N-Heterocyclic Carbene Catalyzed Asymmetric Cycloaddition/Annulation Reactions of Enals and α-Chloroaldehydes

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

vorgelegte von

Sun Li

Master of Science

aus

Shandong, China

Bereichter: Universitätsprofessor Dr. rer. nat. Dieter Enders

Universitätsprofessor Dr. rer. nat. Markus Albrecht

Tag der mündlichen Prüfung: 10. 04. 2018

Diese Dissertation ist auf den Internetseiten der Universitätsbibliothek verfügbar.

The work presented in this thesis was carried out in the Institute of Organic Chemistry of RWTH Aachen University from September 2015 to April 2018 under the supervision of Prof. Dr. Dieter Enders.

Parts of this work have been published:

1. "N-Heterocyclic-Carbene-Catalyzed Domino Reactions via Two or More Activation Modes"
Xiang-Yu Chen, **Sun Li** (Co-first author), Fabrizio Vetica, Mukesh Kumar, Dieter Enders*, *iScience* **2018**, *2*, 1 - 26.

2. "N-Heterocyclic Carbene Catalyzed Asymmetric Synthesis of Dihydropyrano Thiazoles *via* Azolium Enolate Intermediates"
Sun Li, Xiang-Yu Chen, He Sheng, Carolina von Essen, Kari Rissanen, Dieter Enders*, *Synthesis*, **2018**, *50*, 1047 - 1052.

3. "N-Heterocyclic Carbene Catalyzed [3+2] Cycloaddition of Enals with Masked Cinnamates for the Asymmetric One-Pot Synthesis of Adipic Acid Derivatives"
Xiang-Yu Chen, **Sun Li** (Co-first author), He Sheng, Qiang Liu, Ehsan Jafari, Carolina von Essen, Kari Rissanen, Dieter Enders*, *Chem. Eur. J.* **2017**, *23*, 13042 - 13045.

4. "N-Heterocyclic Carbene-Catalyzed Activation of α-Chloroaldehydes: Asymmetric Synthesis of 5-Cyano-Substituted Dihydropyranones"
Sun Li, Xiang-Yu Chen, Qiang Liu, Anssi Peuronen, Kari Rissanen, Dieter Enders*, *Synthesis* **2017**, *49*, 4861 - 4868.

5. "Switchable Access to Different Spirocyclopentane Oxindoles *via N*-Heterocyclic Carbene-Catalyzed Reactions of Isatin-Derived Enals and N-Sulfonyl Ketimines"
Lei Wang, **Sun Li** (Co-first author), Marcus Blümel, Rakesh Puttreddy, Anssi Peuronen, Kari Rissanen, Dieter Enders*, *Angew. Chem. Int. Ed.* **2017**, *56*, 8516 - 8521.

6. "Asymmetric Synthesis of Five-Membered Spiropyrazolones *via N*-Heterocyclic Carbene-Catalyzed [3+2] Annulations"
Sun Li, Lei Wang, Pankaj Chauhan, Anssi Peuronen, Kari Rissanen, Dieter Enders*, *Synthesis* **2017**, *49*, 1808 - 1815.

Contributions to other projects:

7. "Control of *N*-Heterocyclic Carbene Catalyzed Reactions of Enals: Asymmetric

Synthesis of Oxindole-*γ*-Amino Acid Derivatives"
Xiang-Yu Chen, Jia-Wen Xiong, Qiang Liu, **Sun Li**, He Sheng, Carolina von Essen, Kari Rissanen, Dieter Enders*, *Angew. Chem. Int. Ed.* **2018**, 57, 300 - 304.

8. "Two-Step Synthesis of α,β-Unsaturated γ-Amino Acid Esters *via N*-Heterocyclic Carbene Catalyzed [4+2] Cycloadditions of Enals and Nitroso Compounds"
Qiang Liu, Xiang-Yu Chen, **Sun Li**, Fabrizio Vetica, Gerhard Raabe, Dieter Enders*, *Synthesis* **2018**, *50*, 127 - 133.

9. "*N*-Heterocyclic Carbene-catalyzed [4+2] Annulation of β-Methyl Enals and Cyclic Trifluoromethyl Ketimines for the Asymmetric Synthesis of Dihydroquinazolinone Derivatives"
Qiang Liu, Xiang-Yu Chen, **Sun Li**, Ehsan Jafari, Gerhard Raabe, Dieter Enders*, *Chem. Commun.* **2017**, *53*, 11342 - 11344.

10. "*N*-Heterocyclic Carbene Catalyzed [4+2] Annulation of Enals *via* a Double Vinylogous Michael Addition: Asymmetric Synthesis of 3,5-Diaryl Cyclohexenones"
Xiang-Yu Chen, Qiang Liu, Pankaj Chauhan, **Sun Li**, Anssi Peuronen, Kari Rissanen, Ehsan Jafari, Dieter Enders*, *Angew. Chem. Int. Ed.* **2017**, *56*, 6241 –6245.

11. "Asymmetric Synthesis of Spirobenzazepinones with Atroposelectivity and Spiro-1,2-Diazepinones by NHC-Catalyzed [3+4] Annulation Reactions"
Lei Wang, **Sun Li**, Marcus Blümel, Arne R. Philipps, Ai Wang, Rakesh Puttreddy, Kari Rissanen, Dieter Enders*, *Angew. Chem. Int. Ed.* **2016**, *55*, 11110 –11114.

12. "Asymmetric, Three-Component, One-Pot Synthesis of Spiropyrazolones and 2,5-Chromenediones from Aldol Condensation/NHC-Catalyzed Annulation Reactions"
Lei Wang, **Sun Li**, Pankaj Chauhan, Daniel Hack, Arne R. Philipps, Rakesh Puttreddy, Kari Rissanen, Gerhard Raabe, Dieter Enders*, *Chem. Eur. J.* **2016**, *22*, 5123 – 5127.

Table of Contents

1. Introduction

The isolation of the stable carbenes by Arduengo[1] *et al.* has greatly attracted the attention of synthetic organic chemists because of their properties and reactivity.[2] *N*-heterocyclic carbenes (NHCs) are a special kind of singlet carbenes, which contain at least one nitrogen atom connected directly to the divalent carbonic center (Figure 1).[3]

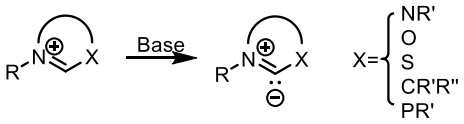


Figure 1 General structure and synthesis of N-heterocyclic carbenes

In the presence of a weak base, the acidic C-H bond of the azolium salts can be easily deprotonated, forming electron-rich nucleophilic *N*-heterocyclic carbenes. Comparing with other carbenes, NHCs have electrophilic properties.[4] Benefits from the connected nitrogen center, which has both σ-electron-withdrawing and π-electron-donating character, the NHCs are sufficiently stable as ligands or as organocatalysts in the reactions (Figure 2).[5]

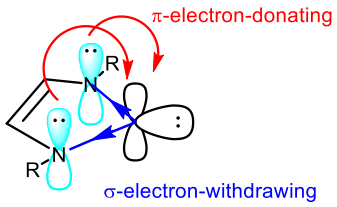


Figure 2 Structural features of the N-heterocyclic carbenes

1.1 Historical background of the *N*-heterocyclic carbenes (NHCs)

The isolation of the stable carbenes has been a big challenge for a long time, with attempted syntheses from as early as 1835[2]. In 1943, Ukai and co-workers have originally used thiazolium salts as catalysts in the benzoin reaction of aldehydes.[6] Later in 1958, Breslow *et al.* reported the proposed mechanism of this reaction, in which a free carbene was generated from the thiazolium salt in the presence of base. The

obtained active species attacked the additional aldehyde to form the named Breslow intermediate (Figure 3).[7]

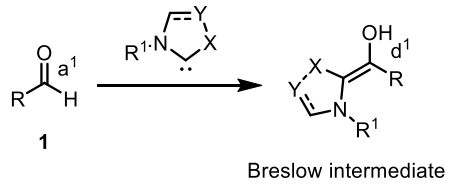


Figure 3 NHC-catalyzed formation of Breslow intermediate

Until the early 1960s, the reactivity and stability of NHCs were firstly investigated by Wanzlick,[8] which then opened a new field of using NHCs as ligands in organometallic chemistry.[9] On the other hand, the enantioselectivity of a chiral thiazolium pre-catalyst in the benzoin reaction was investigated by Sheehan and Hunneman in 1966.[10] In the same year, Noyori and co-workers reported the first chiral copper-carbene-catalyst for the asymmetric synthesis of cyclopropanes.[11] The evolution of NHCs in the next twenty years was mainly developed by Lappert *et al.*.[12] The laboratory curiosity was greatly attracted by the nucleophilic carbenes until the first stable (phosphin)(silyl)carbene was isolated by Bertrand and co-workers in 1988.[13] However, the chemical reactivity of Bertrand's phosphinocarbene appeared to resemble more a phosphaacetylene. Three years later, the isolation and full characterization of the stable, free NHC 1,3-di(adamantyl)imidazol-2-ylidene (IAd) by Arduengo *et al.* attracted great attention in the chemistry field. The generated "bottle-able" carbene was formed from the depronation of its imidazolium precursor.[1]

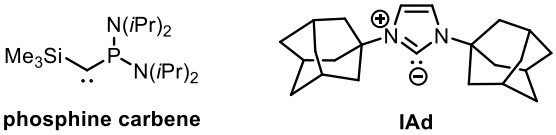


Figure 4 The first stable phosphine carbene and N-heterocyclic carbene

In 1995, Enders and co-workers changed the use of thiazolylidene or imidazolylidene carbenes to triazolylidene carbenes in organocatalysis.[14] Since then, numerous studies of chiral variants of triazolylidene carbenes were reported, and even chiral bicyclic triazolylidene scaffolds were realized in the improvement of stereoselectivity in a series

of NHC-catalyzed reactions.[15]

The application of NHCs can be divided into three main classes (Figure 5).[2] Inspired by the structural features, NHCs are used as ubiquitous ligands for transition metals[16], and the formed bonds with metal centers are stronger than most classical ligands, such as phosphine ligands. The generated transition metal complexes are stable in the whole reaction process, thus avoiding the initial addition of excess pre-catalysts.[5] The beneficial features of NHCs also lead to the coordination to *p*-block elements *via* the formation of highly stable, non-labile complexes.[17] The nucleophilic effect, due to the free electron pair on the carbon atom of the free NHCs, has the propensity to coordinate to carbon-electrophiles, thus NHCs can also be used as organocatalysts in the reactions.[15c, 18]

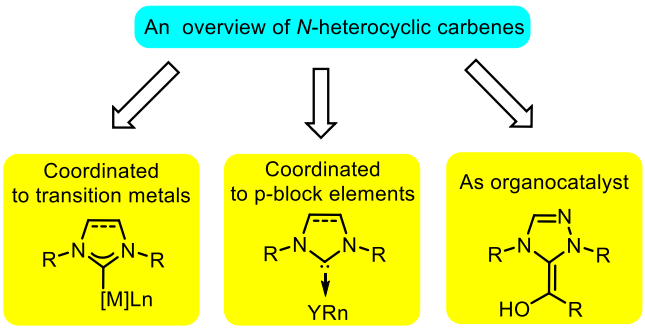


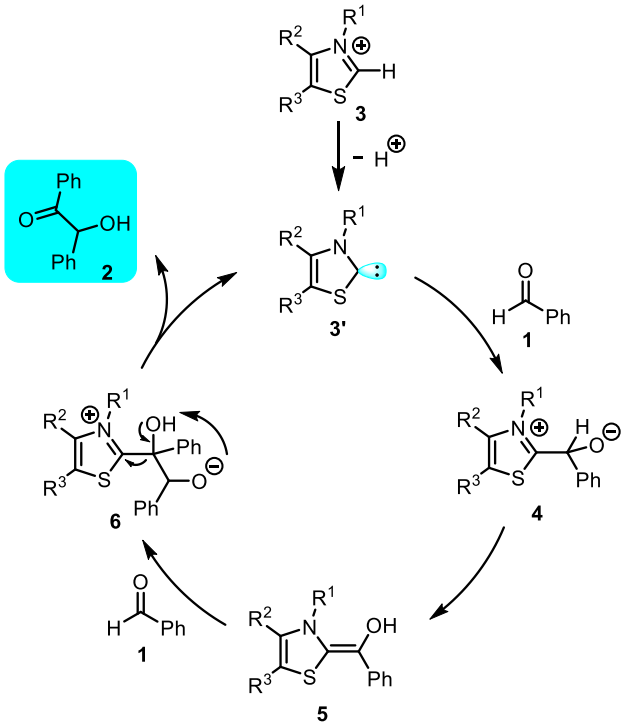
Figure 5 Major applications of NHCs

1.2 *N*-heterocyclic carbenes as organocatalysts

1.2.1 Benzoin reaction

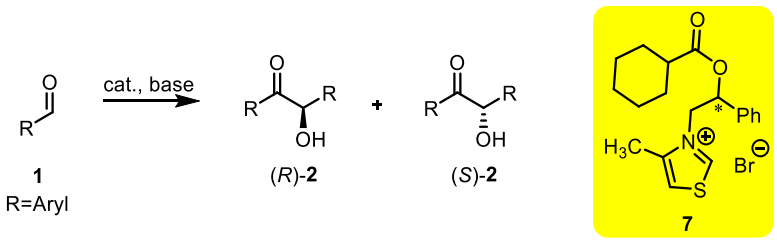
The benzoin condensation is one of the most investigated reactions *via N*-heterocyclic carbene catalysis. The first example of the benzoin reaction dates back to 1832 when the cyanide-catalyzed coupling of benzaldehyde to benzoin was reported by Wöhler and Liebig.[19] The proposed mechanism of this reaction was described in 1903 by Lapworth, in which benzaldehyde was deprotonated by the additional hydrogen cyanide, forming an carbanion intermediate, which bears nucleophilic reactivity.[20] As mentioned earlier, Ukai *et al.* reported the first benzoin reaction catalyzed by

thiazolium salts and the proposed mechanism was postulated by Breslow in 1958 (Scheme 1).[6, 7]



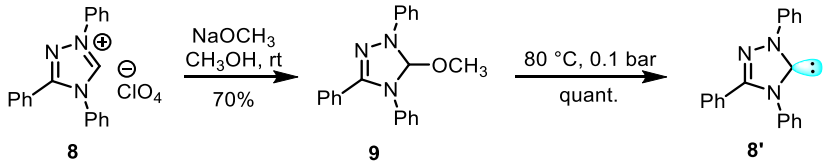
Scheme 1 Catalytic cycle of the benzoin reaction as proposed by Breslow

In the proposed mechanism, thiazolin-2-ylidene **3'** was formed from the thiazolium salt **3** by deprotonation at the most acidic position of **3**. Then, the nucleophilic ylidene **3'** attacks the carbonyl group of the aldehyde **1** to generate the adduct **4**, which leads to the Breslow intermediate **5**. Subsequently, the Breslow intermediate **5** reacts with the second equivalent aldehyde **1** to form the intermediate **6**. The NHC-elimination of **6** leads to the desired benzoin product **2** and regenerats the original free carbene catalyst **3'**.



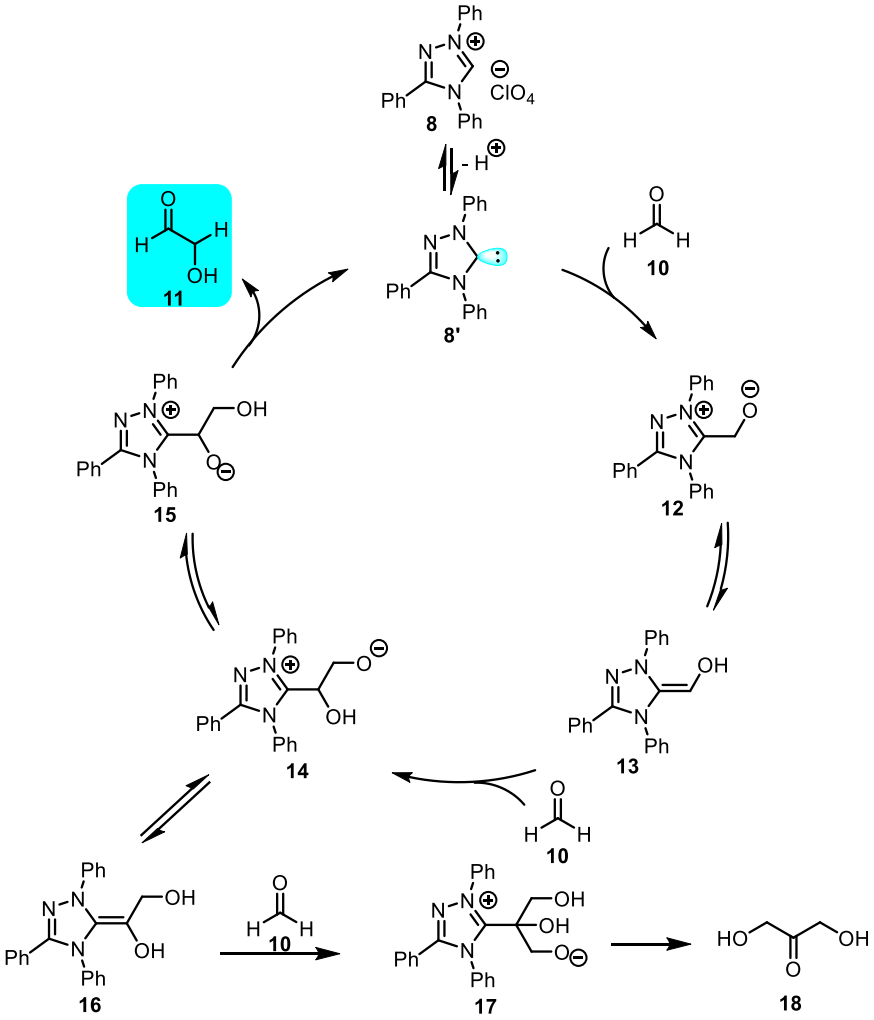
Scheme 2 Asymmetric benzoin reaction

On the basis of the works by Ukai and Breslow, the first asymmetric benzoin condensation was presented by Sheehan and Hunneman in 1966 (Scheme 2).[10]



*Scheme 3 Synthesis of stable carbene **8'***

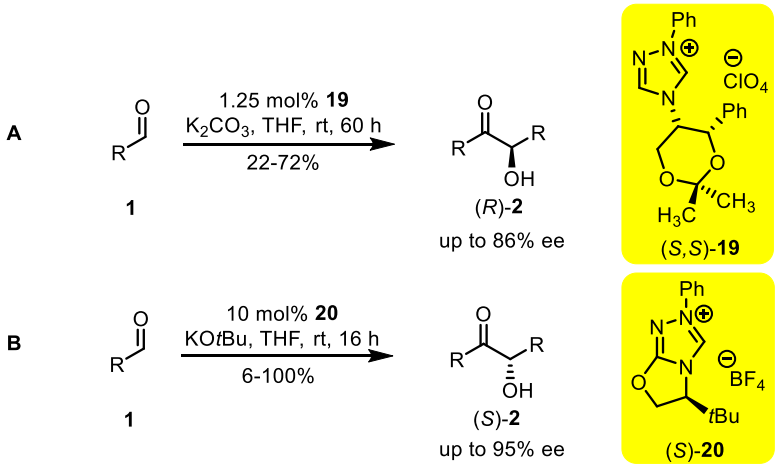
However, the reaction result was not good in the presence of the thiazolium salt **7**, with the *ee* of only around 22%. The optimization of the catalyst for this reaction was investigated in the next decades.[21] Until the isolation of the first stable, free NHC by Arduengo in 1991, numerous studies of the synthesis and applications of NHCs were reported. The situation that organocatalysis was dominated by thiazolylidene or imida-



Scheme 4 Proposed mechanism of the formoin condensation

zolylidene has changed when the stable triazolylidene carbene was synthesized by Enders and Teles in 1995 (Scheme 3).[14]

The triazolium salt precursor **8** gave the satisfying result in the catalyzed "formoin reaction" of formaldehyde **10** to glycolaldehyde **11**. The postulated mechanism of this reaction is shown in Scheme 4. The deprotonation of triazolium salt **8** leaded to free carbene **8'**, followed by the nucleophilic addition to formaldehyde **10**. The Breslow intermediate **13** was formed from the resonance stabilization of triazolium salt adduct **12**. The adduct **14** was then generated *via* the reaction of **13** with a second equivalent of formaldehyde **10**. In the catalytic cycle, the resonance of intermediate **14** followed by the elimination afforded the glycolaldehyde **11** with the release of the catalyst **8'**. Besides, the intermediate **14** was also able to form another Breslow intermediate **16**, which reacted with a third equivalent of formaldehyde **10** and obtained the cosmetic important DHA **18**.



Scheme 5 Asymmetric benzoin condensation of aromatic aldehydes

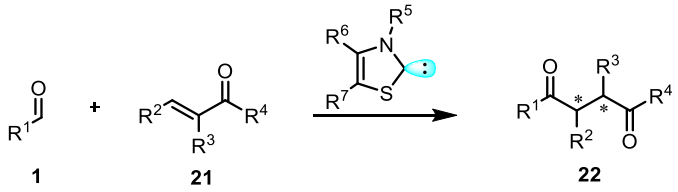
Inspired by the previous described works, a series of chiral triazolium salts were synthesized for the benzoin reaction by our group.[22] The result of the original asymmetric benzoin reaction by Sheehan and Hunneman was greatly improved by the usage of the catalyst (*S*,*S*)-**19** (Scheme 5, **A**). Utilizing the improved chiral bicyclic triazolium salt (*S*)-**20**, an enantiomeric excess of 90% accompanied by a yield of 83% of the benzion (*S*)-**2** was obtained.[23] The substrate scope of numerous aromatic aldehydes **1** also proceeded smoothly under the reaction conditions (Scheme 5, **B**).

The study of the asymmetric benzoin reaction was never suspended with continuous investigations employing different kinds of catalysts, such as axially chiral *N*-arylthiazolium salts[24], *N*-alkyl-benzimidazolium and thiazolium salts[25], rotaxanes[26], thiazolium- and imidazolium-ion based ionic liquids[27] and vitamin B1 catalyst[28].

By the extension of the benzoin reaction, the cross-coupling of different aldehydes or of aldehydes and ketons were broadly studied. The thiazolium salt catalyst precursors were applied in the intermolecular cross benzoin reaction to improve the selectivity of the products.[29] Breaking through the limitation of the crossed benzoin condensation of aldehyde-aldehyde coupling catalyzed by NHCs, a series of researches on aldehydes with many kinds of ketones, aldimines[30], arylsulfonylamides[31], and unactivated imines[32], and also the cross coupling of acylsilanes to imines[33] were investigated.

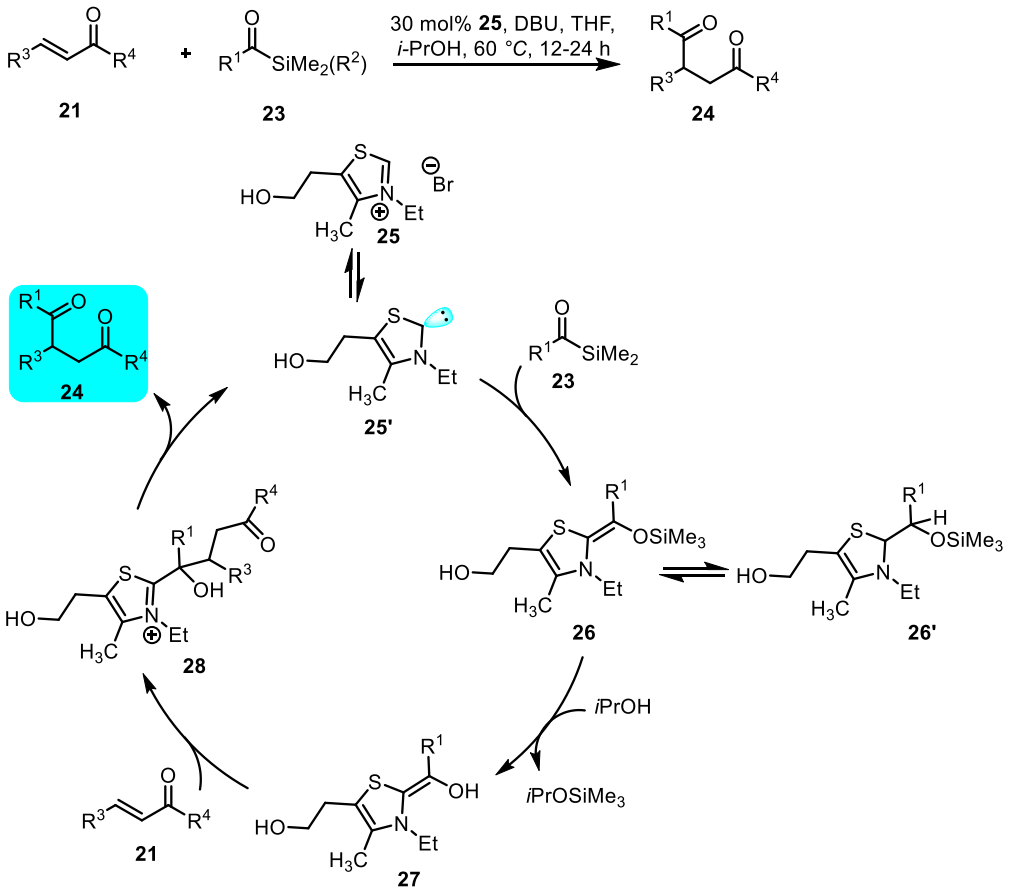
Other than the intermolecular crossed benzoin reactions, the intramolecular condensations have also been studied, despite lacking of earlier reports. The first intramolecular acyloin condensation catalyzed by NHC was reported by Cookson and Lane in 1976.[34] Independently, various five- and six-membered cyclic acyloins were synthesized by our group and Suzuki *et al.* as well.[35] The development of asymmetric studies of the intramolecular crossed benzoin reaction by both groups gave the corresponding products with high enantioselectivities and good yields.[36]

1.2.2 Stetter reaction



Scheme 6 Stetter reaction

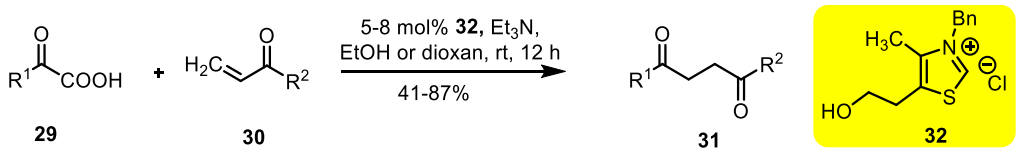
The thiazolium salt was employed for the substrate class of Michael acceptors in the early 1970s by Stetter and co-workers. The Stetter reaction was named from the catalytic 1,4-addition of aldehydes **1** to an acceptor bearing an actived double bond, such as **21**, resulted in 1,4-bifunctional moleculars **22** (Scheme 6).[37]



Scheme 7 Postulated mechanism for the Sila-Stetter reaction

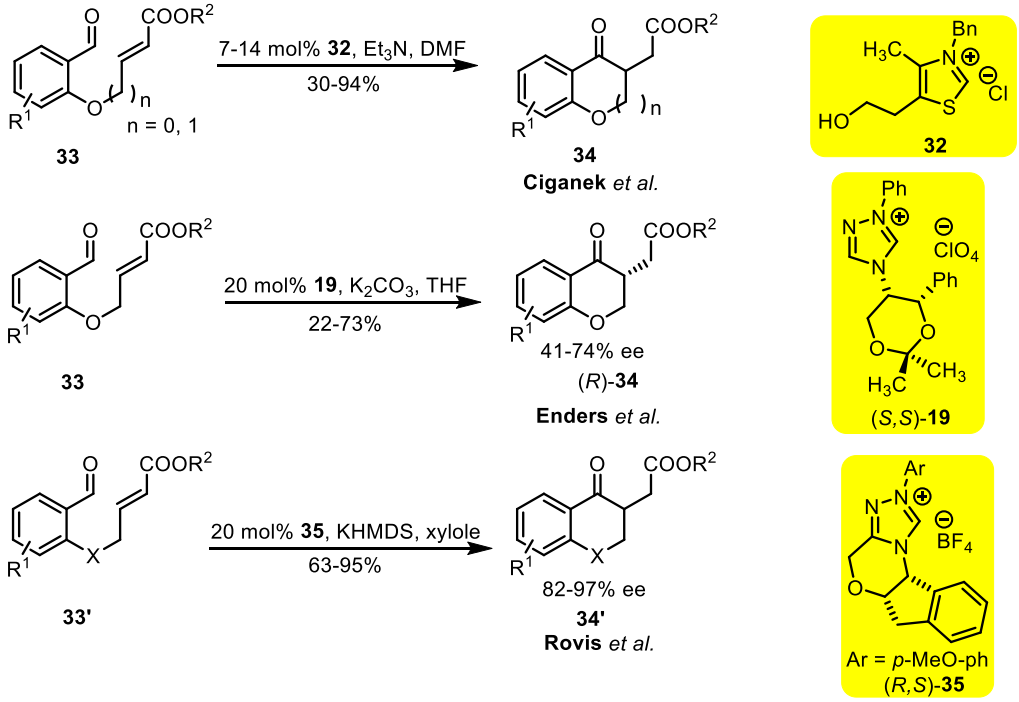
Since then, the Stetter reaction opened a new pathway for the synthesis of 1,4-diketones, 4-ketoesters and 4-ketonitriles.[38] Inspired by the previous results, the enantiomeric activity of the NHCs in the intermolecular Stetter reaction was investigated by our group.[39] Unfortunately, the enantiomeric excess was not satisfactory along with the low yield. Continuous research of the intermolecular Stetter reaction did not provide desired results applying either thiazolium salts or triazolium salts.[38b] Many years later, Scheidt and co-workers developed a special intermolecular Sila-Stetter reaction, in which the aldehydes were replaced by acylsilanes **23**, and catalyzed by thiazolium carbene precursor **25** to form 1,4-dicarbonyl compounds **24** in good yields and applicable to broad substrate scope.[40] As shown in Scheme 7, deprotonation of thiazoliun salt **25** resulted in free carbene catalyst **25'**, followed by the nucleophilic addition to acylsilanes **23** to form the intermediate **26**, which was by deprotonation/reprotonation in equilibrium with **26'**. In the presence of alcohol and

base, the Breslow intermediate **27** was formed, resulted in the conjugate addition to the acceptor **21**, leading to the formation of **28**. Lastly the product **24** was generated with the release of the free carbene **25'**.



Scheme 8 Thiazolium catalyzed reaction of α-ketoacids with enones

The intermolecular Stetter reaction is not limited to the aldehyde or acylsilanes. In 1985, Stetter and Lorenz extended the reaction by utilizing α-ketoacids **29** to react with active acceptors **30** under the thiazolium carbene catalyst **32** and yielded **31** with good outcome (Scheme 8).[41]



Scheme 9 Intramolecular Stetter reaction

The intramolecular Stetter reaction was also realized by Ciganek *et al.* in 1995,[42] followed by the study of the enantiomeric efficiency by our group and Rovis group (Scheme 9).[15b, 43] Extension of the NHC-catalyzed Stetter reaction generated various important structural units, which occur in many natural products and pharmaceuticals.[44]

From the previous description, NHCs have been one of the most powerful catalysts in the class of a^1-d^1 umpolung[45], including the benzoin reaction and Stetter reaction. However, the α,β-unsaturated aldehydes were converted to the homoenolate equivalents **36'** (Figure 6) by the activation of NHCs, which show different reactivity compared to the saturated aldehydes.

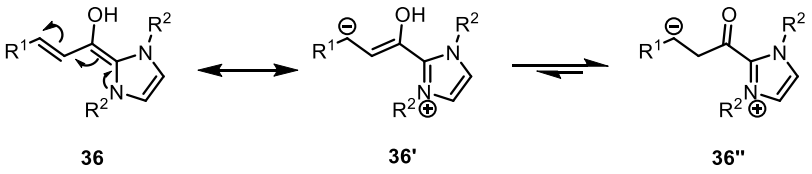


Figure 6 Homoenolate reactivity

During the reactions, the activation of the Breslow intermediate was reported *via* three modes: homoenolate equivalent, azolium enolate equivalent and unsaturated acylazolium intermediate (Figure 7), which will be comprehensively discussed in next sections.

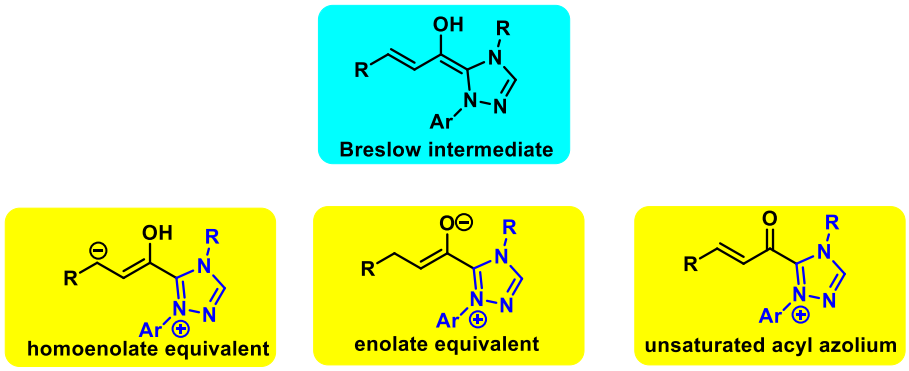


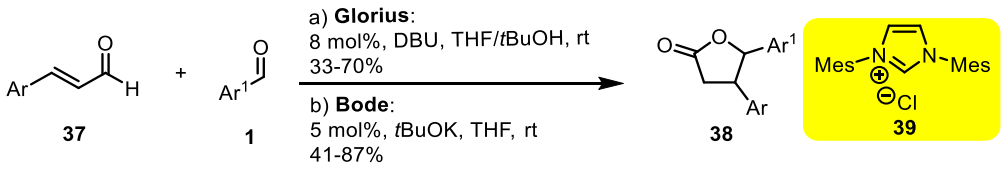
Figure 7 Activation models of the Breslow intermediate

1.3 NHC-catalyzed reactions *via* homoenolate equivalents

1.3.1 Formation of heterocycles

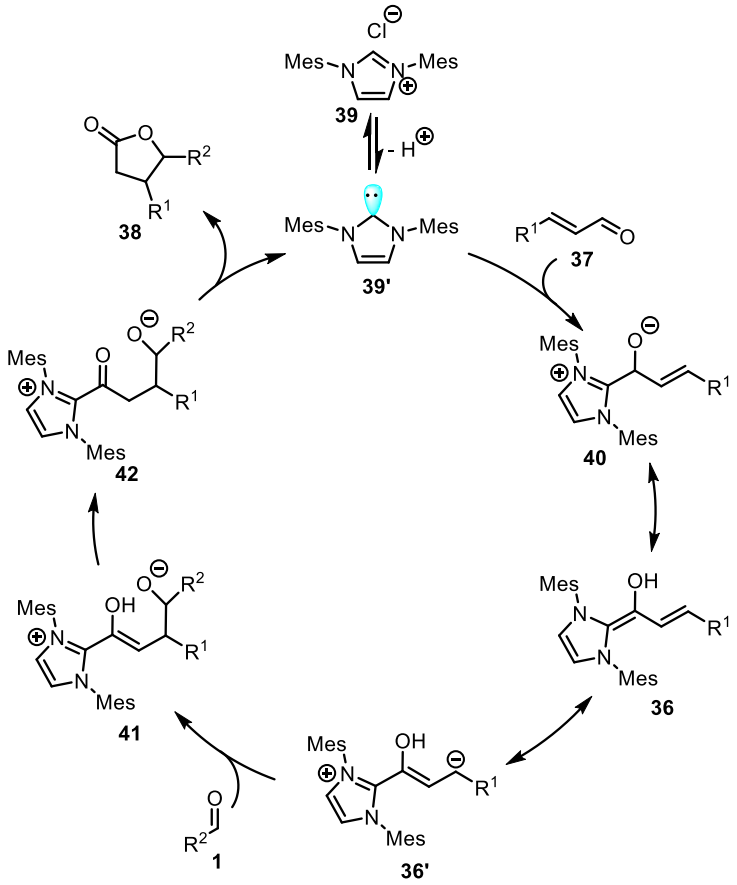
The first example of the NHC-catalyzed reaction *via* homoenolate equivalents was developed independently by Glorius [46] and Bode [47]. In both approaches, the α,β-unsaturated aldehydes **37** were employed to the [3+2] cycloaddition with aldehydes

1 to form γ-butyrolactones **38**. Both reaction conditions were tolerated for the aromatic aldehydes under the using of *N*-heterocyclic bisarylimidazolium salt **39**, resulted the γ-butyrolactone **38** in good yield (Scheme 10).



