N-Heterocyclic Carbene Catalyzed Asymmetric Cycloaddition/Annulation Reactions *via* Homoenolates and Azolium Dienolates

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

vorgelegt von

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Parts of this work have been published:

1. "Asymmetric Synthesis of Spirooxindole ε-Lactones through N-Heterocyclic Carbene Catalysis"
Qiang Liu, Sun Li, Xiang-Yu Chen, Kari Rissanen, Dieter Enders*, *Org. Lett*. **2018**, *20*, 3622.

2 "Highly Enantioselective Kinetic Resolution of Michael Adducts through N-Heterocyclic Carbene Catalysis: An Efficient Asymmetric Route to Cyclohexenes"
Xiang-Yu Chen, Sun Li, **Qiang Liu** (Co-first author), Mukesh Kumar, Anssi Peuronen, Kari Rissanen, and Dieter Enders*, *Chem. Eur. J*. **2018**, *24*, 9735.

3. "N-Heterocyclic Carbene Catalysis via Azolium Dienolates: An Efficient Strategy for Enantioselective Remote Functionalizations"
Xang-Yu Chen, **Qiang Liu** (Co-first author), Pankaj Chauha, Dieter Enders*, *Angew. Chem. Int. Ed*. **2018**, *57*, 3862.

4. "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.

5**. "**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.

6**. "**Squaramide-Catalyzed Domino Michael/aza-Henry [3+2] Cycloaddition: Asymmetric Synthesis of Functionalized 5-Trifluoromethyl and 3-Nitro- Substituted Pyrrolidines"
Qiang Liu, Kun Zhao, Ying Zhi, Gerhard Raabe, Dieter Enders*, *Org. Chem. Frontiers*. **2017**, *4*, 1416.

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.

8. "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, He Sheng, **Qiang Liu**, Ehsan Jafari, Carolina von Essen, Kari Rissanen, Dieter Enders*, *Chem. Eur. J.* **2017**, *23*, 13042.

9. "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.

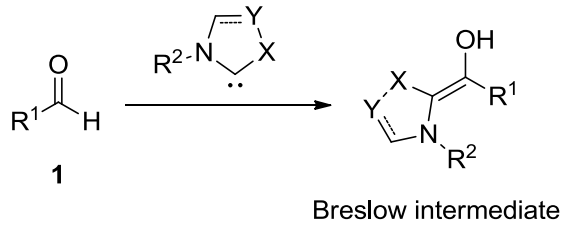
10. "*N*-Heterocyclic Carbene Catalyzed [4+2] Annulation of Enals *via* a Double Vinylogous Michael Addition: Asymmetric Synthesis of 3,5-Diaryl Cyclohexenones"
Xiang-Yu Chen, **Qiang Liu**, Pankaj Chauhan, Sun Li, Anssi Peuronen, Kari Rissanen, Ehsan Jafari, Dieter Enders*, *Angew. Chem. Int. Ed.* **2017**,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

Table of Contents

1. Introduction

1.1 Background of the *N*-heterocyclic carbenes (NHCs)

Carbenes with a bivalent carbon atom and two non bonding electrons are considered as a type of highly reactive compounds. *N*-heterocyclic carbenes (NHCs), as heterocyclic species including at least one nitrogen atom and a divalent carbonic center within the ring structure, have attracted considerable attention among chemists. In 1943, Ukai and co-workers originally achieved the thiazolium salts-catalyzed benzoin reaction of aldehydes.[1] Until 1958, Breslow determined the possible mechanism of this benzoin reaction.[2] With the aid of a base, the thiazolium salt generated the thiazolium carbene, which combined with aldehyde to form the Breslow intermediate (Scheme 1).



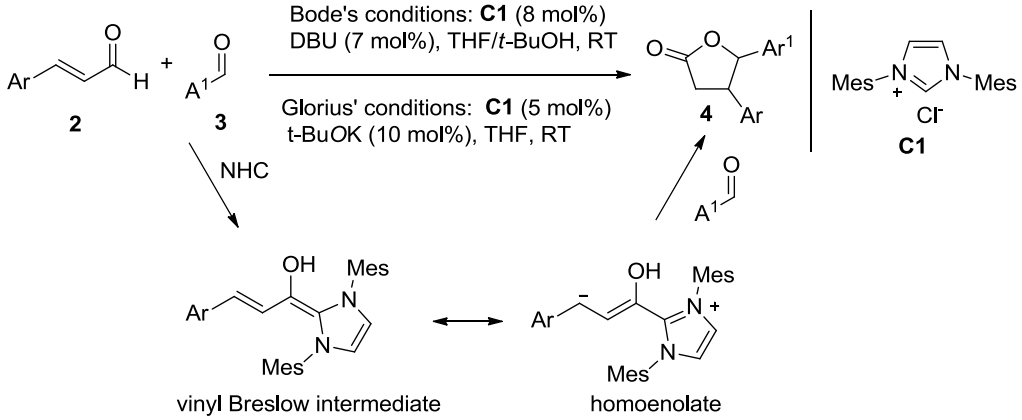
Scheme 1 NHC-catalyzed generation of Breslow intermediate

Later in 1966, Sheehan and Hunneman reported the first example of NHC catalyzed asymmetric benzoin condensation reaction by employing chiral thiazolium salts as NHC pre-catalysts.[3] In the early 1970s Stetter and co-workers successfully developed Michael additions of aldehydes via an "acyl anion" approach.[4] Since then, a variety of NHC-catalyzed reactions of aldehydes, for instance the Stetter reaction and the benzoin reaction, were well explored.[5] In 1990 Enders and coworkers developed the first asymmetric intermolecular Stetter reactions by using new chiral thiazolium salt derived NHCs.[6] Then they firstly described the synthesis of chiral triazolium derived carbenes in 1995.[7] After that, several chiral variants of the triazolylidene were developed, finally resulted in the evolution of chiral bicyclic triazolylidene scaffolds, which sharply enhanced the asymmetric induction of a variety of NHC-catalyzed reactions.[8]

The isolation of stable cabenes remained a challenge for a long time although the attempted syntheses may date back to as early as 1835.[9] Since the seminal independent preparation of stable phosphanylsilycarbene by Bertrand *el al.*[10] in 1988 and imidazolium carbenes by Arduengo *et al.*[11] in 1991, the unambiguous characterization and reactivity of carbenes have stimulated broad interest among chemistry workers. *N*-heterocyclic carbenes (NHCs), as the most important carbene species, have been widely used in various transition-metal catalyzed reactions as excellent ligands. Moreover, NHCs were proved to be efficient catalysts and played a significant role in organocatalysis.

