*), 139.1 (Ar-*C*), 132.7 (Ar-*C*), 131.7 (Ar-*C*), 130.3 (Ar-*C*), 129.8 (Ar-*C*), 128.6 (2C, Ar-*C*), 128.41 (2C, Ar-*C*), 128.39 (2C, Ar-*C*), 128.2 (2C, Ar-*C*), 126.6 (Ar-*C*), 122.0 (Ar-*C*), 119.2 (Ar-*C*), 33.1 (*C*H_2CO), 30.3 (Ar*C*H_2) ppm.

MS (EI, 70 eV): m/z (%) = 390.8 (5) [M^+], 241.8 (18), 130.7 (40), 104.6 (100), 91.4 (23), 77.7 (39).

HRMS (ESI): calcd. for $C_{22}H_{18}N_2O_5$ $[M+Na]^+$: 413.1108; found: 413.1095.

N-Phenyl-3-phenylpropylamido 3-phenylpropanoate (153p)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 154.0 mg, 83%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

Melting point: 59.0-60.0 ^{o}C.

IR (ATR): 3844, 3350, 3030, 2916, 2695, 2491, 2320, 2049, 1949, 1779, 1684, 1593, 1491, 1447, 1379, 1332, 1214, 1078, 983, 910, 778, 739, 695 cm^{-1}.

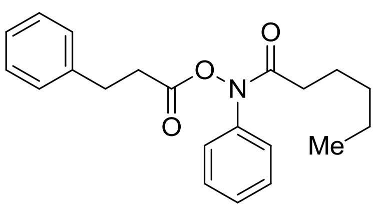
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.38-7.15 (m, 15H, Ar-*H*), 3.03-2.98 (m, 4H, 2×PhCH_2), 2.78 (t, *J* = 7.8 Hz, 2H, CH_2COO), 2.53 (t, *J* = 7.8 Hz, 2H, NCOCH_2) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (CH_2*C*OO), 167.7 (N*C*OCH_2), 140.6 (Ar-*C*), 139.5 (Ar-*C*), 139.1 (Ar-*C*), 129.5 (Ar-*C*), 128.6 (2C, Ar-*C*), 128.5 (4C, Ar-*C*), 128.5 (2C, Ar-*C*), 128.2 (2C, Ar-*C*), 126.5 (2C, Ar-*C*), 126.3 (2C, Ar-*C*), 35.4 (*C*H_2COO), 33.3 (NCO*C*H_2), 31.0 (Ph*C*$H_2$$CH_2$COO), 30.6 (NCO$CH_2$*C*$H_2$Ph) ppm.

MS (EI, 70 eV): m/z (%) = 374.4 (20) [M^+], 241.4 (100), 224.7 (16).

Elemental Analysis: calcd. for $C_{24}H_{23}NO_3$ (373.17) C, 77.19; H, 6.21; N, 3.75 found: C, 77.11; H, 6.12; N, 4.21.

N-Phenyl-1-hexylamido 3-phenylpropanoate (153q)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as a white solid.

Yield: 133.1 mg, 78%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

Melting point: 45.5-46.0 °C.

IR (ATR): 3842, 3358, 2935, 2865, 2671, 2483, 2318, 2194, 2107, 1979, 1775, 1684, 1593, 1489, 1451, 1376, 1313, 1230, 1190, 1090, 998, 917, 777, 736, 696 cm^{-1}.

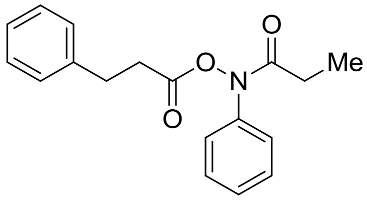
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.41 (s, 5H, Ar-*H*), 7.26-7.15 (m, 5H, Ar-*H*), 3.01 (t, *J* = 7.2 Hz, 2H, $NCOCH_2$), 2.77 (t, *J* = 7.8 Hz, 2H, $ArCH_2$) , 2.19 (t, *J* = 7.2 Hz, 2H, CH_2COO) , 1.66-1.61 (m, 2H, $NCOCH_2CH_2$) , 1.25-1.21 (m, 4H, $CH_2CH_2CH_3$) , 0.86 (t, *J* = 6.6 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (2C, CH_2COO and NCOCH$_2$), 139.6 (Ar-*C*), 139.3 (2C, Ar-*C*), 129.4 (Ar-*C*), 128.6 (2C, Ar-*C*), 128.2 (4C, Ar-*C*), 126.5 (2C, Ar-*C*), 33.3 (CH_2COO), 31.2 (2C, $PhCH_2$, $CH_2CH_2CH_3$), 30.6 ($NCOCH_2$), 24.5 ($NCOCH_2CH_2$), 22.3(CH_2CH_3), 13.9 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 340.0 (20) [M^+], 240.5 (100).

Elemental Analysis: calcd. for $C_{21}H_{25}NO_3$ (339.18) C, 74.31; H, 7.42; N, 4.13 found: C, 74.68; H, 7.69; N, 4.07.

N-Phenyl-1-propanylamido 3-phenylpropanoate (153r)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as colourless oil.

Yield: 124.6 mg, 84%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 2:1).

IR (ATR): 3553, 3030, 2982, 2937, 2345, 1958, 1788, 1692, 1595, 1492, 1454, 1371, 1286, 1209, 1087, 942, 850, 754, 698, 548, 498 cm^{-1}.

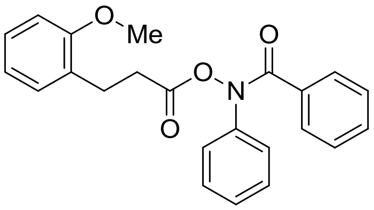
^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.41 (s, 5H, Ar-*H*), 7.25 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.20-7.15 (m, 3H, Ar-*H*), 3.01 (t, *J* = 7.8 Hz, 2H NCOC*H*$_2$), 2.77 (t, *J* = 7.8 Hz, 2H, ArC*H*$_2$), 2.20 (q, *J* = 7.2 Hz, 2H, C*H*$_2$COO), 1.11 (t, *J* = 7.2 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 170.1 (2C, CH$_2$*C*OO and N*C*OCH$_2$), 139.5 (Ar-*C*), 139.3 (Ar-*C*), 129.4 (Ar-*C*), 128.6 (4C, Ar-*C*), 128.2 (4C, Ar-*C*), 126.5 (Ar-*C*), 33.4(*C*H$_2$COO), 30.6 (NCO*C*H$_2$), 26.8(*C*H$_2$CH$_3$), 8.9 (*C*H$_3$) ppm.

MS (EI, 70 eV): m/z (%) = 297.1 (27) [M$^+$], 241.3 (100), 148.4 (54), 132.6 (19), 105.4 (37), 91.3 (38), 77.4 (13).

HRMS (ESI): calcd. for $C_{18}H_{19}NO_3$ [M+Na]$^+$: 320.1257; found: 320.1246.

N-Phenyl-1-phenylformamido 3-(2-methoxy)propanoate (153s)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 10:1). The product was obtained as lightyellow oil.

Yield: 141.1 mg, 75%.

TLC: R$_f$ = 0.3 (*n*-pentane: Et$_2$O = 2:1).

IR (ATR): 3061, 2918, 2844, 2169, 2047, 1785, 1675, 1593, 1490, 1454, 1340, 1244, 1085, 1030, 914, 844, 751, 698 cm^{-1}.

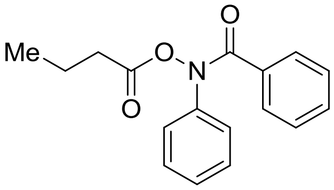
^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.54 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.37 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.28-7.19 (m, 7H, Ar-*H*), 7.09 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.84 (dd, J_1 = 13.8 Hz, J_2 = 7.8 Hz, 2H, Ar-*H*), 3.79 (s, 3H, OCH_3), 2.96 (t, *J* = 7.8 Hz, 2H, ArCH_2), 2.75 (t, *J* = 7.8 Hz, 2H, CH_2CO) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 170.6 (CH$_2$*C*O), 166.9 (*C*OAr), 157.4 (Ar-*C*), 140.5 (Ar-*C*), 135.5 (Ar-*C*), 131.0 (Ar-*C*), 130.0 (Ar-*C*), 129.1 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.2 (Ar-*C*), 128.1 (2C, Ar-*C*), 127.9 (2C, Ar-*C*), 126.6 (Ar-*C*), 120.5 (2C, Ar-*C*), 110.2 (Ar-*C*), 55.1 (O*C*H$_3$), 31.6 (*C*H$_2$CO), 25.9 (Ar*C*H$_2$) ppm.

MS (ESI, M+Na$^+$): 398.1.

HRMS (ESI): calcd. for $C_{23}H_{21}NO_4$ [M+Na]$^+$: 398.1363; found: 398.1361.

N-Phenyl-1-phenylformamido butanoate (153t)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 10:1). The product was obtained as colourless oil.

Yield: 114.2 mg, 81%.

TLC: R$_f$ = 0.4 (*n*-pentane: Et$_2$O = 2:1).

IR (ATR): 3840, 3341, 3063, 2964, 2878, 2671, 2323, 2100, 1785, 1675, 1592, 1489, 1452, 1340, 1127, 1065, 915, 849, 766, 698 cm^{-1}.