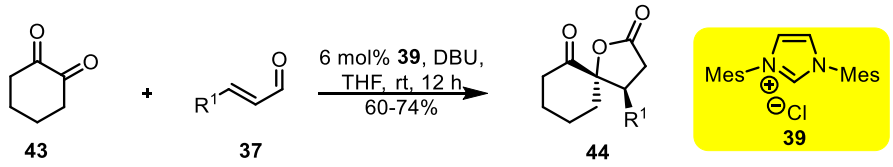
Scheme 10 NHC-catalyzed [3+2] annulations of enals with aldehydes

The plausible catalytic cycle as depicted in Scheme 11 showed that the deprotonation of the pre-catalyst **39** generated the free NHC-catalyst **39'**, which then reacted with the enals **37** to form the zwitterionic intermediates **40**. The Breslow intermediates **36** were



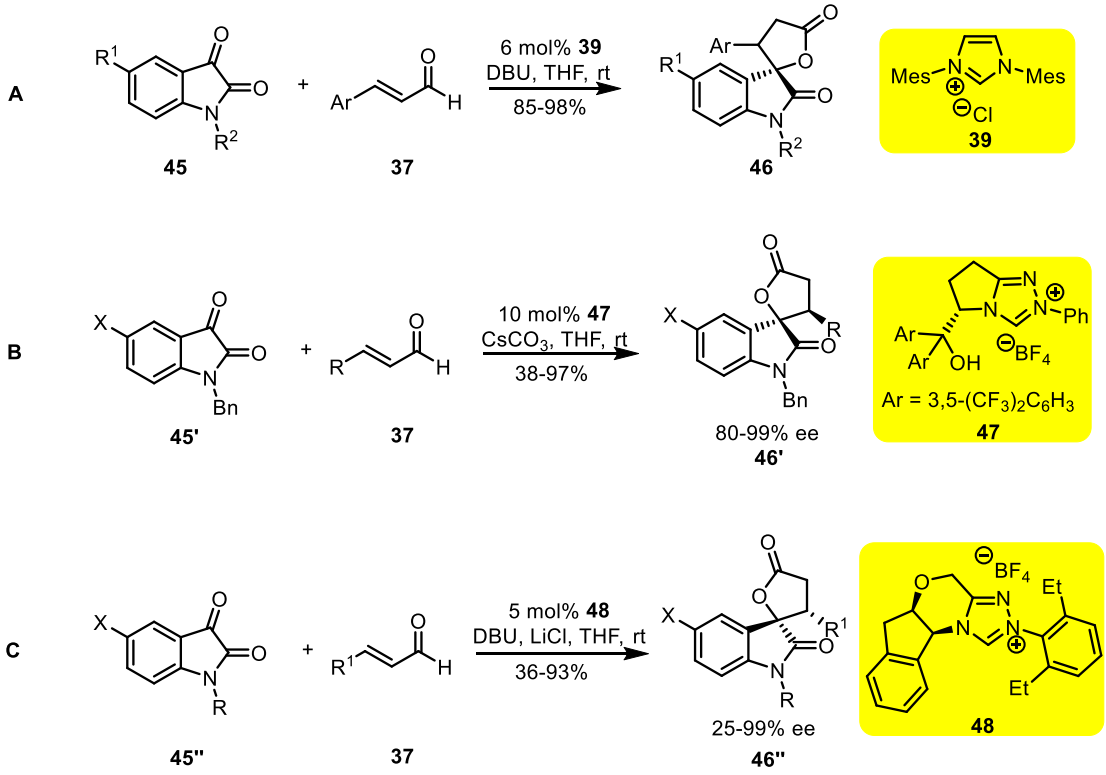
Scheme 11 Postulated catalytic cycle for the carbene-catalyzed formation of γ-butyrolactones

obtained *via* the tautomerization, which were in equilibrium with the homoenolate equivalent **36'**. Subsequently, the Michael addition of **36'** to aldehydes **1** afforded the alcoholates **41,** then tautomerized to the acyl imidazolium intermediate **42**. The intramolecular attack of the alcoholate oxygen atom to the carbonyl group closed the cycle to give the γ-butyrolactone products **38** with the regeneration of the catalyst **39'**. The conjugate umpolung of α,β-unsaturated aldelydes *via* homoenolate equivalents opened a new pathway for the annulation reactions catalyzed by NHCs. Since then, further applications have been developed for these reactive intermediates.[48]



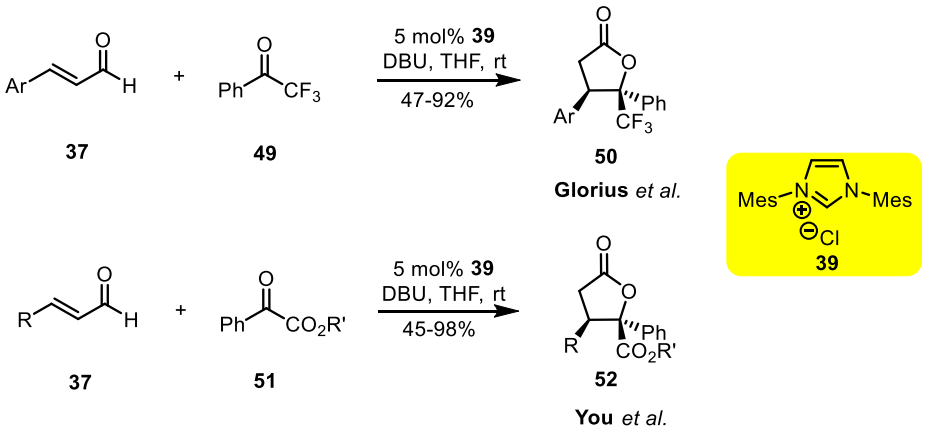
Scheme 12 First carbene-catalyzed spiro γ-butyrolactone reaction

The first spiro γ-butyrolactone was reported by Nair and co-workers in 2006, in which the reaction of 1,2-cyclohexanedione was used with a variety of α,β-unsaturated aldehydes (Scheme 12).[49] Nair *et al.* also developed NHC-catalyzed [3+2] cycloaddi-



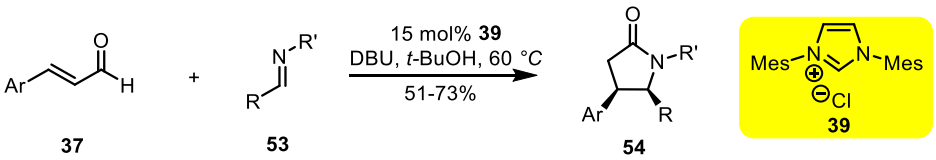
Scheme 13 NHC-catalyzed [3+2] annulations of enals with isatins

tions for the synthesis of spirocyclic oxindole-γ-lactones employing enals with 1,2-diketones and isatins. (Scheme 13, **A**).[49] After that, Ye and co-workers reported enantioselective oxindole-γ-lactones with excellent enantiomeric excess and with moderate yield. (Scheme 13, **B**).[50] Further approaches of Scheidt also described the asymmetric synthesis of spirocyclic structures catalyzed by NHC/Lewis acid with broad range of products (Scheme 13, **C**).[51]



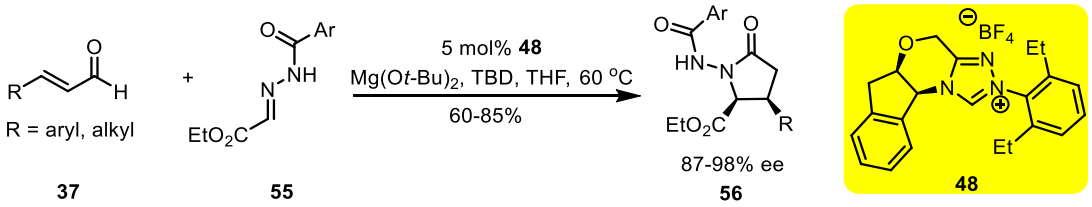
Scheme 14 NHC-catalyzed [3+2] annulations of enals with ketones

Furthermore, the development of γ-butyrolactones bearing quaternary stereocenters was reported by Glorius[52] and You[53] in 2008. The use of electron-deficient ketones **49** and **51** furnished the reaction products **50** and **52** with good results (Scheme 14).



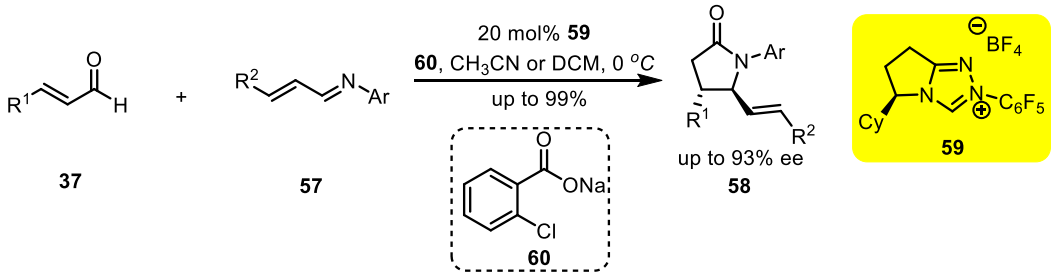
Scheme 15 NHC-catalyzed [3+2] annulations of enals with imines

Beside the nucleophilic addition to carbonyl group, He and Bode reported the first synthesis of *cis*-γ-lactams **54** *via* the condensation of homoenolates with imines **53**.[54] A series of functionalized α,β-unsaturated aldehydes **37** and different imines **53** were screened and afforded the corresponding γ-lactams **54** in very good yields (Scheme 15).



Scheme 16 Lewis acids/NHC co-catalysis for the synthesis of cis-γ-lactams

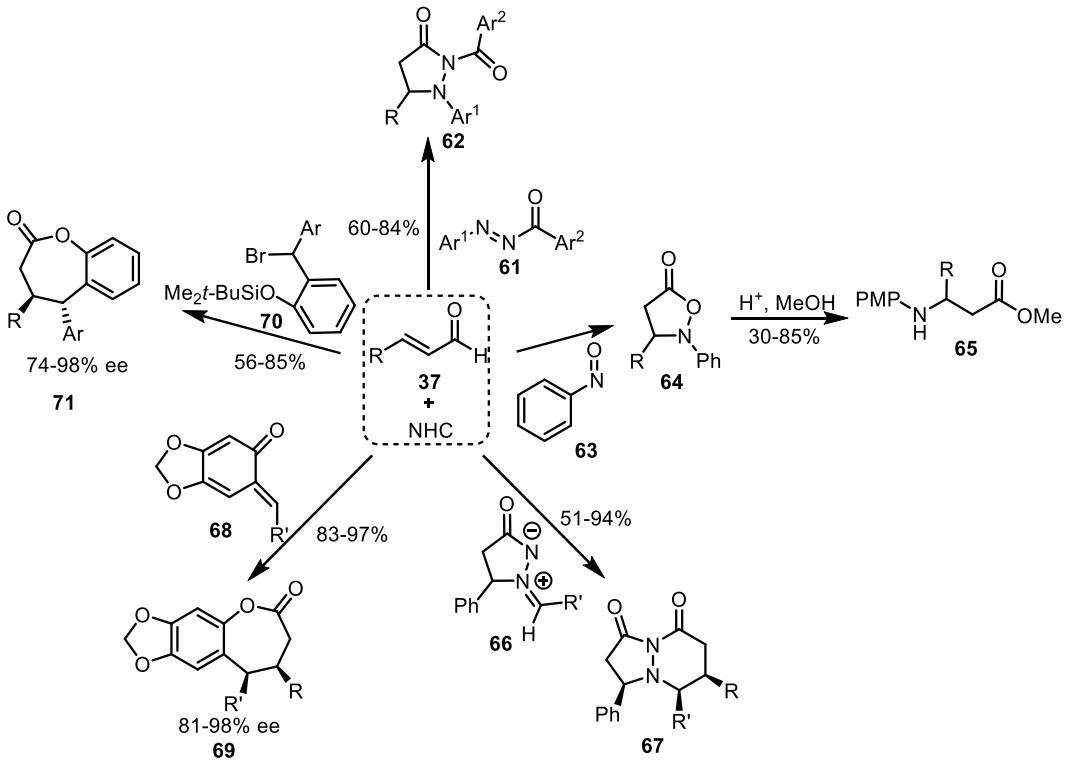
The enantiomeric study of the *cis*-γ-lactams was developed by Scheidt and co-workers in 2010, utilizing the Lewis acid/NHC-catalysis.[55] The combination of NHC precursor triazolium salt **48** and a catalytic amount of $Mg(Ot\text{-}Bu)_2$ furnished the [3+2] cycloaddition very well (Scheme 16).



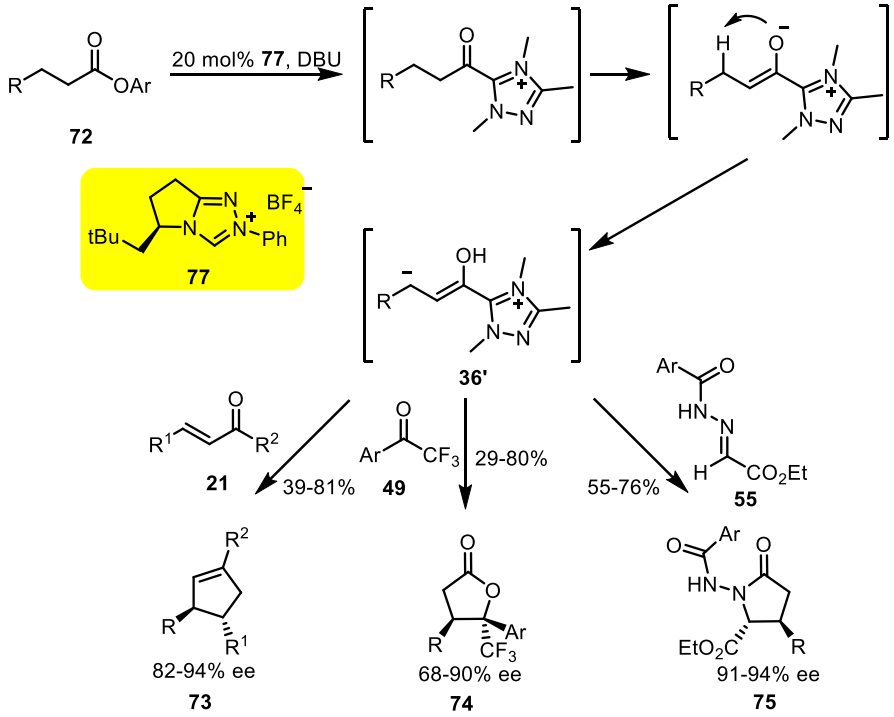
Scheme 17 Brønsted acids/NHC co-catalysis for the synthesis of trans-γ-lactams

In 2011, the combination of NHCs and Brønsted acids was realized by Rovis and co-workers[56], which is a great challenge in the field of organic chemistry. The imines were activated *via* the carboxylate **60** and reacted with the NHC-activated homoenolate intermediate smoothly to give the trans-γ-lactams **58** in good yields with excellent enantioselectivities (Scheme 17).

The homoenolate equivalents obtained from α,β-unsaturated aldehydes with NHCs can also be used in the synthesis of pyrazolidinones **62**[57], oxazolidinones **64**[58], bicyclic pyrazolones **67**[59] and oxepinones **69** and **70**[60] (Scheme 18).



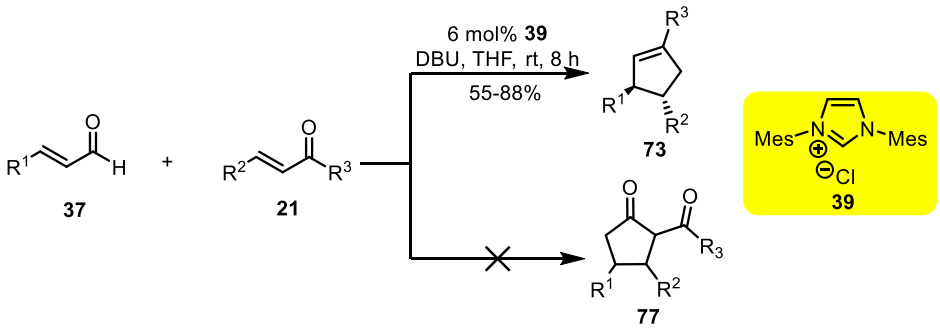
Scheme 18 Selected examples of NHC-catalyzed annulations



Scheme 19 Homoenolate intermediates generated from saturated esters

Very recently, Chi and co-workers described that the homoenolate intermediates could be generated from saturated esters.[61] Both enones and imines worked well in the presence of NHC and somehow the results are even better than the reactions with enals (Scheme 19).

1.3.2 Formation of all carbon cycles

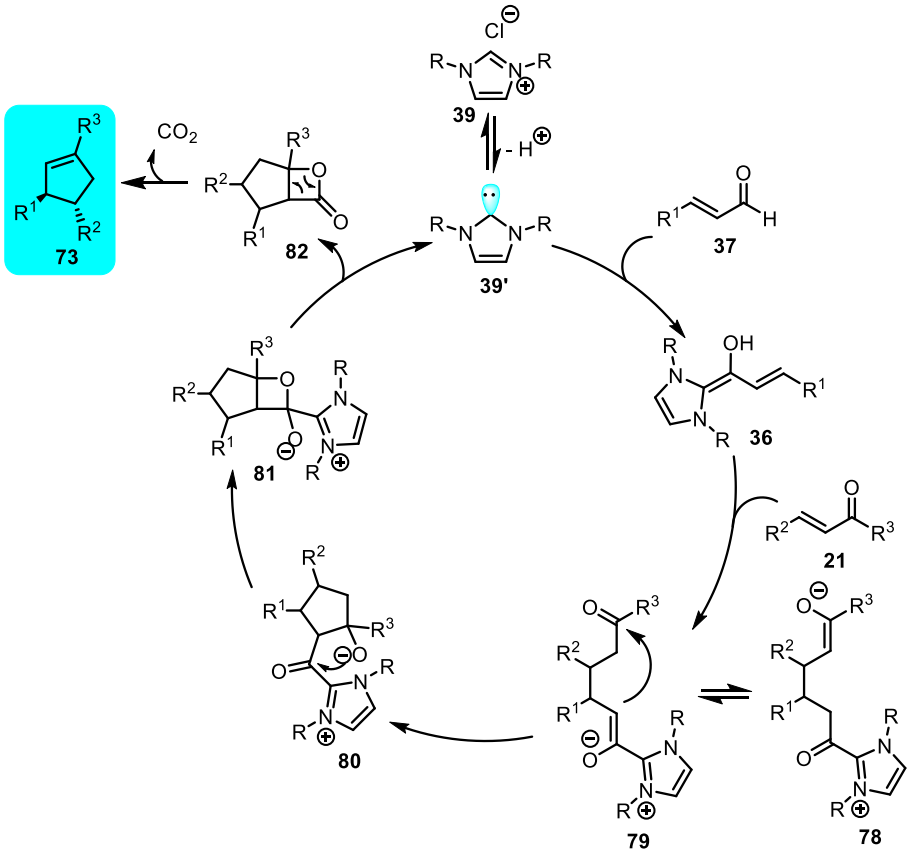


Scheme 20 The homoenolate/enolate domino reactions

During the NHC-catalyzed heterocycle formation *via* homoenolate intermediates, another interesting discovery was by Nair and co-workers developing the cross-condensation of enals and α,β-unsaturated ketones to form the unexpected cyclopentene **73** instead of β-ketocyclopentanone **77** *via* homoenolate/enolate domino reactions (Scheme 20).[62]

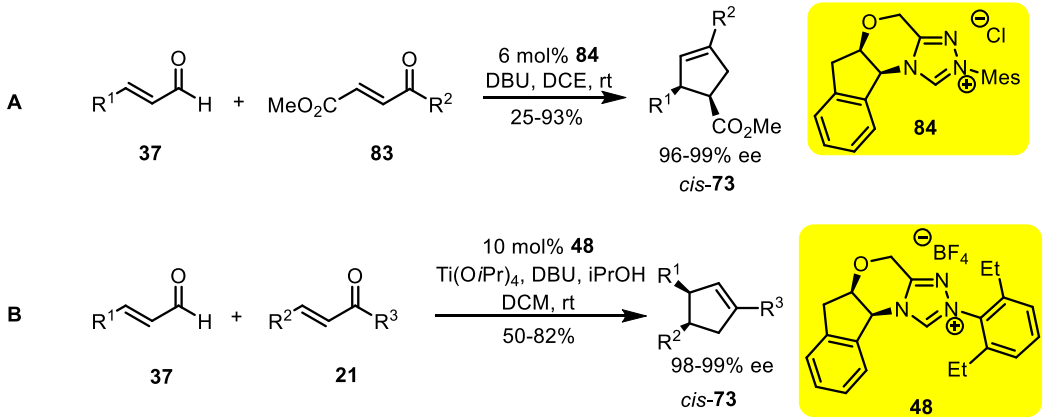
The catalytic cycle showed the Michael addition of the homoenolate **36** to the α,β-unsaturated ketone **21** to form the zwitterionic enolate **79**, followed by an intramolecular aldol reaction to give **80**. Undergoing the β-lactonization, the catalytic cycle was closed with the regeneration of the catalyst **39'**. The formed bicyclic lactones **82** were then converted into the trisubstituted cyclopentenes **73** with the release of CO_2 (Scheme 21).

In 2007, Bode and co-workers expanded the reaction of 4-oxoenones with enals to achieve the *cis*-cyclopentenes of high enantiomerpurity by employing the chiral catalyst **84** (Scheme 22, **A**). [63] The wider substrate scope and excellent stereoselectivities were



Scheme 21 Proposed catalytic cycle for the reaction of α,β-unsaturated ketones with homoenolates

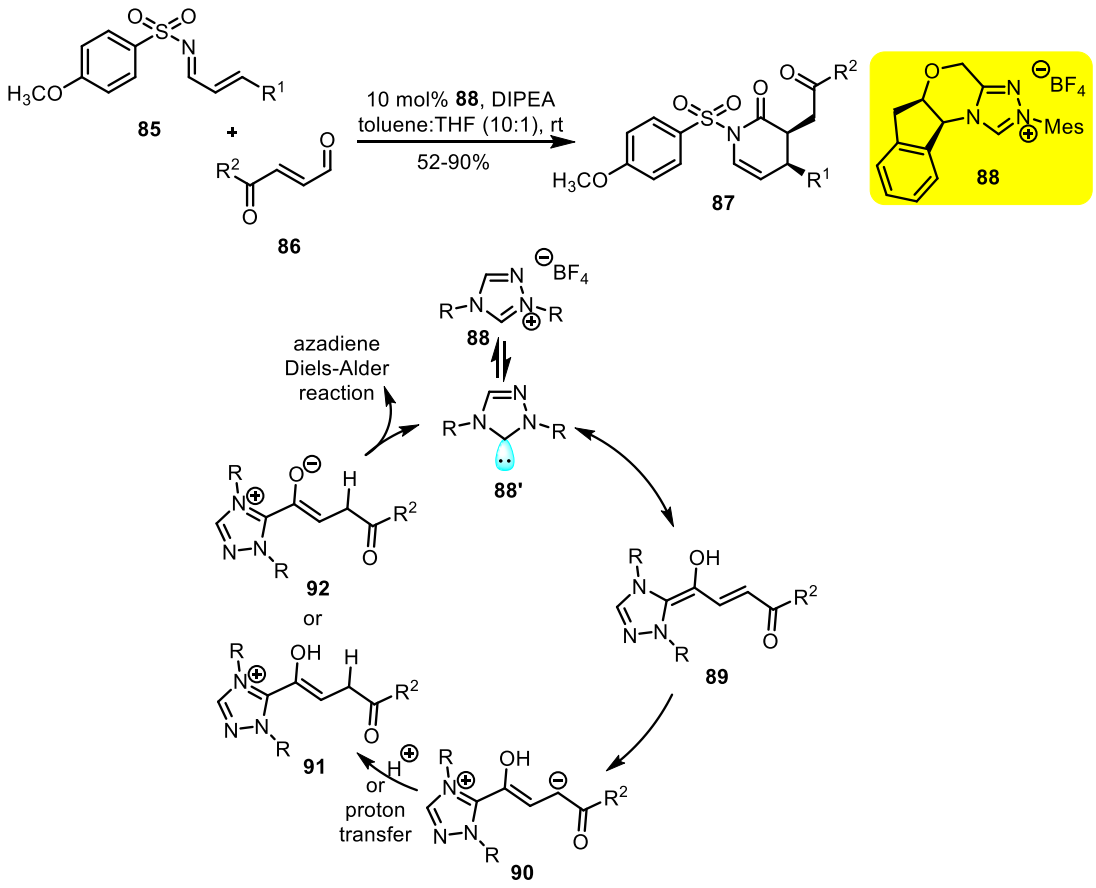
achieved *via* the combination of a Lewis acid Ti(O*i*Pr)$_4$ with NHC **48**.[64] Interestingly, the *cis*-diastereomers of the cyclopentenes were generated (Scheme 22, **B**).



Scheme 22 Enantioselective synthesis of cis-cyclopentenes

1.4 NHC-catalyzed reactions *via* azolium enolate equivalents

1.4.1 Generation *via* α,β-unsaturated aldehydes



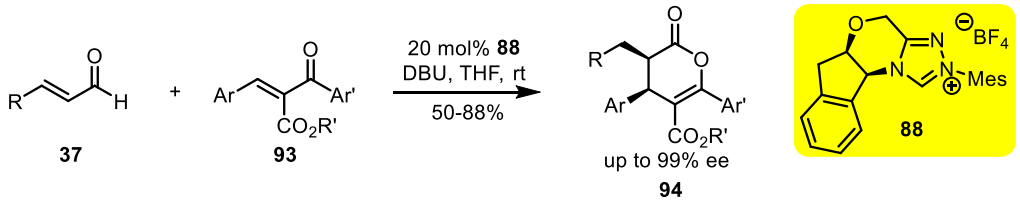
Scheme 23 Enantioselective aza-diene Diels-Alder reaction and postulated cascade for the dienophile formation

The active azolium enolate equivalent could be generated *via* protonation of the homoenolate equivalent, meaning that most of the active α,β-unsaturated aldehyde for the generation of homoenolate was also suitable in the formation of the azolium enolate intermediate.

The original generation of the azolium enolate was developed by Bode and co-workers during the NHC-catalyzed Diels-Alder reaction.[65] The key step of the reaction was the formation of the dienophile **91** or **92**, followed by the cycloaddition with *N*-protected α,β-unsaturated imines **85** to obtain the desired Diels-Alder products **87** (Scheme 23).

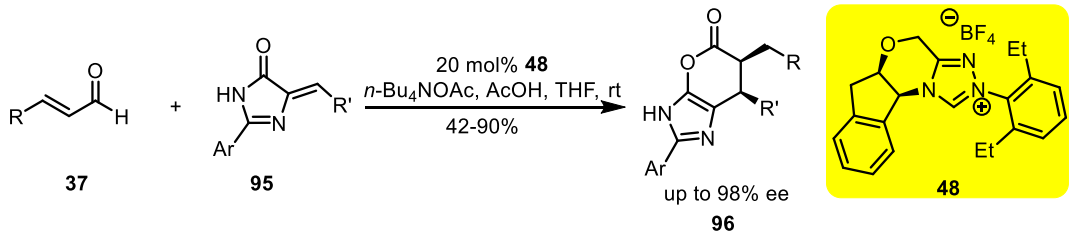
Later, Chi and co-workers investigated the NHC-catalyzed [4+2] cycloaddition

employing enals and enones. Under the catalytic conditions, the dihydropyranones were obtained in good yields with excellent stereoselectivities (Scheme 24).[66]



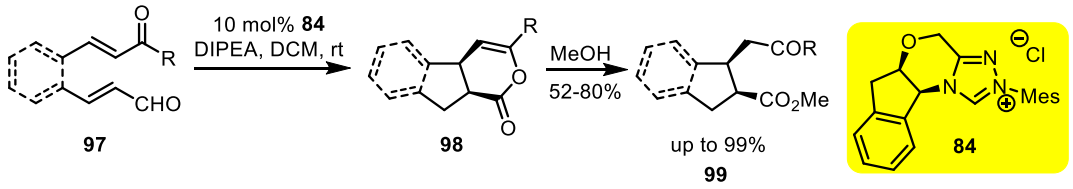
Scheme 24 NHC-catalyzed [4+2] annulation of enals with enones

The reaction between α,β-unsaturated aldehydes with imidazolidinones *via* azolium enolate equivalents for the formation of biologically and pharmaceutically important imidazoles was developed by Scheidt *et al.*.[67] The [4+2] annulation products were obtained in good yields with high stereoselectivities (98% *ee*, 20:1 d.r.) (Scheme 25).



Scheme 25 NHC-catalyzed [4+2] annulation of enals with enones imidazolidinones

Scheidt and co-workers introduced this azolium enolate activated mode to the intramolecular Michael/lactonization reaction, in which tricyclic acylated enols **98** were formed under the catalytic conditions, subsequently hydrolyzed by the addition of MeOH to afford the favored *cis*-bicyclic adducts **99** (Scheme 26).[68]

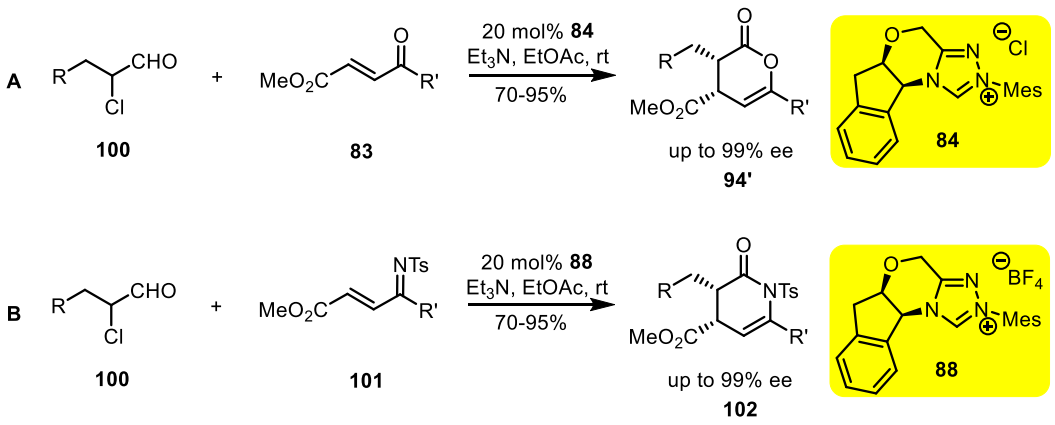


Scheme 26 The intramolecular [4+2] annulation of enals

1.4.2 Generation *via* α-functionalized aldehydes

The aldehydes bearing a leaving group on the α-position could also be activated by NHCs, followed by sequential elimination of the leaving group in the presence of base.

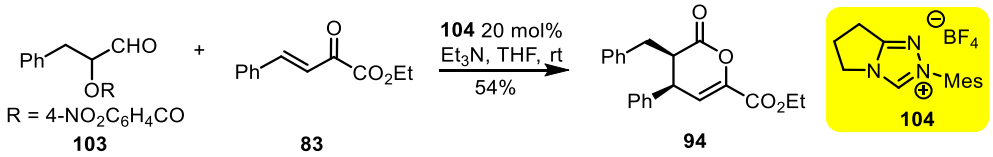
The formed azolium enolates were intensely studied in the catalytic reactions. The first cycloaddition example for the generation of azolium enolates from α-chloroaldehydes was developed by Bode and co-workers.[69] Under the optimized conditions, the oxa-Diels-Alder [4+2] reaction proceeded smoothly with a broad range of substrate scope, in most cases with good yields and excellent stereoselectivities (Scheme 27, **A**). Ye's work extended this strategy to 1-azadienes instead of enones. It also showed great catalytic efficiency *via* the generated dihydropyridinones **102** in good yields with excellent enantioselectivties (Scheme 27, **B**).[70]



Scheme 27 NHC-catalyzed [4+2] annulation of α-chloroaldehydes

Recently, our group developed the NHC-catalyzed annulation of α-chloroaldehydes with nitrovinylindoles[71] or benzothiazoles[72]. Ye and co-workers[73] also investigated the reaction of α-chloroaldehydes with azomethine imines *via* azolium enolate activation, affording the products in good yields with excellent enantioselectivities.

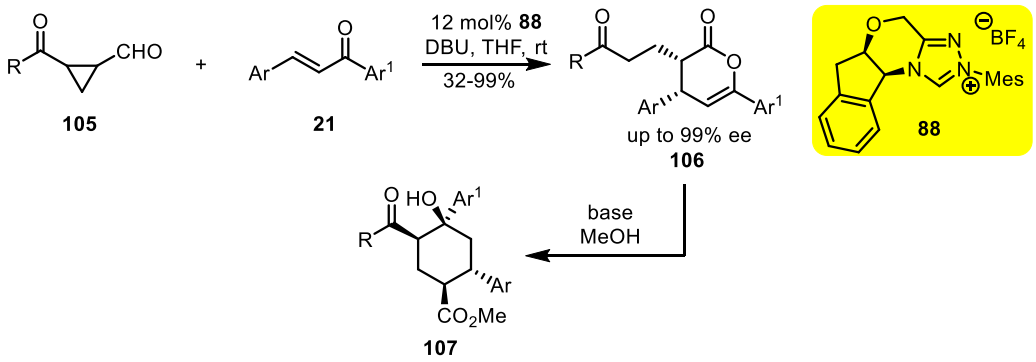
In 2011, Smith extended this method to the utilization of α-aroyloxyaldehydes **103** in the NHC-catalyzed cycloadditions. The more stable and convenient α-aroyloxyaldehydes worked very well under the catalytic conditions (Scheme 28).[74]



Scheme 28 NHC-catalyzed [4+2] annulation of α-aroyloxyaldehydes

In the same year, the formylcyclopropanes **105** as azolium enolate precursors for the

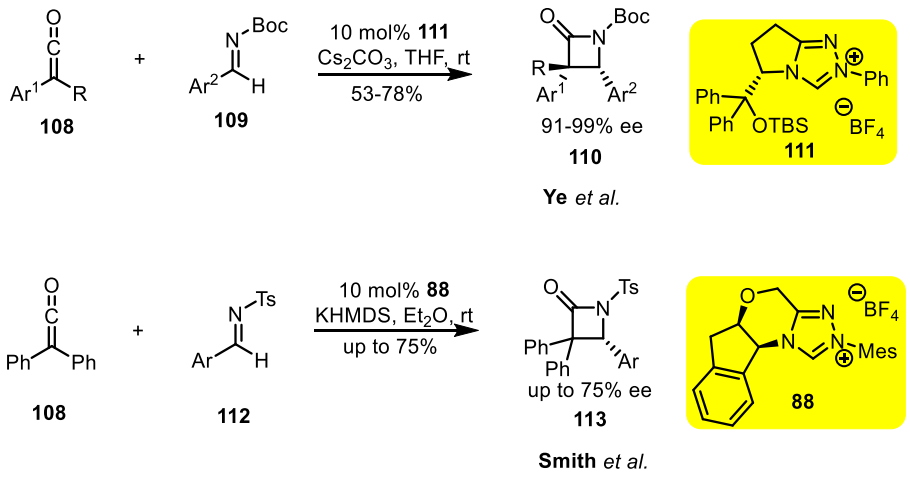
[4+2] cydoaddition were reported by Chi *et al.*,[75] in which δ-lactones **106** were obtained in good yields with high enantioselectivities, followed by transformations in the presence of MeOH and base to afford the cyclohexane **107** with good enantiomeric excesses (Scheme 29).



Scheme 29 NHC-catalyzed [4+2] annulation of formylcyclopropanes

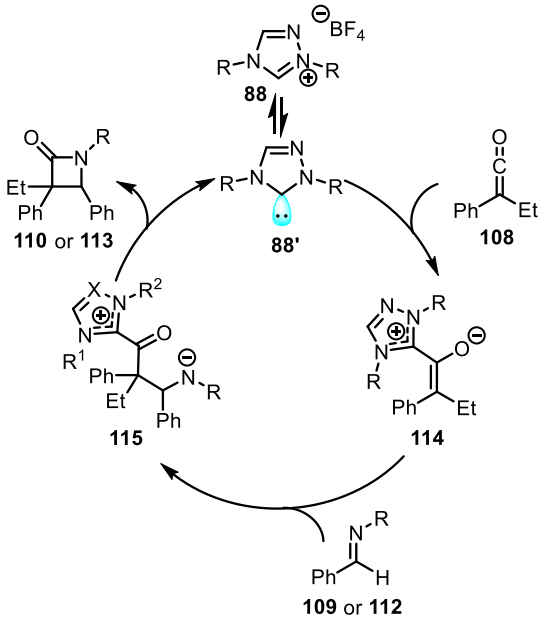
1.4.3 Generation *via* ketenes

Another intensively studied precursor to generate the azolium enolate is ketene that has adjoining C=C and C=O bonds. Simultaneously, Ye[76] and Smith[77] independently reported the NHC-catalyzed Staudinger-type ketene/imine [2+2] cycloaddition for the synthesis of β-lactams, which have attracted great attention due to their extensive bioactivities. Both reactions afforded the β-lactams in good yields with good enantioselectivities (Scheme 30).



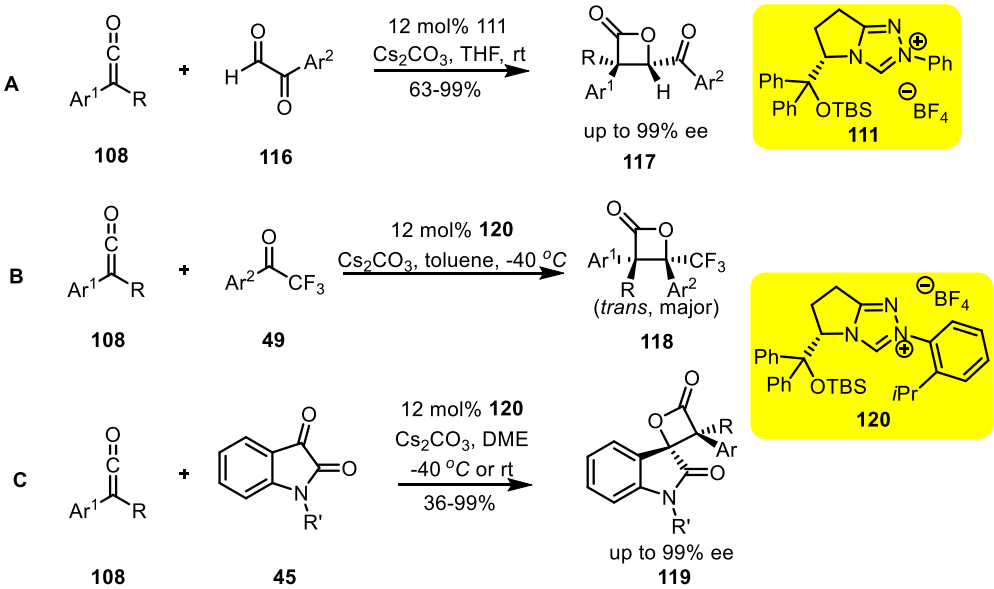
Scheme 30 NHC-catalyzed [2+2] annulation of ketenes with imines

The catalytic cycle shown in Scheme 31 describes the activation of the ketene by the NHC with direct formation of the azolium enolate intermediate. The imines reacted with enolate **114** to form intermediate **115**, followed by the lactamization to obtain the products **110** or **113** with the regeneration of the free NHC-catalyst **88'** (Scheme 31).



Scheme 31 proposed catalytic cycle for the NHC- catalyzed [2+2] annulations

Inspired by the above results, a series of aldehydes were introduced as electrophiles in the NHC-catalyzed reactions with ketenes, to afford β-lactones with excellent enantio-

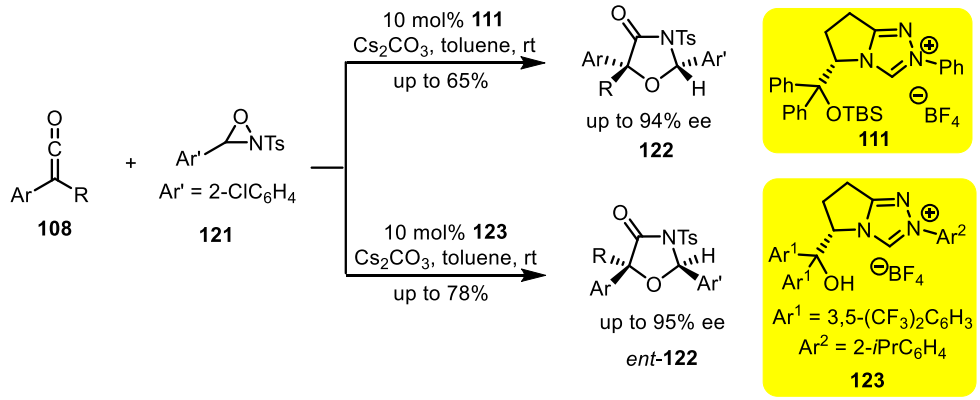


Scheme 32 NHC-catalyzed [2+2] annulation of ketenes with aldehydes and ketones

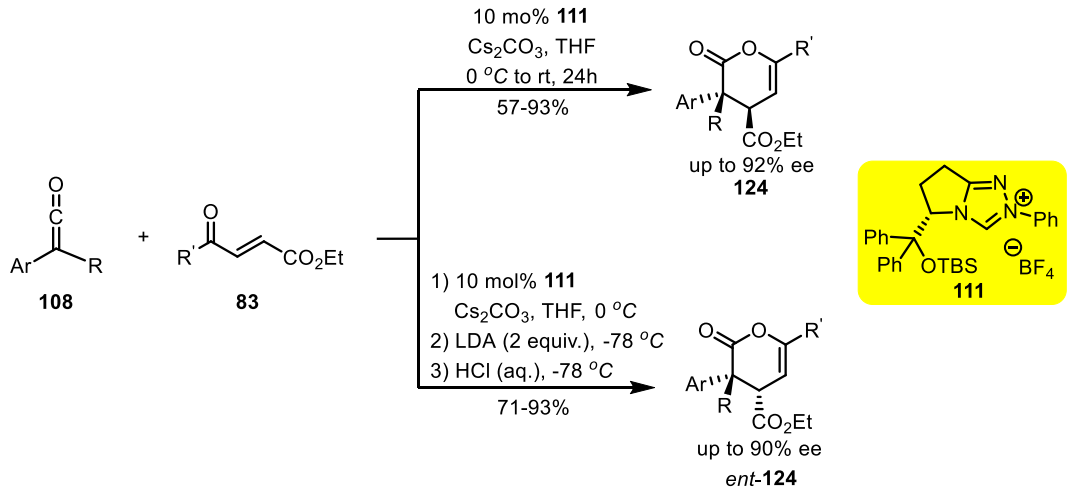
meric excesses (Scheme 32, **A**).[78] Ye's group extended the method to the reactions with ketones by employing trifluoromethyl ketones **49**[79] and isatins **45**[80].

The good yields and high enantioselectivities confirmed the catalytic efficiency of the *N*-heterocyclic carbenes by the formation of the azolium enolate with ketenes (Scheme 32, **B** and **C**).

In 2011, the generation of azolium enolate *via* ketenes was successfully extended to [3+2] reactions.[81] The reaction of ketenes **108** with oxaziridine **121** gave the corresponding [3+2] cycloadolition products **122** in good yields with good enantioselectivities using catalyst **111**. When the catalyst **111** was switched to **123**, which contains a free hydroxy group, the enantiomer *ent*-**122** was obtained with even better results (Scheme 33).