1.2 NHC-catalyzed cyclization reactions *via* homoenolates

1.2.1 Generation *via* α,β-unsaturated aldehydes for the construction of heterocycles

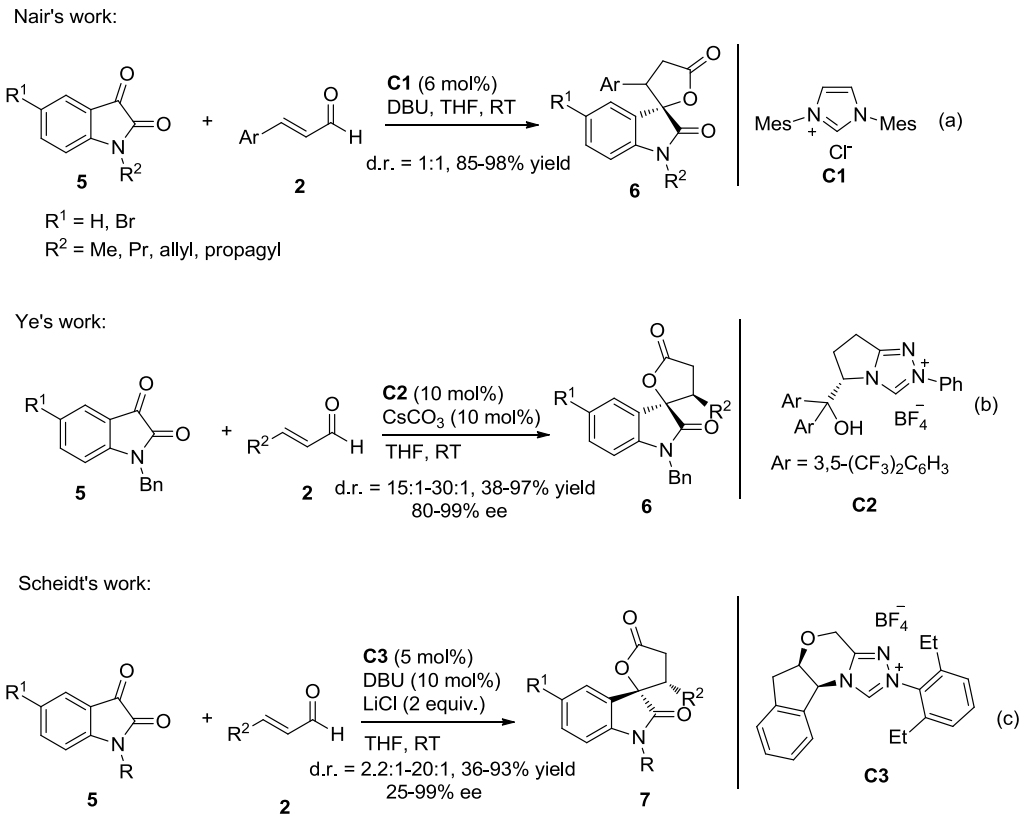


Scheme 2 NHC-catalyzed [3+2] annulations of enals and aromatic aldehydes

The development of the NHC-catalyzed cyclization reactions was relatively slow and the breakthrough progress was achieved until 2004. Bode[12] and Glorius[13] and their coworkers independently developed the pioneering NHC-catalyzed [3+2] annulation reaction of enals with aromatic aldehydes *via* homoenolate equivalents. The reaction was found to be tolerable for both the aromatic aldehydes **2** and α,β-unsaturated aldehydes **3** under the imidazolium salt **C1** conditions, furnishing the targeted

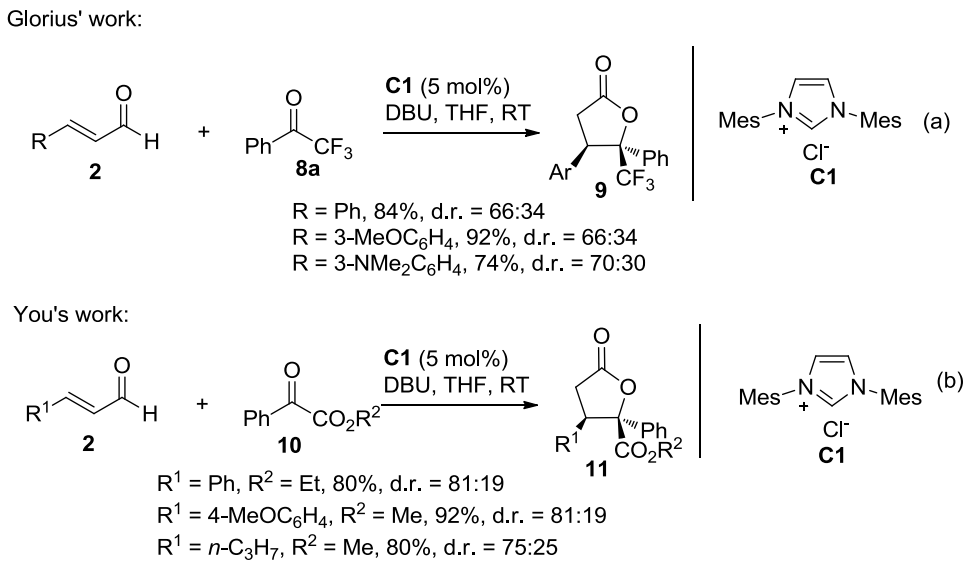
γ-butyrolactones **4** in good yields (Scheme 2). This discovery greatly promoted the development of the NHC-catalyzed cyclization reactions.

In 2006, Nair and co-workers reported the NHC-catalyzed [3+2] annulation of enals with 1,2-diketones and isatins for the preparation of spirocyclic oxindole-γ-lactone derivatives (Scheme 1a).[14] Then the asymmetric version was successfully achieved by Ye and co-workers in 2011 (Scheme 1b).[15] Later on, Scheidt and co-workers prepared these spirocyclic structures by employing an N-heterocyclic carbene/Lewis acid strategy (Scheme 1c).[16] A series of ketones and enals reacted well to furnish corresponding products with quaternary carbon centers in good yields with high enantioselectivities .