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.53-7.52 (m, 2H, Ar-*H*), 7.37-7.34 (m, 1H, Ar-*H*), 7.32-7.23 (m, 7H, Ar-*H*), 2.40 (t, *J* = 7.8 Hz, 2H, CH_2CO), 1.71-1.65 (m, 2H,

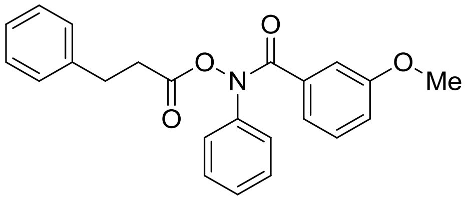
CH_3CH_2), 0.93 (t, *J* = 7.2 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.7 (CH_2*C*O), 166.9 (*C*OAr), 140.6 (Ar-*C*), 133.4 (Ar-*C*), 131.0 (2C, Ar-*C*), 129.1 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.2 (Ar-*C*), 128.1 (2C, Ar-*C*), 126.6 (Ar-*C*), 33.5 (*C*H_2CO), 18.2 (CH_3*C*H_2), 13.5 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 283.6 (99) [M$^+$], 213.0 (42), 196.7 (100), 105.7 (10).

HRMS(ESI): calcd. for $C_{17}H_{17}NO_3$ [M+K]$^+$: 322.0840; found: 322.0833.

N-Phenyl-1-(3-methoxyphenyl)formamido 3-phenylpropanoate (153u)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 10:1). The product was obtained as lightyellow oil.

Yield: 172.4 mg, 92%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 2:1).

IR (ATR): 3867, 3462, 3024, 2939, 2326, 2093, 1996, 1784, 1676, 1590, 1487, 1451, 1335, 1225, 1088, 1038, 950, 906, 825, 736, 694 cm^{-1}.

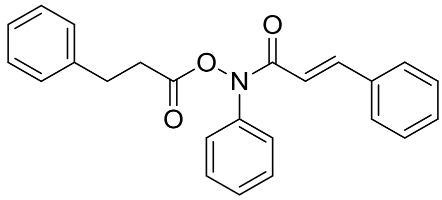
^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.30-7.25 (m, 7H, Ar-*H*), 7.20 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.17-7.13 (m, 3H, Ar-*H*), 7.09-7.06 (m, 2H, Ar-*H*), 6.91-6.89 (m, 1H, Ar-*H*), 3.71 (s, 3H, OC*H*$_3$), 3.00 (t, *J* = 7.8 Hz, 2H ArC*H*$_2$), 2.77 (t, *J* = 7.8 Hz, 2H, C*H*$_2$CO) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.1 (CH_2*C*O), 166.5 (*C*OAr), 159.2 (Ar-*C*), 140.5 (Ar-*C*), 139.6 (Ar-*C*), 134.4 (Ar-*C*), 129.2 (2C, Ar-*C*), 129.1 (Ar-*C*), 128.6 (2C, Ar-*C*), 128.3 (Ar-*C*), 128.2 (2C, Ar-*C*), 126.7 (Ar-*C*), 126.5 (2C, Ar-*C*), 121.2 (Ar-*C*), 117.6 (Ar-*C*), 113.6 (Ar-*C*), 55.3 (O*C*H$_3$), 33.3 (*C*H$_2$CO), 30.5 (Ar*C*H$_2$) ppm.

MS (ESI, M+Na$^+$): 398.1.

HRMS (ESI): calcd. for $C_{23}H_{21}NO_4$ [M+Na]$^+$: 398.1363; found: 398.1361.

N-Phenyl-N-((3-phenylpropanoyl)oxy)cinnamamide (153v)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 10:1). The product was obtained as colourless oil.

Yield: 147.8 mg, 80%.

TLC: R$_f$ = 0.4 (*n*-pentane: Et$_2$O = 2:1).

IR (ATR): 3561, 3042, 2932, 2622, 2081, 1956, 1787, 1671, 1623, 1489, 1350, 1199, 1080, 989, 909, 850, 752, 691 cm^{-1}.

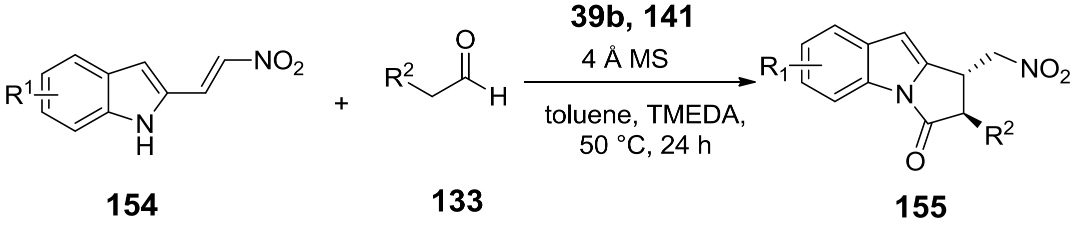
^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.81 (d, *J* = 15.6 Hz, 1H, Ar-*H*), 7.45-7.17 (m, 15H, Ar-*H* and PhC*H*), 6.43 (d, *J* = 15.6 Hz, 1H, COC*H*), 3.05 (t, *J* = 8.0 Hz, 2H, ArC*H*$_2$), 2.84 (t, *J* = 8.0 Hz, 2H, C*H*$_2$CO) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ = 170.1 (CH$_2$*C*O), 162.7 (*C*OAr), 144.0 (Ph*C*H), 139.6 (Ar-*C*), 139.1 (Ar-*C*), 134.6 (Ar-*C*), 130.1 (Ar-*C*), 129.5 (2C, Ar-*C*), 129.2 (Ar-*C*), 128.8 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.3 (2C, Ar-*C*), 128.1 (2C, Ar-*C*), 127.5 (Ar-*C*), 126.5 (2C, Ar-*C*), 116.3 (CO*C*H), 33.4 (*C*H$_2$CO), 30.6 (Ar*C*H$_2$) ppm.

MS (EI, 70 eV): m/z (%) = 370.9 (100) [M$^+$], 239.3 (19), 222.7 (94), 131.7 (85), 103.7 (22).

HRMS (ESI): calcd. for $C_{24}H_{21}NO_3$ [M+Na]$^+$: 394.1414; found: 394.1403.

General Procedure and Analytical Data of Synthesized Compounds for Project 2

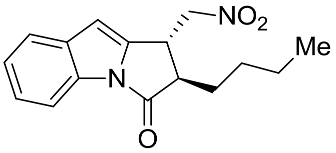


General Procedure 2 (GP2)

Base (0.22 mmol) was added under argon to the solution of (E)-2-(2-Nitrovinyl)-1H-indoles (0.2 mmol), aldehydes (1.0 mmol), oxidants (0.2 mmol), triazolium salt **39b** (0.02 mmol), and molecular sieve 4Å (100 mg) in toluene (2 mL). The mixture was stirred at 50 ℃ for until completion (monitored by TLC). After purification by column chromatography on silica gel the desired products were obtained as yellow syrup.

Analytical Data of Synthesized Compounds

(1*S*,2*R*)-2-Butyl-1-(nitromethyl)-1H-pyrrolo[1,2-a]indol-3(2H)-one (155a)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 5:1). The product was obtained as yellow syrup.

Yield: 34.8 mg, 61%.

TLC: $R_f = 0.5$ (*n*-pentane: Et_2O = 1:1).

Optical rotation: $[\alpha]_D^{21} = +19.4$ (c = 0.77, $CHCl_3$).

dr: >20:1.

ee: 96%.

Anal. chiral HPLC: Daicel AD, *n*-heptane:*i*-propanol = 9:1, 0.7 mL/min, t_R = 13.46 min (minor), 14.67 min (major).

IR (ATR): 3455, 3058, 2930, 2864, 2320, 2090, 1992, 1911, 1734, 1553, 1451, 1375, 1314, 1172, 1101, 1024, 937, 905, 809, 750, 672 cm^{-1}.

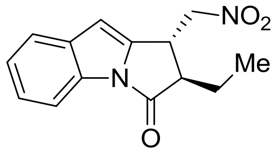
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 7.6 Hz, 1H, Ar-*H*), 7.53-7.51 (m, 1H, Ar-*H*), 7.34-7.26 (m, 2H, Ar-*H*), 6.37 (s, 1H, Ar-*H*), 4.68-4.60 (m, 2H, CH_2NO_2), 3.96-3.91 (m, 1H, $CHCH_2NO_2$), 2.98-2.94 (m, 1H, $CHHC_3H_7$), 2.03-1.94 (m, 1H, CHC_4H_9), 1.88-1.78 (m, 1H, $CHHC_3H_7$), 1.47-1.33 (m, 4H, $C_2H_4CH_3$), 0.92 (t, J = 5.4 Hz, 3H, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (*C*O), 140.1 (Ar-*C*), 134.7 (Ar-*C*), 130.4 (Ar-*C*), 124.5 (Ar-*C*), 124.4 (Ar-*C*), 121.2 (Ar-*C*), 113.9 (Ar-*C*), 102.3 (Ar-*C*), 77.4 (CH_2NO_2), 50.8 (CHC_4H_9), 37.1 ($CHCH_2NO_2$), 31.0 ($CH_2C_3H_7$), 28.4 ($CH_2C_2H_5$), 22.6 (CH_2CH_3), 13.8 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 286.2 (100) [M^+], 239.2 (46), 183.1 (68).

HRMS (ESI): calcd. for $C_{16}H_{18}N_2O_3$ $[M+Na]^+$: 309.1210; found: 309.1213.

(1*S*,2*R*)-2-Ethyl-1-(nitromethyl)-1H-pyrrolo[1,2-a]indol-3(2H)-one (155b)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 5:1). The product was obtained as yellow syrup.

Yield: 29.6 mg, 57%.

TLC: $R_f = 0.5$ (*n*-pentane: Et_2O = 1:1).