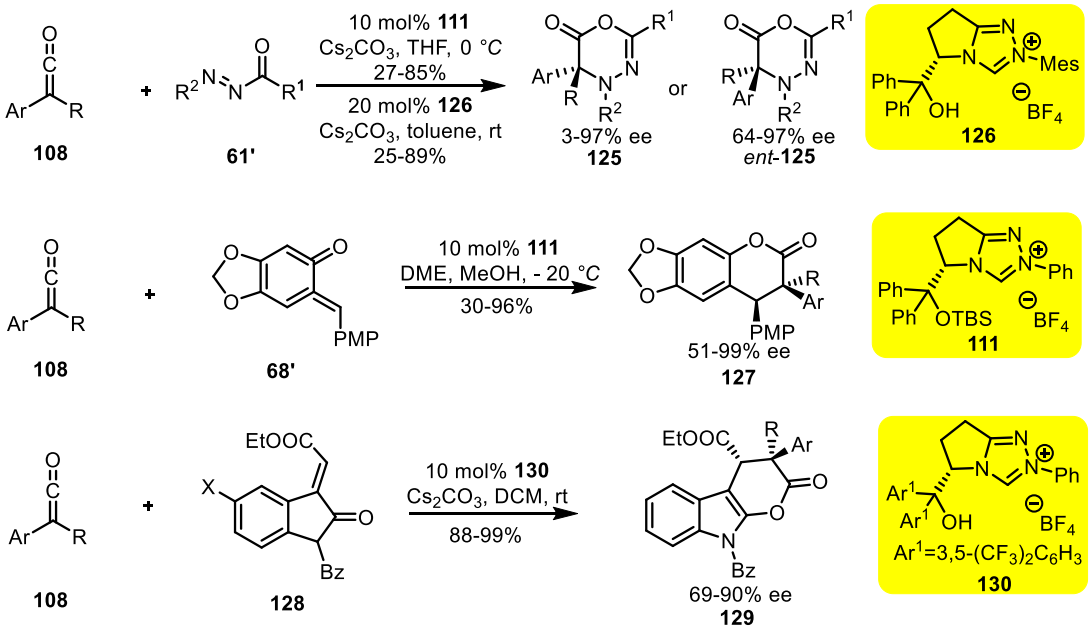


Scheme 33 NHC-catalyzed [3+2] annulation of ketenes with oxaziridine



Scheme 34 NHC-catalyzed [4+2] annulation of ketenes with enones

In 2008, Ye and co-workers also developed the [4+2] cycloaddition of ketenes with enones *via* the direct formation of azolium enolates from the nucleophilic addition of the NHC to ketenes, resulting in an efficient approach for the synthesis of six-membered heterocycles (Scheme 34).[82]

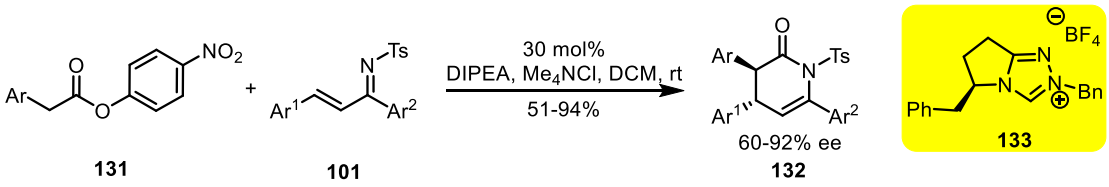


Scheme 35 NHC-catalyzed formal [4+2] cycloadditions of ketene-derived azolium enolates

Further development of this methodology was investigated for the reaction of ketenes with *N*-benzoyldiazenes **61'**[83], *o*-quinone methides **68'**[84] and 3-alkenyloxindoles **128**[85] (Scheme 35). The corresponding products were generated in good yields with good enantioselectivities.

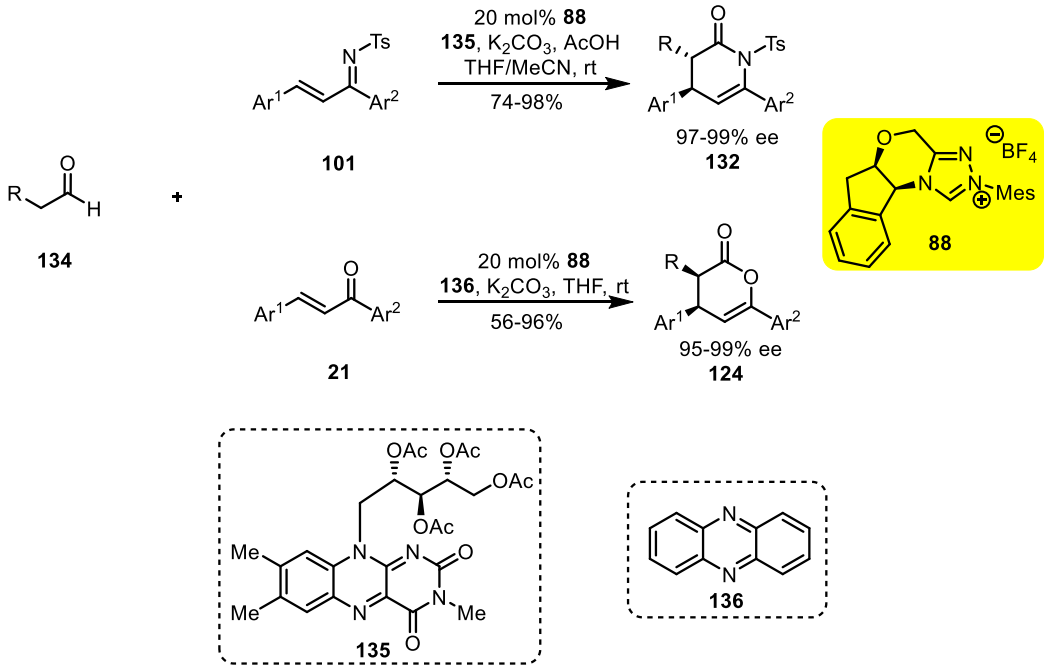
1.4.4 Generation *via* esters and aldehydes

A new method to form the azolium enolate intermediate was reported by Chi *et al.* in 2012.[86] The azolium enolate was easily formed after the addition of NHCs to esters, which reacted with azadienes through *aza*-Diels-Alder pathway in the presence of base. The products were obtained in good yields (51-94%) with high enantioselectivities (60-92% *ee*) (Scheme 36).



Scheme 36 Generation of azolium enolate from esters

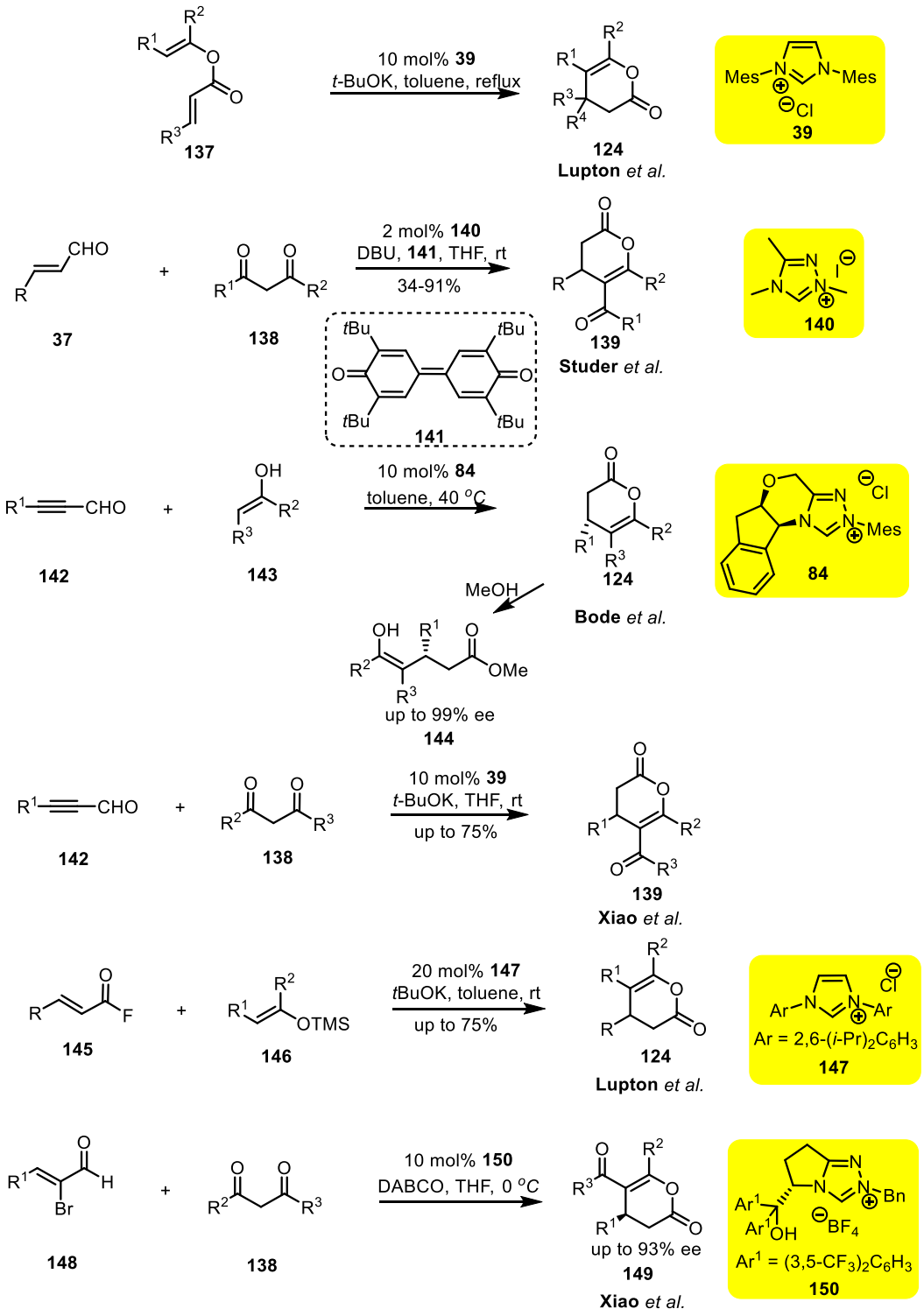
Extension of the strategy to asymmetric [4+2] cycloaddition using simple aliphatic aldehydes with enones was investigated by Rovis and co-workers.[87] The addition of an



Scheme 37 Generation of azolium enolates from aliphatic aldehydes

oxidant promoted the formation of the azolium enolates of NHCs with aldehydes. *cis*-Lactones **124** were afforded in high yields with excellent enantioselectivities, as well as in the reaction with azadiens to form the *trans*-lactams **132** (Scheme 37).

1.5 NHC-catalyzed reactions *via* α,β-unsaturated acylazolium intermediates



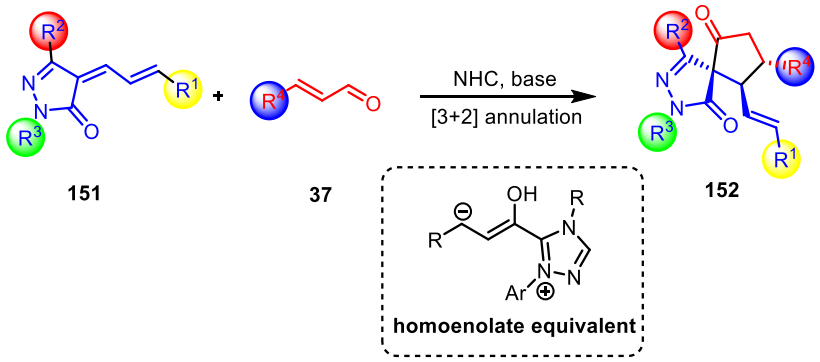
Scheme 38 Generation of α,β-unsaturated acyl azolium intermediates from different substrates

Another activation mode *via* NHC-catalyzed reactions was the formation of unsaturated acylazolium intermediates. As shown in Scheme 38, the initially generated α,β-unsaturated acylazolium from α,β-unsaturated esters **137** was described by Lupton *et al.* in 2009 for the synthesis of dihydropyranones **124**.[88] The δ-lactones were generated in good yields. Inspired by this result, Studer and co-workers also developed the generation of α,β-unsaturated acylazolium intermediate *via* oxidation of the homoenolate **37** for the synthesis of δ-lactones **139**.[89] The work of Bode *et al*. disclosed the formation of α,β-unsaturated acylazolium *via* the activation of ynals **142**, resulted in the kojic acid derivatives **144** in excellent yields and enantiopurity.[90] A similar protocol was also described by Xiao and co-workers.[91] Furthermore, the acylazolium intermediate could also be generated *via* α,β-unsaturated acyl fluorides **145**[92] and bromoenals **148**[93] for the synthesis of dihydropyranones. This methodology also opened a new pathway for the synthesis of δ-lactams.[94]

1.6 Overview of the doctoral work

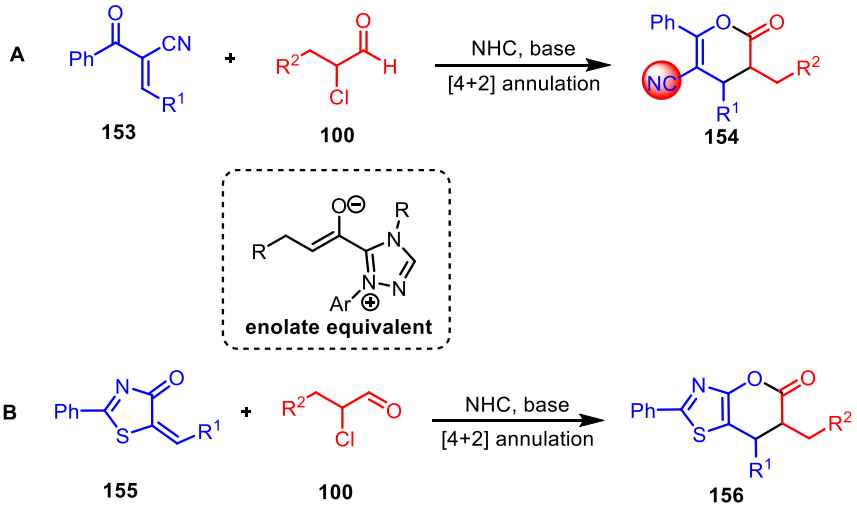
NHCs have attracted great attention and developed rapidly in the past decades. Inspired by the wide application of NHC organocatalysts, this doctoral work focused on the asymmetric reactions of enals and α-chloroaldehydes catalyzed by NHCs. There are three research projects included in this thesis.

The first project focused on the asymmetric synthesis of five-membered spiropyrazolones. In the reaction, cinnamaldehydes **37** were employed as catalytic precursors in the formation of the homoenolate equivalent. As shown in Scheme 39, the desired spiropyrazolones **152** were generated with the flexible variation of all four substituents R^1-R^4.



Schem 39 NHC-catalyzed [3+2] reaction via homoenolate equivalent

Project 2 and 3 focused on the generation of azolium enolate equivalents *via* α-chloroaldehydes **100**. (*E*)-2-benzoyl-3-phenylacrylonitriles **153** (Scheme 40, **A**) and 5-alkenyl thiazolones **155** (Scheme 40, **B**) were introduced as electrophiles in the NHC-catalyzed reactions with α-chloroaldehydes, a series of 5-cyano-substituted dihydropyranones **154** and dihydropyrano thiazoles **156** were synthesized, which contain the crucial structural feature of many natural and medical products.



Scheme 40 NHC-catalyzed [4+2] reaction via enolate equivalents

2. Results and Discussion

2.1 NHC-catalyzed asymmetric synthesis of five-membered spiropyrazolones

2.1.1 Background and motivation

Recently, pyrazolones and related heterocyclic-fused analogues turned out to play an important role in many biological and pharmaceutical products.[95] For instance, the spiropyrazolones bearing a cyclopentane or cyclohexane ring showed type-4 phosphodiesterase inhibitor activities (Figure 8, **157**, **158**)[96] and anticancer activities (Figure 8, **159**).[97]

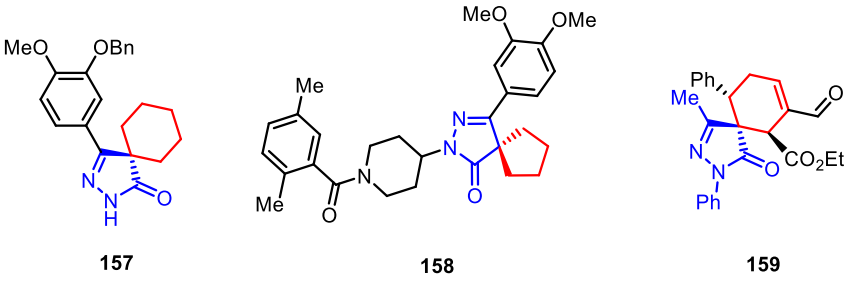
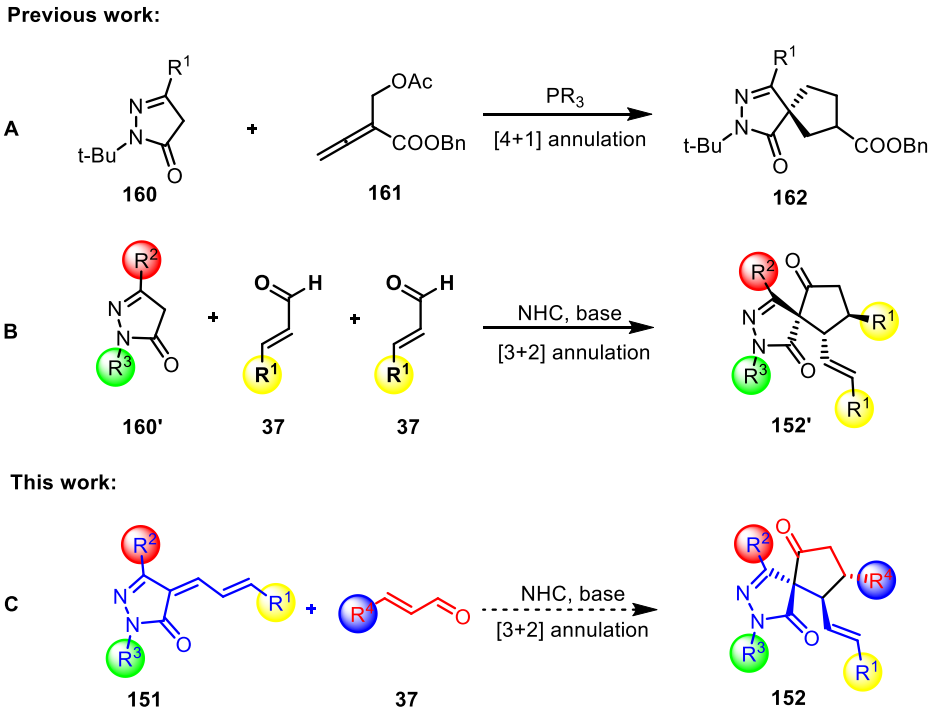


Figure 8 Selected pharmaceutically active spiropyrazolones

However, most of the synthetic methodologies employed special reagents[98] and organocatalysts [99] for the construction of the six-membered carbocyclic spiropyrazolones. In 2004, an asymmetric synthesis of pyrazolone-fused spirocyclopentane was investigated by Lu's group through a phosphine catalyzed [4+1] annulations reaction (Scheme 41, **A**).[100] NHCs have developed rapidly and emerged as an important class of organocatalyst in the past decades. Very recently, our group reported an NHC-catalyzed three-component one-pot asymmetric synthesis of spiropyrazolones (Scheme 41, **B**).[101] Based on the previous work, we have developed an NHC-catalyzed [3+2] annulation reaction through a new strategy for the asymmetric synthesis of spiropyarozolones bearing a five-membered carbocycle, in which all four substituents R^1 - R^4 are variable (Scheme 41, **C**).



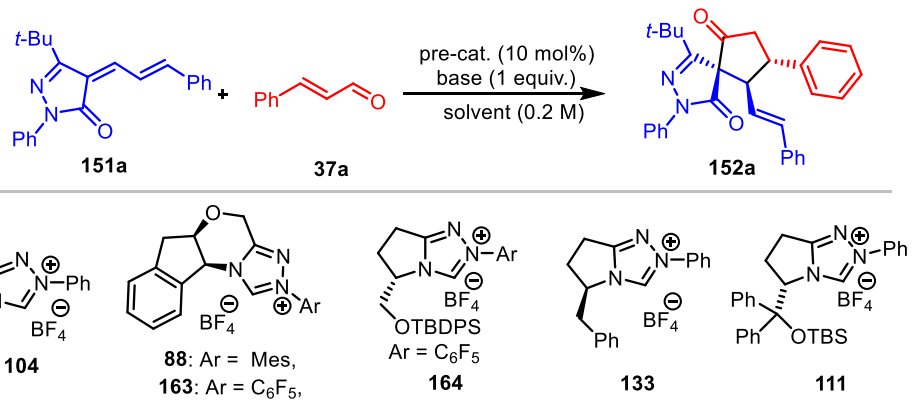
Scheme 41 Selected strategies for the asymmetric synthesis of spiropyrazolones

2.1.2 Optimization of the reaction conditions

To test the feasibility of our above described strategy, unsaturated pyrazolone **151a** and cinnamaldehyde **37a** were used as model substrates to conduct a systematic screening of the reaction conditions. Initially, the readily available substituted pyrazolone **151a** and cinnamaldehyde **37a** were exposed to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DCM at room temperature for 12 h in the presence of pre-catalyst **104** as catalyst. To our delight, the expected reaction proceeded smoothly and the corresponding product **152a** was isolated in 45% yield with excellent diastereoselectivity (Table 1, entry 1). Encouraged by the initial result, a series of chiral NHC pre-catalysts was examined with DBU as base in DCM (Table 1, entries 2-6). The catalyst **88** gave the desired product **152a** in 49% yield with high *ee* of 92%, however the diastereoselectivity was not good with 5:1 d.r.. Switching the catalyst to **163** the product was afforded in 42% yield with slightly improved *ee* of 93% and only 1:1 d.r.. The pre-catalyst **164**, **133** and **111** were also screened for the reaction. The desired

product **152a** was obtained with lower yield and enantiselectivity (Table1, entries 4-6). Thus the catalyst **88** was employed for the subsequent screening. Some inorganic bases (Table 1, entries 7-10) and organic bases (Table 1, entries 11-13) were screened for this reaction. It turned out that the when DMAP was employed as the base, the reaction proceeded smoothly to give the product **152a** in 51% yield with 93% *ee* and > 20:1 d.r.. Although the inorganic base Cs_2CO_3 gave the product with 94% *ee*, the diastereoselectivity was lower (d.r. = 1:1). Utilizing the catalyst **88** and DMAP as the base in different solvents (Table 1, entries 14-19), we found that the enantioselectivity was not influenced albeit with a big improvement in the yield when the reaction was carried out in DCE. The product was obtained in 71% yield with 93% *ee* and > 20:1 d.r. in the presence of triazolium salts **88** as the pre-catalyst, DMAP as base in DCE (Table 1, entry 18).

Table 1 Optimization of the reaction conditions[a]



Entry	Pre-cat.	Solvent	Base	Yield(%)[b]	d.r.[c]	*ee* (%)[d]
1	**104**	CH_2Cl_2	DBU	45	> 20:1	--
2	**88**	CH_2Cl_2	DBU	49	5:1	92
3	**163**	CH_2Cl_2	DBU	42	1:1	93
4	**164**	CH_2Cl_2	DBU	23	>20:1	90
5	**133**	CH_2Cl_2	DBU	27	>20:1	88
6	**111**	CH_2Cl_2	DBU	15	>20:1	86
7	**88**	CH_2Cl_2	Cs_2CO_3	45	1:1	94
8	**88**	CH_2Cl_2	K_3PO_4	24	>20:1	92
9	**88**	CH_2Cl_2	KO*t*-Bu	11	>20:1	93
10	**88**	CH_2Cl_2	KOAc	42	>20:1	92
11	**88**	CH_2Cl_2	DMAP	51	>20:1	93

12	**88**	CH_2Cl_2	DABCO	39	1:2	89
13	**88**	CH_2Cl_2	DIPEA	20	5:1	93
14	**88**	EtOAc	DMAP	51	>20:1	88
15	**88**	THF	DMAP	54	>20:1	85
16	**88**	toluene	DMAP	44	>20:1	90
17	**88**	1,4-dioxane	DMAP	71	>20:1	85
18	**88**	**DCE**	**DMAP**	**71**	**>20:1**	**93**
19	**88**	MeCN	DMAP	57	>20:1	89

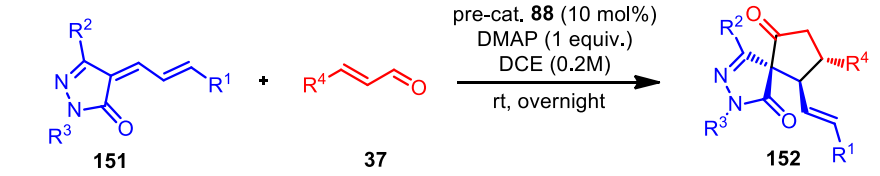
[a]Reaction conditions: **151a** (0.4 mmol, 1.0 equiv.), **37a** (0.8 mmol, 2.0 equiv.), pre-cat (0.04 mmol, 10 mol%), base (0.4 mmol, 1.0 equiv.), solvent (2mL), at r.t. for 12 h. [b]Yield of **152a** after column chromatography. [c]The d.r. was determined by ^{1}H NMR of the crude reaction mixture. [d]The *ee* value was determined by HPLC on a chiral stationary phase.

2.1.3 Investigation of the substrate scope

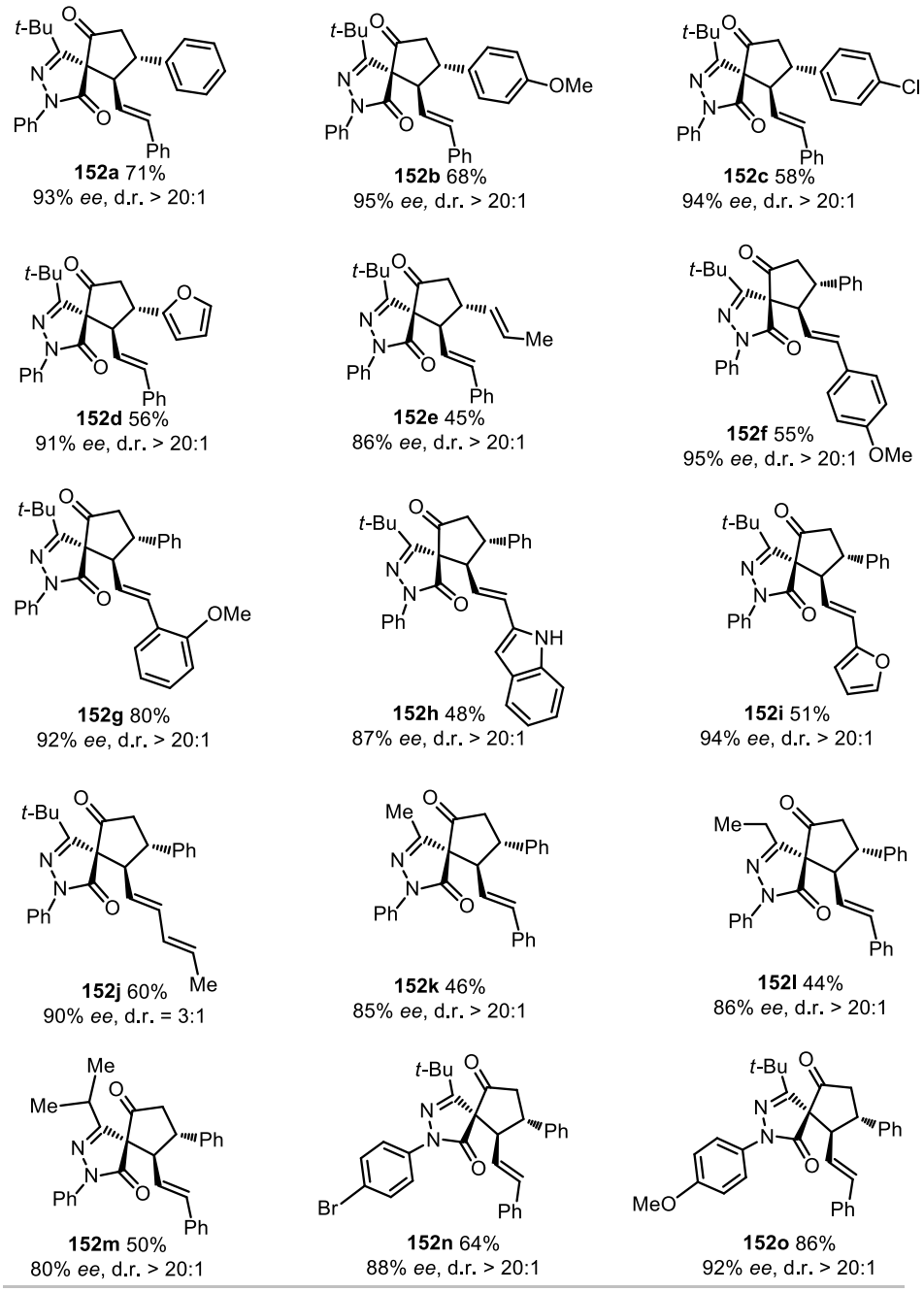
With the optimized reaction conditions in hand, we next investigated the substrate scope. Firstly, a series of enals **37** with different substituents were tested. The cinnamaldehyde derivatives bearing electron-donating and electron-withdrawing groups reacted efficiently with pyrazolone **151a** to provide the spirocyclopentane pyrazolones in good yields with high enantioselectivities and excellent diastereoselectivities (Table 2, **152a–c)**. The enals bearing 2-furyl and 1-propenyl groups also reacted smoothly and the desired product **152d** and **152e** were obtained in good yields and exellent enantio- and diastereoselectivities. Next, the variation of the substituted pyrazolones **151** was tested and showed perfect tolerance in this reaction. Substrates with substituents both at the *ortho*- and *para*-position on the phenyl ring of R^1 proceeded smoothly to give the corresponding products (Table 2, **152f** and **152g**) in good yields with very good enantioselectivities and diastereoselectivities. Instead of the phenyl ring, substrates with indole group, 2-furyl and 1-propenyl group (Table 2, **152h-j**), the reaction products were obtained in good yields with good to excellent enantio- and diastereoselectivities. Substituents (R^2) at the *ortho*-position of the pyrazolones, such as methyl, ethyl and isobutyl groups (Table 2, **152k-m**) were also tolerated in this reaction without significant influence of the yield, enantio- and diastereoselectivity. Variations of the N-aryl groups of the pyrazolones (Table 2,

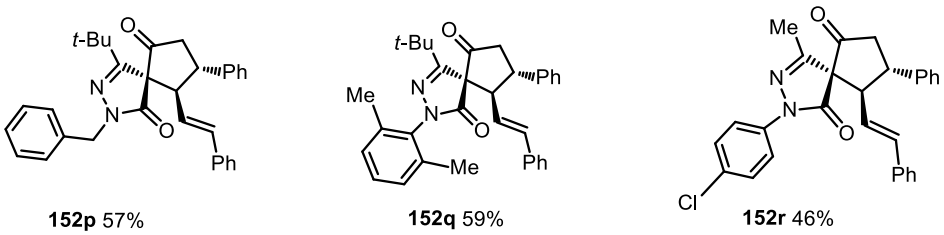
152n-r) furnished the desired products in good yields with very good stereoselectivities.

Table 2 Substrate scope of the spirocyclopentane pyrazolones[a,b,c,d]



151 + 37 → 152





[a]Reaction conditions: **151** (0.4 mmol, 1.0 equiv.), **37** (0.8 mmol, 2.0 equiv.), **88** (0.04 mmol, 10 mol%), DMAP (0.4 mmol, 1.0 equiv.), solvent (2 mL), at r.t. for 12h. [b]Yield of **152** after column chromatography. [c]The d.r. was determined by ^{1}H NMR of the crude reaction mixture. [d]The *ee* value was determined by HPLC on a chiral stationary phase.

2.1.4 Determination of the absolute configuration

The relative and absolute configuration of the spiropyrazolone **152p** was determined by X-ray crystal structure analysis (Figure 9),[102] and the configuration of all other products **152** was assigned accordingly.

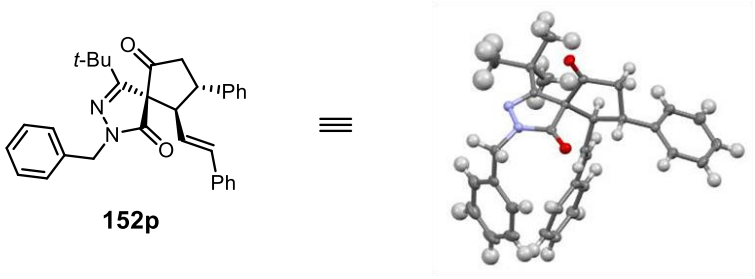
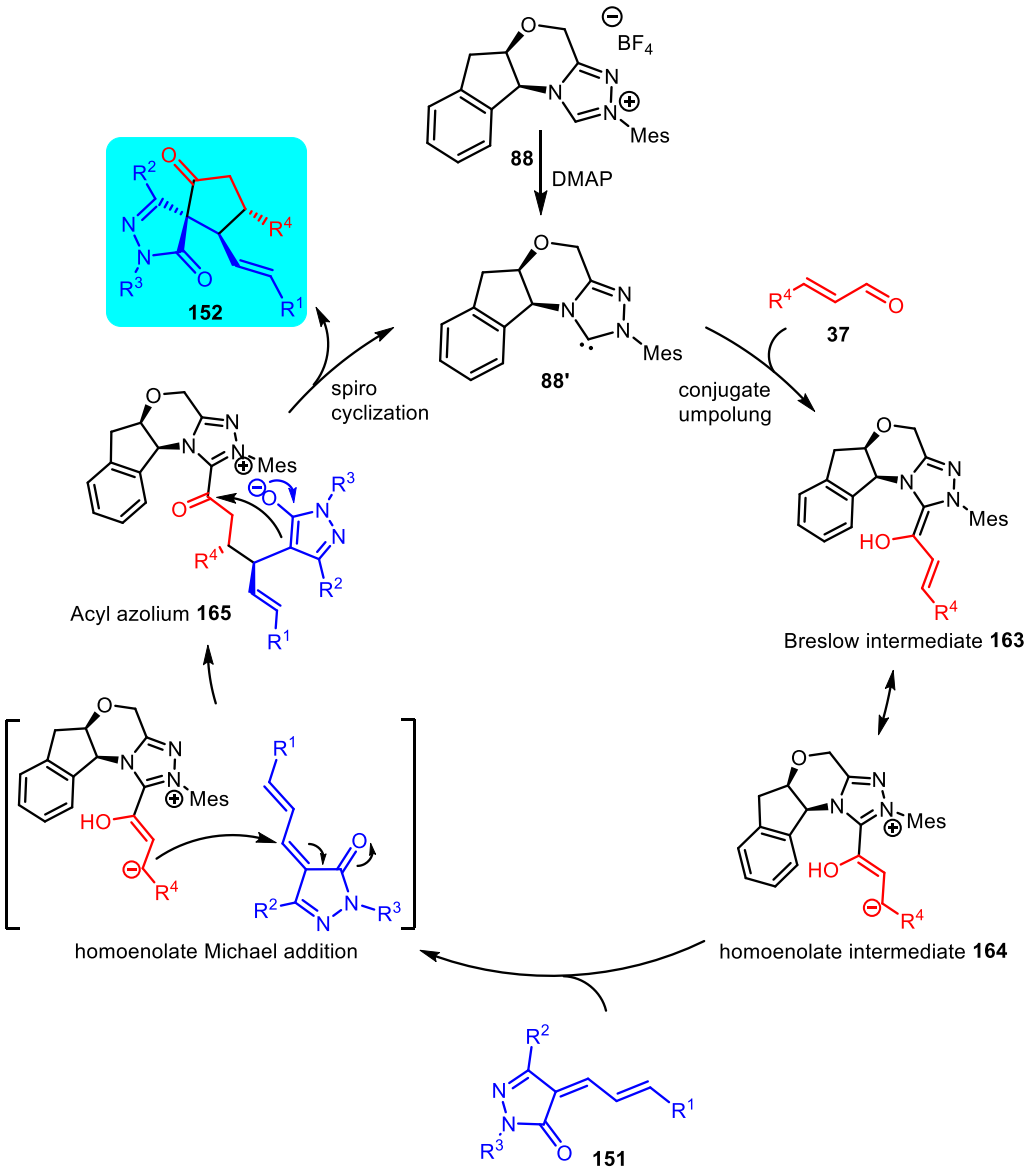


*Figure 9 X-ray crystal structure of the spiropyrazolone **152p***

2.1.5 Proposed mechanism

The plausible catalytic cycle is depicted in Scheme 42. The desired spiropyrazolones **152** were formed by the addition of the free NHC **88'**, which were obtained under the basic conditions, to the enals **37** to generate the Breslow intermediate **163**, which then tautomerized to the homoenolate intermediate **164**. Adducts **165** were afforded *via* a Michael addition to the substituted pyrazolones **151.** The followed spirocyclization gave the final annulation products **152** and regenerated the free NHC catalyst **88'** for further cycles.



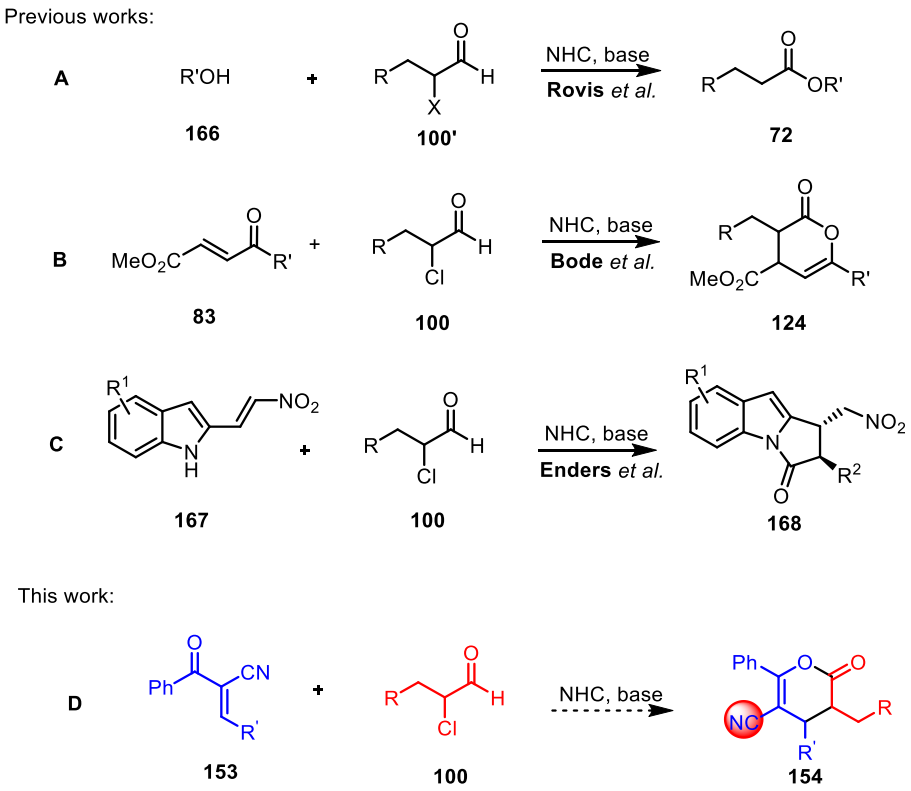
Scheme 42 Proposed catalytic cycle of the asymmetric spiropyrazolone synthesis

2.2 NHC-catalyzed asymmetric synthesis of 5-cyano-substituted dihydropyranones

2.2.1 Background and motivation

Over the past two decades, NHCs have become one of the most powerful organocatalysts, especially in the asymmetric synthesis of heterocycles.[2, 83, 86, 103] The activation of α-haloaldehydes by NHCs was originally investigated by Rovis and co-workers in 2004.[104] In the internal redox reaction, the α-haloaldehyde was

activated by the NHCs to form the Breslow intermediate bearing a leaving group at the β-position. After the tautomerization, the acyl azolium intermediate reacted with the alcohol to form esters (Scheme 43, **A**). In 2006, Bode *et al.* expanded the use of α-haloaldehydes in hetero-Diels-Alder reactions *via* the enolate equivalents (Scheme 43, **B**).[69] The α-chloroaldehyde was employed as a precursor as the catalytic inhibitor, which then reacted with oxodienes to form δ-lactones. Later, our group has also reported the NHC-catalyzed asymmetric annulations of α-chloroaldehydes with nitroalkenes *via* enolate intermediates (Scheme 43, **C**).[71] Based on the previous works, we have developed an NHC-catalyzed asymmetric [4+2] cycloaddition of (*E*)-2-benzoyl-3-arylacrylonitriles with α-chloroaldehydes to generate the 5-cyano-substituted dihydropyranones *via* the azolium enolate equivalent (Scheme 43, **D**). The presence of the cyano group and in particular the α,β-unsaturated acrylonitrile moiety are of considerable importance in organic chemistry as it occurs in many natural and pharmaceutical products.