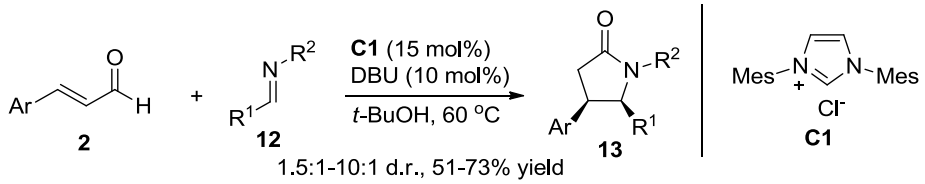
Scheme 3 NHC-catalyzed [3+2] annulations of enals with isatins

In further investigations, Glorius[17] and You[18] and their coworkers extended this concept to prepare γ-butyrolactones with quaternary stereocentres. Several electron-deficient ketones as electrophiles were tolerable to offer the desired product under their conditions (Scheme 4).



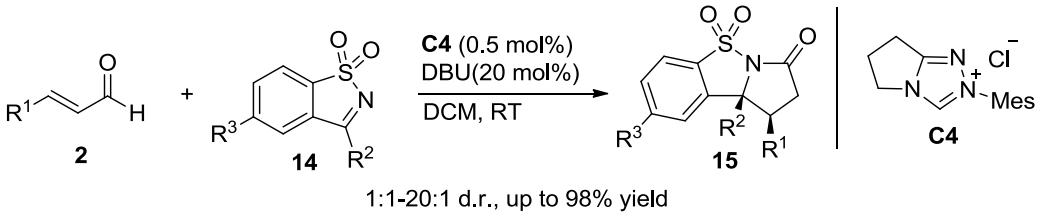
Scheme 4 NHC-catalyzed [3+2] annulations of enals with ketones

In 2005, Bode and co-workers reported the development of NHC-catalyzed [3+2] annulations of enals with N-sulfonylimines **12** employing a similar strategy.[19] A series of γ-lactams **13** were synthesized in good yields (Scheme 5).



Scheme 5 NHC-catalyzed [3+2] annulations of enals with imines

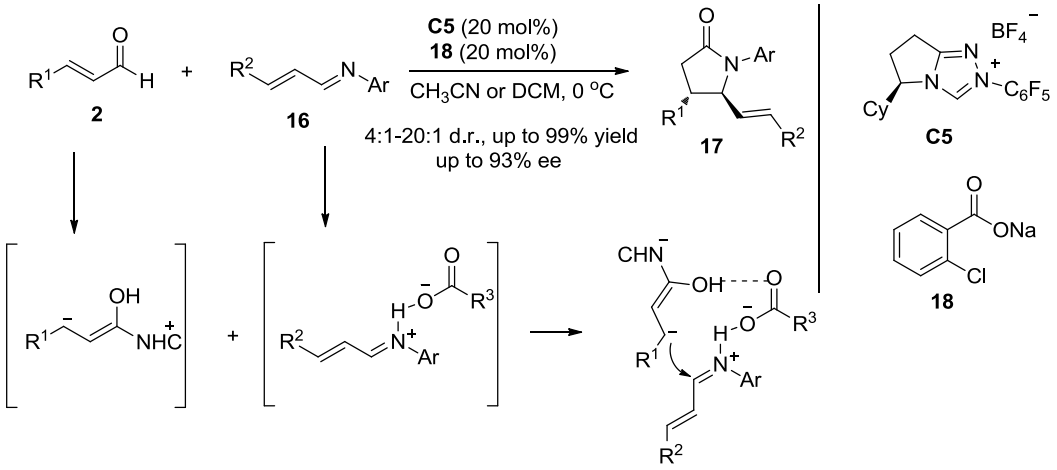
Then the same group further developed the reaction of enals with cyclic N-sulfonylimines **14**.[20] They found that the reaction proceeded efficiently in the presence of NHC pre-catalyst **C4** to give the desired product **15** in good to excellent yields (Scheme 6).



Scheme 6 NHC-catalyzed [3+2] annulations of enals with cyclic imines

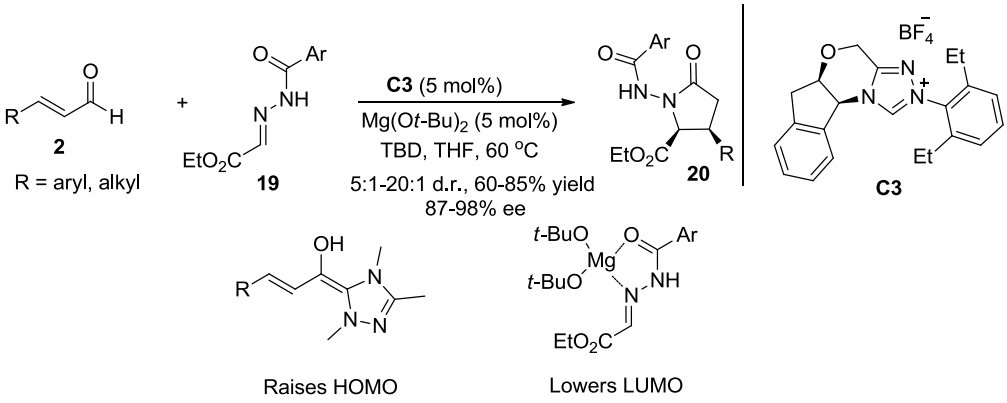
In 2011, employing the Brønsted acid/NHC co-catalysis strategy, Rovis and

co-workers achieved the asymmetric NHC-catalyzed [3+2] cyclization reactions of enals with α,β-unsaturned imines.[21] They disclosed that the simultaneous use of the NHC pre-catalyst **C5** with 20 mol% carboxylate **18** activated the imines, enhancing the enantioselectivity and yield of the transformation (Scheme 7).