Optical rotation: $[\alpha]_D^{21} = +48.8$ ($c = 0.99$, $CHCl_3$).

dr: >20:1.

ee: 98%.

Anal. chiral HPLC: Daicel OD, *n*-heptane:EtOH = 7:3, 1.0 mL/min, $t_R = 6.99$ min (minor), 9.04 min (major).

IR (ATR): 3455, 3058, 2965, 2877, 2744, 2322, 2097, 1909, 1733, 1552, 1450, 1375, 1313, 1217, 1172, 1101, 1031, 966, 929, 872, 810, 750, 670 cm^{-1}.

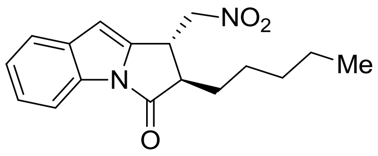
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.06 (d, J = 8.4 Hz, 1H, Ar-*H*), 7.53 (d, J = 7.2 Hz, 1H, Ar-*H*), 7.34-7.29 (m, 2H, Ar-*H*), 6.38 (s, 1H, Ar-*H*), 4.69-4.62 (m, 2H, CH_2NO_2), 3.96-3.94 (m, 1H, $CHCH_2NO_2$), 2.96-2.93 (m, 1H, $CHHCH_3$), 2.06-1.99 (m, 1H), 1.96-1.89 (m, 1H, $CHHCH_3$), 1.07 (t, J = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.1 (*C*O), 140.1 (Ar-*C*), 134.7 (Ar-*C*), 130.4 (Ar-*C*), 124.5 (Ar-*C*), 124.4 (Ar-*C*), 121.2 (Ar-*C*), 113.9 (Ar-*C*), 102.3 (Ar-*C*), 77.4 (CH_2NO_2), 52.0 (C_2H_5CH), 36.5 ($CHCH_2NO_2$), 24.2 (CH_2CH_3), 10.6 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 258.1 (93) [M^+], 211.1 (95), 183.1 (100), 168.1 (20), 154.1 (15), 115.1 (11).

HRMS (ESI): calcd. for $C_{16}H_{18}N_2O_3$ $[M+Na]^+$: 281.0897; found: 281.0897.

(1*S*,2*R*)-1-(Nitromethyl)-2-pentyl-1H-pyrrolo[1,2-a]indol-3(2H)-one (155e)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 5:1). The product was obtained as yellow syrup.

Yield: 19.7 mg, 31%.

TLC: $R_f = 0.5$ (*n*-pentane: Et_2O = 1:1).

Optical rotation: $[\alpha]_D^{21} = +30.6$ ($c = 0.83$, $CHCl_3$).

dr: >20:1.

ee: 97%.

Anal. chiral HPLC: Daicel IA, *n*-heptane:EtOH = 7:3, 0.7 mL/min, t_R = 9.76 min (major), 13.01 min (minor).

IR (ATR): 3454, 3058, 2928, 2861, 2324, 2102, 2014, 1909, 1735, 1553, 1451, 1374, 1315, 1173, 1102, 1029, 943, 851, 808, 749, 670 cm^{-1}.

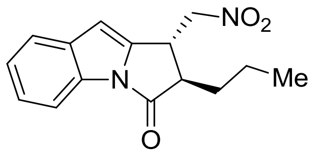
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.06 (d, J = 7.8 Hz, 1H, Ar-*H*), 7.55-7.50 (m, 1H, Ar-*H*), 7.34-7.28 (m, 2H, Ar-*H*), 6.38 (s, 1H, Ar-*H*), 4.68-4.62 (m, 2H, CH_2NO_2), 3.96-3.93 (m, 1H, $CHCH_2NO_2$), 2.98-2.96 (m, 1H, $CHHC_4H_9$), 2.01-1.95 (m, 1H, CHC_5H_{11}), 1.86-1.80 (m, 1H, $CHHC_4H_9$), 1.50-1.40 (m, 2H, $CH_2C_3H_7$), 1.37-1.30 (m, 4H, $C_2H_4CH_3$), 0.89 (t, J = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 171.3 (*C*O), 140.1 (Ar-*C*), 134.7 (Ar-*C*), 130.4 (Ar-*C*), 124.5 (Ar-*C*), 124.4 (Ar-*C*), 121.2 (Ar-*C*), 113.9 (Ar-*C*), 102.3 (Ar-*C*), 77.4 (CH_2NO_2), 50.8 (CHC_5H_{11}), 37.1 ($CHCH_2NO_2$), 31.6 ($CH_2C_4H_9$), 31.2 ($CH_2C_3H_7$), 26.0 ($CH_2C_2H_5$), 22.4 (CH_2CH_3), 14.0 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 300.3 (48) [M$^+$], 253.3 (48), 183.1 (100), 154.1 (18).

HRMS (ESI): calcd for $C_{17}H_{20}N_2O_3$ [M+Na]$^+$: 323.1366; found: 323.1366.

(1*S*,2*R*)-1-(Nitromethyl)-2-propyl-1H-pyrrolo[1,2-a]indol-3(2H)-one (155d)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 5:1). The product was obtained as yellow syrup.

Yield: 21.1 mg, 39%.

TLC: R_f = 0.5 (*n*-pentane: Et$_2$O = 1:1).

Optical rotation: $[\alpha]_D^{21}$ = +27.1 (*c* = 0.97, CHCl$_3$).

dr: >20:1.

ee: 96%.

Anal. chiral HPLC: Daicel AD, *n*-heptane:EtOH = 7:3, 1.0 mL/min, t_R = 7.74 min (major), 10.02 min (minor).

IR (ATR): 3455, 3056, 2955, 2871, 2740, 2323, 2101, 1997, 1908, 1735, 1553, 1449, 1373, 1172, 1104, 1010, 946, 868, 807, 751, 670 cm^{-1}.

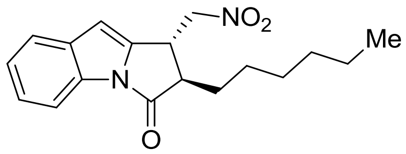
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.06 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.53 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.34-7.27 (m, 2H, Ar-*H*), 6.38 (s, 1H, Ar-*H*), 4.68-4.62 (m, 2H, CH_2NO_2), 3.95-3.92 (m, 1H, $CHCH_2NO_2$), 2.99-2.96 (m, 1H, $CHHC_2H_5$), 2.00-1.94 (m, 1H, CHC_3H_7), 1.85-1.79 (m, 1H, $CHHC_2H_5$), 1.53-1.46 (m, 2H, CH_2CH_3), 0.99 (t, *J* = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 171.3 (*C*O), 140.1 (Ar-*C*), 134.7 (Ar-*C*), 130.4 (Ar-*C*), 124.5 (Ar-*C*), 124.4 (Ar-*C*), 121.2 (Ar-*C*), 113.9 (Ar-*C*), 102.3 (Ar-*C*), 77.4 (CH_2NO_2), 50.7 (CHC_3H_7), 37.2 ($CHCH_2NO_2$), 33.4 ($CH_2C_2H_5$), 19.7 (CH_2CH_3), 13.9 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 272.2 (100) [M$^+$], 225.2 (37), 183.1 (83).

HRMS (ESI): calcd for $C_{15}H_{16}N_2O_3$ [M+Na]$^+$: 295.1053; found: 295.1054.

(1*S*,2*R*)-2-Hexyl-1-(nitromethyl)-1H-pyrrolo[1,2-a]indol-3(2H)-one (155e)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 5:1). The product was obtained as yellow syrup.

Yield: 30.5 mg, 49%.

TLC: R_f = 0.5 (*n*-pentane: Et$_2$O = 1:1).

Optical rotation: $[\alpha]_D^{21}$ = +19.7 (*c* = 0.96, CHCl$_3$).

dr: >20:1.

ee: 96%.

Anal. chiral HPLC: Daicel OD, *n*-heptane:*i*-propanol = 7:3, 1.0 mL/min, t_R = 7.98 min (minor), 13.44 min (major).

IR (ATR): 3457, 3059, 2926, 2859, 2662, 2331, 2100, 1993, 1917, 1736, 1553, 1451, 1374, 1315, 1172, 1102, 939, 887, 809, 749, 672 cm^{-1}.

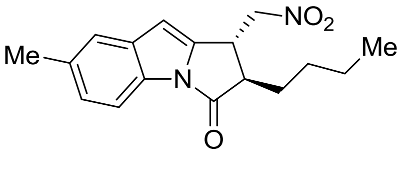
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.52-7.50 (m, 1H, Ar-*H*), 7.34-7.26 (m, 2H, Ar-*H*), 6.36 (s, 1H, Ar-*H*), 4.67-4.59 (m, 2H, CH_2NO_2), 3.95-3.90 (m, 1H, $CHCH_2NO_2$), 2.97-2.93 (m, 1H, $CHHC_5H_{11}$), 2.02-1.93 (m, 1H, CHC_6H_{13}), 1.87-1.77 (m, 1H, $CHHC_5H_{11}$), 1.49-1.24 (m, 8H, $C_4H_8CH_3$), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3 (*C*O), 140.1 (Ar-*C*), 134.7 (Ar-*C*), 130.4 (Ar-*C*), 124.5 (Ar-*C*), 124.4 (Ar-*C*), 121.2 (Ar-*C*), 113.9 (Ar-*C*), 102.3 (Ar-*C*), 77.4 (CH_2NO_2), 50.8 (CHC_6H_{13}), 37.1 ($CHCH_2NO_2$), 31.5 ($CH_2C_5H_{11}$), 31.3 ($CH_2C_4H_9$), 29.1 ($CH_2C_3H_7$), 26.3 ($CH_2C_2H_5$), 22.5 (CH_2CH_3), 14.0 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 314.2 (100) [M^+], 267.2 (54), 183.1 (68).