Scheme 43 NHC catalyzed reactions of α-haloaldehydes

The acrylonitrile group has attracted much attention of the chemists due to their

significant and wide spectrum of biological activities.[105] For examples, the 6-cyanomorphinan (Figure 10, **169**) was found to have antinocoception activity in biological studies.[106] In 2006, it was found that the nucleosides (*E*)-**170a** and (*Z*)-**170a** acted as an inhibitor of AdcHcy hydrolase whereas (*E*)-**170b** acted as active site directed irreversible inhibitor by the formation of a covalent labeling of AdcHcy hydrolase (Figure 10, **170**).[107] The reported TCE, which was abbreviated from tricycles containing non-enolizable cyano enone, beared two cyano enones and treated as essential factor in inflammatory diseases and cancer (Figure 10, **171**).[108] In addition, the cyano group is also very important in the transformation to the nitro group, amino group and amide group, which are requisite in many natural products and pharmaceuticals.[109] Beside the importance of the cyano group, the δ-lactone structure is also a crucial structural feature in many biological and medicinal products.[110] One example is the nepetalactone, which is a prominent attractant for cats (Figure 10, **172**).[111]

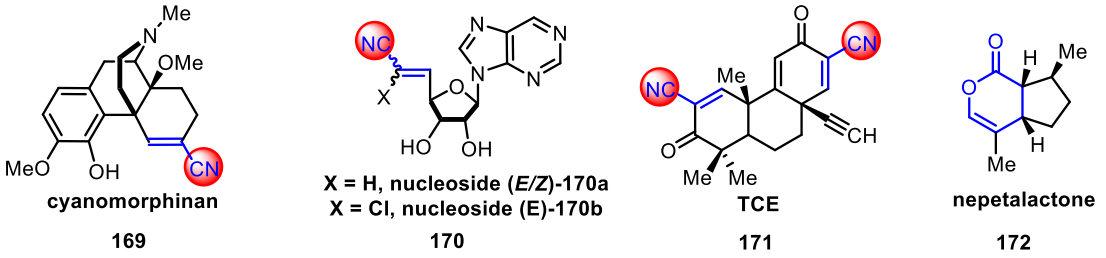


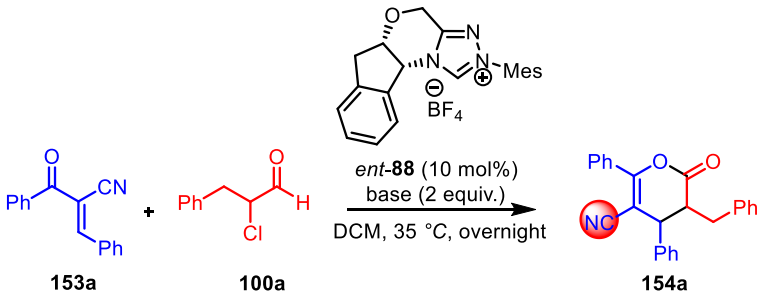
Figure 10 Typical examples of natural products and pharmaceuticals containing the acrylonitrile and δ-lactone moieties

2.2.2 Optimization of the reaction conditions

The evaluation of the reaction conditions started by employing α-cyanoenone **153a** and α-chloroaldehyde **100a** as model compounds in the presence of *N*-mesityl-substituted triazolium salt *ent*-**88** as the pre-catalyst and DABCO as the base in DCM at 35 °C (Table 3, entry 1). To our delight, the desired cyano-substituted δ-lactone **154a** was generated in 85% yield with 49% *ee*. Subsequently, a series of inorganic and organic bases were tested under the previous conditions (Table 3, entries 2-8). The strong organic base DBU (Table 3, entry 3) gave only trace amount of the desired product

154a, while the others provided good results in terms of yield and *ee*. When KOAc (Table 3, entry 8) was used as base, we found the excellent result (93% yield, 99% *ee*). In all cases, the diastereoselectivities were higher than 20:1.

Table 3 Optimization of the reaction conditions[a,d]



Entry	Base	Yield (%)[b]	*ee* (%)[c]
1	DABCO	85	49
2	TMEDA	75	55
3	DBU	trace	nd
4	NEt_3	70	99
5	DIPEA	90	97
6	K_3PO_4	87	60
7	Cs_2CO_3	68	84
8	**KOAc**	**93**	**99**

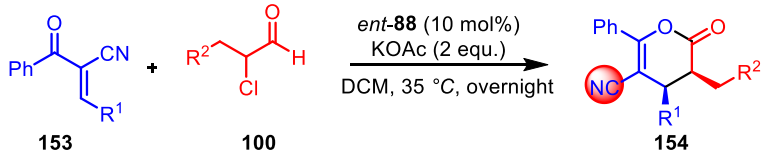
[a]Reaction conditions: **153a** (0.2 mmol, 1.0 equiv.), **100a** (0.6 mmol, 3.0 equiv.), *ent*-**88** (0.02 mmol, 10 mol%), base (0.4 mmol, 2.0 equiv.), solvent (1 mL), at r.t. for 12h. [b]Yield of **154a** after column chromatography. [c]The *ee* value was determined by HPLC on a chiral stationary phase. [d]In all cases, the d.r. is >20:1.

2.2.3 Investigation of the substrate scope

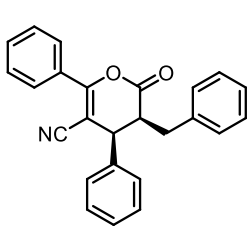
Under the established optimal conditions, the substrate scope of both enones **153** and α-chloroaldehydes **100** was investigated. As indicated in Table 4, a number of substituted α-cyanoenones **153** were found to be suitable for this reaction, irrespective of the *para*-substituents are electron-donating groups (4-$MeOC_6H_4$, 4-MeC_6H_4) or electron-withdrawing groups (4-ClC_6H_4, 4-BrC_6H_4 and 4-FC_6H_4). The corresponding dihydropyranones (Table 4, **154b-f**) were generated in high yield with excellent

enantio- and diastereoselectivities. The *meta*-substituents (3-MeC_6H_4 and 3-ClC_6H_4) of the enones **153** were also tolerated and afforded the desired [4+2] cycloaddition products (Table 4, **154g** and **154h**) in good yield with both 99% *ee*. Variations of the steric hindrance of R^1 (2-$MeOC_6H_4$, 2-MeC_6H_4 and 2-ClC_6H_4) were tested and the yields of the corresponding products (Table 4, **154i - k**) were slightly decreased without influencing the enantio- and diastereoselectivities. The extension of R^1 to 1-naphthyl and benzodioxol groups also worked successfully, providing the δ-lactone products (Table 4, **154l** and **154m**) in excellent yields with excellent *ee*, albeit with lower d.r. of 2:1 in the case of **154l**. Furthermore, investigation of the aliphatic α-chloroaldehydes also showed excellent tolerance and the desired products (Table 4, **154n-q**) were afforded in good yields and almost enantiopure.

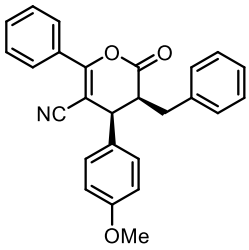
Table 4 Substrate scope of the dihydropyranones[a,c,d,e]



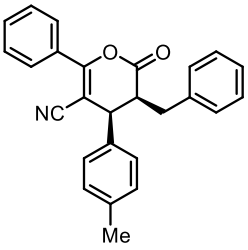
153 **100** **154**



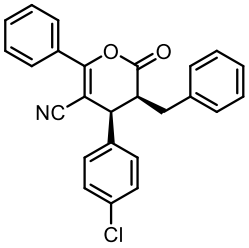
154a 93%
99% *ee*, d.r. > 20:1



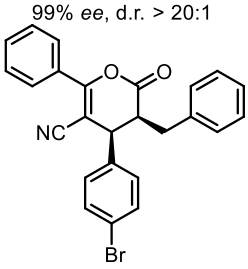
154b 87%
99% *ee*, d.r. > 20:1



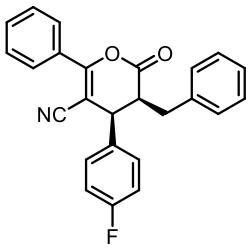
154c 86%
99% *ee*, d.r. > 20:1



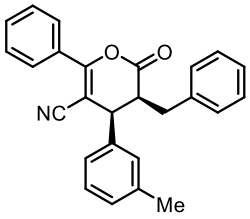
154d 92%
98% *ee*, d.r. > 20:1



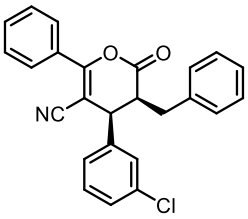
154e 93%
98% *ee*, d.r. > 20:1



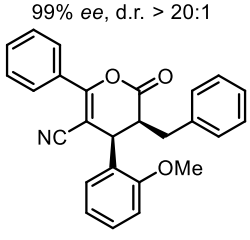
154f 87%
99% *ee*, d.r. > 20:1



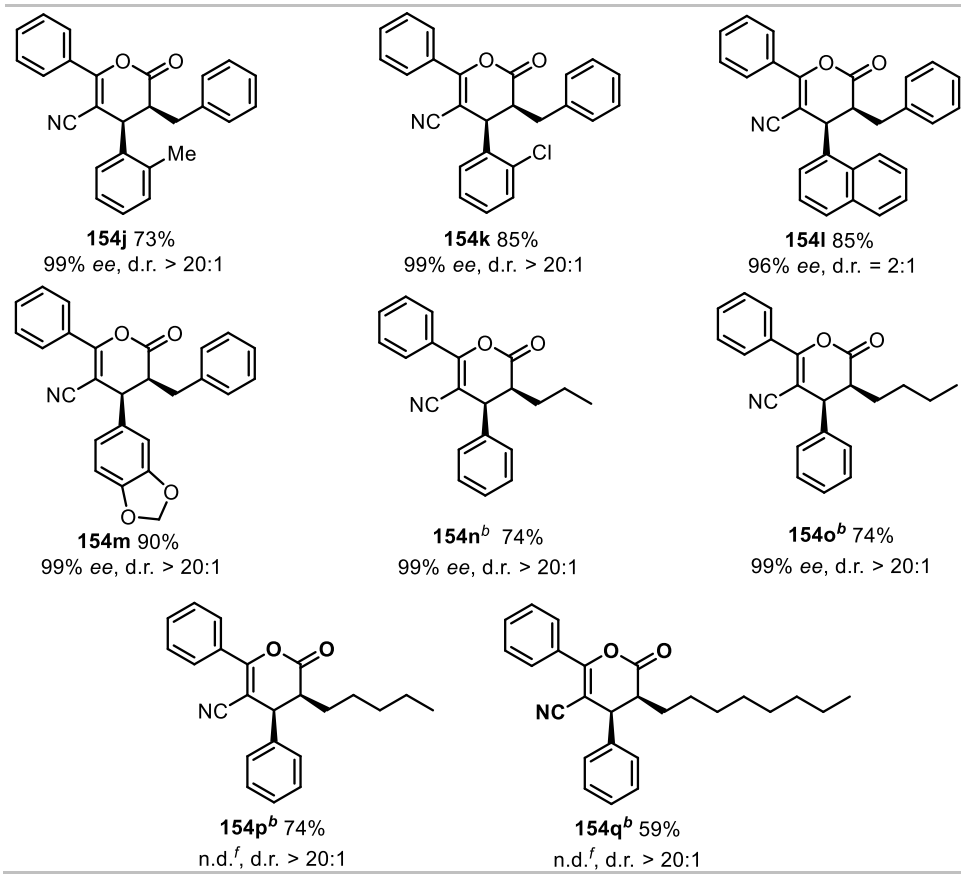
154g 89%
99% *ee*, d.r. > 20:1



154h 92%
99% *ee*, d.r. > 20:1



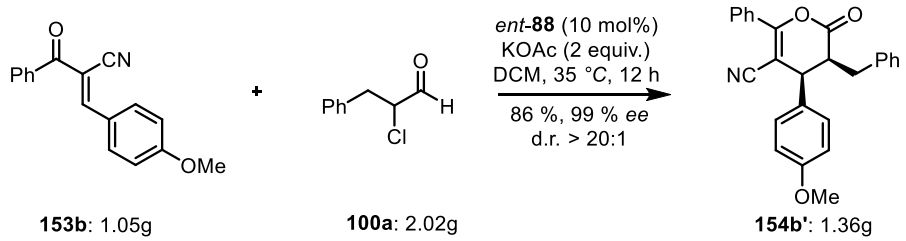
154i 88%
97% *ee*, d.r. > 20:1



[a]Reaction conditions: **153** (0.4 mmol, 1.0 equiv.), **100** (1.2 mmol, 3.0 equiv.), *ent*-**88** (0.04 mmol, 10 mol%), base (0.8 mmol, 2.0 equiv.), solvent (2 mL), at r.t. for 12h. [b]0 °C ~ r.t., 24 h. [c]Yield of **154** after column chromatography. [d]The d.r. was determined by ^{1}H NMR of the crude reaction mixture. [e]The *ee* value was determined by HPLC on a chiral stationary phase. [f]The two enantiomers could not be separated on a Daicel Column

2.2.4 Gram scale reaction and determination of the absolute configuration

A gram-scale asymmetric synthesis of **154b** using the current NHC catalysis system worked very well without affecting the efficiency and stereochemical outcome of the reaction (Scheme 44).



*Scheme 44 Gram-scale synthesis of the cyano-substituted dihydropyranone **154b***

The absolute configuration of the cyano-substituted dihydropyranone **154b** was established by X-ray crystal structure analysis and the other product configurations were assigned by analogy.[112]

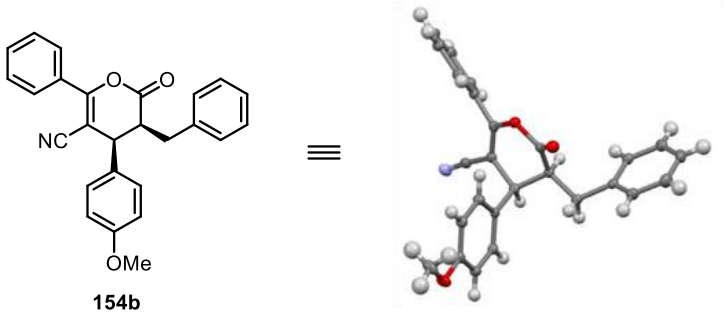
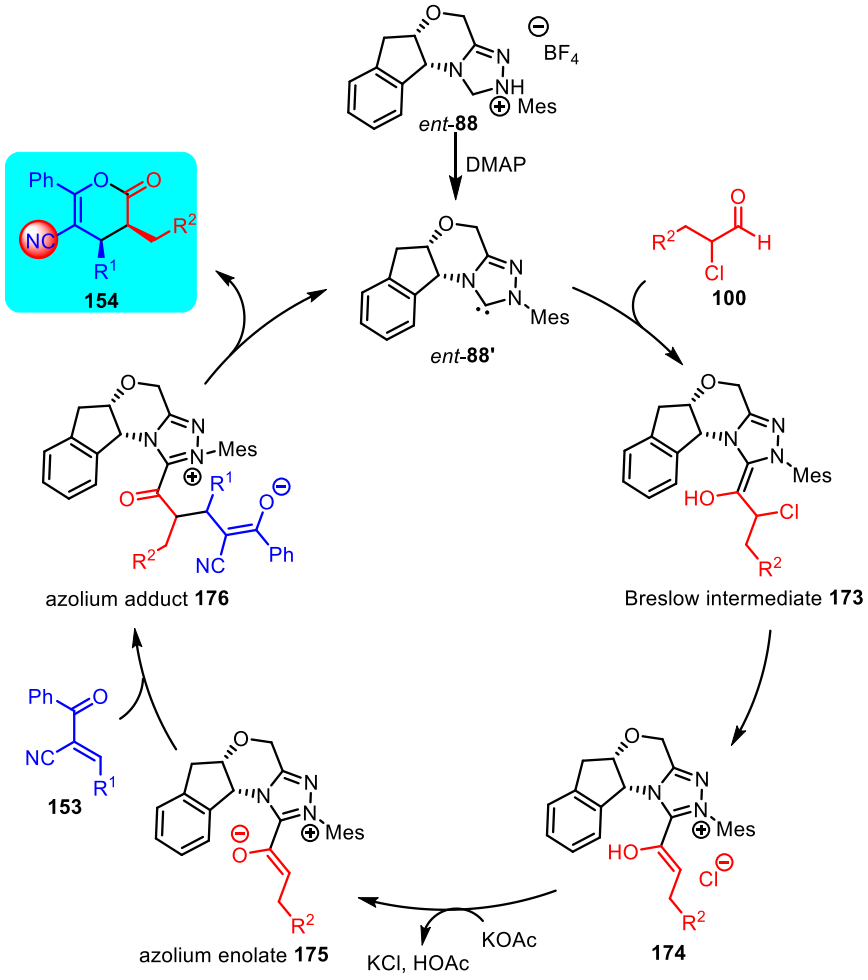


*Figure 11 X-ray crystal structure of the dihydropyanone **154b***

2.2.5 Proposed mechanism



Scheme 45 Proposed catalytic cycle of the asymmetric dihydropyranone synthesis

In the postulated catalytic cycle, the α-chloroaldehyde **100** is attacked by the *in situ* formed carbene *ent*-**88**. The resulting Breslow intermediate **173** with β-leaving group is then converted to the intermediate **174**. In the presence of base, the azolium enolate equivalent **175** is generated, followed by a Michael addition to the (*E*)-2-benzoyl-3-arylacrylonitriles **153** giving the azolium adduct **176**. Subsequently, the lactonization formed the final dihydropyranone **154** with the release of the free carbene catalyst *ent*-**88'** for further cycles (Scheme 45).

2.3 Asymmetric synthesis of dihydropyrano thiazoles *via* NHC catalysis

2.3.1 Background and motivation

Thiazole and δ-lactone skeletons are found in many drugs as well as bioactive compounds. It was found that *N*-bis(trifluoromethyl)alkyl-N'-thiazoyl ureas (Figure 12, **177**)[113] has shown *in vitro* antiproliferative activity against the human cancer cell lines. Evaluation of thiazole derivatives **178**[114] and **179**[115] indicated anticancer activities, especially compound **178** showed significant anticancer effect on both prostate DU-145 and hepatocarcinoma Hep-G2 cancer cell lines. In the report by Hu and co-workers, compound **180** [116] has antitumor activity. Further studies showed that, phenoxmethylthiazole derivative **181**[117] has antipsychotic activity. As well as the δ-lactone derivative Salvinorin A **182**[118] and a series of derivatives have shown antinociceptive effect and acted as KOP agonists.

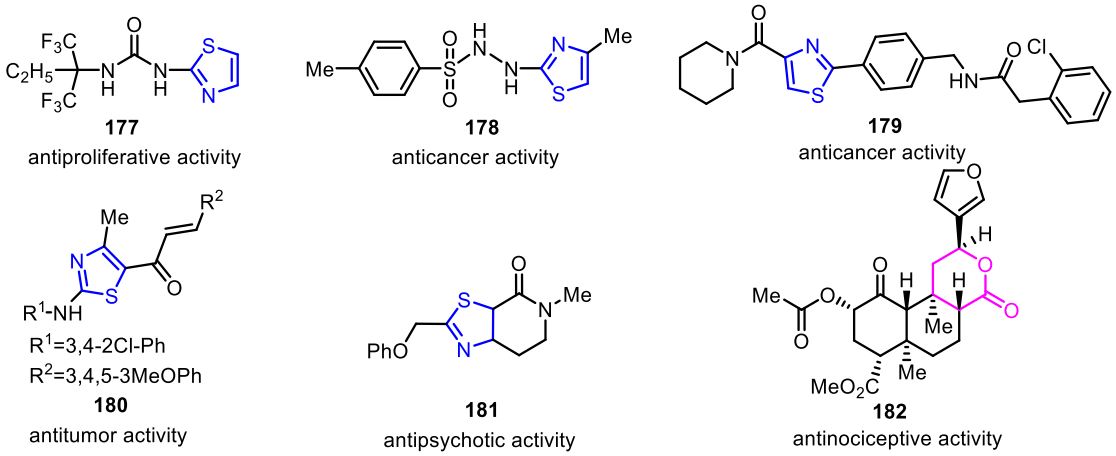
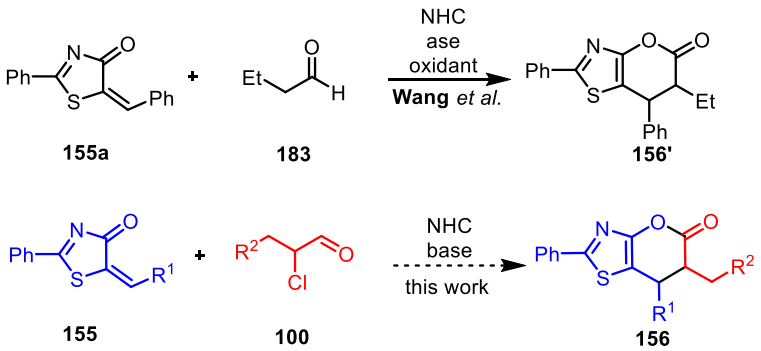


Figure 12 Selected examples of natural products and pharmaceuticals containing the thiazole and δ-lactone moieties

Inspired by these results, we implemented a new strategy to combine these two important cores in one compound by NHC-catalysis. In 2005, an NHC-catalyzed annulation of thiazolo pyrones employing 5-alkenyl thiazoles and simple aliphatic aldehydes under oxidative conditions was reported by Wang's group.[119] Compared to Wang's work, herein we disclosed a more efficient method to obtain the highly functionalized chiral dihydropyrano thiazoles by using 5-phenyl thiazolones and α-chloroaldehydes. A series of substituted thiazolone derivatives and aliphatic α-chloroaldehydes were examined for the reaction.



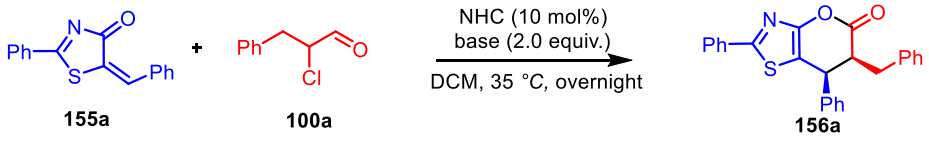
Scheme 46 NHC catalyzed reactions of thiazolo pyrones

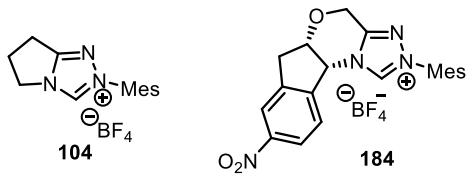
2.3.2 Optimization of the reaction conditions

Initially, we evaluated the model reaction of 5-alkenyl thiazolone **155a** with α-chloroaldehyde **100a** in the presence of achiral triazolium salt **104**. To our delight,

the desired [4+2] annulations product **156a** was obtained in 77% yield with excellent diastereoselectivity (Table 5, entry 1). Test of the chiral NHC catalyst **184** with TMEDA as base and reacted in DCM surprisingly afforded the product **156a** in 72% yield with 99% *ee*, although with low diastereoselectivity of 1:1 d.r. value (Table 5, entry 2). Switching the base to DMAP, the yield of the product **156a** was greatly improved without affecting the enantioselectivity. However, the diastereoselectivity remained low (Table 5, entry 3). Different bases were also examined for this reaction (Table 5, entries 4 - 11). The diastereoselectivity was continuously improved when DBU (Table 5, entry 9) was employed in the reaction. The diastereoselectivity became excellent but with slightly decreased yield. Utilizing KOAc gave an unchanged yield even though the stereoselectivity was kept perfect. Gratifyingly, NaOAc showed more reactivity for the reaction, and the desired bicyclic dihydropyrano thiazole **156a** was generated in excellent yield of 94% and excellent enantio- and diastereoselectivity (Table 5, entry 11).

Table 5 Optimization of the reaction conditions[a]





Entry	Pre-cat.	Base	Yield (%)[b]	d.r.[c]	*ee* (%)[d]
1	**104**	TMEDA	77	>20:1	--
2	**184**	TMEDA	72	1:1	99
3	**184**	DMAP	97	1:1	99
4	**184**	DIPEA	97	3:1	99
5	**184**	DABCO	92	6:1	99
6	**184**	K_3PO_4	68	9:1	99
7	**184**	NEt_3	88	12:1	99

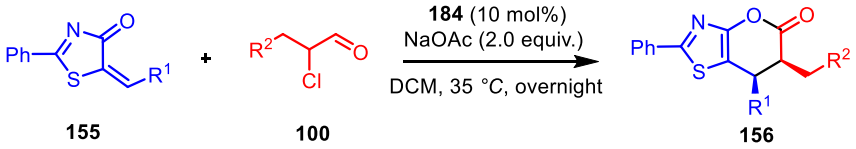
8	**184**	K_2CO_3	98	15:1	99
9	**184**	DBU	86	> 20:1	99
10	**184**	KOAc	88	> 20:1	99
11	**184**	**NaOAc**	**94**	**> 20:1**	**99**

[a]Reaction conditions: **155a** (0.2 mmol, 1.0 equiv.), **100** (0.6 mmol, 3.0 equiv.), pre-cat. (0.02 mmol, 10 mol%), base (0.4 mmol, 2.0 equiv.), solvent (1 mL), at r.t. for 12h. [b]Yield of **156a** after column chromatography. [c]The d.r. was determined by ^{1}H NMR of the crude reaction mixture. [d]The *ee* value was determined by HPLC on a chiral stationary phase.

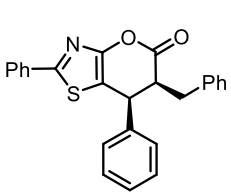
2.3.3 Investigation of the substrate scope

The substrate scope of the reaction was then investigated with the optimized reaction conditions in hand. It was found that, both electron-donating (4-$MeOC_6H_4$ and 4-MeC_6H_4) and electron-withdrawing groups (4-ClC_6H_4, 4-FC_6H_4 and 4-PhC_6H_4) on the *para*-position of the aromatic ring R^1 worked very well for the reaction, and the corresponding [4+2] annulation products (Table 6, **156b-f**) were obtained in very good yields with excellent enantio- and diastereoselectivities. Similar outcomes were obtained with *meta*-substituents (Table 6, **156g** and **156h**) on the phenyl ring R^1. The challenging *ortho*-substituted aryl substituents on R^1 were also tolerated under the same reaction conditions, affording the desired dihydropyrano thiazole products (Table 6, **156i** and **156j**) in good yields and excellent stereoselectivities. The reaction of the benzodioxole-substituted thiazolone with α-chloroaldehyde gave the product (Table 6, **156k**) in 79% yield with 95% *ee*. In addition, aliphatic α-chloroaldehyde were examined and worked as well as the aromatic ones, generating the desired products (Table 6, **156l** and **156m**) in good yields with excellent enantio- and diastereoselectivities.

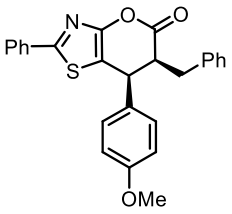
Table 6 Substrate scope of the dihydropyrano thiazoles[a,c,d,e]



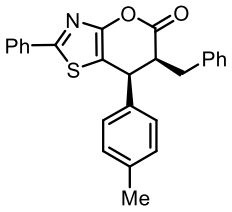
155 + **100** → **156**



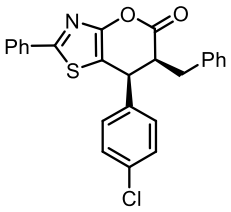
156a
92 %, 99 % *ee*



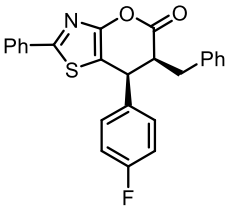
156b[b]
88 %, 88 % *ee*



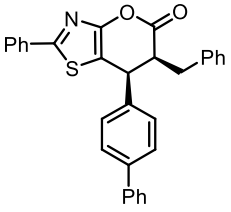
156c
93 %, 99 % *ee*



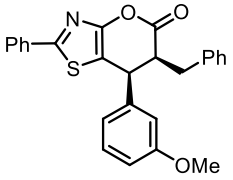
156d
89 %, 99 % *ee*



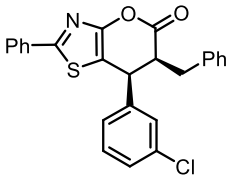
156e
96 %, 97 % *ee*



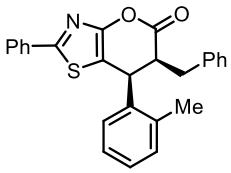
156f
87 %, 99 % *ee*



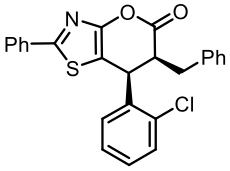
156g
92 %, 99 % *ee*



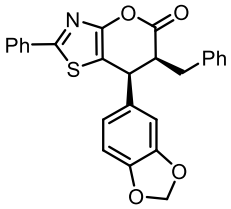
156h
93 %, 92 % *ee*



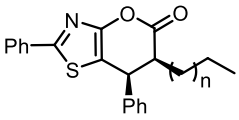
156i[b]
91 %, 99 % *ee*



156j
78 %, 99 % *ee*



156k[b]
79 %, 95 % *ee*



156l n = 1
93 %, 99 % *ee*
156m n=2
83 %, 99 % *ee*

[a]Reaction conditions: **155** (0.4 mmol, 1.0 equiv.), **100** (1.2 mmol, 3.0 equiv.), **184** (0.04 mmol, 10 mol%), NaOAc (0.8 mmol, 2.0 equiv.), DCM (2 mL), at 35 °*C* for 12h. [b]reaction time for 36 h. [c]Yield of **156** after column chromatography. [d]The *ee* value was determined by HPLC on a chiral stationary phase. [e]In all cases, the d.r. is > 20:1.

2.3.4 Determination of the absolute configuration

The absolute configuration of the bicyclic dihydropyrano thiazole **156d** was determined by X-ray crystal structure analysis (Figure 13) and the configuration of all

other products **156** was assigned accordingly.[120]

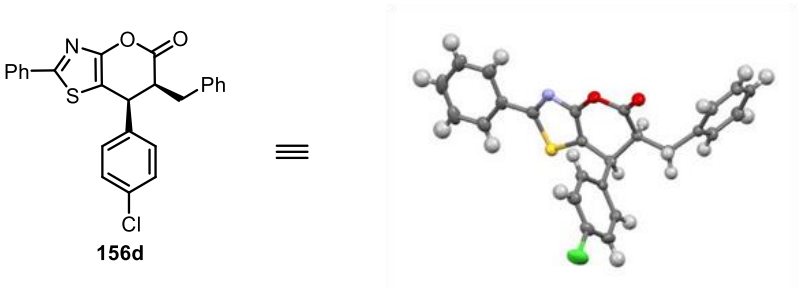
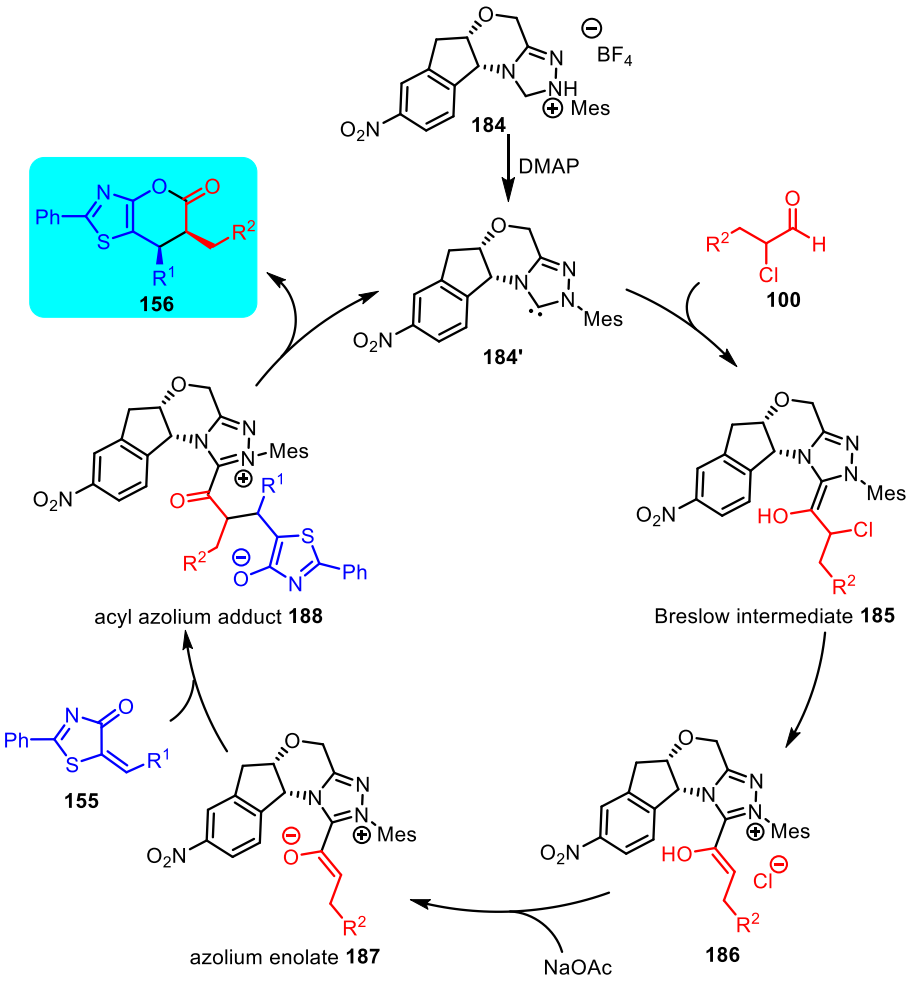


*Figure 13 X-ray crystal structure of the bicyclic dihydropyrano thiazole **156d***

2.3.5 Proposed mechanism



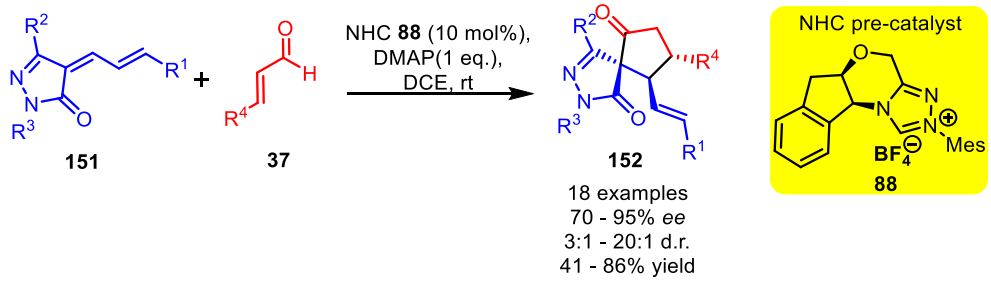
Scheme 47 Proposed catalytic cycle of the asymmetric dihydropyrano thiazole synthesis

A plausible catalytic cycle for the NHC catalyzed [4+2] annulation of α-chloroaldehydes **100** and 5-alkenyl thiazolone **155** is depicted in Scheme 47. The active catalyst, NHC **184'**, was generated from the triazolium salts **184** in the presence of the base. The addition of NHC to the α-chloroaldehyde **155** gave the corresponding Breslow intermediate **185**, which is decomposed to afford the azolium enol **186** *via* elimination of the leaving group. In the presence of base, the azolium enolate **187** was afforded. The [4+2] annulation of azolium enolate **187** and 5-alkenyl thiazolone **155** gave the adduct **188**. The elimination of the NHC catalyst from adduct **188** generated the final product dihydropyrano thiazole **156**.

3. Research Summary and Outlook

In this thesis, three *N*-heterocyclic carbene catalyzed organocatalytic methodologies *via* homoenolate equivalents and azolium enolate equivalents have been presented and the research results were published in peer-reviewed journals. The conclusion of these three projects will be briefly listed as follows:

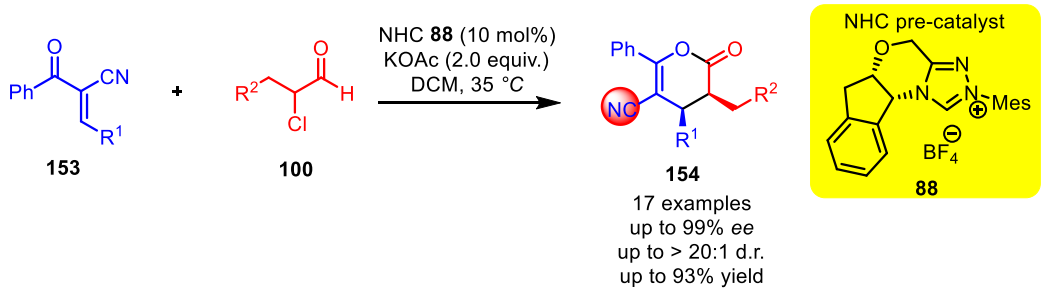
3.1 NHC-catalyzed [3+2] annulation reactions of spiropyrazolones *via* homoenolate intermediates



In this project the highly enantiomerically enriched spirocyclopentane pyrazolones (up to 95% *ee*) were synthesized in moderate to good yields (up to 86%) with excellent diastereoselectivities (d.r. > 20:1) under the optimized conditions. The substituted unsaturated pyrazolones reacted smoothly with numerous enals. The broad substrate scope enabled the flexible variation of all four substituents at will.

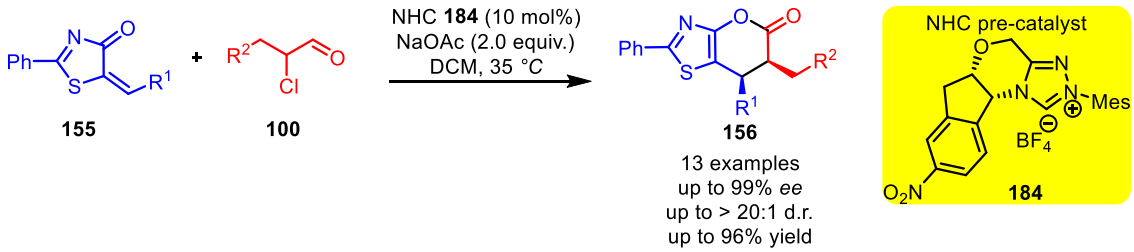
3.2 NHC-catalyzed [4+2] cycloadditions of 5-cyano-substituted dihydropyranones *via* azolium enolate intermediates

In this project, an efficient strategy for the asymmetric synthesis of cyano-substituted dihydropyranones was reported. The triazolium salt **88** treated as catalytic precursor for the nucleophilic addition to α-chloroaldehydes to form the enolate intermediate. Then the reaction with α-cyanoenones gave the corresponding δ-lactone derivatives in good to excellent yields with perfect stereoselectivities.



The new protocol can easily to be scaled up to gram amounts. The cyano substituent and δ-lactone moiety in this structure are crucial structural features in many biological and medical products.

3.3 NHC-catalyzed [4+2] annulation reactions of dihydropyrano thiazoles *via* azolium enolate intermediates



In this project, a combination of the medically active thiazole moiety and δ-lactone moiety was realized in the asymmetric NHC-catalyzed [4+2] annulations of 5-alkenyl thiazolones and α-chloroaldehydes *via* azolium enolate equivalents. The reaction proceeded smoothly to obtain a broad substrate scope in good to excellent yields with excellent enantio- and diastereoselectivities. Inspired by the medicinal activities of the thiazole and δ-lactone derivatives, the resulted dihydropyrano thiazole core in this project shows great potential of biological and pharmaceutical effects.