Scheme 7 Brønsted acid/NHC co-catalysis for the preparation of trans-substituted-γ-lactams

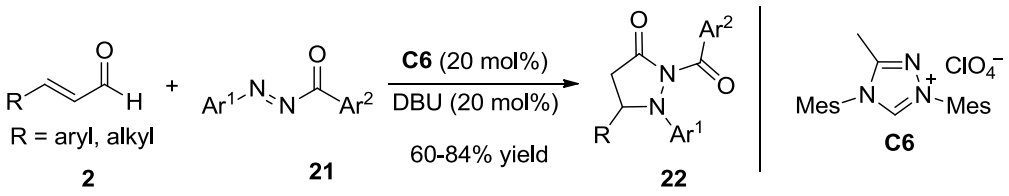
NHCs are known as excellent ligands in many transition-metal catalyzed reactions. Surprisingly, Scheidt and co-workers successfully achieved the asymmetric synthesis of highly substituted *cis*-γ-lactams by using NHC precursor triazolium salt **C3** and Mg(O*t*-Bu)$_2$ co-catalysis strategy (Scheme 8). [22]



Scheme 8 Lewis acid/NHC co-catalysis for the preparation of cis-substitued-γ-lactams

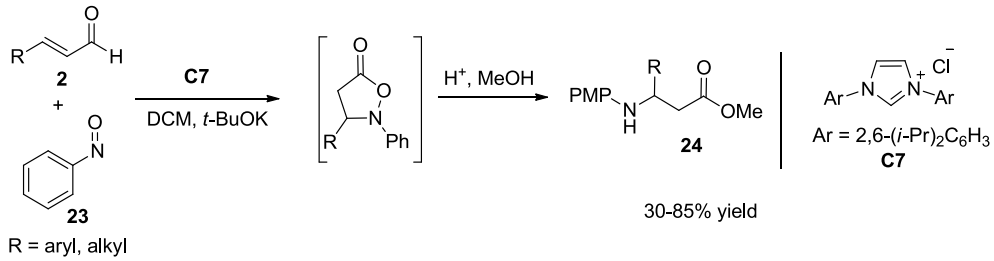
NHC-generated homoenolate intermediates can react not only with aldehydes, ketones and imines, but also with other electrophiles. For instance, Scheidt and co-workers

reported NHC-catalyzed [3+2] annulations of enals and azodicarboxylates, affording the desired pyrazolidinone compounds **22** in good yields (Scheme 9).[23]



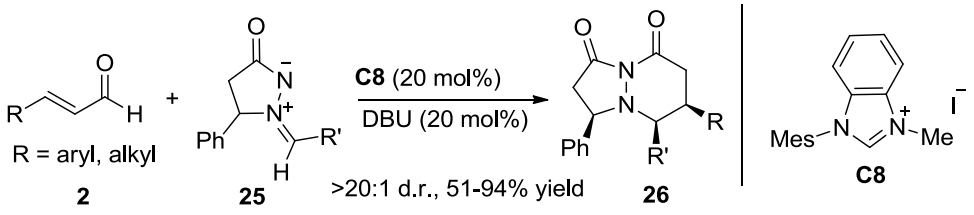
Scheme 9 NHC-catalyzed [3+2] annulations of enals with azodicarboxylates

In the same year, the NHC-catalyzed [3+2] reaction of enals and nitroso compounds was successfully developed employing NHC **C7** as pre-catalyst by Ying and co-workers (Scheme 10).[24]



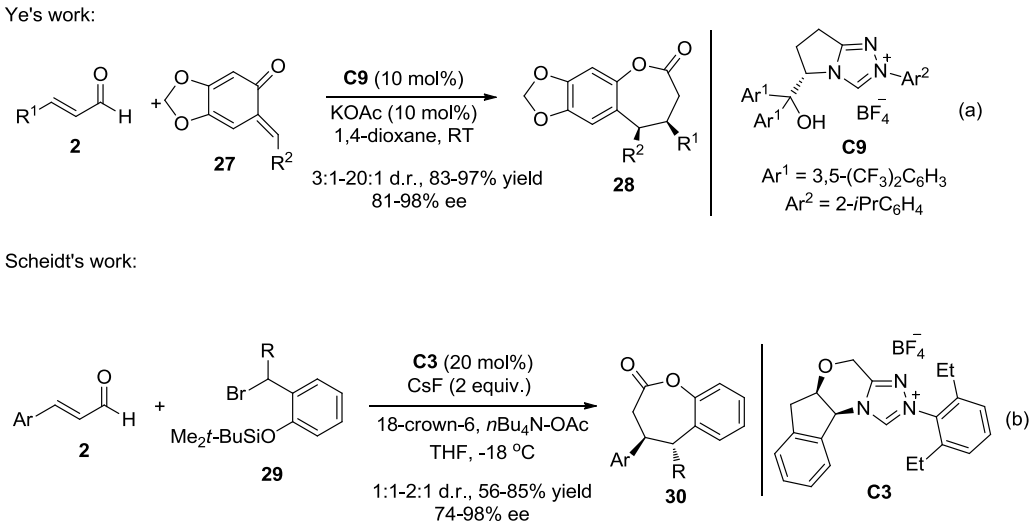
Scheme 10 NHC-catalyzed [3+2] annulations of enals with nitroso compounds

In 2007 Scheidt and co-workers realized the N-heterocyclic carbene-catalyzed enantioselective [3+3] annulation reaction of enals with azomethine imines.[25] The desired bicyclic heterocycles were obtained in moderate to excellent yields with excellent diastereoselectivities under the catalysis of pre-catalyst **C8** (Scheme 11).



Scheme 11 NHC-catalyzed [3+3] annulations of enals with azomethine imines

To further extend the reactions of NHC-generated homoenolate intermediates, Ye[26] and Scheidt[27] and their coworkers independently developed the [3+4] annulations of enals with aurones and *o*-quinone methides, affording the desired ε-lactone compounds in good yieds and asymmetric induction (Scheme 12).