HRMS (ESI): calcd for $C_{18}H_{22}N_2O_3$ $[M+Na]^+$: 337.1523; found: 337.1529.

(1*S*,2*R*)-2-Butyl-7-methyl-1-(nitromethyl)-1H-pyrrolo[1,2-a]indol-3(2H)-one (155f)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 5:1). The product was obtained as yellow syrup.

Yield: 26.5 mg, 44%.

TLC: $R_f = 0.5$ (*n*-pentane: Et_2O = 1:1).

Optical rotation: $[\alpha]_D^{21} = +17.5$ (c = 0.75, $CHCl_3$).

dr: >20:1.

ee: 97%.

Anal. chiral HPLC: Daicel IA, *n*-heptane:EtOH = 7:3, 0.7 mL/min, t_R = 11.45 min (major), 16.41 min (minor).

IR (ATR): 3453, 2928, 2864, 2736, 2320, 2091, 1909, 1733, 1553, 1466, 1362, 1315, 1290, 1238, 1168, 1119, 1029, 976, 932, 877, 809, 743, 697, 661 cm^{-1}.

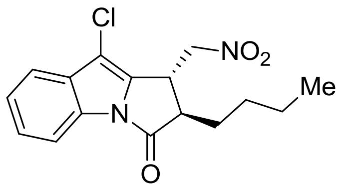
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.30 (s, 1H, Ar-*H*), 7.13 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.28 (s, 1H, Ar-*H*), 4.67-4.58 (m, 2H, $C\mathit{H}_2NO_2$), 3.93-3.88 (m, 1H, $C\mathit{H}CH_2NO_2$), 2.95-2.91 (m, 1H, $CH\mathit{H}C_3H_7$), 2.43 (s, 3H, $ArC\mathit{H}_3$), 2.01-1.93 (m, 1H, $C\mathit{H}C_4H_9$), 1.86-1.77 (m, 1H, $C\mathit{H}HC_3H_7$), 1.46-1.32 (m, 4H, $C_2\mathit{H}_4CH_3$), 0.91 (t, *J* = 6.8 Hz, 3H, $CH_2C\mathit{H}_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (*C*O), 140.2 (Ar-*C*), 134.9 (Ar-*C*), 134.3 (Ar-*C*), 128.6 (Ar-*C*), 125.7 (Ar-*C*), 121.1 (Ar-*C*), 113.5 (Ar-*C*), 102.1 (Ar-*C*), 77.5 ($\mathit{C}H_2NO_2$), 50.8 ($\mathit{C}HC_4H_9$), 37.1 ($\mathit{C}HCH_2NO_2$), 31.0 ($\mathit{C}H_2C_3H_7$), 28.4 ($\mathit{C}H_2C_2H_5$), 22.6 ($\mathit{C}H_2CH_3$), 21.6 ($Ar\mathit{C}H_3$), 13.8 ($CH_2\mathit{C}H_3$) ppm.

MS (EI, 70 eV): m/z (%) = 300.2 (97) [M^+], 253.2 (48), 197.1 (100).

HRMS (ESI): calcd for $C_{17}H_{20}N_2O_3$ $[M+Na]^+$: 323.1366; found: 323.1366.

(1*S*,2*R*)-2-Butyl-9-chloro-1-(nitromethyl)-1H-pyrrolo[1,2-a]indol-3(2H)-one (155g)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 5:1). The product was obtained as yellow syrup.

Yield: 24.1 mg, 38%.

TLC: $R_f = 0.4$ (*n*-pentane: Et_2O = 1:1).

Optical rotation: $[\alpha]_D^{21} = -21.1$ (c = 0.92, $CHCl_3$).

dr: >20:1.

ee: 97%.

Anal. chiral HPLC: Daicel AD, *n*-heptane:EtOH = 7:3, 1.0 mL/min, t_R = 5.03 min (major), 6.18 min (minor).

IR (ATR): 3465, 3060, 2929, 2865, 2663, 2320, 2104, 1991, 1911, 1741, 1605, 1554, 1448, 1363, 1310, 1232, 1173, 1112, 1037, 1000, 937, 902, 855, 750, 670 cm^{-1}.

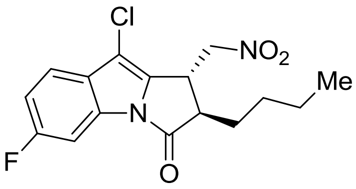
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08-8.04 (m, 1H, Ar-*H*), 7.58-7.54 (m, 1H, Ar-*H*), 7.42-7.37 (m, 2H, Ar-*H*), 5.01 (dd, J_1 = 13.2 Hz, J_2 = 4.2 Hz, 1H, $CHHNO_2$), 4.66 (dd, J_1 = 13.2 Hz, J_2 = 9.0 Hz, 1H $CHHNO_2$), 3.99-3.96 (m, 1H, $CHCH_2NO_2$), 3.18-3.15 (m, 1H, $CHHC_3H_7$), 1.98-1.93 (m, 1H, CHC_4H_9), 1.89-1.83 (m, 1H, $CHHC_3H_7$), 1.48-1.34 (m, 4H, $C_2H_4CH_3$), 0.92 (t, J = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0 (*C*O), 133.8 (Ar-*C*), 132.1 (Ar-*C*), 129.4 (Ar-*C*), 125.6 (Ar-*C*), 125.0 (Ar-*C*), 118.6 (Ar-*C*), 114.1 (Ar-*C*), 106.3 (Ar-*C*), 75.4 (CH_2NO_2), 51.6 (CHC_4H_9), 36.8 ($CHCH_2NO_2$), 31.1 ($CH_2C_3H_7$), 28.1 ($CH_2C_2H_5$), 22.5 (CH_2CH_3), 13.8 (CH_3) ppm.

MS (EI, 70 eV): m/z (%) = 320.2 (67) [M^+], 273.1 (46), 217.1 (100).

HRMS (ESI): calcd for $C_{16}H_{17}ClN_2O_3$ $[M+ Na]^+$: 343.0820; found: 343.0823.

(1*S*,2*R*)-2-Butyl-9-chloro-6-fluoro-1-(nitromethyl)-1H-pyrrolo[1,2-a]indol-3(2H)-one (155h)



The compound was prepared according to the ***GP2*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 5:1). The product was obtained as yellow syrup.

Yield: 22.4mg, 33%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 1:1).

Optical rotation: $[\alpha]_D^{21} = -17.2$ (*c* = 0.79, $CHCl_3$).

dr: >20:1.

ee: 96%.

Anal. chiral HPLC: Daicel AD, *n*-heptane:EtOH = 7:3, 0.7 mL/min, t_R = 6.85 min (major), 8.69 min (minor).

IR (ATR): 3841, 3388, 3096, 2931, 2865, 2728, 2327, 2102, 1997, 1921, 1745, 1617, 1555, 1484, 1443, 1363, 1249, 1189, 1114, 987, 934, 854, 809, 747, 684 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.76 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, Ar-*H*), 7.49

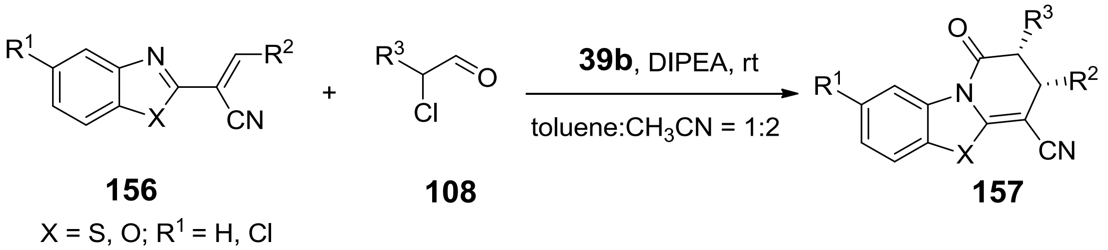
(dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H, Ar-*H*), 7.14 (td, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H, Ar-*H*), 4.98 (dd, J_1 = 13.2 Hz, J_2 = 4.2 Hz, 1H, CH*H*NO_2), 4.68 (dd, J_1 = 13.2 Hz, J_2 = 9.0 Hz, 1H, C*H*HNO_2), 3.97-3.94 (m, 1H, C*H*CH_2NO_2), 3.18-3.16 (m, 1H, CH*H*C_3H_7), 1.98-1.93 (m, 1H, C*H*C_4H_9), 1.88-1.82 (m, 1H, C*H*HC_3H_7), 1.46-1.33 (m, 4H, $C_2H_4CH_3$), 0.92 (t, *J* = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9 (*C*O), 161.3 (d, $J_{F\text{-}C}$ = 243.5 Hz, Ar-*C*), 134.0 (d, $J_{F\text{-}C}$ = 3.9 Hz, Ar-*C*), 129.3 (d, $J_{F\text{-}C}$ = 12.8 Hz, Ar-*C*), 128.4 (Ar-*C*), 119.7 (d, $J_{F\text{-}C}$ = 9.8 Hz, Ar-*C*), 113.5 (d, $J_{F\text{-}C}$ = 24.5 Hz, Ar-*C*), 106.1 (Ar-*C*), 101.5 (d, $J_{F\text{-}C}$ = 27.6 Hz, Ar-*C*), 75.3 (*C*H_2NO_2), 51.5 (*C*HC_4H_9), 36.8 (*C*HCH_2NO_2), 31.1 (*C*$H_2C_3H_7$), 28.1 (*C*$H_2C_2H_5$), 22.5 (*C*H_2CH_3), 13.8 (*C*H_3) ppm.