3.4 Perspectives and outlook

As discussed earlier, the application of *N*-heterocyclic carbenes for annulation/cycloaddtion reactions was developed rapidly. The strategy of NHC-catalyzed reactions for the synthesis of many biologically and medicinally active

structures was also significantly investigated.

NHCs as non-toxic, environment friendly organic catalysts that can be commercially synthesized are active and more efficient on many kinds of organic synthesis. Thus, the design of more suitable and valuable substrates for the NHC-catalyzed reactions is still desired.

4. Experimental Part

4.1 General remarks

All reagents purchased from Sigma-Aldrich, Fluorochem, Acros, Alfa Aesar, TCI Europe and Apollo Chemicals were used without further purification unless otherwise stated. All other reagents used were available from chemical store. Dried syringes and cannulas were used to inject the solvents and reagents into the reaction mixtures. The organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator.

4.1.1 Solvents

All solvents were distilled and dried by standard procedures prior to use. Absolute THF, toluene and Et_2O were distilled over sodium-lead alloy (Solvona®) under argon. Absolute mesitylene was distilled over Solvona® under reduced pressure. MeCN was distilled from CaH_2. EtOAc was distilled from K_2CO_3. Absolute CH_2Cl_2 was purchased directly from Acros.

4.1.2 Chromatographic methods

The reactions were monitored by TLC using silica gel pre-coated aluminium sheet (SIL G-25 UV254 from MACHERY-NAGEL) and visualized with UV light at 254 nm or by diving with potassium permanganate stains, followed by heating with a heat gun. Glass columns with appropriate diameters and lengths were used for different scale purification. When running the column, a low air over-pressure (max. 0.5 bar) was used to push the eluting solvent. Flash column chromatography was performed using Merck silica gel 60, particle size 0.040 – 0.063 mm (230 – 240 mesh). After isolation and collection, the desired products were concentrated with a rotary evaporator under reduced pressure.

4.2 Analytical methods

4.2.1 NMR-spectroscopy

^{1}H and ^{13}C NMR spectra were recorded at room temperature on Mercury 300 (300 MHz), VNMRS 600 (600 MHz) and Inova 400 (400 MHz) instruments. The chemical shifts are reported in ppm downfield of tetramethylsilane and referenced to residual solvent peaks resonance as internal standard. For the ^{1}H-NMR data, the order of citation in parentheses is multiplicity (s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, td = triplet of doublet, m = multiplet); *J*: coupling constants; number of protons and assignment.

4.2.2 Mass spectra

The EI mass spectra were measured on Finningen SSQ7000 at 70 eV and the high resolution mass spectra on a ThermoFisher Scientific LTQ Orbitrap XL (ESI).

4.2.3 IR spectroscopy

IR spectra was measured on a Perkin-Elmer FT-IR Spectrum 100 with Diamant/KRS5 ATR. The absorption bands are reported in cm^{-1}.

4.2.4 HPLC analyses

The measurements were performed on Hewlett-Packard 1050 Series or Agilent 1100 instrument with achiral or Daicel chiral columns. The chiral stationary phases are as follows:

Chiralpak IB (10 µm) (250 mm x 4.6 mm)

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 OJ (10 µm) (250 mm x 4.6 mm)

Chiralpak AS (10 µm) (250 mm x 4.6 mm)

4.2.5 Melting points

Melting points (°*C*) were determined in capillaries with a Büchi B-540 apparatus.

4.2.6 Optical rotation values

The optical rotation values were measured on a Perkin-Elmer 241 polarimeter at room temperature using a light frequency of 589 nm (D-line of a sodium vapor lamp) in a cuvette (length d = 1 dm). HPLC grade $CHCl_3$ and CH_2Cl_2 were used as solvents. The concentrations (c) are given in g·100 mL^{-1}.

4.3 General procedure and analytical data

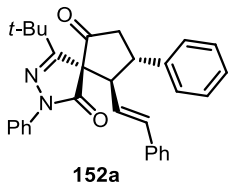
4.3.1 Spiropyrazolone synthesis

4.3.1.1 General procedure I (GP I)

A dried and argon-filled Schlenk tube was charged with unsaturated pyrazolones **151** (0.4 mmol, 1.0 equiv.) and triazolium salt **88** (0.04 mmol, 10 mol%) in anhydrous 1,2-dichloroethane (2 mL). Subsequently, α,β-unsaturated aldehydes **37** (0.8 mmol, 2.0 equiv.) and DMAP (0.4 mmol, 1.0 equiv.) were introduced. The resulting mixture was stirred at room temperature and the reaction was completed as monitored by TLC. After purification by column chromatorgraphy on silica gel (*n*-pentane:EtOAc = 15:1) the desired spirocyclopentane pyrazolones **152** were obtained as yellow oils or a colorless solid. The racemic substrates of the corresponding **152** were prepared by using the pre-catalyst **104** with DMAP in DCE.

4.3.1.2 Analytical data of the synthesized compounds

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-2,8-diphenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152a)



152a

Compound **152a** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (120 mg, 65% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralcel OD; *n*-heptane/EtOH = 95/5, flow rate: 0.5 mL/min, retention time: t_R = 12.66 min (major), 11.11 min (minor); T= 30 °*C*; 94% *ee*.

$\mathbf{[\alpha]_D^{27}}$ = + 277.2 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.89 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.41 – 7.39 (m, 2H, Ar*H*), 7.37 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.34 (d, *J* = 7.0 Hz, 2H, Ar*H*), 7.28 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.21 (dd, *J* = 7.7, 6.4 Hz, 3H, Ar*H*), 7.18 – 7.14 (m, 3H, Ar*H*), 6.20 – 6.15 (m, 2H, C*H*=C*H*), 4.34 (td, *J* = 11.7, 8.5 Hz, 1H, C*H*CH=CH), 3.90 (dd, *J* = 11.3, 7.2 Hz, 1H, C*H*CH_2), 3.19 (dd, *J* = 19.3, 8.4 Hz, 1H, C*H*HCO), 2.86 (dd, *J* = 19.3, 12.1 Hz, 1H, CH*H*CH), 1.39 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

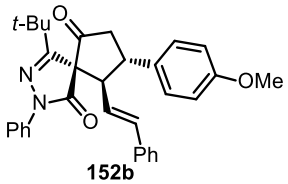
δ = 205.5 (CH_2*C*O), 168.5 (N*C*O), 165.8 (*C*NN), 139.9 (C_{Ar}), 137.6 (C_{Ar}), 136.1 (C_{Ar}), 135.0 (*C*H=CHPh), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 127.8 (CH=*C*HPh), 127.5 (2 x C) (C_{Ar}), 127.4 (C_{Ar}), 126.4 (2 x C) (C_{Ar}), 125.4 (C_{Ar}), 123.8 (C_{Ar}), 119.3 (C_{Ar}), 75.7 (CO*C*CO), 55.4 (CO*C*H_2), 45.9 (*C*HCH=CH), 44.5 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 2970, 1750, 1693, 1595, 1494, 1368, 1296, 1196, 1132, 1063, 952, 837, 747, 689 cm^{-1}.

MS (ESI): *m/z* = 463.2 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{31}O_2N_2$: 463.2380, found 463.2380.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-8-(4-methoxyphenyl)-2-phenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152b)



152b

Compound **152b** was prepared according to **GP I** and isolated after flash chromatography as yellow oil (134 mg, 68% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IB; *n*-heptane/*i*PrOH = 9/1, flow rate: 1.0 mL/min, retention time: t_R = 7.23 min (major), 5.16 min (minor); T = 30 °*C*; 95% *ee*.

$[\alpha]_D^{27}$ = + 264.6 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.89 (dd, *J* = 8.9, 1.1 Hz, 2H, Ar*H*), 7.40 (dd, *J* = 8.6, 7.3 Hz, 2H, Ar*H*), 7.26 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.23 – 7.16 (m, 6H, Ar*H*), 6.91 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.20 – 6.19 (m, 2H, C*H*=C*H*), 4.30 (td, *J* = 11.7, 8.4 Hz, 1H, C*H*CH=CH), 3.87 – 3.83 (m, 1H, C*H*CH_2), 3.80 (s, 3H, OC*H*$_3$), 3.17 (dd, *J* = 19.3, 8.4 Hz, 1H, C*H*HCO), 2.82 (dd, *J* = 19.3, 12.2 Hz, 1H, CH*H*CH), 1.40 (s, 9H, C(C*H*$_3$)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

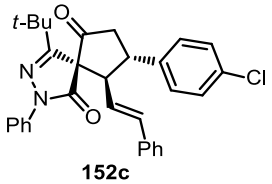
δ = 205.6 (CH_2*C*O), 168.5 (N*C*O), 165.8 (*C*NN), 158.7 (*C*$_{Ar}$), 137.6 (*C*$_{Ar}$), 136.2 (*C*$_{Ar}$), 135.0 (*C*H=CHPh), 131.8 (*C*$_{Ar}$), 128.8 (2 x C) (*C*$_{Ar}$), 128.4 (4 x C) (*C*$_{Ar}$), 127.8 (CH=*C*HPh), 126.4 (2 x C) (*C*$_{Ar}$), 125.4 (*C*$_{Ar}$), 123.9 (*C*$_{Ar}$), 119.3 (2 x C) (*C*$_{Ar}$), 114.3 (2 x C) (*C*$_{Ar}$), 75.7 (CO*C*CO), 55.5 (CO*C*H_2), 55.3 (O*C*H_3), 46.0 (*C*HCH=CH), 43.8 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3363, 2969, 2320, 1740, 1607, 1496, 1367, 1220, 1035, 948, 852, 746, 682 cm^{-1}.

MS (ESI): *m/z* = 493.2 $[M+H]^+$, 515.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}O_3N_2$: 493.2485, found 493.2480.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-8-(4-chlorophenyl)-2-phenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152c)



152c

Compound **152c** was prepared according to **GP I** and isolated after flash

chromatography as yellow oil (115 mg, 58% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 9/1, flow rate: 1.0 mL/min, retention time: t_R = 5.12 min (major), 4.34 min (minor); T = 30 °*C*; 94% *ee*.

$\mathbf{[\alpha]_D^{27}}$ = +263.3 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.89 (dd, *J* = 8.8, 1.2 Hz, 2H, Ar*H*), 7.41 (dd, *J* = 8.7, 7.4 Hz, 2H, Ar*H*), 7.36 – 7.34 (m, 3H, Ar*H*), 7.28 – 7.26 (m, 2H, Ar*H*), 7.22 – 7.19 (m, 3H, Ar*H*), 7.19 – 7.16 (m, 2H, Ar*H*), 6.19 – 6.18 (m, 2H, C*H*=C*H*), 4.34 (td, *J* = 11.7, 8.4 Hz, 1H, C*H*CH=CH), 3.85 – 3.82 (m, 1H, C*H*CH_2), 3.18 (dd, *J* = 19.2, 8.4 Hz, 1H, C*H*HCO), 2.81 (dd, *J* = 19.2, 12.1 Hz, 1H, CH*H*CH), 1.39 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

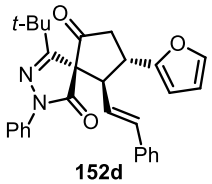
δ = 204.9 (CH_2*C*O), 168.4 (N*C*O), 165.6 (*C*NN), 138.4 (C_{Ar}), 135.9 (C_{Ar}), 135.3 (*C*H=CHPh), 133.1 (C_{Ar}), 130.2 (C_{Ar}), 129.2 (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.0 (CH=*C*HPh), 126.5 (C_{Ar}), 126.4 (C_{Ar}), 125.5 (C_{Ar}), 123.4 (C_{Ar}), 120.8 (C_{Ar}), 119.3 (2 x C) (C_{Ar}), 75.6 (CO*C*CO), 55.4 (CO*C*H_2), 45.6 (*C*HCH=CH), 43.9 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR(KBr): 3461, 2966, 2320, 1742, 1596, 1490, 1369, 1297, 1203, 1088, 960, 826, 749, 686 cm^{-1}.

MS (EI): *m/z* (%) = 57.2 (11), 77.1 (17), 91.1 (14), 125.0 (13), 138.0 (17), 165.0 (11), 227.0 (11), 242.0 (11), 243.0 (100), 144.0 (15), 330.1 (18), 331.1 (23), 496.0 (10).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{31}H_{30}O_2N_2Cl$: 497.1990, found 497.1981.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-8-(furan-2-yl)-2-phenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152d)



152d

Compound **152d** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (101 mg, 56% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 9/1, flow rate: 1.0 mL/min, retention time: t_R = 8.73 min (major), 10.65 min (minor); T = 30 °*C*; 91% *ee*.

$[\alpha]_D^{27}$ = + 290.8 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.88 – 7.86 (m, 2H, Ar*H*), 7.42 – 7.38 (m, 3H, Ar*H*), 7.25 – 7.18 (m, 6H, Ar*H*), 6.31 – 6.28 (m, 2H, Ar*H*), 6.22 – 6.18 (m, 2H, C*H*=C*H*), 4.39 (td, *J* = 11.4, 8.4 Hz, 1H, C*H*CH=CH), 4.01 (dd, *J* = 11.2, 8.3 Hz, 1H, C*H*CH_2), 3.08 (dd, *J* = 19.2, 8.4 Hz, 1H, C*H*HCO), 2.99 (dd, *J* = 19.2, 11.7 Hz, 1H, CH*H*CH), 1.37 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

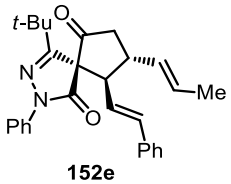
δ = 204.7 (CH_2*C*O), 168.4 (N*C*O), 165.8 (*C*NN), 152.4 (C_{Ar}), 142.0 (C_{Ar}), 137.6 (C_{Ar}), 136.2 (C_{Ar}), 135.1 (*C*H=CHPh), 128.8 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 127.9 (CH=*C*HPh), 126.4 (2 x C) (C_{Ar}), 125.4 (C_{Ar}), 123.7 (C_{Ar}), 119.2 (2 x C) (C_{Ar}), 110.4 (C_{Ar}), 107.8 (C_{Ar}), 75.2 (CO*C*CO), 52.4 (CO*C*H_2), 42.9 (*C*HCH=CH), 38.4 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.4 (3 x C) (C(*C*H_3)$_3$) ppm.

IR(KBr): 3458, 2970, 2328, 1739, 1366, 1216, 1095, 906, 752, 687 cm^{-1}.

MS (EI): *m/z* (%) = 51.2 (15), 55.2 (21), 57.2 (58), 65.2 (17), 66.2 (11), 77.1 (54), 83.1 (12), 91.1 (53), 92.1 (13), 94.1 (41), 105.1 (18), 115.0 (19), 121.0 (12), 128.0 (11), 141.0 (12), 165.0 (11), 168.0 (20), 210.0 (34), 227.0 (11), 242.0 (11), 243.0 (100), 244.1 (15), 331.1 (18), 452.1 (6).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}O_3N_2$: 453.2172, found 453.2161.

(5*S*,8*R*,9*R*)-4-(*tert*-Butyl)-2-phenyl-8-((*E*)-prop-1-en-1-yl)-9-((*E*)-styryl)-2,3-diaza-spiro-[4.4]non-3-ene-1,6-dione (152e)



152e

Compound **152e** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (77 mg, 45% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak AD; *n*-heptane/*i*PrOH = 97/3, flow rate: 1.0 mL/min, retention time: t_R = 9.29 min (major), 10.56 min (minor); T = 30 °*C*; 86% *ee*.

$[\alpha]_D^{27}$ = + 282.8 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.87 – 7.85 (m, 2H, Ar*H*), 7.39 – 7.37 (m, 2H, Ar*H*), 7.30 – 7.17 (m, 6H, Ar*H*), 6.48 (d, *J* = 15.9 Hz, 1H, Ar*H*), 6.21 (dd, *J* = 15.9, 8.6 Hz, 1H, Ar*H*), 5.64 – 5.60 (m, 1H, CH=C*H*Ph), 5.44 – 5.40 (m, 1H, CHC*H*=CH), 3.71 (td, *J* = 11.5, 5.8 Hz, 1H, C*H*CH=CH), 3.48 (dd, *J* = 11.5, 8.6 Hz, 1H, C*H*CH_2), 2.92 (dd, *J* = 19.0, 8.6 Hz, 1H, C*H*HCO), 2.48 (dd, *J* = 19.0, 11.5 Hz, 1H, CH*H*CH), 1.72 – 1.70 (m, 3H, C*H*$_3$), 1.33 (s, 9H, C(C*H*$_3$)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

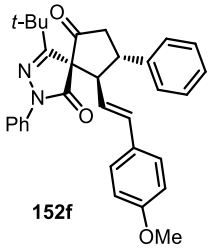
δ = 205.9 (CH_2*C*O), 168.5 (N*C*O), 165.8 (*C*NN), 137.6 (*C*H=CHCH$_3$), 134.9 (*C*H=CHPh), 130.4 (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 128.4 (2 x C) (C_{Ar}), 127.8 (C_{Ar}), 126.5 (2 x C) (C_{Ar}), 125.3 (CH=*C*HCH$_3$), 124.4 (CH=*C*HPh), 119.2 (2 x C) (C_{Ar}), 75.3 (CO*C*CO), 53.9 (CO*C*H$_2$), 44.3 (CH_2*C*H), 41.7 (C*C*H), 36.3 (*C*(CH$_3$)$_3$), 29.4(3 x C) (C(*C*H$_3$)$_3$), 18.0 (CH=CH*C*H$_3$) ppm.

IR(KBr): 3370, 2967, 2318, 1696, 1598, 1491, 1369, 1296, 1201, 1088, 961, 825, 749, 686 cm^{-1}.

MS (EI): *m/z* (%) = 184.1 (18), 227.0 (14), 242.0 (28), 243.0 (100), 244.1 (19), 309.0 (20), 322.1 (17), 331.1 (51), 332.1 (12), 426.1 (43).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{31}O_2N_2$: 427.2380, found 427.2378.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-9-((*E*)-4-methoxystyryl)-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152f)



152f

Compound **152f** was prepared according to **GP I** and isolated after flash chromatography as yellow oil (108 mg, 55% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak AD; *n*-heptane/*i*PrOH = 97/3, 1.0 mL/min, t_R = 20.12 min (major), 24.64 min (minor); T = 30 °*C*; 95% *ee*.

$[\alpha]_D^{27}$ = + 260.4 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.87 (dd, *J* = 8.7, 1.2 Hz, 2H, Ar*H*), 7.40 – 7.31 (m, 6H, Ar*H*), 7.28 – 7.25 (m, 1H, Ar*H*), 7.21 – 7.18 (m, 1H, Ar*H*), 7.08 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.73 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.11 (d, *J* = 15.8 Hz, 1H, CH=C*H*Ph), 6.04 (dd, *J* = 15.9 Hz, 8.2, 1H, CHC*H*=CH), 4.31 (td, *J* = 11.7, 8.4 Hz, 1H, C*H*CH=CH), 3.88 (d, *J* = 8.1 Hz, 1H, C*H*CH_2), 3.74 (s, 3H, OCH_3), 3.17 (dd, J = 19.3, 8.4 Hz, 1H, C*H*HCHO), 2.84 (dd, J = 19.3, 12.1 Hz, 1H, CH*H*CH), 1.38 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

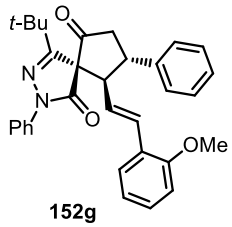
δ = 205.7 (CH_2*C*O), 168.6 (N*C*O), 165.8 (*C*NN), 159.4 (C_{Ar}), 140.0 (C_{Ar}), 137.6 (C_{Ar}), 134.4 (*C*H=CHPh), 129.0 (2 x C) (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (CH=*C*HPh), 127.6 (2 x C) (C_{Ar}), 127.5 (2 x C) (C_{Ar}), 127.3 (C_{Ar}), 125.4 (C_{Ar}), 121.4 (C_{Ar}), 119.3 (2 x C) (C_{Ar}), 113.8 (2 x C) (C_{Ar}), 75.8 (CO*C*CO), 55.4 (CO*C*H_2), 55.3 (O*C*H_3), 45.9 (*C*HCH=CH), 44.5 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3454, 2930, 2320, 1740, 1598, 1493, 1368, 1223, 1117, 958, 752, 688 cm^{-1}.

MS (EI): *m/z* (%) = 57.2 (37), 77.1 (47), 78.1 (14), 91.1 (45), 92.1 (13), 103.0 (34), 104.1 (48), 105.1 (11), 115.0 (20), 121.0 (45), 128.0 (10), 131.0 (47), 145.0 (12), 165.0 (11), 227.0 (12), 243.0 (100), 244.0 (16), 250.0 (25), 492.1 (3).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}O_3N_2$: 493.2485, found 493.2479.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-9-((*E*)-2-methoxystyryl)-2,8-diphenyl-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152g)



152g

Compound **152f** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (158 mg, 80% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IA; *n*-heptane/*i*PrOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 11.34 min (major), 9.74 min (minor); T = 30 °*C*; 92% *ee*.

$[\alpha]_D^{20}$ = +257.7 (c = 6.2, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.92 (d, *J* = 8.6 Hz, 2H, Ar*H*), 7.44 – 7.35 (m, 6H, Ar*H*), 7.31 – 7.26 (m, 1H, Ar*H*), 7.22 – 7.18 (m, 2H, Ar*H*), 7.15 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.81 (t, *J* = 10.9 Hz, 1H, Ar*H*), 6.74 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.53 (d, *J* = 16.1 Hz, 1H, CH=C*H*Ph), 6.22 – 6.16 (m, 1H, CHC*H*=CH), 4.41 – 4.33 (m, 1H, C*H*CH=CH), 3.98 – 3.91 (m, 1H, C*H*CH_2), 3.59 (s, 3H, OCH_3), 3.20 (dd, *J* = 19.3, 8.4 Hz, 1H, C*H*HCO), 2.87 (dd, *J* = 19.3, 12.1 Hz, 1H, CH*H*CH), 1.42 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

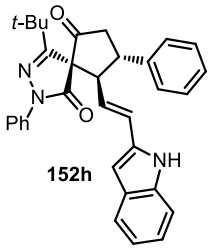
δ = 205.8 (CH_2*C*O), 168.6 (N*C*O), 165.9 (*C*NN), 156.6 (C_{Ar}), 140.1 (C_{Ar}), 137.7 (*C*H=CHPh), 130.0 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 127.6 (2 x C) (C_{Ar}), 127.3 (2 x C) (C_{Ar}), 126.9 (CH=*C*HPh), 125.5 (C_{Ar}), 125.3 (C_{Ar}), 124.2 (C_{Ar}), 120.5 (C_{Ar}), 119.2 (2 x C) (C_{Ar}), 110.9 (C_{Ar}), 75.8 (CO*C*CO), 55.7 (CO*C*H_2), 55.3 (O*C*H_3), 46.1 (*C*HCH=CH), 44.4 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.6 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3483, 2964, 2304, 2079, 1969, 1879, 1748, 1689, 1594, 1468, 1367, 1296, 1244, 1191, 1122, 1031, 958, 841, 751, 686 cm^{-1}.

MS (ESI): *m/z* = 493.2 $[M + H]^+$, 515.2 $[M + Na]^+$.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{32}O_3N_2Na$: 515.2305, found 515.2296.

(5*S*,8*S*,9*R*)-9-((*E*)-2-(1H-Indol-2-yl)vinyl)-4-(*tert*-butyl)-2,8-diphenyl-2,3-diazaspiro-[4.4]non-3-ene-1,6-dione (152h)



152h

Compound **152h** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (96 mg, 48% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IC; *n*-heptane/EtOH = 97:3, flow rate: 1.0 mL/min, retention time: t_R = 5.07 min (major), 7.06 min (minor); T = 30 °*C*; 87% *ee*.

$[\alpha]_D^{27}$ = + 292.7 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 8.16 (broad s, 1H, N*H*), 7.93 – 7.90 (m, 2H, Ar*H*), 7.47 – 7.46 (m, 1H, Ar*H*), 7.41 – 7.36 (m, 4H, Ar*H*), 7.34 – 7.32 (m, 2H, Ar*H*), 7.30 – 7.27 (m, 1H, Ar*H*), 7.23 – 7.19 (m, 2H, Ar*H*), 7.13 – 7.11 (m, 1H, Ar*H*), 7.04 – 7.01 (m, 1H, Ar*H*), 6.28 (dd, *J* = 2.1, 1.0 Hz, 1H, Ar*H*), 6.21 (d, *J* = 16.1 Hz, 1H, CH=C*H*Ph), 6.06 – 6.02 (m, 1H, CHC*H*=CH), 4.34 (td, *J* = 11.7, 8.5 Hz, 1H, C*H*CH=CH), 3.93 (dd, *J* = 11.2, 8.7 Hz, 1H, C*H*CH_2), 3.20 (dd, *J* = 19.4, 8.5 Hz, 1H, C*H*HCO), 2.89 (dd, *J* = 19.4, 12.1 Hz, 1H, CH*H*CH), 1.41 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

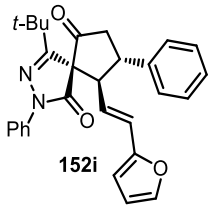
δ = 205.1 (CH_2*C*O), 168.6 (N*C*O), 165.9 (*C*NN), 139.6 (C_{Ar}), 137.5 (C_{Ar}), 136.7 (C_{Ar}), 134.5 (*C*H=CHPh), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.3 (2 x C) (C_{Ar}), 127.5 (2 x C) (C_{Ar}), 125.8 (CH=*C*HPh), 125.6 (C_{Ar}), 123.0 (C_{Ar}), 121.7 (C_{Ar}), 120.6 (C_{Ar}), 120.1 (C_{Ar}), 119.3 (2 x C) (C_{Ar}), 110.7 (C_{Ar}), 103.9 (C_{Ar}), 75.8 (CO*C*CO), 55.4 (CO*C*H_2), 45.8 (*C*HCH=CH), 44.8 (CH_2*C*H), 36.4 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3352, 2323, 2096, 1727, 1644, 1370, 1279, 1218, 1116, 681 cm^{-1}.

MS (ESI): *m/z* = 502.2 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{32}O_2N_3$: 502.2489, found 502.2482.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-9-((*E*)-2-(furan-2-yl)vinyl)-2,8-diphenyl-2,3-diazaspiro-[4.4]non-3-ene-1,6-dione (152i)



152i

Compound **152i** was prepared according to **GP I** and isolated after flash chromatography as yellow oil (92 mg, 51% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IC; *n*-heptane/EtOH = 97:3, flow rate: 1.0 mL/min, retention time: t_R = 14.11 min (major), 15.28 min (minor); T = 30 °*C*; 94% *ee*.

$[\alpha]_D^{27}$ = + 356.5 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.90 – 7.88 (m, 2H, Ar*H*), 7.42 – 7.27 (m, 7H, Ar*H*), 7.23 – 7.19 (m, 2H, Ar*H*), 6.25 (dd, *J* = 3.3, 1.8 Hz, 1H, Ar*H*), 6.14 (dd, *J* = 15.9, 8.5 Hz, 1H, CH=C*H*Ph), 6.05 (d, *J* = 3.3 Hz, 1H, Ar*H*), 5.98 (d, *J* = 15.9 Hz, 1H, CHC*H*=CH), 4.33 (td, *J* = 11.7, 8.5 Hz, 1H, C*H*CH=CH), 3.86 (dd, *J* = 11.3, 8.5 Hz, 1H, C*H*CH_2), 3.18 (dd, *J* = 19.3, 8.4 Hz, 1H, C*H*HCO), 2.83 (dd, *J* = 19.3, 12.1 Hz, 1H, CH*H*CH), 1.38 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

δ = 205.4 (CH_2*C*O), 168.3 (N*C*O), 165.6 (*C*NN), 151.5 (C_{Ar}), 142.1 (C_{Ar}), 139.9 (C_{Ar}), 137.6 (*C*H=CHPh), 128.9 (2 x C) (C_{Ar}), 128.8 (CH=*C*HPh), 127.5 (2 x C) (C_{Ar}), 127.4 (2 x C) (C_{Ar}), 125.4 (C_{Ar}), 122.9 (C_{Ar}), 122.1 (C_{Ar}), 119.3 (2 x C) (C_{Ar}), 111.1 (C_{Ar}), 108.3 (C_{Ar}), 75.6 (CO*C*CO), 55.0 (CO*C*H_2), 46.0 (*C*HCH=CH), 44.4 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

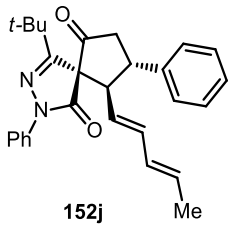
IR (KBr): 3461, 2964, 2331, 1743, 1597, 1490, 1368, 1211, 1113, 952, 749, 689 cm^{-1}.

MS (EI): *m/z* (%) = 51.2 (23), 55.2 (12), 57.2 (30), 65.2 (17), 77.1 (47), 78.1 (22), 91.1

(80), 92.1 (14), 103.0 (36), 104.1 (57), 105.1 (25), 115.0 (28), 117.0 (12), 118.0 (10), 128.0 (12), 129.0 (10), 131.0 (100), 132.0 (23), 133.0 (15), 173.0 (12), 219.0 (13), 243.0 (51), 264.0 (13), 452.1 (8).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{29}O_3N_2$: 453.2172, found 453.2171.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-9-((1*E*,3*E*)-penta-1,3-dien-1-yl)-2,8-diphenyl-2,3-diaza-spiro-[4.4]non-3-ene-1,6-dione (152j)



152j

Compound **152j** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (103 mg, 60% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralcel OJ; *n*-heptane/EtOH = 97:3, flow rate: 0.7 mL/min, retention time: t_R = 10.64 min (major), 7.54 min (minor); T = 30 °*C*; 90% *ee*.

$\mathbf{[\alpha]_D^{20}}$ = + 279.6 (c = 3.2, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

(major) δ = 7.88 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.43 – 7.35 (m, 4H, Ar*H*), 7.33 – 7.26 (m, 3H, Ar*H*), 7.22 – 7.18 (m, 1H, Ar*H*), 5.87 – 5.74 (m, 2H, CHC*H*=C*H*), 5.54 – 5.41 (m, 2H, C*H*=C*H*CH_3), 4.27 – 4.19 (m, 1H, C*H*CH=CH), 3.74 (dd, *J* = 11.7, 8.5 Hz, 1H, C*H*CH_2), 3.13 (dd, *J* = 19.3, 8.5 Hz, 1H, C*H*HCO), 2.78 (dd, J = 19.3, 11.7 Hz, 1H, CH*H*CH), 1.62 (d, J = 7.3 Hz, 3H, CH=CHCH_3), 1.35 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (150 MHz, $CDCl_3$):

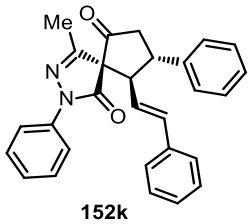
(major) δ = 205.7 (CH_2*C*O), 168.5 (N*C*O), 165.8 (*C*NN), 140.1 (C_{Ar}), 137.7 (CH*C*H=CH), 135.3 (C_{Ar}), 130.6 (*C*H=CHPh), 130.2 (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 127.5 (2 x C) (C_{Ar}), 127.2 (2 x C) (C_{Ar}), 125.3 (CHCH=*C*H), 124.0 (CH=*C*HPh), 119.2 (2 x C) (C_{Ar}), 75.7 (CO*C*CO), 54.9 (CO*C*H_2), 46.1 (*C*HCH=CH), 44.4 (CH_2*C*H), 36.2 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$), 17.9 (CH=CH*C*H_3) ppm.

IR (KBr): 3482, 2967, 2297, 2061, 1952, 1748, 1694, 1595, 1493, 1368, 1294, 1198, 1124, 1061, 986, 941, 849, 754, 687 cm^{-1}.

MS (ESI): *m/z* = 427.2 $[M + H]^+$, 875.5 $[2M + Na]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{31}O_2N_2$: 427.2380, found 427.2380.

(5*S*,8*S*,9*R*)-4-Methyl-2,8-diphenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152k)



152k

Compound **152k** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (77 mg, 71% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak AS; *n*-heptane/*i*PrOH = 9:1, flow rate: 1.0 mL/min, retention time: t_R = 8.29 min (major), 6.20 min (minor); T = 30 °*C*; 85% *ee*.

$[\alpha]_D^{20}$ = + 54.5 (c = 1.7, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.82 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.40 – 7.36 (m, 2H, Ar*H*), 7.36 – 7.30 (m, 4H, Ar*H*), 7.28 – 7.26 (m, 1H, Ar*H*), 7.22 – 7.18 (m, 3H, Ar*H*), 7.18 – 7.14 (m, 3H, Ar*H*), 6.26 – 6.21 (m, 1H, CH=C*H*Ph), 6.17 – 6.13 (m, 1H, CHC*H*=CH), 4.37 (td, *J* = 11.2, 9.0 Hz, 1H, C*H*CH=CH), 3.46 (dd, *J* = 11.2, 8.5 Hz, 1H, C*H*CH_2), 3.27 (dd, *J* = 19.6, 9.0 Hz, 1H, C*H*HCO), 2.72 (dd, *J* = 19.6, 11.2 Hz, 1H, CH*H*CH), 2.19 (s, 3H, CH_3) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

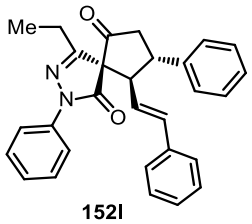
δ = 205.0 (CH_2*C*O), 167.9 (N*C*O), 157.2 (*C*NN), 139.8 (C_{Ar}), 137.4 (C_{Ar}), 135.9 (C_{Ar}), 135.1 (*C*H=CHPh), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 128.0 (2 x C) (C_{Ar}), 127.4 (2 x C) (C_{Ar}), 126.5 (2 x C) (C_{Ar}), 125.5 (CH=*C*HPh), 123.3 (C_{Ar}), 119.3 (2 x C) (C_{Ar}), 75.7 (CO*C*CO), 55.7 (CO*C*H_2), 46.0 (*C*HCH=CH), 43.7 (CH_2*C*H), 14.4 (C*C*H_3) ppm.

IR (KBr): 3437, 3030, 2927, 2847, 2635, 2324, 2101, 1894, 1712, 1594, 1495, 1450, 1368, 1304, 1222, 1076, 1020, 897, 838, 754, 694 cm^{-1}.

MS (EI) *m/z* (%) = 51.4 (20), 57.4 (11), 65.3 (11), 77.3 (76), 78.3 (20), 79.3 (10), 91.2 (100), 92.2 (17), 103.2 (29), 104.2 (64), 105.2 (51), 107.2 (14), 115.2 (49), 116.2 (11), 117.2 (11), 120.2 (13), 121.2 (12), 127.1 (17), 128.1 (32), 129.2 (18), 131.1 (33), 132.1 (18), 133.2 (11), 141.2 (14), 150.1 (10), 153.2 (11), 155.2 (11), 174.2 (14), 185.2 (18), 200.1 (15), 201.2 (53), 202.2 (14), 203.2 (12), 205.2 (42), 206.2 (11), 262.2 (12), 263.2 (18), 288.2 (21), 289.3 (56), 290.2 (12), 420.4 (4).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{25}O_2N_2$: 421.1911, found 421.1914.

(5*S*,8*S*,9*R*)-4-Ethyl-2,8-diphenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152l)



152l

Compound **152l** was prepared according to the **GP I** and isolated after flash chromatography as yellow oil (76 mg, 44% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IB; *n*-heptane/*i*PrOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 9.31 min (major), 10.02 min (minor); T = 30 °*C*; 86% *ee*.

$\mathbf{[\alpha]_D^{20}}$ = + 99.4 (c = 2.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.86 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.39 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.37 – 7.34 (m, 2H, Ar*H*), 7.33 – 7.30 (m, 2H, Ar*H*), 7.28 – 7.24 (m, 2H, Ar*H*), 7.22 – 7.19 (m, 2H, Ar*H*), 7.19 – 7.14 (m, 3H, Ar*H*), 6.24 – 6.14 (m, 2H, C*H*=C*H*), 4.36 (td, *J* = 20.2, 11.3 Hz, 1H, C*H*CH=CH), 3.49 (dd, *J* = 11.3, 8.1 Hz, 1H, C*H*CH_2), 3.25 (dd, *J* = 19.6, 8.8 Hz, 1H, C*H*HCO), 2.73 (dd, *J* = 19.6, 11.3 Hz, 1H, CH*H*CH), 2.59 – 2.44 (m, 2H, CH_2CH_3), 1.34 (t, *J* = 7.4 Hz, 3H, CH_2CH_3) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

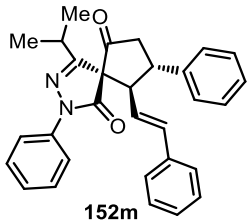
δ = 205.2 (CH_2CO), 168.1 (N*C*O), 161.0 (*C*NN), 139.8 (C_{Ar}), 137.6 (C_{Ar}), 135.9 (C_{Ar}), 135.0 (*C*H=CHPh), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 127.9 (2 x C) (C_{Ar} and CH=*C*HPh), 127.4 (2 x C) (C_{Ar}), 126.5 (2 x C) (C_{Ar}), 125.5 (C_{Ar}), 123.4 (C_{Ar}), 119.3 (2 x C) (C_{Ar}), 75.6 (CO*C*CO), 55.6 (CO*C*H_2), 46.1 (*C*HCH=CH), 43.8 (CH_2*C*H), 22.2 (*C*H_2CH_3), 9.6 (CH_2*C*H_3) ppm.

IR (KBr): 3440, 3031, 2925, 2647, 2321, 2098, 1992, 1887, 1694, 1595, 1494, 1455, 1350, 1227, 1137, 1061, 961, 901, 834, 751, 691 cm^{-1}.

MS (EI): *m/z* (%) = 77.3 (32), 78.3 (11), 91.2 (57), 103.2 (25), 104.2 (72), 105.2 (26), 115.2 (25), 128.2 (14), 131.2 (22), 188.2 (13), 205.3 (20), 214.2 (17), 215.2 (100), 216.3 (14), 303.3 (18), 434.4 (4).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{29}H_{27}O_2N_2$: 435.2067, found 435.2065.

(5*S*,8*S*,9*R*)-4-Isopropyl-2,8-diphenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152m)



152m

Compound **152m** was prepared according to **GP I** and isolated after flash chromatography as yellow oil (90 mg, 50% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IB; *n*-heptane/*i*PrOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 7.92 min (major), 8.73 min (minor); T = 30 °*C*; 80% *ee*.

$\mathbf{[\alpha]_D^{20}}$ = + 188.9 (c = 2.7, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.86 (d, *J* = 7.7 Hz, 2H, Ar*H*), 7.41 – 7.37 (m, 2H, Ar*H*), 7.37 – 7.34 (m, 2H, Ar*H*), 7.34 – 7.31 (m, 2H, Ar*H*), 7.28 – 7.26 (m, 1H, Ar*H*), 7.22 – 7.18 (m, 3H, Ar*H*), 7.18 – 7.14 (m, 3H, Ar*H*), 6.23 – 6.15 (m, 2H, C*H*=C*H*), 4.33 (td, *J* = 11.6, 8.5 Hz, 1H,

C*H*CH=CH), 3.57 (dd, *J* = 11.4, 6.5, Hz, 1H, C*H*CH$_2$), 3.22 (dd, *J* = 19.4, 8.5 Hz, 1H, C*H*HCO), 2.82 – 2.74 (m, 2H, CH*H*CH), 1.36 (d, *J* = 6.9 Hz, 3H, CC*H*$_3$), 1.31 (d, *J* = 6.9 Hz, 3H, CC*H*$_3$) ppm.