Scheme 12 NHC-catalyzed [3+4] annulations of enals with aurones and o-quinone methides

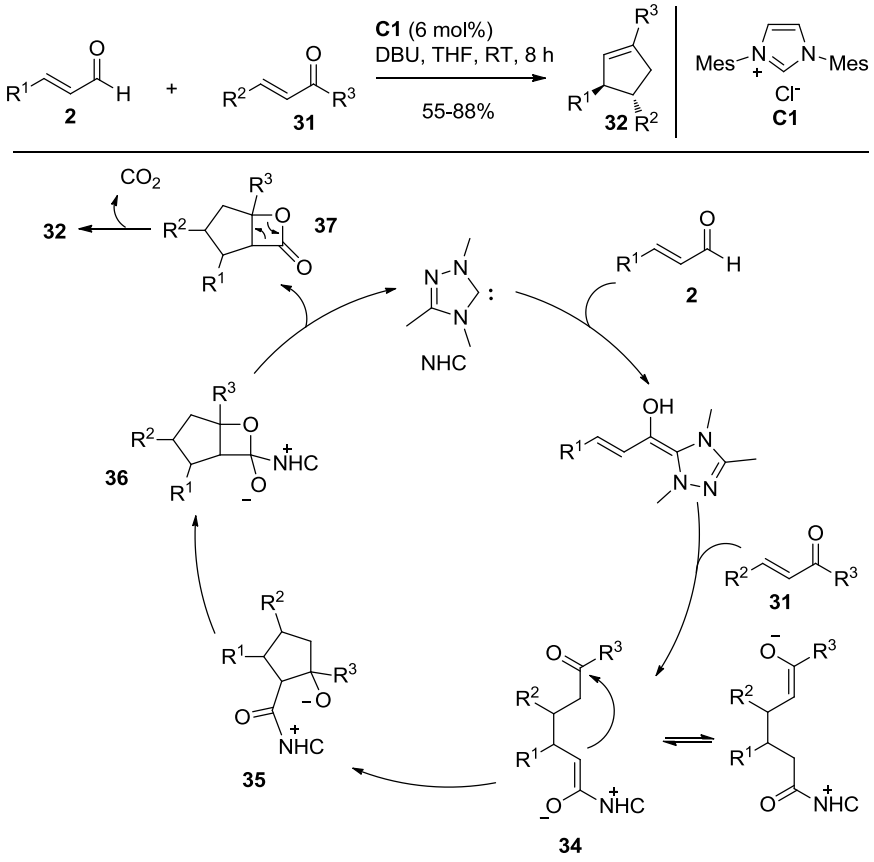
1.2.2 Generation *via* α,β-unsaturated aldehydes for the construction of all carbon cycles

The homoenolate equivalent could also be used to prepare all carbon cycle compounds *via* homoenolate/enolate domino reactions. In 2006, Nair and co-workers initially developed the NHC-catalyzed [3+2] annulation of enals with chalcones, providing diverse cyclopentenes in good yields.[28] The proposed mechanism involved the Michael addition of the homoenolate to the chalcone delivered enolate intermediate **34**, which underwent an intramolecular aldol reaction to afford adduct **35**. The β-lactonization of intermediate **35** returned the pre-catalyst and led to the unstable β-lactone **37**. The decarboxylation of unstable β-lactone **37** furnished the desired cyclopentene **32** (Scheme 13).

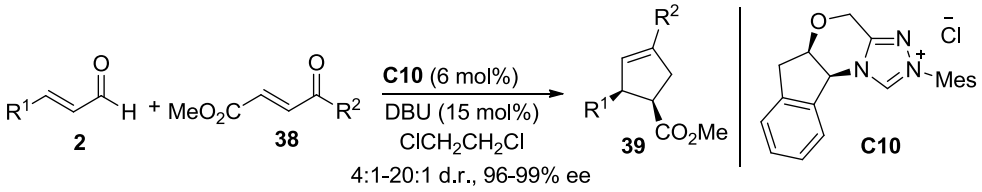
Then the asymmetric cycloadditions of 4-oxoenones with enals were successfully realized by Bode and co-workers.[29] The *cis*-cyclopentenes were efficiently prepared in good yields with excellent enantioselectivities and good diastereoselectivities under the catalysis of NHC **C10** (Scheme 14).

In 2010 Scheidt and co-workers further developed this method and they revealed that the combination of $Ti(O\textit{i}\text{-}Pr)_4$ with an NHC could realize better results on both the

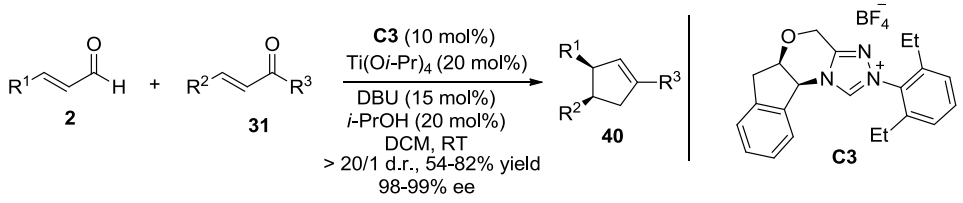
tolerance of substrate scope and stereoselectivity.[30] Interestingly, compared with Nair's work, the *cis* diastereomer was furnished by employing the combination of NHC catalysis and Lewis acid catalysis (Scheme 15).



Scheme 13 The domino homoenolate/enolate annulations



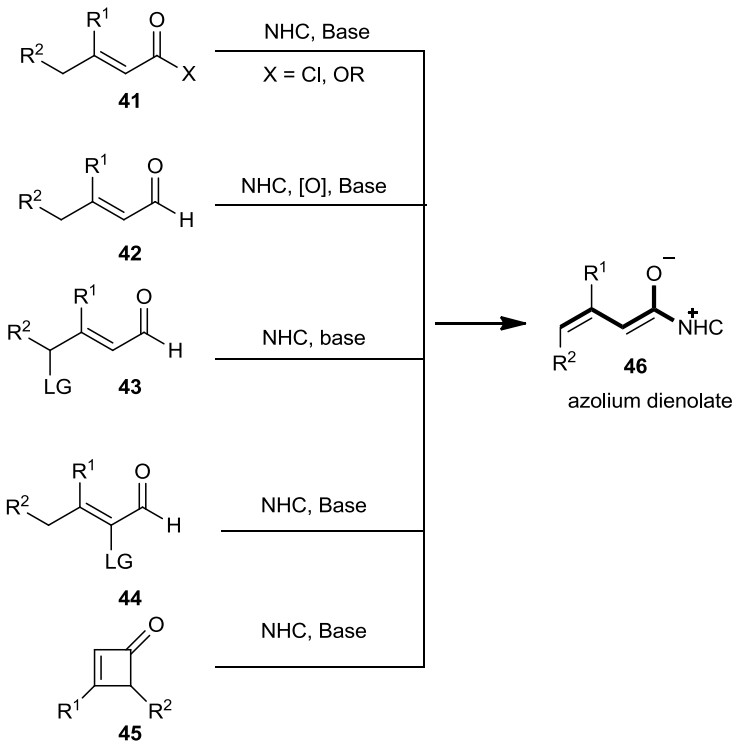
Scheme 14 Asymmetric synthesis of cis-cyclopentenes



Scheme 15 Asymmtric synthesis of cis-cyclopentenes

1.3 NHC-catalyzed cyclizations *via* Azolium Dienolates

The azolium dienolate intermediates can be generated from the combination of NHCs and carbonyl compounds with an acidic γ-hydrogen atom. The most commonly used methods to access NHC-derived azolium dienolate intermediates relie on redox activation of α,β-unsaturated aldehydes, α,β-unsaturated acid derivatives and cyclobutenones (Scheme 16). The NHC generated azolium dienolates offer a valuable method for the remote functionalization reactions, which have attracted the increasing attention of many chemists.