MS (EI, 70 eV): m/z (%) = 338.1 (63) [M^+], 291.1 (49), 235.1 (100).

HRMS (ESI): calcd for $C_{16}H_{16}ClFN_2O_3$ $[M+Na]^+$: 361.0726; found: 361.0729.

General Procedure and Analytical Data of Synthesized Compounds for Project 3



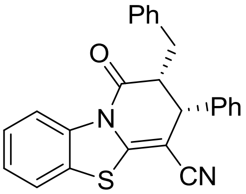
General Procedure 3 (GP3)

To a dried and argon-filled Schlenk flask was added (*E*)-2-styrylbenzo[*d*]thiazole (**156**) (0.5 mmol, 1.0 equiv.), α-chloroaldehyde (**108**) (0.75 mmol, 1.5 equiv.), triazolium salt **39b** (0.05 mmol, 10 mol%) and DIPEA (1.0 mmol, 2.0 equiv.) in 5 mL of a mixed solvent of toluene/CH_3CN (V/V = 1:2). The mixture was stirred at room temperature and monitored by TLC until completion of the reaction. After removal of the solvent under vacuum, the residue was purified by flash chromatography on silica gel

(n-pentane/Et_2O 15:1) to afford the products **157a-l** as colorless or light yellow solids.

Analytical Data of Synthesized Compounds

(2*R*,3*R*)-2-Benzyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157a)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (n-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 183.2 mg, 93%.

TLC: R_f = 0.4 (n-pentane: Et_2O = 5:1).

Melting point: 140-142 °C.

Optical rotation: $[\alpha]_D^{21} = -501.5$ (c = 1.0, $CHCl_3$).

dr: 7:1.

ee: 96%.

Anal. chiral HPLC: Daicel IC, n-heptane:EtOH = 9:1, 0.5 mL/min, t_R = 11.01 min (minor), 13.47 min (major).

IR (ATR): 3446, 3026, 2938, 2321, 2196, 2103, 1948, 1719, 1605, 1493, 1455, 1364, 1314, 1223, 1135, 1065, 1027, 983, 919, 849, 748, 697 cm^{-1}.

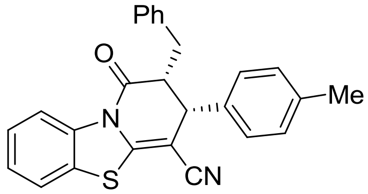
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.44 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.38-7.24 (m, 9H, Ar-*H*), 7.07 (d, *J* = 7.2 Hz, 4H, Ar-*H*), 3.66-3.63 (m, 1H, C*H*Ph), 3.55-3.52 (m, 1H, C*H*Bn), 3.46 (dd, J_1 = 14.4 Hz, J_2 = 4.2 Hz, 1H, CH*H*Ph), 2.49 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 169.3 (*C*O), 152.3 (S*C*CCN), 138.1 (Ar-*C*), 137.5 (Ar-*C*), 136.5 (Ar-*C*), 129.3 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.5 (Ar-*C*), 127.7 (2C, Ar-*C*), 127.1 (Ar-*C*), 126.8 (Ar-*C*), 126.0 (Ar-*C*), 123.8 (Ar-*C*), 121.9 (Ar-*C*), 117.9 (Ar-*C*), 117.3 (*C*N), 83.5 (*C*CN), 48.0 (*C*HPh), 43.1 (*C*HBn), 31.5 (*C*H$_2$Ph) ppm.

MS (ESI): [M+H]$^+$ = 395.1215.

HRMS (ESI): calcd for $C_{25}H_{18}N_2OS$ [M+Na]$^+$: 417.1032; found: 417.1030.

(2*R*,3*R*)-2-Benzyl-1-oxo-3-(p-tolyl)-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157b)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 15:1). The product was obtained as a colorless solid.

Yield: 151.8 mg, 74%.

TLC: R$_f$ = 0.4 (*n*-pentane: Et$_2$O = 5:1).

Melting point: 133-135 °C.

Optical rotation: $[\alpha]_D^{21}$ = –509.4 (*c* = 1.0, $CHCl_3$).

dr: 9:1.

ee: 96%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:*i*-propanol = 97:3, 1.0 mL/min, t_R = 16.05 min (minor), 27.22 min (major).

IR (ATR): 3441, 3024, 2928, 2324, 2196, 2100, 1978, 1718, 1606, 1508, 1456, 1364, 1313, 1223, 1134, 1029, 982, 934, 813, 748, 702 cm^{-1}.

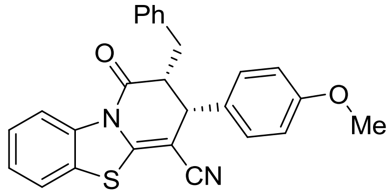
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.38-7.22 (m, 6H, Ar-*H*), 7.13 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.07 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 6.95 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 3.60 (d, *J* = 6.6 Hz, 1H, C*H*Ar), 3.52-3.48 (m, 1H, C*H*Bn), 3.44 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H, CH*H*Ph), 2.49 (dd, J_1 = 14.4 Hz, J_2 = 9.0 Hz, 1H, C*H*HPh), 2.34 (s, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4 (*C*O), 152.0 (S*C*CCN), 138.22 (Ar-*C*), 138.16 (Ar-*C*), 137.5 (Ar-*C*), 133.4 (Ar-*C*), 129.9 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 127.5 (2C, Ar-*C*), 127.1 (Ar-*C*), 126.8 (Ar-*C*), 125.9 (Ar-*C*), 123.8 (Ar-*C*), 121.8 (Ar-*C*), 117.9 (Ar-*C*), 117.3 (*C*N), 83.7 (*C*CN), 48.1 (*C*HAr), 42.7 (*C*HBn), 31.5 (CH_2Ph), 21.1 (CH_3) ppm.

MS (ESI): $[M+H]^+$ = 409.1373.

HRMS (ESI): calcd for $C_{26}H_{20}N_2OS$ $[M+Na]^+$: 431.1189; found: 431.1188.

(2*R*,3*R*)-2-Benzyl-3-(4-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo [3,2-a]pyridine-4-carbonitrile (157c)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 152.0 mg, 72%.

TLC: $R_f = 0.3$ (*n*-pentane: Et_2O = 5:1).

Melting point: 96-98 °C.

Optical rotation: $[\alpha]_D^{21} = -500.9$ (c = 2.89, $CHCl_3$).

dr: 8:1.

ee: 94%.

Anal. chiral HPLC: Daicel AD, *n*-heptane:EtOH = 7:3, 0.5 mL/min, t_R = 18.94 min (minor), 25.78 min (major).

IR (ATR): 3455, 3017, 2956, 2841, 2631, 2321, 2195, 2102, 2063, 2008, 1908, 1727, 1605, 1509, 1455, 1366, 1224, 1132, 1029, 930, 826, 747, 701 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, J = 8.4 Hz, 1H, Ar-*H*), 7.41-7.22 (m, 6H, Ar-*H*), 7.08 (d, J = 7.2 Hz, 2H, Ar-*H*), 6.98 (d, J = 8.4 Hz, 2H, Ar-*H*), 6.86 (d, J = 8.4 Hz, 2H, Ar-*H*), 3.80 (s, 3H, OCH_3), 3.59 (d, J = 7.2 Hz, 1H, C*H*Ar), 3.52-3.49 (m, 1H, C*H*Bn), 3.44 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H, CH*H*Ph), 2.49 (dd, J_1 = 15.0 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

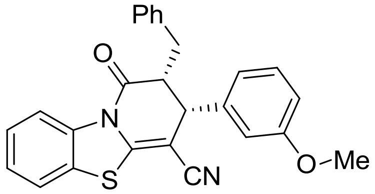
^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.4 (*C*O), 159.6 (S*C*CCN), 151.8 (Ar-*C*), 138.1

(Ar-*C*), 137.4 (Ar-*C*), 128.9 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.4 (Ar-*C*), 127.1 (Ar-*C*), 126.8 (Ar-*C*), 126.0 (Ar-*C*), 123.8 (Ar-*C*), 121.9 (Ar-*C*), 118.0 (Ar-*C*), 117.2 (*C*N), 114.6 (2C, Ar-*C*), 83.9 (*C*CN), 55.3 (OCH_3), 48.2 (*C*HAr), 42.4 (*C*HBn), 31.5 (CH_2Ph) ppm.

MS (ESI): $[M+H]^+$ = 425.1315.

HRMS (ESI): calcd for $C_{26}H_{20}N_2O_2S$ $[M+Na]^+$: 447.1138; found: 447.1137.

(2*R*,3*R*)-2-Benzyl-3-(3-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157d)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a light yellow solid.

Yield: 200.6 mg, 94%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 5:1).

Melting point: 134-135 °C.

Optical rotation: $[\alpha]_D^{21}$ = –491.0 (*c* = 1.0, $CHCl_3$).

dr: 6:1.

ee: 98%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:*i*-propanol = 9:1, 1.0 mL/min, t_R = 11.62

min (minor), 14.60 min (major).

IR (ATR): 3425, 3023, 2937, 2839, 2641, 2322, 2195, 2088, 1989, 1922, 1715, 1599, 1454, 1312, 1255, 1140, 1039, 932, 862, 748, 702 cm^{-1}.