^{13}C NMR (151 MHz, CDCl$_3$):

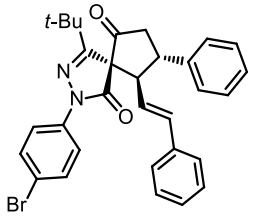
δ = 205.1 (CH$_2$*C*O), 168.2 (N*C*O), 164.1 (*C*NN), 139.7 (*C*$_{Ar}$), 137.6 (*C*$_{Ar}$), 136.0 (*C*$_{Ar}$), 135.0 (*C*H=CHPh), 128.9 (2 x C) (*C*$_{Ar}$), 128.8 (2 x C) (*C*$_{Ar}$), 128.5 (2 x C) (*C*$_{Ar}$), 127.9 (2 x C) (*C*$_{Ar}$ and CH=*C*HPh), 127.4 (2 x C) (*C*$_{Ar}$), 126.4 (2 x C) (*C*$_{Ar}$), 125.4 (*C*$_{Ar}$), 123.7 (*C*$_{Ar}$), 119.3 (2 x C) (*C*$_{Ar}$), 75.6 (CO*C*CO), 55.3 (CO*C*H$_2$), 46.2 (*C*HCH=CH), 44.2 (CH$_2$*C*H), 29.3 (*C*(CH$_3$)$_2$), 21.3 (C(*C*H$_3$)$_2$), 19.8 (C(*C*H$_3$)$_2$) ppm.

IR (KBr): 3031, 2971, 2324, 2098, 1953, 1880, 1748, 1691, 1596, 1494, 1455, 1345, 1240, 1130, 1065, 963, 905, 837, 749, 689 cm^{-1}.

MS (EI): *m/z* (%) = 77.3 (44), 78.3 (17), 91.2 (71), 92.2 (13), 103.2 (36), 104.2 (100), 105.2 (24), 115.2 (31), 128.2 (19), 129.2 (11), 131.2 (33), 141.2 (10), 228.2 (15), 229.3 (92), 230.3 (13), 317.3 (13), 448.4 (3).

HRMS (EI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{29}O_2N_2$: 449.2224, found 449.2229.

(5*S*,8*S*,9*R*)-2-(4-Bromophenyl)-4-(*tert*-butyl)-8-phenyl-9-((*E*)-styryl)-2,3-diazaspiro-[4.4]non-3-ene-1,6-dione (152n)



152n

Compound **152n** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (138 mg, 64% yield).

TLC: R$_f$ = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IB; *n*-heptane/*i*PrOH = 9:1, flow rate: 0.7 mL/min, retention time: t$_R$ = 7.06 min (major), 7.84 min (minor); T = 30 °*C*; 88% *ee*.

$[\alpha]_D^{20}$ = + 270.5 (c = 1.3, CHCl$_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.80 (d, *J* = 8.9 Hz, 2H, Ar*H*), 7.52 – 7.48 (m, 2H, Ar*H*), 7.39 – 7.34 (m, 2H, Ar*H*), 7.34 – 7.31 (m, 2H, Ar*H*), 7.29 – 7.26 (m, 1H, Ar*H*), 7.23 – 7.15 (m, 3H, Ar*H*), 7.15 – 7.12 (m, 2H, Ar*H*), 6.17 – 6.15 (m, 2H, C*H*=C*H*), 4.30 (td, *J* = 11.7, 8.4 Hz, 1H, C*H*CH=CH), 3.92 – 3.87 (m, 1H, C*H*CH_2), 3.18 (dd, *J* = 19.3, 8.4 Hz, 1H, C*H*HCO), 2.86 (dd, *J* = 19.3, 12.1 Hz, 1H, CH*H*CH), 1.38 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

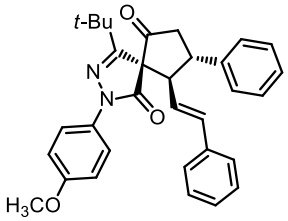
δ = 205.3 (CH_2*C*O), 168.4 (N*C*O), 166.2 (*C*NN), 139.7 (C_{Ar}), 136.6 (C_{Ar}), 136.1 (C_{Ar}), 135.1 (*C*H=CHPh), 131.8 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 127.9 (CH=*C*HPh), 127.5 (2 x C) (C_{Ar}), 127.4 (C_{Ar}), 126.4 (2 x C) (C_{Ar}), 123.5 (C_{Ar}), 120.6 (2 x C) (C_{Ar}), 118.3 (C_{Ar}), 75.7 (CO*C*CO), 55.3 (CO*C*H_2), 45.9 (*C*HCH=CH), 44.5 (CH_2*C*H), 36.4 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3476, 2966, 2319, 2072, 1899, 1691, 1597, 1482, 1367, 1293, 1199, 1126, 1059, 963, 824, 731 cm^{-1}.

MS (ESI): *m/z* = 541.1 $[M + H]^+$, 563.1 $[M + Na]^+$.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{31}H_{29}O_2N_2BrNa$: 563.1305, found 563.1305.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-2-(4-methoxyphenyl)-8-phenyl-9-((*E*)-styryl)-2,3-diaza-spiro-[4.4]non-3-ene-1,6-dione (152o)



152o

Compound **152o** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (170 mg, 86% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IC; *n*-heptane/*i*PrOH = 9:1, flow rate: 1.0 mL/min, retention time: t_R = 5.17 min (major), 4.11 min (minor); T = 30 °*C*; 92% *ee*.

$[\alpha]_D^{20}$ = + 299.6 (c = 5.23, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.75 (d, *J* = 9.0 Hz, 2H, Ph*H*), 7.39 – 7.35 (m, 2H, Ar*H*), 7.35 – 7.32 (m, 2H, Ar*H*), 7.29 – 7.27 (m, 1H, Ar*H*), 7.23 – 7.19 (m, 2H, Ar*H*), 7.19 – 7.14 (m, 3H, Ar*H*), 6.94 – 6.91 (m, 2H, Ar*H*), 6.23 – 6.15 (m, 2H, C*H*=C*H*), 4.34 (td, *J* = 11.7, 8.5 Hz, 1H, C*H*CH=CH), 3.90 (dd, *J* = 11.3, 7.3 Hz, 1H, C*H*CH_2), 3.82 (s, 3H, OCH_3), 3.18 (dd, *J* = 19.3, 8.5 Hz, 1H, C*H*HCO), 2.86 (dd, *J* = 19.3, 12.1 Hz, 1H, CH*H*CH), 1.38 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

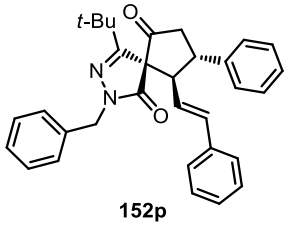
δ = 205.7 (CH_2*C*O), 168.1 (N*C*O), 165.7 (*C*NN), 157.3 (C_{Ar}), 139.9 (C_{Ar}), 136.2 (C_{Ar}), 134.9 (*C*H=CHPh), 130.9 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.5 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.5 (CH=*C*HPh), 127.4 (2 x C) (C_{Ar}), 126.4 (2 x C) (C_{Ar}), 123.9 (C_{Ar}), 121.2 (2 x C) (C_{Ar}), 114.0 (2 x C) (C_{Ar}), 75.5 (CO*C*CO), 55.5 (CO*C*H_2), 55.3 (O*C*H_3), 45.9 (*C*HCH=CH), 44.5 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.5 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3489, 3027, 2966, 2305, 2059, 1957, 1880, 1749, 1688, 1596, 1508, 1455, 1371, 1296, 1246, 1182, 1131, 1062, 1030, 950, 831, 749, 695, 662 cm^{-1}.

MS (ESI): *m/z* = 493.2 $[M + H]^+$, 515.2 $[M + Na]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{33}O_3N_2$: 493.2486, found 493.2476.

(5*S*,8*S*,9*R*)-2-Benzyl-4-(*tert*-butyl)-8-phenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152p)



152p

Compound **152p** was prepared according to **GP I** and isolated after flash chromatography as a colorless solid (108 mg, 57% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IC; *n*-heptane/*i*PrOH = 9:1, flow rate: 0.5 mL/min, retention time: t_R = 7.24 min (major), 20.72 min (minor); T = 30 °*C*; 85% *ee*.

Melting Point: 122 – 124 °*C*.

$[\alpha]_D^{20}$ = + 151.5 (c = 6.4, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.38 – 7.34 (m, 2H, Ar*H*), 7.34 – 7.31 (m, 2H, Ar*H*), 7.29 – 7.26 (m, 1H, Ar*H*), 7.25 – 7.22 (m, 2H, Ar*H*), 7.22 – 7.19 (m, 2H, Ar*H*), 7.19 – 7.16 (m, 1H, Ar*H*), 7.14 – 7.09 (m, 4H, Ar*H*), 6.18 – 6.10 (m, 2H, C*H*=C*H*), 4.97 (d, *J* = 15.5 Hz, 1H, C*H*HN), 4.76 (d, *J* = 15.5 Hz, 1H, CH*H*Ph), 4.31 (dd, *J* = 20.2, 11.4 Hz, 1H, C*H*CH=CH), 3.86 (dd, *J* = 11.1, 7.0 Hz, 1H, C*H*CH_2), 3.15 (dd, *J* = 19.1, 8.3 Hz, 1H, C*H*HCO), 2.83 (dd, *J* = 19.1, 12.2 Hz, 1H, CH*H*CH), 1.31 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

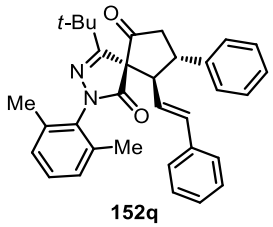
δ = 206.2 (CH_2*C*O), 170.1 (N*C*O), 165.5 (*C*NN), 140.0 (C_{Ar}), 136.2 (C_{Ar}), 136.2 (*C*H=CHPh), 134.8 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 128.4 (2 x C) (C_{Ar}), 127.8 (2 x C) (C_{Ar} and CH=*C*HPh), 127.5 (2 x C) (C_{Ar}), 127.3 (2 x C) (C_{Ar}), 126.4 (2 x C) (C_{Ar}), 124.2 (C_{Ar}), 74.3 (CO*C*CO), 54.9 (CO*C*H_2), 47.9 (*C*H_2Ph), 46.1 (*C*HCH=CH), 44.3 (CH_2*C*H), 36.1 (*C*(CH_3)$_3$), 29.6 (3 x C) (C(*C*H_3)$_3$) ppm.

IR (KBr): 3368, 2967, 2322, 2079, 1963, 1888, 1744, 1690, 1592, 1492, 1455, 1367, 1271, 1186, 1140, 1113, 1067, 1029, 963, 904, 849, 747, 695 cm^{-1}.

MS (ESI): *m/z* = 477.3 $[M + H]^+$, 499.2 $[M + Na]^+$.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{32}H_{32}O_2N_2Na$: 499.2356, found 499.2346.

(5*S*,8*S*,9*R*)-4-(*tert*-Butyl)-2-(2,6-dimethylphenyl)-8-phenyl-9-((*E*)-styryl)-2,3-diaz-aspiro-[4.4]non-3-ene-1,6-dione (152q)



152q

Compound **152q** was prepared according to **GP I** and isolated after flash chromatography as pale yellow oil (116 mg, 59% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IA; *n*-heptane/EtOH = 7:3, flow rate: 0.5 mL/min, retention time: t_R = 12.35 min (major), 10.74 min (minor); T = 30 °*C*; 85% *ee*.

$[\alpha]_D^{20}$ = + 148.7 (c = 4.4, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.38 – 7.31 (m, 4H, Ar*H*), 7.28 – 7.26 (m, 1H, Ar*H*), 7.26 – 7.23 (m, 2H, Ar*H*), 7.22 – 7.19 (m, 3H, Ar*H*), 7.18 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.12 (d, *J* = 7.5 Hz, 1H, Ar*H*), 7.04 (d, *J* = 7.5 Hz, 1H, Ar*H*), 6.36 – 6.25 (m, 2H, C*H*=C*H*), 4.34 (td, *J* = 11.8, 8.3 Hz, 1H, C*H*CH=CH), 3.94 (dd, *J* = 11.2, 8.3 Hz, 1H, C*H*CH_2), 3.18 (dd, *J* = 19.1, 8.3 Hz, 1H, C*H*HCO), 2.87 (dd, *J* = 19.1, 12.3 Hz, 1H, CH*H*CH), 2.24 (s, 3H, PhCH_3), 2.02 (s, 3H, PhCH_3), 1.38 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

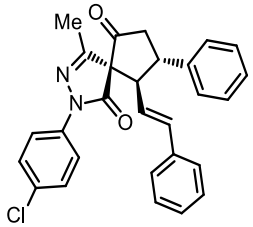
δ = 206.0 (CH_2*C*O), 169.0 (N*C*O), 166.2 (*C*NN), 139.9 (C_{Ar}), 137.3 (C_{Ar}), 135.0 (*C*H=CHPh), 129.2 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 128.4 (C_{Ar}), 128.2 (2 x C) (C_{Ar}), 127.9 (2 x C) (C_{Ar} and CH=*C*HPh), 127.4 (2 x C) (C_{Ar}), 127.3 (2 x C) (C_{Ar}), 126.3 (2 x C) (C_{Ar}), 124.5 (C_{Ar}), 74.4 (CO*C*CO), 54.9 (CO*C*H_2), 46.1 (*C*HCH=CH), 44.4 (CH_2*C*H), 36.3 (*C*(CH_3)$_3$), 29.7 (3 x C) (C(*C*H_3)$_3$), 18.3 (Ph*C*H_3), 18.1 (Ph*C*H_3) ppm.

IR (KBr): 3812, 3460, 3091, 2971, 2323, 2058, 1898, 1739, 1595, 1469, 1369, 1294, 1225, 1035, 961, 801, 729 cm^{-1}.

MS (ESI): *m/z* = 491.3 $[M + H]^+$, 513.3 $[M + Na]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{33}H_{35}O_2N_2$: 491.2693, found 491.2693.

(5*S*,8*S*,9*R*)-2-(4-Chlorophenyl)-4-methyl-8-phenyl-9-((*E*)-styryl)-2,3-diazaspiro[4.4]non-3-ene-1,6-dione (152r)



152r

Compound **152r** was prepared according to **GP I** and isolated after flash chromatography as yellow oil (93 mg, 46% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 15:1).

HPLC: Chiralpak IC; *n*-heptane/*i*PrOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 4.52 min (major), 4.98 min (minor); T = 30 °*C*; 70% *ee*.

$[\alpha]_D^{20}$ = +57.0 (c = 2.2, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

(major) δ = 7.80 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.37 – 7.33 (m, 4H, Ar*H*), 7.33 – 7.30 (m, 2H, Ar*H*), 7.28 – 7.26 (m, 1H, Ar*H*), 7.23 – 7.19 (m, 2H, Ar*H*), 7.19 – 7.13 (m, 3H, Ar*H*), 6.23 (d, *J* = 15.8 Hz, 1H, CH=C*H*Ph), 6.13 (dd, *J* = 15.8, 8.6 Hz, 1H, CHC*H*=CH), 4.35 (td, *J* = 11.3, 9.0 Hz, 1H, C*H*CH=CH), 3.46 (dd, *J* = 11.4, 8.6 Hz, 1H, C*H*CH_2), 3.27 (dd, *J* = 19.7, 9.0 Hz, 1H, C*H*HCO), 2.72 (dd, *J* = 19.7, 11.2 Hz, 1H, CH*H*CH), 2.19 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

(major) δ = 204.8 (CH_2*C*O), 167.9 (N*C*O), 157.5 (*C*NN), 139.6 (C_{Ar}), 136.0 (C_{Ar}), 135.8 (C_{Ar}), 135.2 (*C*H=CHPh), 130.6 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.5 (C_{Ar}), 128.1 (CH=*C*HPh), 127.5 (2 x C) (C_{Ar}), 127.4 (2 x C) (C_{Ar}), 126.5 (2 x C) (C_{Ar}), 123.1 (C_{Ar}), 120.2 (2 x C) (C_{Ar}), 75.7 (CO*C*CO), 55.7 (CO*C*H_2), 46.0 (*C*HCH=CH), 43.7 (CH_2*C*H), 14.4 (C*C*H_3) ppm.

IR (KBr): 3452, 3023, 2928, 2649, 2322, 2105, 1989, 1907, 1725, 1591, 1492, 1365, 1298, 1219, 1087, 1010, 896, 827, 754, 696 cm^{-1}.

MS (EI): *m/z* (%) = 50.4 (11), 51.5 (47), 63.3 (11), 77.4 (57), 78.3 (16), 79.3 (10), 90.5 (10), 91.3 (100), 103.3 (15), 104.3 (67), 105.3 (29), 107.3 (11), 111.3 (12), 115.2 (20), 125.2 (12), 131.2 (13), 205.2 (24), 322.1 (13), 323.2 (30), 324.2 (12), 325.1 (14), 454.2 (6).

HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{24}O_2N_2Cl$: 455.1521, found 455.1524.

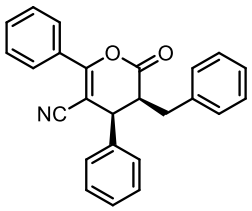
4.3.2 5-Cyano-substituted dihydropyranone synthesis

4.3.2.1 General procedure II (GP II)

A dried and argon-filled Schlenk tube is charged with acrylnitriles **153** (0.4 mmol, 1.0 equiv.), triazolium salt *ent*-**88** (0.04 mmol, 10 mol%), KOAc (0.8 mmol, 2.0 equiv.) and 2.0 mL anhydrous DCM. Subsequently, α-chloroaldehydes **100** (1.2 mmol, 3 equiv.) is successively added. The resulting yellow solution is stirred at 35°*C* until the reaction is complete (as monitored by TLC). After the solvent is evaporated under reduced pressure, the crude product is purified *via* flash chromatography (*n*-pentane:EtOAc = 10:1) to give the cyano-substituted dihydropyranones **154** as colorless solids. The racemic substrates of the corresponding **154** were prepared by using the pre-catalyst **104** with KOAc in DCM.

4.3.2.2 Analytical data of the synthesized compounds

(3*S*,4*S*)-3-Benzyl-2-oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154a)



154a

Compound **154a** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (136 mg, 93% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IA; *n*-heptane/*i*PrOH = 97:3, flow rate: 1.0 mL/min, retention time: t_R = 22.16 min (major), 16.76 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 132 – 134 °*C*.

$[\alpha]_D^{21}$ = + 270.4 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.94 – 7.86 (m, 2H, Ar*H*), 7.55 – 7.43 (m, 3H, Ar*H*), 7.42 – 7.25 (m, 6H, Ar*H*), 7.13 – 7.07 (m, 4H, Ar*H*), 3.77 (d, *J* = 6.8 Hz, 1H, C*H*Ph), 3.51 – 3.43 (m, 1H, C*H*CH_2), 3.29 (dd, *J* = 14.8, 5.2 Hz, 1H, CHCH*H*), 2.48 (dd, *J* = 14.8, 9.6 Hz, 1H, CHC*H*H).

^{13}C NMR (101 MHz, $CDCl_3$):

δ = 167.3 (O*C*OCH), 160.8 (Ph*C*O), 137.3 (C_{Ar}), 135.1 (C_{Ar}), 131.9 (C_{Ar}), 129.9 (C_{Ar}),

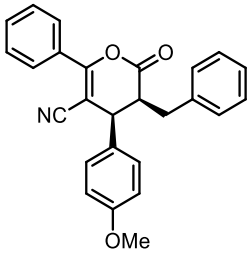
129.4 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.2 (2 x C) (C_{Ar}), 127.7 (2 x C) (C_{Ar}), 127.0, 117.4 (C*C*N), 93.1 (*C*CN), 44.6 (CO*C*H), 44.3 (CH*C*H$_2$), 32.1 (Ph*C*H) ppm.

IR (ATR): 3507, 2926, 2321,2093, 1919, 1716, 1605, 1513, 1302, 1153, 691 cm^{-1}.

MS (ESI): *m/z* = 366.1 [M + H]$^+$, 388.1 [M + Na]$^+$.

HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{25}H_{20}O_2N$: 366.1481, found 366.1489.

(3*S*,4*S*)-3-Benzyl-4-(4-methoxyphenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154b)



154b

Compound **154b** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (146 mg, 87% yield; 1.44 g, 86% yield (**154b'**)).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/EtOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 20.50 min (major), 16.85 min (minor); T = 30 °*C*; 99% *ee* (**154b**); 99% *ee* (**154b'**).

Melting Point: 162 – 164 °*C*.

$[\alpha]_D^{21}$ = + 210.2 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.93 – 7.89 (m, 2H, Ar*H*), 7.54 – 7.50 (m, 1H, Ar*H*), 7.50 – 7.45 (m, 2H, Ar*H*), 7.36 – 7.32 (m, 2H, Ar*H*), 7.30 – 7.27 (m, 1H, Ar*H*), 7.12 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.04 – 7.00 (m, 2H, Ar*H*), 6.91 (d, *J* = 8.4 Hz, 2H, Ar*H*), 3.83 (s, 3H, OCH_3), 3.72 (d, *J* = 6.6 Hz, 1H, C*H*Ph), 3.47 – 3.42 (m, 1H, C*H*CH$_2$), 3.30 (dd, *J* = 14.4, 4.8 Hz, 1H, CHCH*H*), 2.49 (dd, *J* = 15.0, 9.6 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

δ = 167.4 (O*C*OCH), 160.5 (Ph*C*O), 159.9 (C_{Ar}), 137.4 (C_{Ar}), 131.8 (C_{Ar}), 129.9 (C_{Ar}),

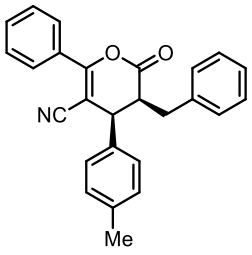
129.3 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 127.7 (2 x C) (C_{Ar}), 127.0 (C_{Ar}), 126.8 (C_{Ar}), 117.5 (C*C*N), 114.8 (2 x C) (C_{Ar}), 93.4 (*C*CN), 55.3 (O*C*H$_3$), 44.8 (CO*C*H), 43.5 (CH*C*H$_2$), 32.1 (Ph*C*H) ppm.

IR (ATR): 3545, 3032, 2939, 2833, 2333, 2207, 2091, 1896, 1778, 1614, 1503, 1444, 1313, 1248, 1177, 1083, 1032, 929, 828, 769, 695 cm^{-1}.

MS (EI): *m/z* (%) = 77.1 (32), 91.0 (23), 105.0 (77), 231.9 (13), 235.9 (19), 261.9 (12), 262.9 (100), 263.9 (26), 304.0 (27), 395.0 (87).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{21}O_3NNa$: 418.1415, found 418.1414.

(3*S*,4*S*)-3-Benzyl-2-oxo-6-phenyl-4-(*p*-tolyl)-3,4-dihydro-2H-pyran-5-carbonitrile (154c)



154c

Compound **154c** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (139 mg, 86% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/*i*PrOH = 9:1, flow rate: 1.0 mL/min, retention time: t_R = 8.52 min (major), 9.84 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 162 – 164 °*C*.

$[\alpha]_D^{21}$ = + 232.6 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.92 – 7.86 (m, 2H, Ar*H*), 7.54 – 7.42 (m, 3H, Ar*H*), 7.36 – 7.25 (m, 3H, Ar*H*), 7.17 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.12 – 7.07 (m, 2H, Ar*H*), 6.97 (d, *J* = 8.0 Hz, 2H, Ar*H*), 3.71 (d, *J* = 6.8 Hz, 1H, C*H*Ph), 3.45 – 3.38 (m, 1H, C*H*CH$_2$), 3.28 (dd, *J* = 14.8, 4.8 Hz, 1H, CHCH*H*), 2.47 (dd, *J* = 14.8, 9.6 Hz, 1H, CHC*H*H), 2.35 (s, 3H, PhC*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

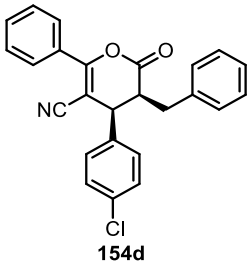
δ = 167.3 (O*C*OCH), 160.6 (Ph*C*O), 138.7 (*C*$_{Ar}$), 137.4 (*C*$_{Ar}$), 131.9 (*C*$_{Ar}$), 131.8 (*C*$_{Ar}$), 130.1 (2 x C) (*C*$_{Ar}$), 129.9 (*C*$_{Ar}$), 128.9 (2 x C) (*C*$_{Ar}$), 128.8 (2 x C) (*C*$_{Ar}$), 128.7 (2 x C) (*C*$_{Ar}$), 128.0 (2 x C) (*C*$_{Ar}$), 127.7 (2 x C) (*C*$_{Ar}$), 127.0 (*C*$_{Ar}$), 117.4 (C*C*N), 93.3 (*C*CN), 44.8 (*C*HCO), 43.9 (CH*C*H$_2$), 32.0 (Ph*C*H), 21.1 (Ph*C*H$_3$) ppm.

IR (ATR): 3494, 3026, 2925, 2653, 2326, 2224, 2104, 1913, 1749, 1647, 1501, 1444, 1328, 1200, 1109, 1029, 933, 818, 770, 707 cm^{-1}.

MS (EI): *m/z* (%) = 77.1 (15), 91.0 (14), 104.0 (10), 105.0 (27), 131.0 (18), 132.0 (11), 231.9 (28), 247.9 (38), 287.9 (51), 379.0 (100).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{21}O_2NNa$: 402.1471, found 402.1465.

(3*S*,4*S*)-3-Benzyl-4-(4-chlorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154d)



154d

Compound **154d** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (155 mg, 92% yield).

TLC: R$_f$ = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IA; *n*-heptane/*i*PrOH = 8:2, flow rate: 0.7 mL/min, retention time: t$_R$ = 11.88 min (major), 10.06 min (minor); T = 30 °*C*; 98 % *ee*.

Melting Point: 128 – 130 °*C*.

$[\alpha]_D^{21}$ = + 272.8 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.94 – 7.90 (m, 2H, Ar*H*), 7.56 – 7.52 (m, 1H, Ar*H*), 7.51 – 7.46 (m, 2H, Ar*H*), 7.40 – 7.33 (m, 4H, Ar*H*), 7.32 – 7.28 (m, 1H, Ar*H*), 7.11 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.04 (d, *J* = 8.4 Hz, 2H, Ar*H*), 3.77 (d, *J* = 7.2 Hz, 1H, C*H*Ph), 3.53 – 3.47 (m, 1H, C*H*CH$_2$), 3.32 (dd, *J* = 14.4, 4.8 Hz, 1H, CHCH*H*), 2.46 (dd, *J* = 15.0, 9.6 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

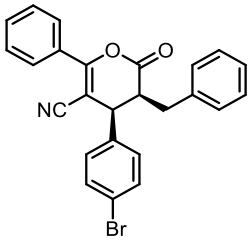
δ = 167.0 (O*C*OCH), 161.0 (Ph*C*O), 137.0 (C_{Ar}), 134.9 (C_{Ar}), 133.6 (C_{Ar}), 132.1 (C_{Ar}), 129.7 (C_{Ar}), 129.6 (2 x C) (C_{Ar}), 129.5 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.2 (C_{Ar}), 117.3 (C*C*N), 92.6 (*C*CN), 44.3 (*C*HCO), 43.6 (CH*C*H$_2$), 32.1 (Ph*C*H) ppm.

IR (ATR): 3501, 3030, 2929, 2680, 2348, 2223, 2132, 1917, 1750, 1649, 1596, 1491, 1327, 1198, 1110, 1025, 933, 829, 694 cm^{-1}.

MS (EI): *m/z* (%) = 77.0 (31), 91.0 (33), 103.0 (10), 104.0 (41), 105.0 (44), 131.0 (100), 132.0 (71), 267.9 (11), 398.9 (78).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{18}O_2N^{35}Cl$: 399.1026, found 399.1021.

(3*S*,4*S*)-3-Benzyl-4-(4-bromophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154e)



154e

Compound **154e** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (165 mg, 93% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/EtOH = 8:2, flow rate: 0.5 mL/min, retention time: t_R = 15.53 min (major), 21.66 min (minor); T = 30 °*C*; 98 % *ee*.

Melting Point: 180 – 182 °*C*.

$\mathbf{[\alpha]_D^{21}}$ = + 245.2 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.92 – 7.88 (m, 2H, Ar*H*), 7.68 – 7.65 (m, 1H, Ar*H*), 7.55 – 7.51 (m, 1H, Ar*H*), 7.50 – 7.45 (m, 2H, Ar*H*), 7.39 – 7.35 (m, 1H, Ar*H*), 7.33 – 7.29 (m, 2H, Ar*H*), 7.28 – 7.23 (m, 2H, Ar*H*), 7.18 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.13 (d, *J* = 7.2 Hz, 2H, Ar*H*), 4.79 (d, *J* =

7.2 Hz, 1H, C*H*Ph), 3.53 (q, *J* = 7.2 Hz, 1H, C*H*CH_2), 3.14 (dd, *J* = 14.4, 6.6 Hz, 1H, CHCH*H*), 2.69 (dd, *J* = 14.4, 6.6 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

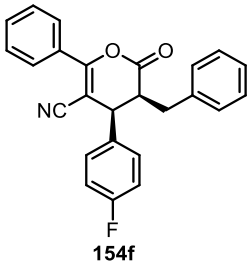
δ = 167.1 (O*C*OCH), 161.3 (Ph*C*O), 137.5 (C_{Ar}), 135.5 (C_{Ar}), 134.0 (C_{Ar}), 132.0 (C_{Ar}), 130.2 (C_{Ar}), 129.8 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (C_{Ar}), 128.8 (4 x C) (C_{Ar}), 127.9 (2 x C) (C_{Ar}), 126.9 (C_{Ar}), 125.6 (C_{Ar}), 117.0 (C*C*N), 91.9 (*C*CN), 44.7 (*C*HCO), 42.5 (CH*C*H_2), 32.3 (Ph*C*H) ppm.

IR (ATR): 3560, 3062, 2941, 2670, 2337, 2208, 2120, 1930, 1787, 1622, 1444, 1378, 1258, 1214, 1132, 1077, 1028, 904, 818, 730, 696 cm^{-1}.

MS (EI): *m/z* (%) = 77.0 (27), 91.0 (33), 103.0 (10), 104.0 (40), 105.0 (35), 130.9 (100), 131.9 (65), 231.9 (14), 351.8 (52), 352.8 (12), 353.8 (49), 442.9 (49).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}O_2N^{79}Br$: 444.0592, found 444.0594.

(3*S*,4*S*)-3-Benzyl-4-(4-fluorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154f)



154f

Compound **154f** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (142 mg, 87% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IA; *n*-heptane/*i*PrOH = 8:2, flow rate: 0.7 mL/min, retention time: t_R = 11.21 min (major), 9.61 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 145 – 147 °*C*.

$[\alpha]_D^{21}$ = + 241.2 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.96 – 7.96 (m, 2H, Ar*H*), 7.56 – 7.51 (m, 1H, Ar*H*), 7.51 – 7.46 (m, 2H, Ar*H*), 7.38

– 7.33 (m, 2H, Ar*H*), 7.32 – 7.28 (m, 1H, Ar*H*), 7.16 – 7.04 (m, 6H, Ar*H*), 3.80 (d, *J* = 6.6 Hz, 1H, C*H*Ph), 3.55 – 3.47 (m, 1H, C*H*CH_2), 3.31 (dd, *J* = 15.0, 4.8 Hz, 1H, CHCH*H*), 2.47 (dd, *J* = 15.0, 9.6 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

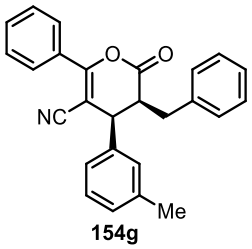
δ = 167.1 (O*C*OCH), 160.9 (Ph*C*O), 137.1 (C_{Ar}), 132.0 (C_{Ar}), 130.9 (C_{Ar}), 130.0 (C_{Ar}), 129.9 (C_{Ar}), 129.8 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (4 x C) (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.2 (C_{Ar}), 117.4 (C*C*N), 116.6 (C_{Ar}), 116.4 (C_{Ar}), 92.9 (*C*CN), 44.5 (*C*HCO), 43.5 (CH*C*H_2), 32.1 (Ph*C*H) ppm.

IR (ATR): 3551, 3030, 2921, 2854, 2695, 2330, 2208, 2111, 1959, 1891, 1782, 1620, 1504, 1449, 1326, 1226, 1085, 1025, 931, 835, 756, 695 cm^{-1}.

MS (EI): *m/z* (%) = 77.0 (26), 91.0 (41), 103.0 (10), 104.0 (43), 104.9 (36), 130.9 (100), 131.9 (66), 132.9 (10), 251.9 (17), 291.9 (55), 292.9 (10), 283.0 (67).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{18}O_2NFNa$: 406.1214, found 406.1214.

(3*S*,4*S*)-3-Benzyl-2-oxo-6-phenyl-4-(*m*-tolyl)-3,4-dihydro-2H-pyran-5-carbonitrile (154g)



154g

Compound **154g** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (95 mg, 59% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/EtOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 11.68 min (major), 14.00 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 179 – 181 °*C*.

$\mathbf{[\alpha]_D^{21}}$ = + 262.0 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.90 – 7.83 (m, 2H, Ar*H*), 7.53 – 7.41 (m, 3H, Ar*H*), 7.32 – 7.20 (m, 5H, Ar*H*), 7.20 – 7.14 (m, 1H, Ar*H*), 7.12 – 7.06 (m, 1H, Ar*H*), 6.99 – 6.91 (m, 2H, Ar*H*), 4.13 (d, *J* = 8.0 Hz, 1H, C*H*Ph), 3.60 – 3.53 (m, 1H, C*H*CH_2), 3.38 (dd, *J* = 14.8, 5.2 Hz, 1H, CHCH*H*), 2.48 (dd, *J* = 14.8, 10.0 Hz, 1H, CHC*H*H), 1.98 (s, 3H, PhCH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

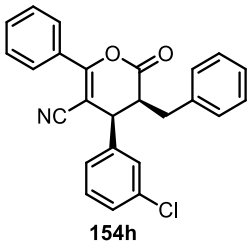
δ = 167.8 (O*C*OCH), 160.3 (Ph*C*O), 137.1 (C_{Ar}), 137.0 (C_{Ar}), 134.6 (C_{Ar}), 131.7 (C_{Ar}), 131.4 (C_{Ar}), 130.1 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.4 (2 x C) (C_{Ar}), 127.0 (2 x C) (C_{Ar}), 126.2 (C_{Ar}), 117.6 (2 x C) (C_{Ar} and C*C*N), 92.9 (*C*CN), 43.6 (*C*HCO), 38.3 (CH*C*H_2), 32.2 (Ph*C*H), 19.5 (Ph*C*H_3) ppm.

IR (ATR): 3336, 3034, 2920, 2650, 2322, 2210, 2036, 1904, 1774, 1624, 1493, 1449, 1373, 1328, 1212, 1085, 1033, 937, 763, 694 cm^{-1}.

MS (EI): *m/z* (%) = 287.9 (13), 379.0 (100).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{21}O_2NNa$: 402.1473, found 402.1465.

(3*S*,4*S*)-3-Benzyl-4-(3-chlorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154h)



154h

Compound **154h** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (156 mg, 92% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AD; *n*-heptane/*i*PrOH = 9:1, flow rate: 1.0 mL/min, retention time: t_R = 12.28 min (major), 8.84 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 121 – 123 °*C*.

$[\alpha]_D^{21}$ = + 161.8 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.91 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.58 – 7.42 (m, 3H, Ar*H*), 7.42 – 7.26 (m, 5H, Ar*H*), 7.19 – 7.02 (m, 3H, Ar*H*), 7.02 – 6.96 (m, 1H, Ar*H*), 3.75 (d, *J* = 6.4 Hz, 1H, C*H*Ph), 3.54 – 3.44 (m, 1H, C*H*CH_2), 3.35 – 3.26 (m, 1H, CHCH*H*), 2.45 (dd, *J* = 14.4, 9.6 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

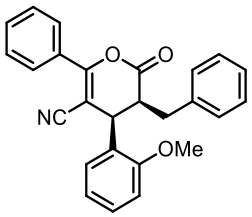
δ = 166.8 (O*C*OCH), 161.2 (Ph*C*O), 137.0 (C_{Ar}), 136.9 (C_{Ar}), 135.2 (C_{Ar}), 132.1 (C_{Ar}), 130.8 (C_{Ar}), 129.7 (C_{Ar}), 129.2 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.6 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.2 (C_{Ar}), 126.1 (C_{Ar}), 117.2 (C*C*N), 92.3 (*C*CN), 44.3 (*C*HCO), 43.9 (CH*C*H_2), 32.1 (Ph*C*H) ppm.

IR (ATR): 3300, 3058, 2917, 2854, 2652, 2327, 2211, 2082, 1930, 1777, 1734, 1634, 1595, 1456, 1377, 1268, 1184, 1079, 1023, 935, 882, 760, 692 cm^{-1}.

MS (EI): *m/z* (%) = 77.1 (18), 91.0 (23), 104.0 (36), 105.0 (29), 130.9 (100), 131.9 (66), 307.9 (58), 308.9 (12), 309.9 (19), 399.0 (62).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{18}O_2NClNa$: 422.0916, found 422.0918.

(3*S*,4*S*)-3-Benzyl-4-(2-methoxyphenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154i)



154i

Compound **154i** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (148 mg, 88% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IC; *n*-heptane/*i*PrOH = 97:3, flow rate: 0.5 mL/min, retention time: t_R = 23.88 min (major), 19.22 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 166 – 168 °*C*.

$[\alpha]_D^{21}$ = + 212.8 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.86 – 7.82 (m, 2H, Ar*H*), 7.51 – 7.42 (m, 3H, Ar*H*), 7.39 – 7.33 (m, 1H, Ar*H*), 7.29 – 7.22 (m, 3H, Ar*H*), 6.97 – 6.90 (m, 4H, Ar*H*), 6.89 – 6.85 (m, 1H, Ar*H*), 3.83 (s, 1H, C*H*Ph), 3.77 (bs, 3H, OCH_3), 3.45 (dd, *J* = 14.4, 3.6 Hz, 1H, C*H*CH_2), 3.38 – 3.32 (m, 1H, CHCH*H*), 2.36 (dd, *J* = 13.8, 10.2 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

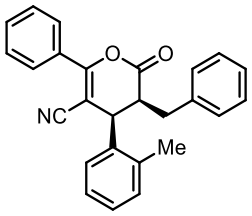
δ = 166.7 (O*C*OCH), 160.3 (Ph*C*O), 157.6 (C_{Ar}), 137.7 (C_{Ar}), 132.4 (C_{Ar}), 131.4 (C_{Ar}), 130.7 (C_{Ar}), 130.2 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.6 (2 x C) (C_{Ar}), 128.5 (2 x C) (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 122.8 (C_{Ar}), 121.1 (C_{Ar}), 117.9 (C*C*N), 110.6 (C_{Ar}), 90.0 (*C*CN), 54.0 (O*C*H_3), 42.7 (*C*HCO), 32.4 (2 x C) (CH*C*H_2 and Ph*C*H) ppm

IR (ATR): 3544, 3030, 2941, 2646, 2323, 2212, 2109, 1896, 1780, 1640, 1591, 1488, 1453, 1370, 1250, 1205, 1100, 1020, 921, 821,754, 691 cm^{-1}.

MS (EI): *m/z* (%) = 91.0 (12), 105.0 (21), 231.9 (73), 232.9 (13), 263.9 (11), 303.9 (100), 304. 9 (22), 395.0 (69).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{21}O_3NNa$: 418.1412, found 418.1414.

(3*S*,4*S*)-3-Benzyl-2-oxo-6-phenyl-4-(*o*-tolyl)-3,4-dihydro-2H-pyran-5-carbonitrile (154j)



154j

Compound **154j** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (85 mg, 53% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/EtOH = 9:1, flow rate: 0.7 mL/min, retention time: t_R = 11.67 min (major), 14.29 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 156 – 158 °*C*.