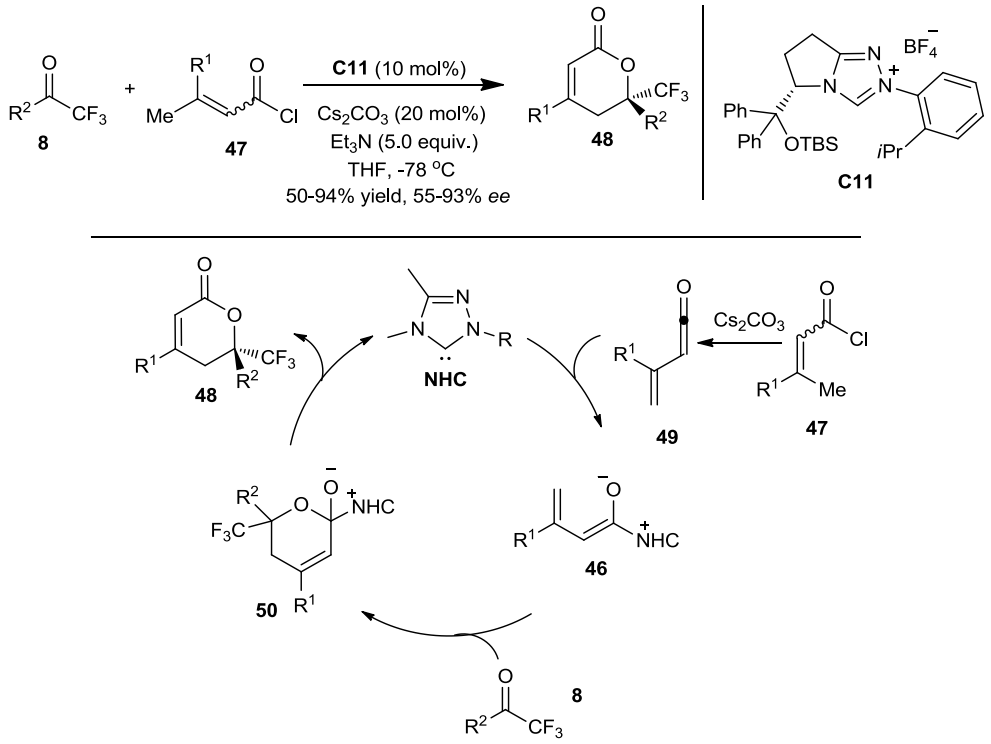


Scheme 16 The approaches to azolium dienolates

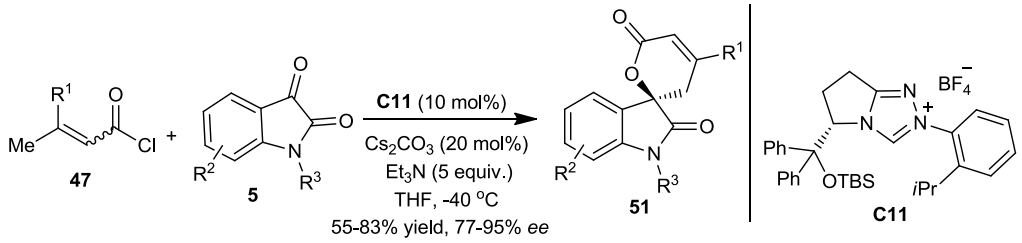
1.3.1 Azolium dienolates generated from α,β-unsaturated acid derivatives

In 2011, Ye and co-workers first reported the azolium dienolate mediated [4+2] cycloaddition of α,β-unsaturated acid chlorides **47** with trifluoromethyl ketones **8** by using an NHC catalyst to accomplish the asymmetric synthesis of δ-lactones.[31] It was

proposed that the vinylketenes **49** were formed *in situ* from the α,β-unsaturated acid chlorides **47** in the presence of Cs_2CO_3. The addition of NHC to the vinylketenes provided the azolium dienolate intermediates **46**, which reacted with the trifluoromethyl ketones **8** to give the zwitterionic intermediates **50**. Finally, the δ-lactones **48** were obtained after the release of the NHC from the zwitterionic intermediate **50** (Scheme 17)**.**



Scheme 17 NHC-catalyzed [4+2] cycloaddition of α,β-unsaturated acid chlorides with trifluoromethyl ketones

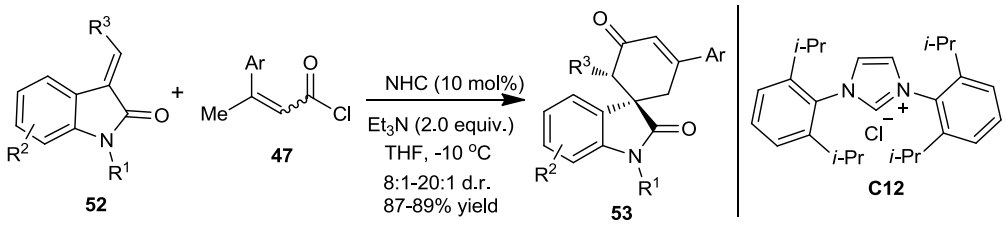


Scheme 18 NHC-catalyzed [4+2] cycloaddition of α,β-unsaturated acid chlorides with isatins