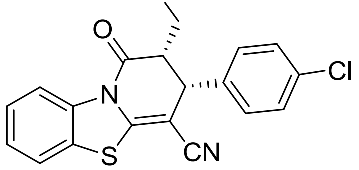
^{1}H NMR (600 MHz, CDCl$_3$): δ = 8.43 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.42-7.19 (m, 7H, Ar-*H*), 7.08 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 6.86 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H, Ar-*H*), 6.67 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.57 (s, 1H, Ar-*H*), 3.76 (s, 3H, OC*H*$_3$), 3.59 (d, *J* = 7.2 Hz, 1H, C*H*Ar), 3.53-3.45 (m, 2H, C*H*Bn and CH*H*Ph), 2.51 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (150 MHz, CDCl$_3$): δ = 169.3 (*C*O), 160.0 (S*C*CCN), 152.3 (Ar-*C*), 138.1 (Ar-*C*), 137.9 (Ar-*C*), 137.4 (Ar-*C*), 130.4 (Ar-*C*), 128.9 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 127.1 (Ar-*C*), 126.8 (Ar-*C*), 126.0 (Ar-*C*), 123.7 (Ar-*C*), 121.8 (Ar-*C*), 119.6 (Ar-*C*), 117.9 (Ar-*C*), 117.3 (*C*N), 113.9 (Ar-*C*), 113.4 (Ar-*C*), 83.3 (*C*CN), 55.2 (O*C*H$_3$), 48.0 (*C*HAr), 43.1 (*C*HBn), 31.5 (*C*H$_2$Ph) ppm.

MS (ESI): [M-H]$^-$ = 423.1194.

Elemental Analysis: calcd. for $C_{26}H_{20}N_2O_2S$ (424.12) C, 73.56; H, 4.75; N, 6.60 found: C, 73.15; H, 5.00; N, 6.35.

(2*R*,3*R*)-2-Benzyl-3-(4-chlorophenyl)-1-oxo-2,3-dihydro-1H-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157e)



The compound was prepared according to the ***GP1*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 10:1). The product was obtained as a colorless solid.

Yield: 180.3 mg, 84%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 5:1).

Melting point: 97-98 °C.

Optical rotation: $[\alpha]_D^{21}$ = –596.0 (*c* = 1.0, $CHCl_3$).

dr: 6:1.

ee: 97%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 0.7 mL/min, t_R = 13.11 min (minor), 17.74 min (major).

IR (ATR): 3450, 3025, 2937, 2639, 2323, 2195, 2104, 1985, 1905, 1721, 1605, 1491, 1458, 1365, 1318, 1222, 1134, 1094, 1015, 934, 825, 747, 701 cm^{-1}.

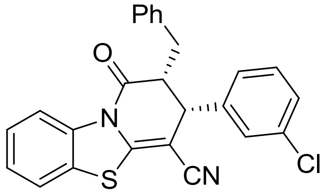
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.43-7.22 (m, 8H, Ar-*H*), 7.05 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 6.98 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 3.61 (d, *J* = 7.2 Hz, 1H, C*H*Ar), 3.56-3.52 (m, 1H, C*H*Bn), 3.46 (dd, J_1 = 14.4 Hz, J_2 = 4.8 Hz, 1H, CH*H*Ph), 2.44 (dd, J_1 = 15.0 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.0 (*C*O), 152.6 (S*C*CCN), 137.6 (Ar-*C*), 137.3 (Ar-*C*), 134.9 (Ar-*C*), 134.4 (Ar-*C*), 129.5 (2C, Ar-*C*), 129.0 (2C, Ar-*C*), 128.80 (2C, Ar-*C*), 128.79 (2C, Ar-*C*), 127.2 (Ar-*C*), 127.0 (Ar-*C*), 126.1 (Ar-*C*), 123.7 (Ar-*C*), 121.9 (Ar-*C*), 117.7 (Ar-*C*), 117.3 (*C*N), 82.8 (*C*CN), 47.7 (*C*HAr), 42.4 (*C*HBn), 31.5 (CH_2Ph) ppm.

MS (ESI): $[M+H]^+$ = 429.0825.

HRMS (ESI): calcd for $C_{25}H_{17}ClN_2OS$ $[M+H]^+$: 429.0823; found: 429.0823.

(2*R*,3*R*)-2-Benzyl-3-(3-chlorophenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157f)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 208.9 mg, 97%.

TLC: $R_f = 0.3$ (*n*-pentane: Et_2O = 5:1).

Melting point: 85-86 °C.

Optical rotation: $[\alpha]_D^{21} = -506.3$ ($c = 1.0$, $CHCl_3$).

dr: 4:1.

ee: 98%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 1.0 mL/min, t_R = 9.42 min (minor), 13.16 min (major).

IR (ATR): 3441, 3025, 2929, 2640, 2322, 2195, 2101, 1979, 1718, 1601, 1458, 1362, 1315, 1221, 1135, 1081, 870, 747, 698 cm^{-1}.

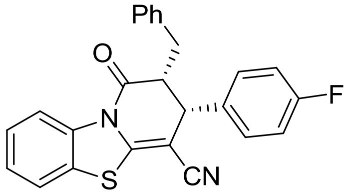
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (d, J = 7.8 Hz, 1H, Ar-*H*), 7.43-7.22 (m, 8H, Ar-*H*), 7.06 (d, J = 7.2 Hz, 2H, Ar-*H*), 7.00-6.99 (m, 1H, Ar-*H*), 6.95 (d, J = 7.2 Hz, 1H, Ar-*H*), 3.61 (d, J = 7.2 Hz, 1H, C*H*Ar), 3.57-3.53 (m, 1H, C*H*Bn), 3.47 (dd, J_1 = 15.0 Hz, J_2 = 4.8 Hz, 1H, CH*H*Ph), 2.45 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.9 (*C*O), 152.9 (S*C*CCN), 138.4 (Ar-*C*), 137.6 (Ar-*C*), 137.3 (Ar-*C*), 134.9 (Ar-*C*), 130.6 (Ar-*C*), 129.11 (Ar-*C*), 129.07 (Ar-*C*), 128.813 (2C, Ar-*C*), 128.805 (2C, Ar-*C*), 128.7 (Ar-*C*), 128.1 (Ar-*C*), 127.2 (Ar-*C*), 127.0 (Ar-*C*), 126.1 (Ar-*C*), 125.6 (Ar-*C*), 121.9 (Ar-*C*), 117.3 (*C*N), 82.5 (*C*CN), 47.7 (*C*HAr), 42.7 (*C*HBn), 31.5 (CH_2Ph) ppm.

MS (ESI): $[M+H]^+$ = 429.0825.

Elemental Analysis: calcd. for $C_{25}H_{17}ClN_2OS$ (428.08) C, 70.00; H, 3.99; N, 6.53 found: C, 69.85; H, 3.82; N, 6.65.

(2*R*,3*R*)-2-Benzyl-3-(4-fluorophenyl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157g)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a light yellow solid.

Yield: 201.3 mg, 97%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 5:1).

Melting point: 64-66 °C.

Optical rotation: $[\alpha]_D^{21} = -486.3$ (c = 1.0, $CHCl_3$).

dr: 4:1.

ee: 97%.

Anal. chiral HPLC: Daicel IA, *n*-heptane:EtOH = 9:1, 1.0 mL/min, t_R = 11.42 min (minor), 17.83 min (major).

IR (ATR): 3448, 3025, 2939, 2651, 2323, 2196, 2106, 1894, 1720, 1603, 1506, 1457, 1363, 1315, 1223, 1138, 1026, 911, 831, 743 cm^{-1}.

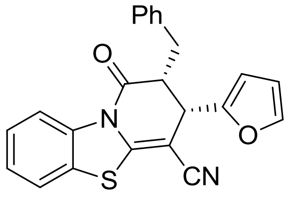
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.43 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H, Ar-*H*), 7.42-7.22 (m, 7H, Ar-*H*), 7.05-6.96 (m, 5H, Ar-*H*), 3.63 (d, *J* = 7.2 Hz, 1H, C*H*Ar), 3.56-3.52 (m, 1H, C*H*Bn), 3.45 (dd, J_1 = 15.0 Hz, J_2 = 4.8 Hz, 1H, CH*H*Ph), 2.45 (dd, J_1 = 14.4 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (*C*O), 162.6 (d, $J_{F\text{-}C}$ = 246 Hz, Ar-*C*), 152.4 (S*C*CCN), 137.7 (Ar-*C*), 137.3 (Ar-*C*), 132.3 (d, $J_{F\text{-}C}$ = 4 Hz, Ar-*C*), 129.4 (d, $J_{F\text{-}C}$ = 8 Hz, 2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 127.2 (Ar-*C*), 126.9 (Ar-*C*), 126.1 (Ar-*C*), 123.7 (Ar-*C*), 121.9 (Ar-*C*), 117.7 (Ar-*C*), 117.3 (*C*N), 116.2 (d, $J_{F\text{-}C}$ = 22 Hz, 2C, Ar-*C*), 83.2 (*C*CN), 47.9 (*C*HAr), 42.3 (*C*HBn), 31.5 (*C*H_2Ph) ppm.

MS (ESI): $[M+H]^+$ = 413.1121.

HRMS (ESI): calcd for $C_{25}H_{17}FN_2OS$ $[M+H]^+$: 413.1118; found: 413.1119.

(2*R*,3*S*)-2-Benzyl-3-(furan-2-yl)-1-oxo-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a] pyridine-4-carbo-nitrile (157h)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 129.8 mg, 68%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 5:1).

Melting point: 76-78 ^{o}C.

Optical rotation: $[\alpha]_D^{21}$ = –444.6 (*c* = 1.0, $CHCl_3$).

dr: 6:1.

ee: 92%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 1.0 mL/min, t_R = 11.21 min (minor), 13.72 min (major).