$\mathbf{[\alpha]_D^{21}}$ = + 213.8 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.89 – 7.85 (m, 2H, Ar*H*), 7.53 – 7.48 (m, 1H, Ar*H*), 7.48 – 7.44 (m, 2H, Ar*H*), 7.32 – 7.28 (m, 2H, Ar*H*), 7.28 – 7.25 (m, 1H, Ar*H*), 7.25 – 7.22 (m, 2H, Ar*H*), 7.21 – 7.16 (m, 1H, Ar*H*), 7.11 – 7.07 (m, 1H, Ar*H*), 6.95 (d, *J* = 7.2 Hz, 2H, Ar*H*), 4.13 (d, *J* = 7.8 Hz, 1H, C*H*Ph), 3.59 – 3.55 (m, 1H, C*H*CH_2), 3.39 (dd, *J* = 14.4, 5.4 Hz, 1H, CHCH*H*), 2.49 (dd, *J* = 14.4, 10.2 Hz, 1H, CHC*H*H), 1.98 (s, 3H, PhCH_3) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

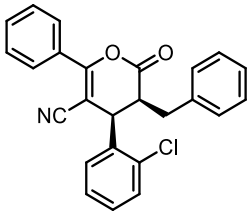
δ = 167.8 (O*C*OCH), 160.3 (Ph*C*O), 137.1 (C_{Ar}), 137.0 (C_{Ar}), 134.6 (C_{Ar}), 131.7 (C_{Ar}), 131.4 (C_{Ar}), 130.0 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.4 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.4 (C_{Ar}), 127.0 (C_{Ar}), 126.2 (C_{Ar}), 117.6 (C*C*N), 92.9 (*C*CN), 43.6 (*C*HCO), 38.3 (CH*C*H_2), 32.2 (Ph*C*H), 19.6 (Ph*C*H_3) ppm.

IR (ATR): 3563, 3041, 2944, 2891, 2652, 2336, 2206, 2107, 1927, 1788, 1617, 1494, 1451, 1374, 1306, 1247, 1209, 1128, 1076, 1034, 955, 821, 729, 691 cm^{-1}.

MS (EI): *m/z* (%) = 51.1 (12), 65.1 (21), 77.0 (99), 78.0 (25), 91.0 (92), 92.0 (11), 103.0 (19), 104.0 (59), 104.9 (100), 114.9 (15), 130.9 (78), 131.9 (43), 217.9 (12), 231.9 (12), 245.9 (12), 247.9 (11), 287.9 (32), 379.0 (39).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{21}O_2NNa$: 402.1472, found 402.1465.

(3*S*,4*R*)-3-Benzyl-4-(2-chlorophenyl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154k)



154k

Compound **154k** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (144 mg, 85% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/EtOH = 8:2, flow rate: 0.5 mL/min, retention time: t_R = 15.01 min (major), 16.96 min (minor); T = 30 °*C*; 99 % *ee*.

$[\alpha]_D^{21}$ = + 302.4 (c = 0.5, CH_2Cl_2).

Melting Point: 169 – 171 °*C*.

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.92 – 7.87 (m, 2H, Ar*H*), 7.54 – 7.50 (m, 1H, Ar*H*), 7.49 – 7.44 (m, 3H, Ar*H*), 7.34 – 7.28 (m, 4H, Ar*H*), 7.27 – 7.24 (m, 1H, Ar*H*), 7.19 – 7.14 (m, 1H, Ar*H*), 7.11 – 7.08 (m, 2H, Ar*H*), 4.76 – 4.66 (m, 1H, C*H*Ph), 3.52 (dd, *J* = 14.4, 7.2 Hz, 1H, C*H*CH_2), 3.18 (dd, *J* = 14.4, 6.6 Hz, 1H, CHCH*H*), 2.65 (dd, *J* = 14.4, 7.2 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

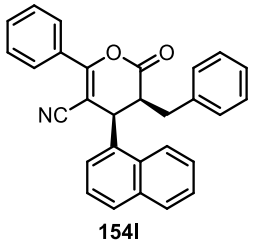
δ = 167.1 (O*C*OCH), 161.4 (Ph*C*O), 137.4 (C_{Ar}), 134.7 (C_{Ar}), 133.6 (C_{Ar}), 132.0 (C_{Ar}), 130.6 (C_{Ar}), 130.0 (C_{Ar}), 129.8 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (3 x C) (C_{Ar}), 128.7 (3 x C) (C_{Ar}), 128.2 (C_{Ar}), 127.9 (2 x C) (C_{Ar}), 126.9 (C*C*N), 117.0 (*C*CN), 44.6 (*C*HCO), 32.2 (2 x C) (CH*C*H_2 and Ph*C*H) ppm.

IR (ATR): 3535, 3276, 3071, 2919, 2670, 2331, 2220, 2126, 1961, 1774, 1640, 1446, 1333, 1256, 1201, 1093, 927, 817, 753, 695 cm^{-1}.

MS (EI): *m/z* (%) = 51.1 (10), 65.1 (11), 77.0 (53), 91.0 (63), 102.9 (18), 104.0 (61), 105.0 (47), 130.9 (90), 131.9 (52), 231.9 (13), 307.9 (70), 308.9 (14), 309.9 (24), 399.0 (100).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{25}H_{18}O_2NClNa$: 422.0918, found 422.0918.

(3*S*,4*S*)-3-Benzyl-4-(naphthalen-1-yl)-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154l)



154l

Compoun**d 154l wa**s prepared according to **GP II** and isolated after flash chromatography as a colorless solid (149 mg, 85% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AS; *n*-heptane/EtOH = 9:1, flow rate: 1.0 mL/min, retention time: t_R = 10.01 min (major), 15.81 min (minor); T = 30 °*C*; 96 % *ee*.

Melting Point: 176 – 178 °*C*.

$[\alpha]_D^{21}$ = + 144.4 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

(major) δ = 7.95 – 7.86 (m, 4H, Ar*H*), 7.79 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.57 – 7.43 (m, 6H, Ar*H*), 7.41 – 7.37 (m, 1H, Ar*H*), 7.23 – 7.14 (m, 3H, Ar*H*), 6.84 – 6.84 (m, 2H, Ar*H*), 4.86 (d, *J* = 7.2 Hz, 1H, C*H*Ph), 3.69 – 3.64 (m, 1H, C*H*CH_2), 3.22 (dd, *J* = 14.4, 5.4 Hz, 1H, CHCH*H*), 2.52 (dd, *J* = 14.4, 8.4 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

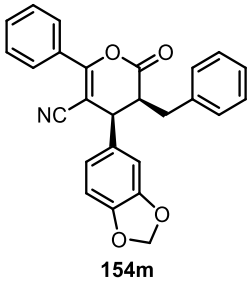
(major) δ = 167.6 (O*C*OCH), 161.1 (Ph*C*O), 137.3 (C_{Ar}), 134.1 (C_{Ar}), 132.2 (C_{Ar}), 131.8 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (C_{Ar}), 129.0 (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.3 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 126.9 (C_{Ar}), 126.8 (C_{Ar}), 126.2 (C_{Ar}), 125.7 (C_{Ar}), 124.5 (C_{Ar}), 122.8 (C_{Ar}), 117.5 (C*C*N), 93.2 (*C*CN), 45.3 (*C*HCO), 32.2 (CH*C*H_2), 29.7 (Ph*C*H) ppm.

IR (ATR): 3302, 2917, 2658, 2322, 2213, 2089, 2004, 1939, 1744, 1608, 1461, 1374, 1249, 1182, 1094, 943, 772, 682 cm^{-1}.

MS (EI): *m/z* (%) = 77.1 (31), 91.0 (27), 105.0 (100), 271.0 (18), 281.9 (31), 283.0 (20), 323.9 (41), 325.0 (11), 415.0 (40).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{21}O_2NNa$: 438.1462, found 438.1465.

(3*S*,4*S*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-3-benzyl-2-oxo-6-phenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154m)



154m

Compound **154m** was prepared according to **GP II** and isolated after flash

chromatography as a colorless solid (156 mg, 90% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak AD; *n*-heptane/*i*PrOH = 9:1, flow rate: 1.0 mL/min, retention time: t_R = 24.67 min (major), 21.08 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 189 – 191 °*C*.

$[\alpha]_D^{21}$ = + 190.4 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.94 – 7.84 (m, 2H, Ar*H*), 7.56 – 7.39 (m, 3H, Ar*H*), 7.40 – 7.24 (m, 3H, Ar*H*), 7.16 – 7.09 (m, 2H, Ar*H*), 6.82 – 7.76 (m, 1H, Ar*H*), 6.60 – 6.52(m, 2H, Ar*H*), 5.98 (d, *J* = 2.0 Hz, 2H, OC*H*$_2$O), 3.70 (d, *J* = 7.2 Hz, 1H, C*H*Ph), 3.47 – 3.37 (m, 1H, C*H*CH$_2$), 3.30 (dd, *J* = 14.8, 4.8 Hz, 1H, CHCH*H*), 2.51 (dd, *J* = 14.8, 9.6 Hz, 1H, CHC*H*H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

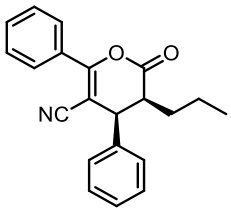
δ = 167.2 (O*C*OCH), 160.6 (Ph*C*O), 148.6 (*C*$_{Ar}$), 148.1 (*C*$_{Ar}$), 137.3 (*C*$_{Ar}$), 131.9 (*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 128.9 (2 x C) (*C*$_{Ar}$), 128.8 (2 x C) (*C*$_{Ar}$), 128.7 (2 x C) (*C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.7 (2 x C) (*C*$_{Ar}$), 127.0 (*C*$_{Ar}$), 122.1 (*C*$_{Ar}$), 117.4 (C*C*N), 108.9 (*C*$_{Ar}$), 107.9 (*C*$_{Ar}$), 101.5 (O*C*H$_2$O), 93.2 (*C*CN), 44.8 (*C*HCO), 44.0 (CH*C*H$_2$), 32.1 (Ph*C*H) ppm.

IR (ATR): 3557, 3074, 2898, 2648, 2330, 2203, 2075, 1995, 1913, 1782, 1622, 1490, 1443, 1322, 1248, 1203, 1035, 920, 816, 731, 687 cm^{-1}.

MS (EI): *m/z* (%) = 105.0 (14), 276.9 (16), 317.9 (33), 409.0 (100).

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{19}O_4NNa$: 432.1205, found 432.1206.

(3*S*,4*S*)-2-Oxo-4,6-diphenyl-3-propyl-3,4-dihydro-2H-pyran-5-carbonitrile (154n)



154n

Compound **154n** was prepared according to **GP II** and isolated after flash chromatography as a colorless solid (94 mg, 74% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IA; *n*-heptane/*i*PrOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 8.05 min (major), 7.17 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 122 – 124 °*C*.

$[\alpha]_D^{21}$ = + 191.4 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.95 – 7.90 (m, 2H, Ar*H*), 7.54 – 7.43 (m, 3H, Ar*H*), 7.38 – 7.29 (m, 3H, Ar*H*), 7.19 – 7.11 (m, 2H, Ar*H*), 3.91 (d, *J* = 6.8 Hz, 1H, C*H*Ph), 3.04 (q, *J* = 6.8 Hz, 1H, C*H*CH_2), 1.75 – 1.66 (m, 1H, CHCH*H*CH_2), 1.53 – 1.41 (m, 1H, CHC*H*HCH_2), 1.30 – 1.19 (m, 2H, C*H*$_2$$CH_3$), 0.90 (t, *J* = 7.2 Hz, 3H, CH_2C*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

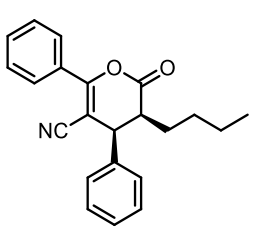
δ = 167.4 (O*C*OCH), 161.0 (Ph*C*O), 135.2 (C_{Ar}), 131.8 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.7 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.7 (2 x C) (C_{Ar}), 117.6 (C*C*N), 92.8 (*C*CN), 45.1 (*C*HCO), 42.9 (Ph*C*H), 28.5 (*C*$H_2CH_2CH_3$), 20.3 (CH_3CH_2), 13.8 (CH_2CH_3) ppm.

IR (ATR): 3524, 3051, 2936, 2213, 2091, 1764, 1641, 1462, 1332, 1231, 1079, 882, 698 cm^{-1}.

MS (EI): *m/z* (100) = 51.1 (14), 55.1 (57), 56.1 (15), 77.0 (72), 83.0 (24), 84.0 (24), 104.9 (91), 114.9 (12), 155.8 (11), 231.9 (21), 232.9 (16), 233.9 (86), 234.9 (14), 245.8 (12), 316.9 (100).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}O_2N$: 318.1482, found 318.1489.

(3*S*,4*S*)-3-Butyl-2-oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154o)



154o

Compound **154o** was prepared according to **GP II** and isolated after flash

chromatography as a colorless solid (105 mg, 74% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IA; *n*-heptane/*i*PrOH = 97:3, flow rate: 0.7 mL/min, retention time: t_R = 9.88 min (major), 9.10 min (minor); T = 30 °*C*; 99 % *ee*.

Melting Point: 105 – 107 °*C*.

$[\alpha]_D^{21}$ = + 187.2 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.95 – 7.90 (m, 2H, Ar*H*), 7.54 – 7.42 (m, 3H, Ar*H*), 7.38 – 7.29 (m, 3H, Ar*H*), 7.18 – 7.13 (m, 2H, Ar*H*), 3.92 (d, *J* = 6.8 Hz, 1H, C*H*Ph), 3.02 (q, *J* = 6.8 Hz, 1H, C*H*CH_2), 1.79 – 1.69 (m, 1H, CHCH*H*CH2), 1.43 – 1.38 (m, 1H, CHCH*H*CH_2), 1.32 – 1.20 (m, 4H, CHC*H*$_2$C*H*$_2$$CH_3$), 0.90 – 0.85 (m, 3H, CH_2C*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

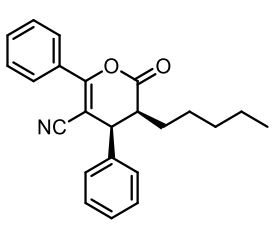
δ = 167.5 (O*C*OCH), 161.0 (Ph*C*O), 135.2 (C_{Ar}), 131.8 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.6 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.7 (2 x C) (C_{Ar}), 117.6 (C*C*N), 92.8 (*C*CN), 45.1 (*C*HCO), 43.2 (Ph*C*H), 29.2 (*C*$H_2C_3H_7$), 26.1 (*C*$H_2C_2H_5$), 22.4 (CH_3*C*H_2), 13.8 (CH_2*C*H_3) ppm.

IR (ATR): 3521, 3063, 2933, 2867, 2652, 2324, 2212, 2128, 1942, 1766, 1640, 1453, 1330, 1207, 1136, 1078, 996, 925, 860, 761, 694 cm^{-1}.

MS (EI): *m/z* (%) = 51.1 (17), 55.1 (100), 56.1 (11), 69.1 (33), 70.1 (23), 77.0 (90), 78.0 (11), 80.0 (16), 91.0 (11), 97.0 (46), 98.0 (24), 104.9 (100), 233.9 (15), 331.0 (3).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{22}H_{21}O_2NNa$: 354.1470, found 354.1465.

(3*S*,4*S*)-2-Oxo-3-pentyl-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile (154p)



154p

Compound **154p** was prepared according to **GP II** and isolated after flash

chromatography as a colorless solid (109 mg, 74% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

Melting Point: 109 – 111 °*C*.

$[\alpha]_D^{21}$ = + 220.0 (c = 0.5, CH_2Cl_2).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.96 – 7.91 (m, 2H, Ar*H*), 7.54 – 7.50 (m, 1H, Ar*H*), 7.50 – 7.46 (m, 2H, Ar*H*), 7.39 – 7.31 (m, 3H, Ar*H*), 7.18 – 7.14 (m, 2H, Ar*H*), 3.94 (d, *J* = 7.2 Hz, 1H, C*H*Ph), 3.04 (q, *J* = 7.2 Hz, 1H, C*H*CH_2), 1.79 – 1.71 (m, 1H, CHCH*H*CH2), 1.50 – 1.38 (m, 2H, CHC*H*HCH*H*), 1.33 – 1.20 (m, 5H, CH_2C*H*HCH_2CH_2), 0.88 (t, *J* = 7.2 Hz, 3H, CH_2CH_3) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

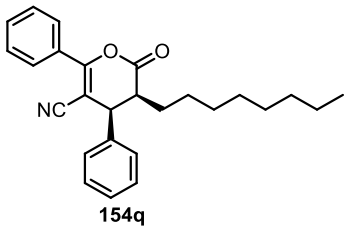
δ = 167.5 (O*C*OCH), 161.0 (Ph*C*O), 135.2 (C_{Ar}), 131.8 (C_{Ar}), 130.0 (C_{Ar}), 129.4 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.7 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.7 (2 x C) (C_{Ar}), 117.6 (C*C*N), 92.8 (*C*CN), 45.1 (*C*HCO), 43.2 (Ph*C*H), 31.5 ($CH_2C_4H_9$), 26.7 ($CH_2C_3H_7$), 26.3 ($CH_2C_2H_5$), 22.4 (CH_3CH_2), 14.0 (CH_2CH_3) ppm.

IR (ATR): 3523, 2934, 2310, 2213, 2086, 1765, 1639, 1457, 1329, 1080, 878, 696 cm^{-1}.

MS (EI): *m/z* (%) = 55.1 (36), 68.1 (23), 69.1 (10), 77.1 (53), 84.0 (14), 105.0 (100), 111.0 (16), 112.0 (14), 115.0 (10), 231.9 (21), 232.9 (28), 233.9 (12), 345.0 (4).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{23}O_2NNa$: 368.1626, found 368.1621.

(3*S*,4*S*)-3-Octyl-2-oxo-4,6-diphenyl-3,4-dihydro-2H-pyran-5-carbonitrile



154q

Compound **154q** was prepared according to **GP II** and isolated after flash chromatography as pale yellow oil (97 mg, 59% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 10:1).

$[\alpha]_D^{21}$ = + 90.2 (c = 0.5, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.95 – 7.89 (m, 1H, Ar*H*), 7.54 – 7.41 (m, 2H, Ar*H*), 7.40 – 7.28 (m, 2H, Ar*H*), 7.16 – 7.11 (m, 1H, Ar*H*), 3.92 (d, *J* = 6.8 Hz, 1H, C*H*Ph), 3.07 – 2.96 (m, 1H, C*H*CH_2), 1.81 – 1.62 (m, 1H, CHCH*H*CH_2), 1.45 – 1.39 (d, *J* = 6.7 Hz, 2H, C*H*HCH*H*CH_2), 1.27 – 1.23 (m, 11H, C*H*$HC_5H_{10}CH_3$), 0.88 – 0.85 (m, 3H, CH_2CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

δ = 167.5 (O*C*OCH), 161.0 (Ph*C*O), 135.1 (C_{Ar}), 131.8 (C_{Ar}), 129.3 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.6 (2 x C) (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 127.7 (2 x C) (C_{Ar}), 117.6 (C*C*N), 92.7 (*C*CN), 45.1 (*C*HCO), 43.2 (Ph*C*H), 31.8 ($CH_2C_7H_{15}$), 29.3 ($CH_2C_6H_{13}$), 29.2 ($CH_2C_5H_{11}$), 29.1 ($CH_2C_4H_9$), 27.0 ($CH_2C_3H_7$), 26.4 ($CH_2C_2H_5$), 22.6 (CH_2CH_3), 14.1 (CH_2CH_3) ppm.

IR (ATR): 3816, 3300, 2911, 2675, 2337, 2091, 1778, 1458, 1328, 1079, 707 cm^{-1}.

MS (EI): *m/z* (%) = 55.1 (44), 57.1 (14), 69.1 (11), 77.0 (43), 83.0 (15), 84.0 (12), 91.0 (12), 97.0 (19), 98.0 (82), 104.9 (100), 111.9 (18), 152.9 (10), 154.9 (11), 155.8 (14), 231.8 (17), 232.8 (15), 233.8 (58), 234.9 (10), 245.8 (11), 387.0 (29).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{29}O_2NNa$: 410.2091, found 410.2091.

4.3.3 Dihydropyrano thiazole synthesis

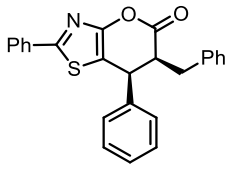
4.3.3.1 General procedure (GP III)

A dried and argon-filled Schlenk tube was charged with 5-alkenyl thiazolones **155** (0.4 mmol, 1.0 equiv.) and triazolium salt **184** (0.04 mmol, 10 mol%) in anhydrous DCM (2 mL). Subsequently, α-chloroaldehydes **100** (1.2 mmol, 3.0 equiv.) and NaOAc (0.8 mmol, 2.0 equiv.) were added. The resulting mixture was stirred at 35°*C* for hours, and the reaction was completed as monitored by TLC. After purification by column chromatorgraphy on silica gel (*n*-pentane/EtOAc = 15:1) the desired bicyclic dihydropyrano thiazoles **156** were obtained as colorless solids or pale yellow oils. The racemic substrates of the corresponding **156** were prepared by using the pre-catalyst

104 with NaOAc in DCM.

4.3.3.2 Analytical data of the synthesized compounds

(6*S*,7*S*)-6-Benzyl-2,7-diphenyl-6,7-dihydro-5H-pyrano[2,3-d]thiazol-5-one (156a)



156a

Compound **156a** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (146 mg, 92% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.5 mL/min, retention time: t_R = 17.35 min (major), 12.73 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 180 – 182 °*C*.

$[\alpha]_D^{22}$ = + 112.2 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.88 – 7.83 (m, 2H, Ar*H*), 7.44 – 7.38 (m, 3H, Ar*H*), 7.37 – 7.31 (m, 5H, Ar*H*), 7.30 – 7.26 (m, 1H, Ar*H*), 7.12 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.08 – 7.02 (m, 2H, Ar*H*), 4.16 (d, *J* = 7.2 Hz, 1H, PhC*H*), 3.64 – 3.56 (m, 1H, COC*H*), 3.39 (dd, *J* = 15.0, 4.8 Hz, 1H, PhCH*H*), 2.51 (dd, *J* = 15.0, 10.2 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

δ = 168.6 (O*C*OCH), 165.3 (S*C*N), 155.6 (S*C*CH), 137.9 (C_{Ar}), 137.8 (N*C*O), 132.8 (C_{Ar}), 130.6 (C_{Ar}), 129.2 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.3 (C_{Ar}), 127.8 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 111.5 (C_{Ar}), 46.8 (CO*C*H), 39.3 (Ph*C*H), 32.8 (Ph*C*H_2) ppm.

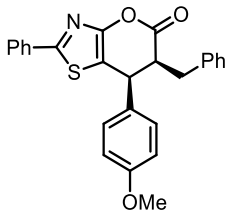
IR (ATR): 3458, 2959, 2299, 2097, 1743, 1364, 1216, 1098, 701 cm^{-1}.

MS (ESI): *m/z* = 398.1 $[M+H]^+$, 420.1 $[M+Na]^+$.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}NO_2S$: 398.1210, found: 398.1209.

(6*S*,7*S*)-6-Benzyl-7-(4-methoxyphenyl)-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d]

thiazol-5-one (156b)



156b

Compound **156b** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (147 mg, 88% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 12.44 min (major), 9.39 min (minor); T = 30 °*C*; 88% *ee*.

Melting Point: 155 – 157 °*C*.

$\mathbf{[\alpha]_D^{22}}$ = + 137.0 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.90 – 7.81 (m, 2H, Ar*H*), 7.43 – 7.38 (m, 3H, Ar*H*), 7.36 – 7.31 (m, 2H, Ar*H*), 7.29 – 7.26 (m, 1H, Ar*H*), 7.15 – 7.11 (m, 2H, Ar*H*), 6.97 – 6.92 (m, 2H, Ar*H*), 6.88 – 6.83 (m, 2H, Ar*H*), 4.11 (d, *J* = 6.6 Hz, 1H, PhC*H*), 3.80 (s, 3H, OCH_3), 3.60 – 3.54 (m, 1H, COC*H*), 3.38 (dd, *J* = 15.0, 4.8 Hz, 1H, PhCH*H*), 2.50 (dd, *J* = 15.0, 10.2 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

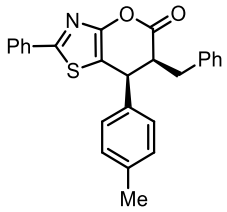
δ = 168.7 (O*C*OCH), 165.1 (S*C*N), 159.4 (S*C*CH), 155.5 (C_{Ar}), 137.9 (N*C*O), 132.9 (C_{Ar}), 130.6 (C_{Ar}), 129.6 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 114.5 (2 x C) (C_{Ar}), 111.9 (C_{Ar}), 55.3 (CO*C*H), 47.0 (O*C*H$_3$), 38.6 (Ph*C*H), 32.7 (Ph*C*H$_2$) ppm.

IR (ATR): 3531, 3035, 2944, 2841, 2270, 2193, 2096, 1893, 1771, 1606, 1558, 1508, 1457, 1359, 1248, 1185, 1067, 965, 829, 753, 686 cm^{-1}.

MS (EI): *m/z* (%) = 91.2 (15), 104.1 (11), 149.1 (22), 164.1 (100), 165.1 (14), 178.1 (14), 192.1 (16), 295.2 (11), 427.2 (9).

HRMS (ESI$^+$): *m/z* $[M + Na]^+$ calcd for $C_{26}H_{21}NO_3NaS$: 450.1135, found: 450.1134.

(6*S*,7*S*)-6-Benzyl-2-phenyl-7-(*p*-tolyl)-6,7-dihydro-5H-pyrano[2,3-d]thiazol-5-one (156c)



156c

Compound **156c** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (153 mg, 93% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 10.90 min (major), 8.20 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 167 – 169 °*C*.

$\mathbf{[\alpha]_D^{22}}$ = + 137.6 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.88 – 7.80 (m, 2H, Ar*H*), 7.43 – 7.37 (m, 3H, Ar*H*), 7.36 – 7.31 (m, 2H, Ar*H*), 7.30 – 7.26 (m, 1H, Ar*H*), 7.14 (t, *J* = 8.4 Hz, 4H, Ar*H*), 6.94 (d, *J* = 8.4 Hz, 2H, Ar*H*), 4.13 (d, *J* = 6.6 Hz, 1H, PhC*H*), 3.62 – 3.55 (m, 1H, COC*H*), 3.39 (dd, *J* = 15.0, 4.8 Hz, 1H, PhCH*H*), 2.52 (dd, *J* = 15.0, 9.6 Hz, 1H, PhC*H*H), 2.35 (s, 3H, PhCH_3) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

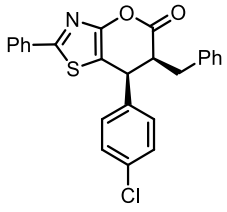
δ = 168.7 (O*C*OCH), 165.1 (S*C*N), 155.6 (S*C*CH), 138.1 (C_{Ar}), 138.0 (N*C*O), 134.7 (C_{Ar}), 132.9 (C_{Ar}), 130.6 (C_{Ar}), 129.9 (2 x C) (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 127.6 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 111.8 (C_{Ar}), 46.8 (CO*C*H), 39.0 (Ph*C*H), 32.8 (Ph*C*H_2), 21.1 (Ph*C*H_3) ppm.

IR (ATR): 3494, 2936, 2314, 1750, 1454, 1358, 1213, 1097, 700 cm^{-1}.

MS (EI): *m/z* (%) = 91.2 (23), 104.2 (15), 115.1 (10), 147.2 (13), 148.2 (100), 149.2 (14), 117.6 (17), 320.2 (25), 411.3 (14).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}NO_2S$: 412.1368, found: 412.1366.

(6*S*,7*S*)-6-Benzyl-7-(4-chlorophenyl)-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d] thiazol-5-one (156d)



156d

Compound **156d** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (154 mg, 89% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 14.19 min (major), 9.96 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 146 – 148 °*C*.

$[\alpha]_D^{22}$ = + 137.2 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.88 – 7.78 (m, 2H, Ar*H*), 7.45 – 7.35 (m, 3H, Ar*H*), 7.35 – 7.22 (m, 5H, Ar*H*), 7.12 – 7.05 (m, 2H, Ar*H*), 6.97 – 6.90 (m, 2H, Ar*H*), 4.12 (d, *J* = 6.8 Hz, 1H, PhC*H*), 3.60 (ddd, *J* = 10.0, 6.8, 4.8 Hz, 1H, COC*H*), 3.39 (dd, *J* = 14.8, 4.8 Hz, 1H, PhCH*H*), 2.45 (dd, *J* = 14.8, 10.0 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

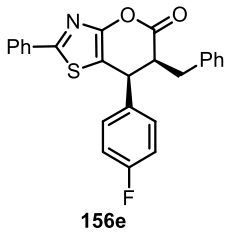
δ = 168.3 (O*C*OCH), 165.6 (S*C*N), 155.7 (S*C*CH), 137.5 (C_{Ar}), 136.2 (N*C*O), 134.2 (C_{Ar}), 132.7 (C_{Ar}), 130.8 (C_{Ar}), 129.4 (2 x C) (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 126.9 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 110.8 (C_{Ar}), 46.5 (CO*C*H), 38.7 (Ph*C*H), 32.7 (Ph*C*H_2) ppm.

IR (ATR): 3335, 3033, 2928, 1750, 1453, 1342, 1237, 1024, 705 cm^{-1}.

MS (EI): *m/z* (%) = 77.1 (19), 91.1 (87), 92.2 (11), 103.1 (23), 104.1 (29), 105.1 (36), 115.1 (13), 129.1 (11), 131.1 (13), 133.0 (27), 168.0 (100), 169.0 (13), 170.0 (36), 196.0 (15), 300.1 (12), 340.1 (14), 431.2 (8).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}NO_2SCl$: 432.0818, found: 432.0820.

(6*S*,7*S*)-6-Benzyl-7-(4-fluorophenyl)-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d] thiazol-5-one (156e)



156e

Compound **156e** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (160 mg, 96% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 13.88 min (major), 9.64 min (minor); T = 30 °*C*; 97% *ee*.

Melting Point: 138 – 140 °*C*.

$[\alpha]_D^{22}$ = +140.0 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.90 – 7.80 (m, 2H, Ar*H*), 7.44 – 7.36 (m, 3H, Ar*H*), 7.35 – 7.29 (m, 2H, Ar*H*), 7.26 – 7.22 (m, 1H, Ar*H*), 7.13 (d, *J* = 7.2 Hz, 2H, Ar*H*), 6.74 (d, *J* = 7.6 Hz, 1H, Ar*H*), 6.51 – 6.48 (m, 1H, Ar*H*), 5.95 (s, 2H, Ar*H*), 4.07 (d, *J* = 6.8 Hz, 1H, PhC*H*), 3.58 – 3.49 (m, 1H, COC*H*), 3.38 (dd, *J* = 14.8, 4.8 Hz, 1H, PhCH*H*), 2.53 (dd, *J* = 14.8, 10.0 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

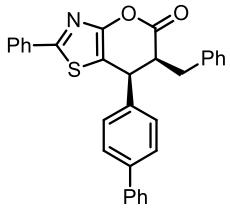
δ = 168.5 (O*C*OCH), 165.3 (S*C*N), 155.5 (S*C*CH), 148.4 (C_{Ar}), 147.5 (C_{Ar}), 137.9 (N*C*O), 132.8 (C_{Ar}), 131.3 (C_{Ar}), 130.6 (C_{Ar}), 129.0 (3 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 121.3 (C_{Ar}), 111.5 (C_{Ar}), 108.6 (C_{Ar}), 107.7 (C_{Ar}), 101.3 (C_{Ar}), 46.9 (CO*C*H), 39.1 (Ph*C*H), 32.7 (Ph*C*H_2) ppm.

IR (ATR): 3031, 2933, 2109, 1754, 1489, 1354, 1214, 1079, 832, 699 cm^{-1}.

MS (EI): *m/z* (%) = 91.1 (21), 103.1 (10), 104.1 (14), 152.0 (100), 153.0 (12), 165.0 (12), 180.0 (14), 284.1 (15), 324.1 (22), 415.1 (17).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}NO_2FS$: 416.1116, found: 416.1115.

(6*S*,7*S*)-7-([1,1'-Biphenyl]-4-yl)-6-benzyl-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d] thiazol-5-one (156f)



156f

Compound **156f** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (165 mg, 90% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 14.11 min (major), 10.55 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 220 – 222 °*C*.

$[\alpha]_D^{22}$ = + 168.4 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.89 – 7.84 (m, 2H, Ar*H*), 7.61 – 7.52 (m, 4H, Ar*H*), 7.48 – 7.39 (m, 5H, Ar*H*), 7.38 – 7.32 (m, 3H, Ar*H*), 7.31 – 7.27 (m, 1H, Ar*H*), 7.18 – 7.14 (m, 2H, Ar*H*), 7.13 – 7.08 (m, 2H, Ar*H*), 4.21 (d, *J* = 6.6 Hz, 1H, PhC*H*), 3.63 (ddd, *J* = 10.2, 6.6, 4.8 Hz, 1H, COC*H*), 3.43 (dd, *J* = 15.0, 4.8 Hz, 1H, PhCH*H*), 2.57 (dd, *J* = 15.0, 10.2 Hz, 1H, CH, PhC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

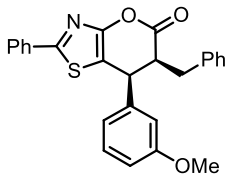
δ = 168.6 (O*C*OCH), 165.3 (S*C*N), 155.7 (S*C*CH), 141.2 (C_{Ar}), 140.2 (C_{Ar}), 137.8 (N*C*O), 136.6 (C_{Ar}), 132.8 (C_{Ar}), 130.7 (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.2 (2 x C) (C_{Ar}), 127.9 (2 x C) (C_{Ar}), 127.6 (C_{Ar}), 127.0 (2 x C) (C_{Ar}), 126.9 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 111.4 (C_{Ar}), 46.8 (CO*C*H), 39.0 (Ph*C*H), 32.8 (Ph*C*H_2) ppm.

IR (ATR): 3031, 2914, 2344, 2103, 1911, 1761, 1563, 1460, 1349, 1200, 1072, 843, 705 cm^{-1}.

MS (ESI): *m/z* = 474.2 $[M + H]^+$.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{31}H_{24}NO_2S$: 474.1523, found: 474.1522.

(6*S*,7*S*)-6-Benzyl-7-(3-methoxyphenyl)-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d] thiazol-5-one (156g)



156g

Compound **156g** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (157 mg, 92% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 12.09 min (major), 9.80 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 175 – 177 °*C*.

$[\alpha]_D^{22}$ = + 150.4 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.88 – 7.81 (m, 2H, Ar*H*), 7.45 – 7.38 (m, 3H, Ar*H*), 7.35 – 7.31 (m, 2H, Ar*H*), 7.29 – 7.23 (m, 2H, Ar*H*), 7.16 – 7.11 (m, 2H, Ar*H*), 6.87 – 6.83 (m, 1H, Ar*H*), 6.67 – 6.62 (m, 1H, Ar*H*), 6.58 – 6.54 (m, 1H, Ar*H*), 4.12 (d, *J* = 6.6 Hz, 1H, PhC*H*), 3.77 (s, 3H, OCH_3), 3.61 – 3.55 (m, 1H, COC*H*), 3.40 (dd, *J* = 15.0, 4.8 Hz, 1H, PhCH*H*), 2.53 (dd, *J* = 15.0, 9.6 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

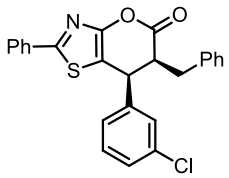
δ = 168.6 (O*C*OCH), 165.3 (S*C*N), 160.0 (S*C*CH), 155.6 (C_{Ar}), 139.2 (C_{Ar}), 137.9 (N*C*O), 132.8 (C_{Ar}), 130.6 (C_{Ar}), 130.3 (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 119.8 (C_{Ar}), 113.6 (C_{Ar}), 113.5 (C_{Ar}), 111.3 (C_{Ar}), 55.2 (OCH_3), 46.7 (CO*C*H), 39.4 (Ph*C*H), 32.8 (PhCH_2) ppm.

IR (ATR): 3434, 2929, 2112, 1750, 1577, 1452, 1355, 1231, 1047, 699 cm^{-1}.

MS (EI): *m/z* (%) = 77.1 (17), 91.1 (84), 103.1 (20), 104.1 (26), 115.1 (11), 121.0 (18), 131.1 (12), 133.1 (18), 134.0 (14), 164.0 (100), 165.0 (16), 336.1 (20), 427.2 (3).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}NO_3S$: 428.1326, found: 428.1315.

(6*S*,7*S*)-6-Benzyl-7-(3-chlorophenyl)-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d] thiazol-5-one (156h)



156h

Compound **156h** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (158 mg, 93% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 17.12 min (major), 10.24 min (minor); T = 30 °*C*; 92% *ee*.

Melting Point: 176 – 178 °*C*.

$[\alpha]_D^{22}$ = + 169.4 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.89 – 7.82 (m, 2H, Ar*H*), 7.46 – 7.39 (m, 3H, Ar*H*), 7.38 – 7.33 (m, 2H, Ar*H*), 7.32 – 7.26 (m, 3H, Ar*H*), 7.11 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.00 – 6.96 (m, 1H, Ar*H*), 6.94 – 6.90 (m, 1H, Ar*H*), 4.13 (d, *J* = 7.2 Hz, 1H, PhC*H*), 3.65 – 3.59 (m, 1H, COC*H*), 3.42 (dd, *J* = 14.4, 4.2 Hz, 1H, PhCH*H*), 2.47 (dd, *J* = 14.4, 10.2 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

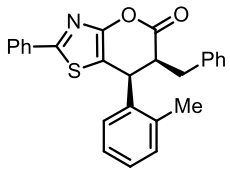
δ = 168.2 (O*C*OCH), 165.7 (S*C*N), 155.8 (S*C*CH), 139.6 (C_{Ar}), 137.4 (N*C*O), 134.9 (C_{Ar}), 130.8 (C_{Ar}), 130.6 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.8 (2 x C) (C_{Ar}), 128.6 (C_{Ar}), 128.3 (C_{Ar}), 127.0 (C_{Ar}), 125.9 (2 x C) (C_{Ar}), 125.7 (C_{Ar}), 110.5 (C_{Ar}), 46.4 (CO*C*H), 39.0 (Ph*C*H), 32.8 (Ph*C*H_2) ppm.

IR (ATR): 3459, 2993, 2193, 1944, 1743, 1563, 1365, 1215, 1081, 912, 692 cm^{-1}.

MS (EI): *m/z* (%) = 77.2 (13), 89.1 (13), 91.1 (70), 103.1 (22), 104.1 (34), 115.1 (10), 131.1 (16), 133.1 (16), 168.0 (100), 169.1 (13), 170.0 (37), 181.1 (12), 300.1 (13), 340.1 (13), 431.1 (5).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}NO_2ClS$: 432.0817, found: 432.0820.

(6*S*,7*S*)-6-Benzyl-2-phenyl-7-(o-tolyl)-6,7-dihydro-5H-pyrano[2,3-d]thiazol-5-one (156i)



156i

Compound **156i** was prepared according to **GP III** and isolated after flash chromatography as pale yellow oil (150 mg, 91% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB, *n*-heptane/EtOH (7:3), 0.7 mL/min, t_R (minor) = 8.22 min, t_R (major) = 8.79 min; T = 30 °*C*; 99% *ee*.

$\mathbf{[\alpha]_D^{22}}$ = + 73.6 (c = 0.5, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.86 – 7.78 (m, 2H, Ar*H*), 7.42 – 7.36 (m, 3H, Ar*H*), 7.28 – 7.23 (m, 3H, Ar*H*), 7.22 – 7.17 (m, 2H, Ar*H*), 7.16 – 7.13 (m, 1H, Ar*H*), 7.12 – 7.08 (m, 1H, Ar*H*), 6.92 – 6.87 (m, 2H, Ar*H*), 4.34 (d, *J* = 7.2 Hz, 1H, PhC*H*), 3.65 – 3.59 (m, 1H, COC*H*), 3.49 (dd, *J* = 14.4, 4.8 Hz, 1H, PhCH*H*), 2.64 (dd, *J* = 14.4, 10.8 Hz, 1H, PhC*H*H), 1.98 (s, 3H, PhCH_3) ppm.