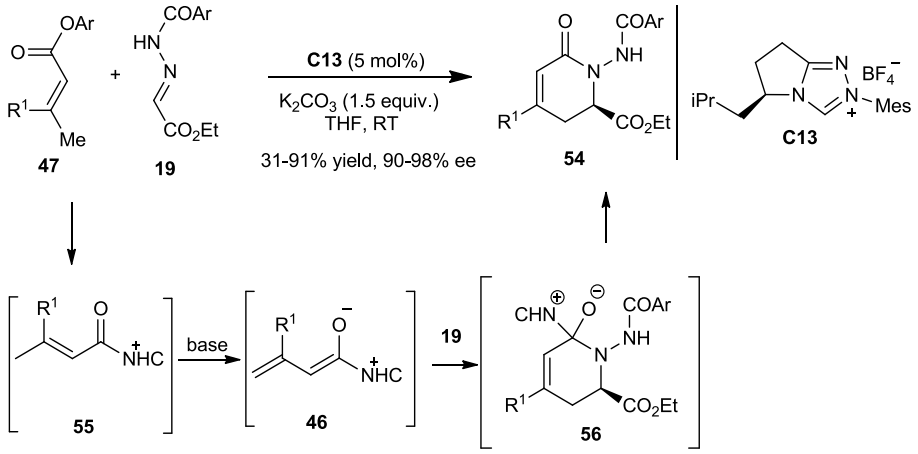
Then Chi's work extended this strategy to the isatins **5** instead of trifluoromethyl ketones.[32] They successfully achieved the enantioselective preparation of a variety of

spirocyclic oxindole-δ-lactones **51** in moderate to good yields with moderate to excellent enantioselectivities by employing the same NHC pre-catalyst**.**

In 2014 Ye and co-workers utilized the NHC-generated azolium dienolate intermediates from α,β-unsaturated acid chlorides to construct spiro-carbocyclic oxindole compounds.[33] The reaction of α,β-unsaturated acid chlorides **47** with 3-alkylenyloxindoles **52** afforded the targeted product **53** in good yields with good to excellent diastereoselectivities by employing imidazole salt **C12** as NHC pre-catalyst (Scheme 19).



Scheme 19 Diastereoselective NHC-catalyzed [4+2] cycloaddition of 3-alkylenyloxindoles with azolium dienolates

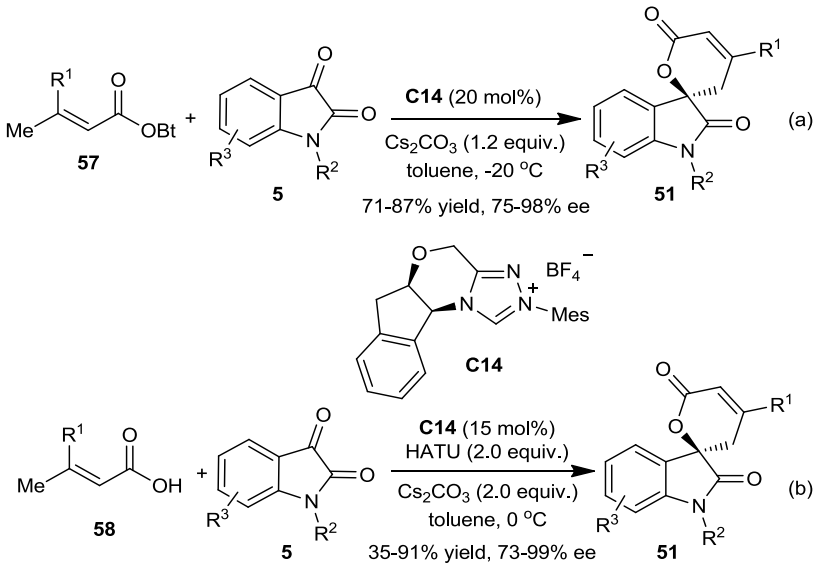


Scheme 20 Unsaturated esters as azolium dienolate precursors for [4+2] cycloaddition with hydrazones

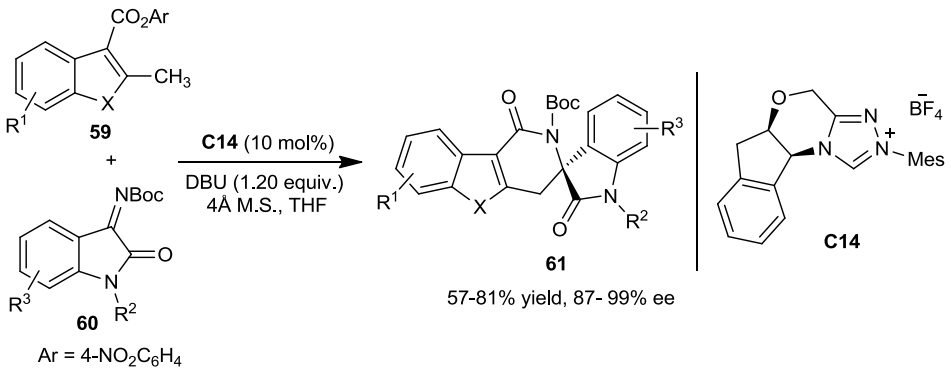
Recently the esters have been applied to NHC catalysis as very useful substrates. Chi and co-workers successfully realized the generation of azolium dienolates **46** from α,β-unsaturated esters **47**.[34] The author offered an interesting method for the enantioselective preparation of δ-lactams from α,β-unsaturated esters **47** and hydrazones **19** (Scheme 20). Both the electron-deficient and electron-rich esters were

tolerable in the optimized condition to deliver the targeted δ–lactams **54** with excellent enantioselectivities.

In 2015 Yao and co-workers reported asymmetric NHC-catalyzed [4+2] cycloaddition reactions of α,β-unsaturated esters and the isatin derivatives affording the spirooxindole derivatives **51** with good to high ee-values.[35] They successfully achieved the generation of azolium dienolates from 1-hydroxybenzotriazole (HOBt) α,β-unsaturated esters **57** (Scheme 21a). Later, the same research group successfully extended the strategy of the NHC-mediated generation of azolium dienolates from α,β-unsaturated carboxylic acid **58**, with in situ activation by HATU (Scheme 21b).[36]