IR (ATR): 3781, 3118, 3065, 3027, 2933, 2719, 2345, 2197, 2040, 1990, 1963, 1790, 1719, 1606, 1579, 1497, 1458, 1361, 1318, 1256, 1227, 1135, 1066, 1012, 922, 865, 814, 789, 743, 702 cm^{-1}.

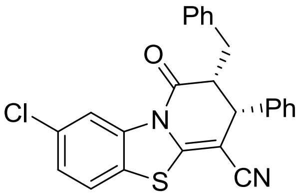
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.40-7.22 (m, 7H, Ar-*H*), 7.13 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 6.35-6.34 (m, 1H, Ar-*H*), 6.19 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 3.67 (d, *J* = 6.6 Hz, 1H, C*H*Ar), 3.54 (dd, J_1 = 14.4 Hz, J_2 = 4.2 Hz, 1H, CH*H*Ph), 3.36-3.32 (m, 1H, C*H*Bn), 2.41 (dd, J_1 = 14.4 Hz, J_2 = 10.8 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 168.8 (*C*O), 153.7 (S*C*CCN), 149.7 (Ar-*C*), 143.1 (Ar-*C*), 138.0 (Ar-*C*), 137.7 (Ar-*C*), 129.0 (2C, Ar-*C*)), 128.8 (2C, Ar-*C*)), 127.1 (Ar-*C*), 126.9 (Ar-*C*), 125.8 (Ar-*C*), 123.7 (Ar-*C*), 121.8 (Ar-*C*), 117.8 (Ar-*C*), 117.4 (*C*N), 110.4 (Ar-*C*), 109.0 (Ar-*C*), 79.9 (*C*CN), 47.4 (*C*HAr), 36.2 (*C*HBn), 31.7 (*C*H_2Ph) ppm.

MS (ESI): [M-H]$^-$ = 383.0845.

HRMS (ESI): calcd for $C_{23}H_{16}N_2O_2S$ [M+H]$^+$: 385.1005; found: 385.1005.

(2*R*,3*R*)-2-Benzyl-8-chloro-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a]pyridine-4-carbonitrile (157i)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 208.3 mg, 97%.

TLC: R_f = 0.3 (*n*-pentane: Et_2O = 5:1).

Melting point: 240-242 ^{o}C.

Optical rotation: $[\alpha]_D^{21}$ = –597.3 (c = 1.0, $CHCl_3$).

dr: 9:1.

ee: 98%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 0.5 mL/min, t_R = 19.67 min (minor), 27.51 min (major).

IR (ATR): 3413, 3124, 3084, 3029, 2920, 2877, 2318, 2190, 2037, 1993, 1955, 1825, 1714, 1602, 1573, 1493, 1457, 1418, 1368, 1297, 1267, 1221, 1135, 1080, 1052, 996, 939, 896, 865, 805, 752, 698, 663 cm^{-1}.

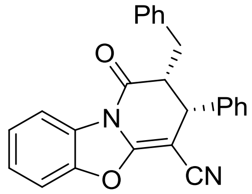
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.47 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.34-7.20 (m, 8H, Ar-*H*), 7.05-7.02 (m, 4H) , Ar-*H*, 3.63 (d, *J* = 6.8 Hz, 1H, C*H*Ar), 3.54-3.49 (m, 1H, C*H*Bn), 3.41 (dd, J_1 = 14.4 Hz, J_2 = 4.4 Hz, 1H, CH*H*Ph), 2.48 (dd, J_1 = 14.8 Hz, J_2 = 9.6 Hz, 1H, C*H*HPh) ppm.

^{13}C NMR (100 MHz, CDCl$_3$): δ = 169.2 (*C*O), 152.0 (S*C*CCN), 138.2 (Ar-*C*), 137.9 (Ar-*C*), 136.2 (Ar-*C*), 133.2 (Ar-*C*), 129.3 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.6 (Ar-*C*), 127.6 (2C, Ar-*C*), 126.9 (Ar-*C*), 126.0 (Ar-*C*), 122.3 (Ar-*C*), 122.2 (Ar-*C*), 117.7 (Ar-*C*), 117.5 (*C*N), 84.3 (*C*CN), 48.0 (*C*HAr), 43.1 (*C*HBn), 31.5 (*C*H$_2$Ph) ppm.

MS (ESI): $[M-H]^-$ = 427.0682.

HRMS (ESI): calcd for $C_{25}H_{17}Cl\,N_2OS$ $[M+H]^+$: 429.0823; found: 429.0817.

(2*R*,3*R*)-2-Benzyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]oxazolo[3,2-a] pyridine-4-carbonitrile (157j)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et$_2$O = 15:1). The product was obtained as a colorless solid.

Yield: 183.8 mg, 97%.

TLC: R_f = 0.4 (*n*-pentane: Et$_2$O = 5:1).

Melting point: 138-140 °C.

Optical rotation: $[\alpha]_D^{21} = -445.9$ (c = 1.0, $CHCl_3$).

dr: 4:1.

ee: 95%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 0.7 mL/min, t_R = 19.07 min (minor), 26.35 min (major).

IR (ATR): 3448, 3028, 2942, 2320, 2204, 2103, 1967, 1893, 1692, 1621, 1471, 1368, 1263, 1225, 1192, 1128, 1089, 1006, 923, 843, 745, 697 cm^{-1}.

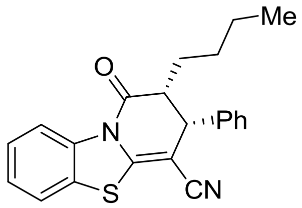
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.01-7.98 (m, 1H, Ar-*H*), 7.34-7.24 (m, 9H, Ar-*H*), 7.07-7.06 (m, 2H, Ar-*H*), 7.03 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 3.68-3.67 (m, 1H, C*H*Ar), 3.51-3.46 (m, 2H, C*H*Bn and CH*H*Ph), 2.50-2.46 (m, 1H, C*H*HPh) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.6 (*C*O), 156.9 (O*C*CCN), 146.9 (Ar-*C*), 137.9 (Ar-*C*), 137.2 (Ar-*C*), 129.3 (2C, Ar-*C*), 128.8 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 128.4 (Ar-*C*), 127.4 (2C, Ar-*C*), 127.1 (Ar-*C*), 126.9 (Ar-*C*), 125.8 (Ar-*C*), 125.0 (Ar-*C*), 116.0 (*C*N), 114.4 (Ar-*C*), 110.4 (Ar-*C*), 66.0 (*C*CN), 47.9 (*C*HAr), 41.3 (*C*HBn), 31.2 (*C*H_2Ph) ppm.

MS (ESI): $[M+Na]^+$ = 401.1260.

Elemental Analysis: calcd. for $C_{25}H_{18}N_2O_2$ (378.14) C, 79.35; H, 4.79; N, 7.40 found: C, 79.06; H, 4.94; N, 7.29.

(2*R*,3*R*)-2-Butyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a] pyridine-4-carbonitrile (157k)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 128.1 mg, 71%.

TLC: $R_f = 0.4$ (*n*-pentane: Et_2O = 5:1).

Melting point: 100-102 °C.

Optical rotation: $[\alpha]_D^{21} = -511.7$ ($c = 0.96$, $CHCl_3$).

dr: 8:1.

ee: 98%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 0.5 mL/min, t_R = 15.59 min (minor), 19.09 min (major).

IR (ATR): 3423, 3029, 2948, 2865, 2196, 1947, 1717, 1606, 1457, 1310, 1226, 1135, 1060, 1028, 908, 846, 740 cm^{-1}.

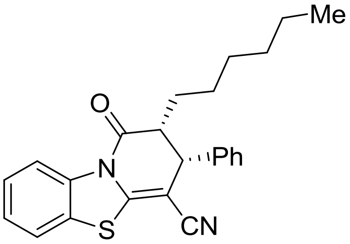
^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.40 (d, J = 7.8 Hz, 1H, Ar-*H*), 7.40-7.23 (m, 6H, Ar-*H*), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 2H, Ar-*H*), 3.84 (d, J = 7.2 Hz, 1H, C*H*Ar), 3.09 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1H, CHC_4H_9), 1.94-1.88 (m, 1H, $CHHC_3H_7$), 1.42-1.21 (m, 5H, $CHHC_3H_7$ and $CH_2C_2H_4CH_3$), 0.88 (t, J = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8 (*C*O), 152.5 (S*C*CCN), 137.6 (Ar-*C*), 136.5 (Ar-*C*), 129.2 (2C, Ar-*C*), 128.3 (Ar-*C*), 127.4 (2C, Ar-*C*), 127.1 (Ar-*C*), 125.9 (Ar-*C*), 123.8 (Ar-*C*), 121.8 (Ar-*C*), 118.1 (Ar-*C*), 117.2 (*C*N), 83.0 (*C*CN), 46.5 (*C*HAr), 43.9 (*C*HC_4H_9), 29.5 (*C*$H_2C_3H_7$), 25.4 (*C*$H_2C_2H_5$), 22.5 (*C*H_2CH_3), 13.9 (*C*H_3) ppm.

MS (ESI): $[M-H]^-$ = 359.1202.

HRMS (ESI): calcd for $C_{22}H_{20}N_2OS$ $[M+Na]^+$: 383.1196; found: 383.1187.

(2*R*,3*R*)-2-Hexyl-1-oxo-3-phenyl-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-a] pyridine-4-carbonitrile (157l)



The compound was prepared according to the ***GP3*** and isolated by flash column chromatography (*n*-pentane: Et_2O = 15:1). The product was obtained as a colorless solid.

Yield: 85.5 mg, 44%.