^{13}C NMR (151 MHz, $CDCl_3$):

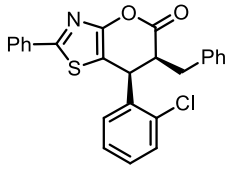
δ = 169.3 (O*C*OCH), 164.6 (S*C*N), 155.1 (S*C*CH), 137.5 (N*C*O), 136.8 (C_{Ar}), 135.3 (C_{Ar}), 132.8 (C_{Ar}), 131.1 (C_{Ar}), 130.6 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 127.8 (C_{Ar}), 127.3 (C_{Ar}), 126.8 (C_{Ar}), 126.4 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 111.3 (C_{Ar}), 45.4 (CO*C*H), 34.1 (Ph*C*H), 32.9 (Ph*C*H_2), 19.6 (Ph*C*H_3) ppm.

IR (ATR): 3523, 3029, 2931, 2323, 2095, 1828, 1768, 1562, 1494, 1452, 1353, 1226, 1184, 1113, 1018, 933, 844, 698 cm^{-1}.

MS (EI): *m/z* (%) = 77.2 (13), 91.2 (100), 105.1 (11), 103.1 (23), 104.1 (21), 105.1 (11), 115.1 (41), 117.1 (12), 128.1 (20), 129.1 (22), 131.1 (12), 133.1 (13), 147.1 (62), 148.1 (90), 149.1 (13), 161.1 (16), 176.1 (18), 219.2 (11), 264.1 (24), 279.2 (10), 280.2 (31), 320.2 (50), 321.2 (12), 411.2 (70).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}NO_2S$: 412.1368, found: 412.1366.

(6*S*,7*S*)-6-Benzyl-7-(2-chlorophenyl)-2-phenyl-6,7-dihydro-5H-pyrano[2,3-d] thiazol-5-one (156j)



156j

Compound **156j** was prepared according to **GP III** and isolated after flash chromatography as pale yellow oil (134 mg, 78% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IC; *n*-heptane/*i*PrOH = 7:3, flow rate: 1.0 mL/min, retention time: t_R = 9.54 min (major), 6.71 min (minor); T = 30 °*C*; 99% *ee*.

$[\alpha]_D^{22}$ = + 120.4 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.87 – 7.75 (m, 2H, Ar*H*), 7.45 – 7.39 (m, 1H, Ar*H*), 7.39 – 7.33 (m, 3H, Ar*H*), 7.30 – 7.16 (m, 6H, Ar*H*), 6.97 (d, *J* = 6.8 Hz, 2H, Ar*H*), 4.77 (d, *J* = 6.4 Hz, 1H, PhC*H*), 3.62 – 3.54 (m, 1H, COC*H*), 3.45 (dd, *J* = 14.4, 4.8 Hz, 1H, PhCH*H*), 2.73 (dd, *J* = 14.4, 9.6 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

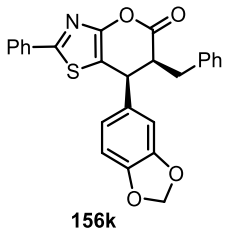
δ = 169.0 (O*C*OCH), 165.2 (S*C*N), 155.5 (S*C*CH), 137.6 (N*C*O), 135.9 (C_{Ar}), 133.5 (C_{Ar}), 132.7 (C_{Ar}), 130.6 (C_{Ar}), 130.3 (C_{Ar}), 129.3 (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.9 (2 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 110.1 (C_{Ar}), 45.6 (CO*C*H), 34.9 (Ph*C*H), 32.9 (Ph*C*H$_2$) ppm.

IR (ATR): 3025, 2660, 2333, 2084, 1947, 1761, 1565, 1456, 1356, 1210, 1094, 704 cm^{-1}.

MS (ESI): *m/z* = 432.1 $[M + H]^+$, 454.1 $[M + Na]^+$.

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}NO_2ClS$: 432.0810, found: 432.0820.

(6*S*,7*S*)-7-(Benzo[d][1,3]dioxol-5-yl)-6-benzyl-2-phenyl-6,7-dihydro-5H-pyrano [2,3-d]thiazol-5-one (156k)



156k

Compound **156k** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (135 mg, 79% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IB; *n*-heptane/EtOH = 7:3, flow rate: 0.7 mL/min, retention time: t_R = 15.11 min (major), 10.81 min (minor); T = 30 °*C*; 95% *ee*.

Melting Point: 156 – 158 °*C*.

$[\alpha]_D^{22}$ = + 144.2 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.88 – 7.78 (m, 2H, Ar*H*), 7.44 – 7.36 (m, 3H, Ar*H*), 7.35 – 7.28 (m, 2H, Ar*H*), 7.26 – 7.22 (m, 1H, Ar*H*), 7.16 – 7.10 (m, 2H, Ar*H*), 6.74 (d, *J* = 7.8 Hz, 1H, Ar*H*), 6.50 – 6.47 (m, 2H, Ar*H*), 5.95 (s, 2H, OCH_2O), 4.07 (d, *J* = 6.8 Hz, 1H, PhC*H*), 3.54 (ddd, *J* = 10.0, 6.8, 4.8 Hz, 1H, COC*H*), 3.38 (dd, *J* = 14.8, 4.8 Hz, 1H, PhCH*H*), 2.53 (dd, *J* = 14.8, 10.0 Hz, 1H, PhC*H*H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

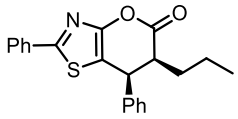
δ = 168.5 (O*C*OCH), 165.3 (S*C*N), 155.5 (S*C*CH), 148.4 (C_{Ar}), 147.5 (C_{Ar}), 137.9 (N*C*O), 132.8 (C_{Ar}), 131.3 (C_{Ar}), 130.6 (C_{Ar}), 129.0 (3 x C) (C_{Ar}), 128.7 (2 x C) (C_{Ar}), 126.8 (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 121.3 (C_{Ar}), 111.5 (C_{Ar}), 108.6 (C_{Ar}), 107.7 (C_{Ar}), 101.3 (C_{Ar}), 46.9 (CO*C*H), 39.1 (Ph*C*H), 32.7 (Ph*C*H_2) ppm.

IR (ATR): 3526, 3024, 2897, 2783, 2257, 2190, 2096, 1916, 1764, 1556, 1489, 1443, 1356, 1239, 1037, 918, 814, 747, 688 cm^{-1}.

MS (EI): *m/z* (%) = 77.2 (13), 78.2 (12), 91.2 (100), 103.1 (19), 104.1 (18), 129.1 (11), 133.1 (18), 178.1 (41), 441.2 (2).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{26}H_{20}NO_4S$: 442.1100, found: 442.1108.

(6*S*,7*S*)-2,7-Diphenyl-6-propyl-6,7-dihydro-5H-pyrano[2,3-d]thiazol-5-one (156l)



156l

Compound **156l** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (130 mg, 93% yield).

TLC: R_f = 0.40 (*n*-pentane:EtOAc = 10:1).

HPLC: Chiralpak IC, *n*-heptane/EtOH = 95:5, flow rate: 0.7 mL/min, retention time: t_R = 19.30 min (major), 18.33 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 150 – 152 °*C*.

$\mathbf{[\alpha]_D^{22}}$ = + 109.0 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.88 – 7.79 (m, 2H, Ar*H*), 7.42 – 7.33 (m, 3H, Ar*H*), 7.32 – 7.21 (m, 3H, Ar*H*), 7.13 – 7.06 (m, 2H, Ar*H*), 4.32 (d, *J* = 6.8 Hz, 1H, PhC*H*), 3.13 (ddd, *J* = 10.2, 6.8, 6.8 Hz, 1H,COC*H*), 1.86 – 1.66 (m, 1H, CH*H*C_2H_5), 1.51 – 1.41 (m, 2H, C*H*HCH*H*CH_3), 1.30 – 1.16 (m, 1H, C*H*HCH_3), 0.88 (t, *J* = 7.2 Hz, 3H, CH_2CH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

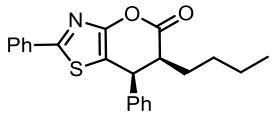
δ = 168.9 (O*C*OCH), 165.1 (S*C*N), 156.0 (S*C*CH), 137.9 (N*C*O), 132.9 (C_{Ar}), 130.6 (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.1 (C_{Ar}), 127.5 (2 x C) (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 111.1 (C_{Ar}), 45.2 (CO*C*H), 40.2 (Ph*C*H), 29.3 ($CH_2C_2H_5$), 20.4 (CH_2CH_3), 13.9 (CH_2CH_3) ppm.

IR (ATR): 3536, 2952, 2869, 2106, 1891, 1773, 1556, 1492, 1454, 1351, 1223, 1134, 1068, 969, 908, 746, 683 cm^{-1}.

MS (EI): *m/z* (%) = 134.1 (82), 135.1 (11), 162.0 (33), 265.0 (34), 266.1 (40), 349.1 (100).

HRMS (ESI$^+$): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{19}NO_2NaS$: 372.1025, found: 372.1029.

(6*S*,7*S*)-6-Butyl-2,7-diphenyl-6,7-dihydro-5H-pyrano[2,3-d]thiazol-5-one (156m)



156m

Compound **156m** was prepared according to **GP III** and isolated after flash chromatography as a colorless solid (120 mg, 83% yield).

TLC: R_f = 0.40 (*n*-petane:EtOAc = 10:1).

HPLC: Chiralpak IC; *n*-heptane/EtOH = 95:5, flow rate: 0.7 mL/min, retention time: t_R = 18.67 min (major), 17.37 min (minor); T = 30 °*C*; 99% *ee*.

Melting Point: 173 – 175 °*C*.

$\mathbf{[\alpha]_D^{22}}$ = + 101.0 (c = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.89 – 7.79 (m, 2H, Ar*H*), 7.42 – 7.33 (m, 3H, Ar*H*), 7.33 – 7.22 (m, 3H, Ar*H*), 7.10 (d, *J* = 6.4 Hz, 2H, Ar*H*), 4.33 (d, *J* = 6.8 Hz, 1H, PhC*H*), 3.11 (ddd, *J* = 13.6, 6.8, 6.8 Hz, 1H, COC*H*), 1.85 – 1.71 (m, 1H, CH*H*C_3H_7), 1.53 – 1.36 (m, 2H, C*H*HCH*H*C_2H_5), 1.35 – 1.20 (m, 3H, C*H*HC*H*$_2$$CH_3$), 0.86 (t, *J* = 7.2 Hz, 3H, CH_2C*H*$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$):

δ = 168.9 (O*C*OCH), 165.1 (S*C*N), 156.0 (S*C*CH), 137.9 (N*C*O), 132.9 (C_{Ar}), 130.6 (C_{Ar}), 129.1 (2 x C) (C_{Ar}), 129.0 (2 x C) (C_{Ar}), 128.1 (C_{Ar}), 127.5 (2 x C) (C_{Ar}), 125.8 (2 x C) (C_{Ar}), 111.1 (C_{Ar}), 45.4 (CO*C*H), 40.2 (Ph*C*H), 29.3 (*C*$H_2C_3H_7$), 26.8 (*C*$H_2C_2H_5$), 22.5 (*C*H_2CH_3), 13.9 (CH_2*C*H_3) ppm.

IR (ATR): 3468, 2934, 2865, 2322, 2094, 1963, 1760, 1560, 1457, 1357, 1209, 1140, 1086, 969, 751, 685 cm^{-1}.

MS (EI): *m/z* (%) = 134.1 (100), 135.1 (13), 162.1 (28), 265.1 (27), 266.1 (35), 363.2 (51).

HRMS (ESI$^+$): *m/z* $[M + H]^+$ calcd for $C_{22}H_{22}NO_2S$: 364.1370, found: 364.1366

5. Acknowledgment

It is my great pleasure to take this opportunity to express my gratitude and thanks to all the people who have helped and encouraged me during my PhD studies. This dissertation could not have been accomplished without their supports and kind suggestions.

Foremost, I especially want to thank my supervisor, Prof. Dr. Dieter Enders, for his constant supports and guidance throughout my PhD research. His intensity, passion, motivation and profound knowledge had motivated me. Prof. Enders has allowed me great freedom in developing projects to work on in the lab and has always been ready for providing valuable advice when I confront the challenges. There is no doubt that what I have benefited from Prof. Enders, a professional chemist and supervisor, will have an extraordinary impact to my future life.

Next, I wish to express my warm and sincere thanks to Prof. Xiuying Yang, my bachelor supervisor in CDTF in China, who has shown me philosophical perspectives when I faced challenges in my life.

I'd also like to thank Dr. Xiang-Yu Chen for his great help and support during my doctor research. Without his help I cannot finish my research so smoothly.

Besides, I also want to give my appreciation to my master supervisor Dr. Lei Wang. Many thanks to all my labmates: Pratap Reddy, Kun Zhao, as well as all the current and former group members for their cooperation and general help during my PhD study, including Qiang Liu, Jiawen Xiong, Tao Shu, Dr. Pankaj Chauhan, Dr. Marcus Blümel *et al.*. I want to thank Fabrizio Vetica, Dr. Stephen Bailey, Dr. Mukesh Kumar, Yee Ann Ho for helping me correct the thesis. I am also grateful to my master students: Tengfei Ji, Yue Zhao, Chen Zhu, He Sheng, Dan Zhao and Ke Wang.

Chapter 5. Acknowledgment

High tribute shall be paid to the administrative and technical staff of the organische institute of RWTH for their support. Especially, thanks to Dr. Wolfgang Bettray for keeping everything well in our group and his supervisor during the research. Also many thanks to Karin Risse and Kristina Deckers for the warmly help during my study here, to Desiree Gilliam and Lena Ronkartz for the analytical help. I am extremely thankful to Prof. G. Raabe, Prof. K. Rissanen, Carolina von Essen, Anssi Peuronen and Ai Wang for the X-ray testing.

Then I would like to thank Prof. Dr. Markus Albrecht as second supervisor of this doctor thesis.

I would also like to express my sincere thank to all my friends in Paderborn and RWTH for their help during the past seven years in Germany, especially thanks to Xiaobing Yu and Duo Zhang for their great help and support for my daily life during the PhD study. I will definitely miss and treasure their friendships.

Last but not least, my deepest gratitude goes to my family for their unflagging love and support throughout my life.

6. Abbreviation

Å	Ångström
Ac	acetyl
Ar-	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
cat.	catalyst
Cy	cyclohexene
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo-[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	dichlorethane
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethylether
DMF	dimethylformamid
d	day
d.r.	diastereomeric ratio
ee	enantiomeric excess
EI	electron Ionization
equiv.	equivalent
ESI	electron spray ionization
Et	ethyl
e.r.	enantiomeric ratio
h	hour
HRMS	high resolution mass spectrometry
Hz	Hertz
IAd	1,3-di(adamantyl)imidazol-2-ylidene
*i*Pr	*iso*-propyl
J	coupling constant (in NMR spectroscopy)
KHMDS	kaliumhexamethyldisilazid
LDA	lithiumdiisopropylamid
Me	methyl
MeCN	acetonitril
Mes	2,4,6-trimethylphenyl

MS	molecular sieve
NHC	*N*-heterocyclic carbene
NMR	nuclear magnetic resonance
n.r.	no reaction
Nu	nucleophile
Ph	phenyl
PMP	polymethylpenten
Quant.	quantitative
rac	racemic
rt	room temperature
TCE	tricycles containing nonenolizable cyano enone
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl

7. References

1. A. J. Arduengo, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361.
2. M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485.
3. a) D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39; b) Y. Canac, M. Soleilhavoup, S. Conejero, G. Bertrand, *J. Organomet. Chem.* **2004**, *689*, 3857; c) P. de Frémont, N. Marion, S. P. Nolan, *Coord. Chem. Rev.* **2009**, *253*, 862; d) K. Öfele, E. Tosh, C. Taubmann, W. A. Herrmann, *Chem. Rev.* **2009**, *109*, 3408; e) O. Schuster, L. Yang, H. G. Raubenheimer, M. Albrecht, *Chem. Rev.* **2009**, *109*, 3445; f) M. Melaimi, M. Soleilhavoup, G. Bertrand, *Angew. Chem. Int. Ed.* **2010**, *49*, 8810.
4. a) L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz, V. César, *Chem. Rev.* **2011**, *111*, 2705; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307.
5. a) T. Strassner, in *Electronic Structure and Reactivity of Metal Carbenes*, Springer-verlag: Heidelberg, Berlin, **2004**; p. 1; b) L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.* **2005**, *690*, 5407; c) S. Díez-González, S. P. Nolan, *Coord. Chem. Rev.* **2007**, *251*, 874; d) O. Kühl, *Coord. Chem. Rev.* **2009**, *253*, 2481; e) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841; f) T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 6940.
6. T. Ukai, R. Tanaka, T. Dokawa, *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.
7. R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719.
8. H. W. Wanzlick, *Angew. Chem. Int. Ed.* **1962**, *1*, 75.
9. a) K. Öfele, *J. Organomet. Chem.* **1968**, *12*, P42; b) H. W. Wanzlick, H. J. Schönherr, *Angew. Chem. Int. Ed.* **1968**, *7*, 141; c) A. J. Arduengo, J. R. Goerlich, R. Krafczyk, W. J. Marshall, *Angew. Chem. Int. Ed.* **1998**, *37*, 1963.
10. J. C. Sheehan, D. H. Hunneman, *J. Am. Chem. Soc.* **1966**, *88*, 3666.
11. H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, *7*, 5239.
12. a) D. J. Cardin, B. Cetinkaya, M. F. Lappert, *Chem. Rev.* **1972**, *72*, 545; b) M. F. Lappert, *J. Organomet. Chem.* **1988**, *358*, 185.
13. A. Igau, H. Grutzmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **1988**, *110*, 6463.

14. D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J. P. Melder, K. Ebel, S. Brode, *Angew. Chem. Int. Ed.* **1995**, *34*, 1021.
15. a) R. L. Knight, F. J. Leeper, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891; b) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2002**, *124*, 10298; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606.
16. A. Ben-Naim, G. Subramanian, F. Glorius, J. T. Hynes, J. P. Klinman, H. H. Limbach, R. L. Schowen, Y. Kazakevich, E. Silva, A. M. Edwards, *J. Am. Chem. Soc.* **2007**, *129*, 8923.
17. a) N. Kuhn, A. Al-Sheikh, *Coord. Chem. Rev.* **2005**, *249*, 829; b) M. J. Fuchter, *Chem. Eur. J.* **2010**, *16*, 12286.
18. P. C. Chiang, J. W. Bode, in *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, RSC Publishing: Cambridge, **2011**, p. 399.
19. F. Wöhler, J. Liebig, *Ann. der Pharm.* **1832**, *3*, 249.
20. A. Lapworth, *J. Chem. Soc.* **1903**, *83*, 995.
21. a) J. C. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *39*, 1196; b) W. Tagaki, Y. Tamura, Y. Yano, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478; c) C. Zhao, S. Chen, P. Wu, Z. Wen, *Huaxue Xuebao* **1988**, *46*, 784; d) J. Martí, J. C. Francisco López-Calahorra, *Tetrahedron Lett.* **1993**, *34*, 521; e) C. A. Dvorak, V. H. Rawal, *Tetrahedron Lett.* **1998**, *39*, 2925.
22. a) D. Enders, K. Breuer, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1217; b) J. Teles, K. Breuer, D. Enders, H. Gielen, *Synth. Commun.* **1999**, *29*, 1; c) D. Enders, K. Breuer, in *Comprehensive Asymmetric Catalysis*, Springer-Verlag: Heidelberg, Germany, **1999**; Vol. 3, p. 1093.
23. D. Enders, U. Kallfass, *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.
24. J. Pesch, K. Harms, T. Bach, *Eur. J. Org. Chem.* **2004**, 2025.
25. a) S. Orlandi, M. Caporale, M. Benaglia, R. Annunziata, *Tetrahedron: Asymmetry* **2003**, *14*, 3827; b) K. I. Iwamoto, M. Hamaya, N. Hashimoto, H. Kimura, Y. Suzuki, M. Sato, *Tetrahedron Lett.* **2006**, *47*, 7175.
26. Y. Tachibana, N. Kihara, T. Takata, *J. Am. Chem. Soc.* **2004**, *126*, 3438.
27. a) J. H. Davis, K. J. Forrester, *Tetrahedron Lett.* **1999**, *40*, 1621; b) L. W. Xu, Y. Gao, J. J. Yin, L. Li, C. G. Xia, *Tetrahedron Lett.* **2005**, *46*, 5317.

28. S. Bag, V. V. Vaze, M. S. Degani, *J. Chemical Res.* **2006**, *4*, 267.
29. a) H. Stetter, G. Dämbkes, *Synthesis* **1977**, 403; b) H. Stetter, G. Dämbkes, *Synthesis* **1980**, 309; c) R. Heck, A. P. Henderson, B. Köhler, J. Rétey, T. G. Bernard, *Eur. J. Org. Chem.* **2001**, 2623.
30. P. Dünkelmann, D. Kolter-Jung, A. Nitsche, A. S. Demir, P. Siegert, B. Lingen, M. Baumann, M. Pohl, M. Müller, *J. Am. Chem. Soc.* **2002**, *124*, 12084.
31. a) J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. Grabowski, P. J. Reider, *J. Am. Chem. Soc.* **2001**, *123*, 9696; b) S. M. Mennen, J. D. Gipson, Y. R. Kim, S. J. Miller, *J. Am. Chem. Soc.* **2005**, *127*, 1654.
32. G. Q. Li, L. X. Dai, S. L. You, *Chem. Commun.* **2007**, 852.
33. A. E. Mattson, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 4363.
34. R. Cookson, R. M. Lane, *J. Chem. Soc. Chem. Commun.* **1976**, 804.
35. H. Takikawa, Y. Hachisu, J. W. Bode, K. Suzuki, *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.
36. a) H. Stetter, M. Schreckenberg, *Angew. Chem. Int. Ed.* **1973**, *12*, 81; b) P. Böhler, C. Tamm, *Fortschr. Chem. Org. Naturst.* **1981**, *40*, 105; c) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725.
37. H. Stetter, *Angew. Chem. Int. Ed.* **1976**, *15*, 639.
38. a) H. Stetter, J. Krasselt, *J. Heterocycl. Chem.* **1977**, *14*, *573*; b) H. Stetter, H. Kuhlmann, *Org. React.* **1991**, *40*, 407; c) Y. Hachisu, J. W. Bode, K. Suzuki, *J. Am. Chem. Soc.* **2003**, *125*, 8432.
39. (a) J. Tiebes, Diploma Thesis, RWTH Aachen, Aachen, Germany, **1990**; (b) D. Enders, In *Stereoselective Synthesis*; Springer-Verlag: Heidelberg, Germany, **1993**; p. 63; (c) D. Enders, B. Bockstiegel, H. Dyker, U. Jegelka, H. Kipphardt, D. Kownatka, H. Kuhlmann, D. Mannes, J. Tiebes, K. Papadopoulos, In *Dechema-Monographies*; VCH: Weinheim, Germany, **1993**; Vol. 129, p. 209.
40. a) A. E. Mattson, A. R. Bharadwaj, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 2314; b) A. E. Mattson, A. R. Bharadwaj, A. M. Zuhl, K. A. Scheidt, *J. Org. Chem.* **2006**, *71*, 5715.
41. H. Stetter, G. Lorenz, *Chem. Ber.* **1985**, *118*, 1115.
42. E. Ciganek, *Synthesis* **1995**, 1311.

43. a) D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899; b) J. L. Moore, M. S. Kerr, T. Rovis, *Tetrahedron* **2006**, *62*, 11477.
44. a) L. Knorr, *Chem. Ber.* **1884**, *17*, 1635; b) C. Paal, *Chem. Ber.* **1885**, *18*, 367; c) H. Stetter, H. Kuhlmann, *Synthesis* **1975**, 379; d) V. Amarnath, D. C. Anthony, K. Amarnath, W. M. Valentine, L. A. Wetterau, D. G. Graham, *J. Org. Chem.* **1991**, *56*, 6924; e) B. D. Roth, C. Blankley, A. Chucholowski, E. Ferguson, M. Hoefle, D. Ortwine, R. Newton, C. Sekerke, D. Sliskovic, M. Wilson, *J. Med. Chem.* **1991**, *34*, 357; f) K. L. Baumann, D. E. Butler, C. F. Deering, K. E. Mennen, A. Millar, T. N. Nanninga, C. W. Palmer, B. D. Roth, *Tetrahedron Lett.* **1992**, *33*, 2283; g) P. E. Harrington, M. A. Tius, *Org. Lett.* **1999**, *1*, 649; h) T. J. Müller, M. Ansorge, D. Aktah, *Angew. Chem. Int. Ed.* **2000**, *39*, 1253; i) R. U. Braun, K. Zeitler, T. J. Müller, *Org. Lett.* **2001**, *3*, 3297; j) C. C. Galopin, *Tetrahedron Lett.* **2001**, *42*, 5589; k) P. E. Harrington, M. A. Tius, *J. Am. Chem. Soc.* **2001**, *123*, 8509; l) A. R. Bharadwaj, K. A. Scheidt, *Org. Lett.* **2004**, *6*, 2465.
45. D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239.
46. C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205.
47. S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370.
48. a) A. Chan, K. A. Scheidt, *Org. Lett.* **2005**, *7*, 905; b) S. S. Sohn, J. W. Bode, *Org. Lett.* **2005**, *7*, 3873.
49. V. Nair, S. Vellalath, M. Poonoth, R. Mohan, E. Suresh, *Org. Lett.* **2006**, *8*, 507.
50. L. H. Sun, L. T. Shen, S. Ye, *Chem. Commun.* **2011**, *47*, 10136.
51. J. Dugal‐Tessier, E. A. O'Bryan, T. B. Schroeder, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 4963.
52. K. Hirano, I. Piel, F. Glorius, *Adv. Synth. Catal.* **2008**, *350*, 984.
53. Y. Li, Z. A. Zhao, H. He, S. L. You, *Adv. Synth. Catal.* **2008**, *350*, 1885.
54. M. He, J. W. Bode, *Org. Lett.* **2005**, *7*, 3131.
55. D. E. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766.
56. X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466.
57. A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2008**, *130*, 2740.
58. J. Seayad, P. K. Patra, Y. Zhang, J. Y. Ying, *Org. Lett.* **2008**, *10*, 953.
59. A. Chan, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 5334.
60. a) J. Izquierdo, A. Orue, K. A. Scheidt, *J. Am. Chem. Soc.* **2013**, *135*, 10634; b) H.

Lv, W. Q. Jia, L. H. Sun, S. Ye, *Angew. Chem. Int. Ed.* **2013**, *52*, 8607.

61. Z. Fu, J. Xu, T. Zhu, W. W. Y. Leong, Y. R. Chi, *Nat. Chem.* **2013**, *5*, 835.
62. V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736.
63. P. C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520.
64. B. Cardinal-David, D. E. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345.
65. M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418.
66. X. Fang, X. Chen, Y. R. Chi, *Org. Lett.* **2011**, *13*, 4708.
67. E. O. B. McCusker, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2013**, *52*, 13616.
68. E. M. Phillips, M. Wadamoto, A. Chan, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3107.
69. M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088.
70. T. Y. Jian, L. H. Sun, S. Ye, *Chem. Commun.* **2012**, *48*, 10907.
71. Q. Ni, H. Zhang, A. Grossmann, C. C. Loh, C. Merkens, D. Enders, *Angew. Chem. Int. Ed.* **2013**, *52*, 13562.
72. X. Song, Q. Ni, C. Zhu, G. Raabe, D. Enders, *Synthesis* **2015**, *47*, 421.
73. Z. H. Gao, X. Y. Chen, J. T. Cheng, W. L. Liao, S. Ye, *Chem. Commun.* **2015**, *51*, 9328.
74. K. B. Ling, A. D. Smith, *Chem. Commun.* **2011**, *47*, 373.
75. H. Lv, J. Mo, X. Fang, Y. R. Chi, *Org. Lett.* **2011**, *13*, 5366.
76. Y. R. Zhang, L. He, X. Wu, P. L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277.
77. N. Duguet, C. D. Campbell, A. M. Slawin, A. D. Smith, *Org. Biomol. Chem.* **2008**, *6*, 1108.
78. L. He, H. Lv, Y.-R. Zhang, S. Ye, *J. Org. Chem.* **2008**, *73*, 8101.
79. X. N. Wang, P. L. Shao, H. Lv, S. Ye, *Org. Lett.* **2009**, *11*, 4029.
80. X. N. Wang, Y. Y. Zhang, S. Ye, *Adv. Synth. Catal.* **2010**, *352*, 1892.
81. P. L. Shao, X. Y. Chen, S. Ye, *Angew. Chem.Int. Ed.* **2010**, *46*, 8412.
82. Y. R. Zhang, H. Lv, D. Zhou, S. Ye, *Chem. Eur. J.* **2008**, *14*, 8473.
83. X. L. Huang, L. He, P. L. Shao, S. Ye, *Angew. Chem. Int. Ed.* **2009**, *48*, 192.
84. H. Lv, L. You, S. Ye, *Adv. Synth. Catal.* **2009**, *351*, 2822.
85. H. Lv, X. Y. Chen, L. H. Sun, S. Ye, *J. Org. Chem.* **2010**, *75*, 6973.
86. L. Hao, Y. Du, H. Lv, X. Chen, H. Jiang, Y. Shao, Y. R. Chi, *Org. Lett.* **2012**, *14*, 2154.

87. X. Zhao, K. E. Ruhl, T. Rovis, *Angew. Chem. Int. Ed.* **2012**, *51*, 12330.
88. S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176.
89. S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2010**, *132*, 1190.
90. J. Kaeobamrung, J. Mahatthananchai, P. Zheng, J. W. Bode, *J. Am. Chem. Soc.* **2010**, *132*, 8810.
91. Z. Q. Zhu, X. L. Zheng, N. F. Jiang, X. Wan, J. C. Xiao, *Chem. Commun.* **2011**, *47*, 8670.
92. S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2011**, *133*, 4694.
93. F. G. Sun, L. H. Sun, S. Ye, *Adv. Synth. Catal.* **2011**, *353*, 3134.
94. a) B. Wanner, J. Mahatthananchai, J. W. Bode, *Org. Lett.* **2011**, *13*, 5378; b) J. Cheng, Z. Huang, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8592.
95. V. Kumar, K. Kaur, G. K. Gupta, A. K. Sharma, *Eur. J. Med. Chem.* **2013**, *69*, 735.
96. a) I. Schlemminger, P. Hummel, A. Hatzelmann, C. Zitt, A. Wohlsen, D. Marx, H. P. Kley, D. Ockert, A. Heuser, J. A. M. Christiaans, G. J . Sterk, W. M. P. B. Menge (Nycomed GmbH, Germany), WO2008138939 **2010**; b) E. Amata, N. D. Bland, R. K. Campbell, M. P. Pollastri, *Tetrahedron Lett.* **2015**, *56*, 2832.
97. Y. Zhang, S. Wu, S. Wang, K. Fang, G. Dong, N. Liu, Z. Miao, J. Yao, J. Li, W. Zhang, *Eur. J. Org. Chem.* **2015**, 2030.
98. a) R. T. Coutts, A. M. El-Hawari, D. F. Biggs, *Can. J. Chem.* **1975**, *53*, 3645; b) M. F. Aly, G. M. El-Nagger, T. I. El-Emary, R. Grigg, S. A. Metwally, S. Sivagnanam, *Tetrahedron* **1994**, *50*, 895; c) U. Uršič, U. Grošelj, A. Meden, J. Svete, B. Stanovnik, *Synthesis* **2009**, 217; d) L. Guideri, R. Noschese, F. Ponticelli, *J. Heterocycl. Chem.* **2012**, *49*, 297.
99. a) S. Gogoi, C. G. Zhao, D. Ding, *Org. Lett.* **2009**, *11*, 2249; b) A. N. R. Alba, A. Zea, G. Valero, T. Calbet, M. Font-Bardía, A. Mazzanti, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2011**, *2011*, 1318; c) Z. Wang, Z. Yang, D. Chen, X. Liu, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2011**, *50*, 4928; d) Z. Yang, Z. Wang, S. Bai, X. Liu, L. Lin, X. Feng, *Org. Lett.* **2011**, *13*, 596; e) A. Zea, A. N. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Org. Biomol. Chem.* **2011**, *9*, 6519; f) F. Li, L. Sun, Y. Teng, P. Yu, J. C. G. Zhao, J. A. Ma, *Chem. Eur. J.* **2012**, *18*, 14255; g) Z. Wang, Z. Chen, S. Bai, W. Li, X. Liu, L. Lin, X. Feng, *Angew. Chem. Int. Ed.* **2012**, *51*, 2776; h) B. Wu, J. Chen, M. Q. Li, J. X. Zhang, X. P. Xu, S. J. Ji, X. W. Wang, *Eur. J. Org.*

Chem. **2012**, *2012*, 1318; i) J. Liang, Q. Chen, L. Liu, X. Jiang, R. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1441; j) P. Chauhan, S. Mahajan, C. C. Loh, G. Raabe, D. Enders, *Org. Lett.* **2014**, *16*, 2954; k) P. Chauhan, S. Mahajan, D. Enders, *Chem. Commun.* **2015**, *51*, 12890; l) D. Hack, P. Chauhan, K. Deckers, Y. Mizutani, G. Raabe, D. Enders, *Chem. Commun.* **2015**, *51*, 2266.

100. X. Han, W. Yao, T. Wang, Y. R. Tan, Z. Yan, J. Kwiatkowski, Y. Lu, *Angew. Chem. Int. Ed.* **2014**, *53*, 5643.
101. L. Wang, S. Li, P. Chauhan, D. Hack, A. R. Philipps, R. Puttreddy, K. Rissanen, G. Raabe, D. Enders, *Chem. Eur. J.* **2016**, *22*, 5123.
102. CCDC 1516205 contains the supplementary crystallographic data of spiropyrozolone **152p**. These data can be obtained free of charge by The Cambridge Crystallographic Data Centre.
103. a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; b) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; d) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; e) J. L. Moore, T. Rovis, in *Asymmetric Organocatalysis*, Springer-verlag, Heidelberg, Berlin, **2010**, pp. 118; f) Y. Wu, W. Yao, L. Pan, Y. Zhang, C. Ma, *Org. Lett.* **2010**, *12*, 640; g) T. Y. Jian, L. He, C. Tang, S. Ye, *Angew. Chem. Int. Ed.* **2011**, *50*, 9104; h) V. Nair, R. S. Menon, A. T. Biju, C. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; i) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; j) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, *44*, 2295; k) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; l) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; m) X. Y. Chen, L. H. Sun, S. Ye, *Chem. Eur. J.* **2013**, *19*, 4441; n) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664; o) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; p) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; q) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; r) A. Lee, K. A. Scheidt, *Chem. Commun.* **2015**, *51*, 3407; s) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040; t) S. R. Yetra, A. Patra, A. T. Biju, *Synthesis* **2015**, *47*, 1357; u) J. L. Li, L. Fu, J. Wu, K. C. Yang, Q. Z. Li, X. J. Gou, C. Peng, B. Han, X. D. Shen, *Chem. Commun.* **2017**, *53*, 6875; v)

E. Reyes, U. Uria, L. Carrillo, J. L. Vicario, *Synthesis* **2017**, *49*, 451.

104. N. T. Reynolds, J. R. de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518.
105. a) A. J. Fatiadi, in *Triple-Bonded Functional Groups*, VCH New York, **1983**, *vol. 2*, pp. 1057; b) R. C. Larock, in *Comprehensive organic transformations: a guide to functional group preparations*, VCH New York, **1999**; c) A. Kleemann, J. Engel, B. Kutschner, D. Reichert, in *Pharmaceutical substances: syntheses, patents, applications*, *4th Ed.*, Georg Theime: Stuttgart, Germany, **2001**; d) J. S. Miller, J. L. Manson, *Acc. Chem. Res.* **2001**, *34*, 563; e) M. B. Smith, J. March, in *March's advanced organic chemistry: reactions, mechanisms, and structure*, *6th Ed.*; Wiley: Hoboken, NJ, **2007**.
106. M. Spetea, E. Greiner, M. D. Aceto, L. S. Harris, A. Coop, H. Schmidhammer, *J. Med. Chem.* **2005**, *48*, 5052.
107. G. Guillerm, M. Muzard, C. Glapski, S. Pilard, E. De Clercq, *J. Med. Chem.* **2006**, *49*, 1223.
108. T. Honda, H. Yoshizawa, C. Sundararajan, E. David, M. J. Lajoie, F. G. Favaloro Jr, T. Janosik, X. Su, Y. Honda, B. D. Roebuck, *J. Med. Chem.* **2011**, *54*, 1762.
109. X. D. An, S. Yu, *Org. Lett.* **2015**, *17*, 5064.
110. a) S. J. Ryan, L. Candish, D. W. Lupton, *J. Am. Chem. Soc.* **2009**, *131*, 14176; b) Z.-Q. Rong, M.-Q. Jia, S.-L. You, *Org. Lett.* **2011**, *13*, 4080; c) S. Bera, C. G. Daniliuc, A. Studer, *Org. Lett.* **2015**, *17*, 4940.
111. L. F. Tietze, *Angew. Chem. Int. Ed.* **1983**, *22*, 828.
112. CCDC 1555938 contains the supplementary crystallographic data of spiropyrozolone **154b**. These data can be obtained free of charge by The Cambridge Crystallographic Data Centre.
113. E. L. Luzina, A. V. Popov, *Eur. J. Med. Chem.* **2009**, *44*, 4944.
114. V. Zaharia, A. Ignat, N. Palibroda, B. Ngameni, V. Kuete, C. N. Fokunang, M. L. Moungang, B. T. Ngadjui, *Eur. J. Med. Chem.* **2010**, *45*, 5080.
115. A. Aliabadi, F. Shamsa, S. N. Ostad, S. Emami, A. Shafiee, J. Davoodi, A. Foroumadi, *Eur. J. Med. Chem.* **2010**, *45*, 5384.
116. H. B. Shi, S. J. Zhang, Q. F. Ge, D. W. Guo, C. M. Cai, W. X. Hu, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6555.
117. J. M. Bartolomé-Nebreda, S. Conde-Ceide, F. Delgado, L. Iturrino, J. Pastor, M. Á.

Pena, A. A. Trabanco, G. Tresadern, C. M. Wassvik, S. R. Stauffer, *J. Med. Chem.* **2013**, *56*, 7243.

118. a) T. F. John, L. G. French, J. S. Erlichman, *Eur. J. Pharmacol.* **2006**, *545*, 129; b) C. R. McCurdy, K. J. Sufka, G. H. Smith, J. E. Warnick, M. J. Nieto, *Pharmacol. Biochem. Behav.* **2006**, *83*, 109; c) T. E. Prisinzano, *J. Nat. Prod.* **2008**, *72*, 581.
119. L. Lin, Y. Yang, M. Wang, L. Lai, Y. Guo, R. Wang, *Chem. Commun.* **2015**, *51*, 8134.
120. CCDC 1587163 contains the supplementary crystallographic data the dihydropyrano thiazole **156d**. These data can be obtained free of charge by The Cambridge Crystallographic Data Centre.

8. Curriculum Vitae of Sun Li

PERSONAL DATA

Name	Li, Sun
Address	Turmstr. 16b, App. 210
	52072, Aachen, Germany
Date of Birth	31.08.1988
Place of Birth	Shandong, P. R. China
Nationality	P. R. China
Marital Status	ledig
Email	sun.li@rwth-aachen.de

EDUCATION

RWTH AACHEN University – Ph. D Aachen, Germany
Major: NHC-catalyzed remote functionalization of unsaturated carbonyl compounds
2015.09-2018.04
Thesis: *N*-heterocyclic Carbene Catalyzed Asymmetric Cycloaddition/Annulation Reactions of Enals and α-Chloroaldehydes
Advisor: Prof. Dr. Dieter Enders

RWTH AACHEN University – Master Aachen, Germany
Major: Bioactive compounds and synthetic methods, catalysts
2013.10-2015.06
Thesis: Asymmetric Three Component One-pot δ-Lactone-Annulation via an Aldol Condensation/NHC-Catalyzed Michael Addition/Lactonization reaction.
Advisor: Prof. Dr. Dieter Enders

Paderborn University – Bachelor Paderborn, Germany
Major: Chemistry *2011.10-2013.09*
Thesis: Kupferkomplex mit Thioharnstoff-Liganden.
Advisor: Prof. Dr. Gerald Henkel

Qingdao University of Science and Technology – Bachelor Qingdao, China
Major: Applied Chemistry *2008.09-2014.07*
Advisor: Prof. Dr. Zijiang Yang and Prof. Xiuying Yang