TLC: R_f = 0.4 (*n*-pentane: Et_2O = 5:1).

Melting point: 123-125 °C.

Optical rotation: $[\alpha]_D^{21}$ = –448.6 (*c* = 1.0, $CHCl_3$).

dr: 5:1.

ee: 96%.

Anal. chiral HPLC: Daicel IC, *n*-heptane:EtOH = 97:3, 0.7 mL/min, t_R = 12.62 min (minor), 14.81 min (major).

IR (ATR): 3427, 3029, 2927, 2858, 2645, 2321, 2196, 2104, 1993, 1804, 1717, 1607, 1457, 1309, 1225, 1135, 1062, 1028, 908, 850, 744 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.40 (d, J = 8.4 Hz, 1H, Ar-H), 7.38 (d, J = 7.8 Hz, 1H, Ar-H), 7.32-7.23 (m, 5H, Ar-H), 7.12 (dd, J_1 = 7.8 Hz, J_2 = 2.4 Hz, 2H, Ar-H), 3.84 (d, J = 7.2 Hz, 1H, CHAr), 3.09 (dd, J_1 = 13.2 Hz, J_2 = 7.2 Hz, 1H, C$H$$C_6H_{13}$), 1.93-1.87 (m, 1H, CH$H$$C_5H_{11}$), 1.43-1.38 (m, 2H, C$HHC_5H_{11}$ and CH_2CH$H$$C_4H_9$), 1.31-1.20 (m, 7H, CH_2CHHC_4H_9 and $C_2H_4C_3$$H_6$$CH_3$), 0.86 (t, J = 7.2 Hz, 3H, CH_3) ppm.

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.8 (CO), 152.5 (SCCCN), 137.6 (Ar-C), 136.5 (Ar-C), 129.2 (2C, Ar-C), 128.3 (Ar-C), 127.4 (2C, Ar-C), 127.1 (Ar-C), 125.9 (Ar-C), 123.7 (Ar-C), 121.8 (Ar-C), 118.1 (Ar-C), 117.2 (CN), 83.0 (CCN), 46.5 (CHAr), 43.9 (CHC_6H_{13}), 31.5 ($C$$H_2C_5H_{11}$), 29.1 ($C$$H_2C_4H_9$), 27.3 ($C$$H_2C_3H_7$), 25.7 ($C$$H_2C_2H_5$), 22.5 ($C$$H_2CH_3$), 14.0 ($C$$H_3$) ppm.

MS (ESI): $[M-H]^-$ = 387.1536.

HRMS (ESI): calcd for $C_{24}H_{24}N_2OS$ $[M+Na]^+$: 411.1504; found: 411.1502.

General Procedure for the synthesis of nitrosobenzenes

General Procedure 4 (GP4)

To a stirred solution of aniline (10 mmol) in MeOH (3 mL) were added H_2O_2 (5.5 mL, 40 mmol, 4 equiv) and H_2O (4.5 mL). Aniline precipitated as fine crystals and then MoO_3 (0.144 g, 1 mmol) and aqueous KOH solution (1 mL, 1 mmol) were added and the solution stirred at 0 °C (for 1-methyl-4-nitrosobenzene) or rt (for 1-nitro-3-nitrosobenzene). The solution became brown and then yellow with formation of a precipitate, pH value 3-3.5. The reaction was monitored by TLC. After 16 h (for 1-methyl-4-nitrosobenzene) or 13 days (for 1-nitro-3-nitrosobenzene), H_2O (15 mL) was added and the desired product formed as an ochre precipitate, which was filtered, washed with H_2O (2 × 10 mL), cold MeOH (5 mL) and dried. Crude product is mainly pure and can be recrystallized by EtOH to give pure compound.

1-Methyl-4-nitrosobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.39 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 2.45 (s, 3H, CH_3) ppm.

1-Nitro-3-nitrosobenzene

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68-8.55 (m, 2H, Ar-*H*), 8.38-8.29 (m, 1H, Ar-*H*), 7890 (dt, J_1 = 7.9 Hz, J_2 = 0.7 Hz, 1H, Ar-*H*) ppm.

The analytical data are in agreement with the previous report.[101]

General Procedure for the synthesis of α-chloroaldehydes 108

General Procedure 5 (GP5)

To a stirred solution of hydrocinnamaldehyde (30 mmol) in dry DCM (60 mL) *L*-proline and NCS were added at 0 °C for 1 h, allowed to reach rt and stirred for additional 1.5 h. The reaction was quenched by addition of pentane 100 mL, filtered through a short plug of celite, the orgnic phase was washed (H_2O, 2 × 50 mL), dried with $MgSO_4$ and concentrated to afford the product **108a** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.60 (t, *J* = 2.1 Hz, 1H, C*H*O), 7.92-6.83 (m, 5H, Ar-*H*), 5.07-4.82 (m, 1H, C*H*Cl) 3.43 (dd, *J* = 14.5, 5.3 Hz, 1H, C*H*H), 3.03 (dd, *J* = 14.4, 8.8 Hz, 1H, CH*H*) ppm.

The analytical data are in agreement with the previous report.[102]

General Procedure for the synthesis of 2-alkenyl-benzothiazole 156

General Procedure 6 (GP6)

To an oven dried round bottle 2-(benzo[*d*]thiazol-2-yl)acetonitrile (10 mmol), benzaldehyde (12 mmol), Et_3N (0.5 mL), 4 Å MS (500 mg) and dry $CHCl_3$ (20 mL) were added. The mixture was refluxed for 8 h and concentrated. The product **156a** was isolated by chromatography on a short silica gel column (*n*-pentane:Et_2O = 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (s, 1H, C*H*), 8.13-8.01 (m, 3H, Ar-*H*), 7.69-7.89 (m, 1H, Ar-*H*), 7.60-7.50 (m, 4H, Ar-*H*), 7.49-7.43 (m, 1H, Ar-*H*) ppm.

The analytical data are in agreement with the previous report.[103]

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My deepest gratitude goes first and foremost to my Ph.D supervisor Prof. Dieter Enders, who gives me the opportunity to study in his group. Without his consistent and illuminating instruction, encouragement and suggestions, I could not finish my thesis smoothly. His patience and kindness are greatly appreciated. I have learnt from him not only about organic chemistry, but also his rigorous scholarship and working with great vigour and enthusiasm.

Then, I would like to express my heartfelt gratitude to my boyfriend Qijian Ni for his great help on the research and daily life during my Ph.D study.

High tribute shall be paid to the administrative and technical staff of the institute for their support. Especially, thanks to Dr. Wolfgang Bettray for keeping everything well in our group and providing mass spectrometry expertise. Also many thanks to Karin Risse for the warmly help during my study here, Sabine Drehsen and Desiree Gilliam for the analytical help. As well as the current and former group members for their general help, including Kun Zhao, Tao Shu, Lei Wang, Chuanjie Loh, Xiaofei Zeng, André Grossmann and my bachelor student Chen Zhu.

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Last but not least, I would like to thank my family for their support all the way from the very beginning of my study. I am thankful to all my family members for their thoughtfulness and encouragement.

6. List of Abbreviations

Å	Ångström
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
cat.	Catalyst
CDI	Carbonyldiimidazole
conv.	conversion
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
dr	diastereomeric ratio
E	Electrophile
ee	enantiomeric excess
EI	Electron Ionization
equiv.	equivalent
ESI	Electron Spray Ionization
Et	Ethyl
EWG	Electron-withdrawing group
h	hour
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz

i-Pr	iso-Propyl
J	coupling constant (in NMR spectroscopy)
Me	Methyl
Mes	2,4,6-Trimethylphenyl
MS	Molecular Sieve
NFSI	N-Fluorobenzenesulfonimide
NHC	N-Heterocyclic Carbene
NMM	N-Methylmorpholine
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu	Nucleophile
PCC	Pyridinium chlorochromate
PG	Protecting Group
Ph	Phenyl
PMP	*para*-Methoxylphenyl
rac	racemic
rt	room temperature
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TEA	Triethylamine
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl

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8. Curriculum Vitae of Xiaoxiao Song

PERSONAL DATA

Name: Xiaoxiao Song
Gender: Female
Date of Birth: Jan. 2nd,1986
Place of Birth: Hebei, P. R. China
Nationality: P. R. China
Marital Status: Single

EDUCATION AND PRACTICE

Sept. 2012-Apr. 2015:	Doctoral Study at Institute of Organic Chemistry, RWTH Aachen University
Advisor:	Prof. Dr. Dieter Enders
Thesis:	NHC Organocatalytic Transformations in One-Pot Sequential and Domino Reactions
Sept. 2009-July 2012:	Master of Engineering, State Key Laboratory of Fine Chemicals, Dalian University of Technology, China
Advisor:	Assoc. Prof. Dr. Chun Liu
Thesis:	Synthesis of Aryl-Substituted Aniline Derivatives *via* the Palladium-Catalyzed Ligand-Free Suzuki Reaction
Sept. 2005-July 2009:	Bachelor of Applied Chemistry, School of Science, Hebei University of Science and Technology, China
Advisor:	Prof. Dr. Jianrong Han
Thesis:	Preparation and Assembly of Crown Ethers Derivatives and Secondary Dialkylammonium Salts

HONORS AND AWARDS

2012-2015	Supported by China Scholarship Council (CSC)
2012	Honored as “Dalian Outstanding Graduates” in Dalian University of Technology
2010-2011	Honored as "Excellent Post-graduates" in Dalian University of Technology
2005-2009	Honored as "Model Class Cadre" in Hebei University of Science and Technology
2005-2009	Second Prize Scholarship in Hebei University of Science and Technology