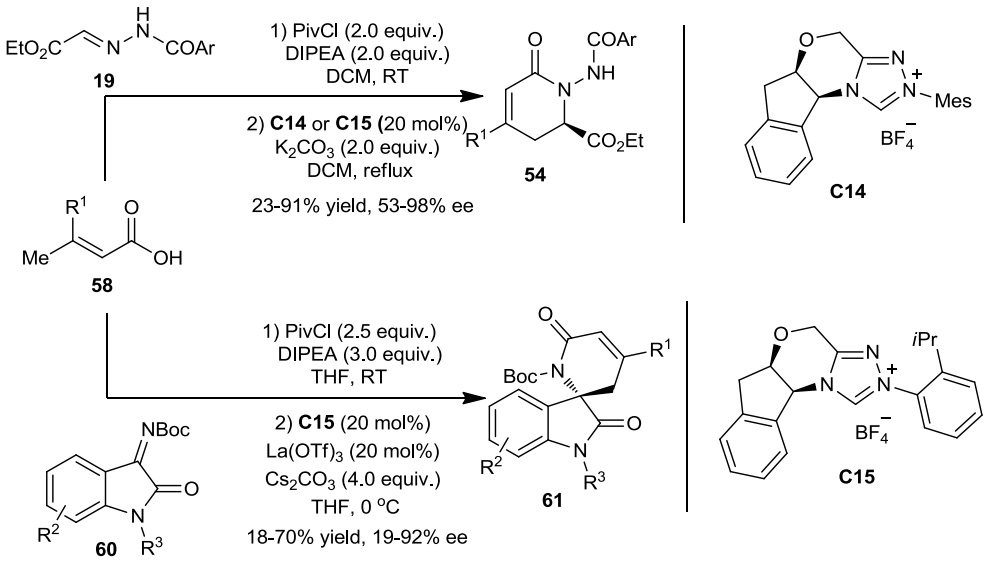
Scheme 21 Generation of azolium dienolates from α,β-unsaturated carboxylic esters and corresponding [4+2] cycloaddtion reactions



Scheme 22 [4+2] Cycloaddition of 2-methyl-heteroarene-3-carboxylic esters with isatin derived ketimines

Later Xu's group extended the strategy from simple α,β-unsaturated carboxylic esters to heteroaryl esters.[37] The asymmetric NHC catalyzed [4+2] cycloaddition of 2-methyl-heteroarene-3-carboxylic esters **59** and the isatin derived ketimines **60** proceeded smoothly to provide the desired spirooxindole δ-lactams **61** in 57-81% yields with 87-99% ee (Scheme 22).

To further extend the NHC-catalyzed [4+2] cycloadditions *via* azolium dienolates, Ye's group achieved the asymmetric synthesis of δ-lactams from α,β-unsaturated carboxylic acid **56** by employing the pivolylchloride as activator (Scheme 23).[38] The cycloaddition reactions were found to be tolerable for both hydrazones **19** and imines **60** to furnish the desired lactams **54** and **61** in moderate to excellent enantioselectivities.

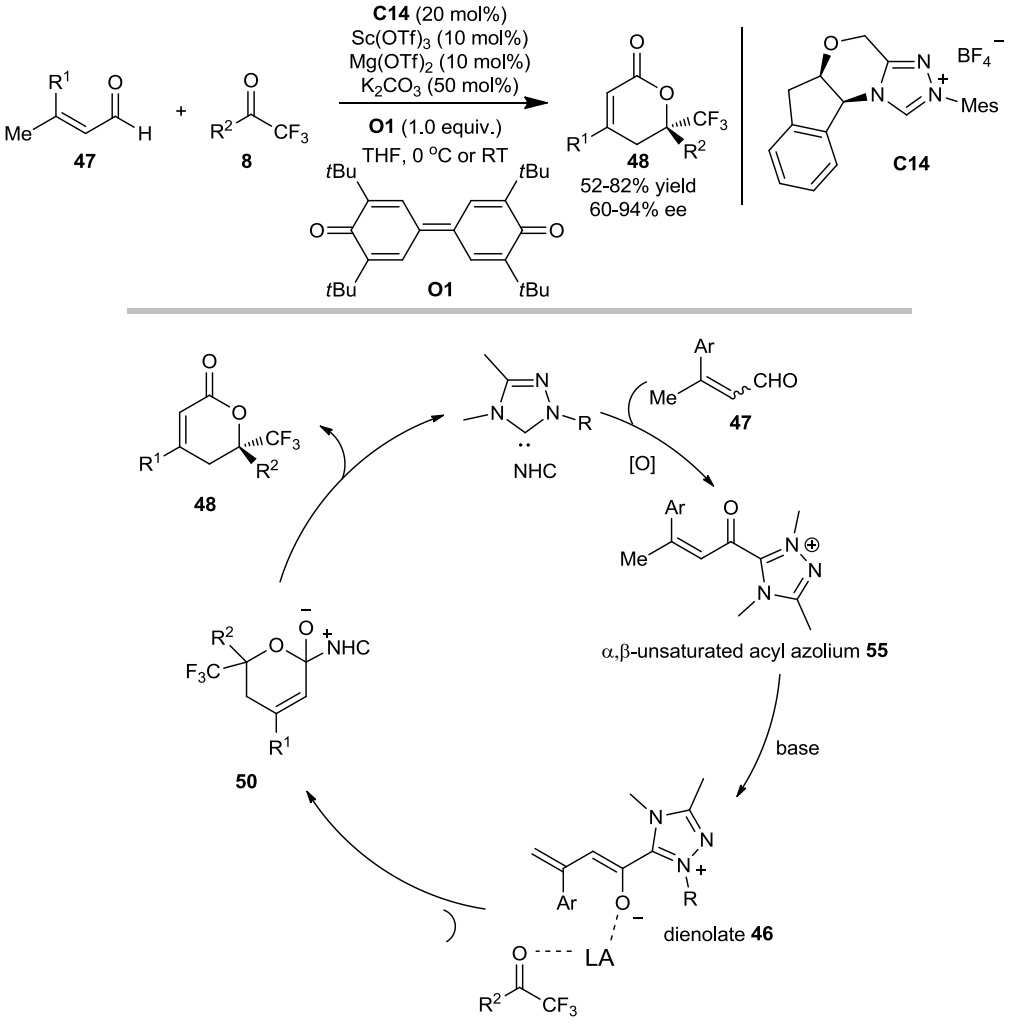


Scheme 23 NHC-catalyzed [4+2] cycloaddition of α,β-unsaturated carboxylic acids for the synthesis of δ-lactams.

1.3.2. Azolium dienolates generated from enals

The azolium dienolate species can also be generated from β-methyl enals under NHC catalysts. In this regard, Chi's group developed this method that using the oxidative γ-functionalization of β-methyl enals in the presence of an oxidant to generate the azolium dienolate intermediate (Scheme 24).[39] They proposed that the addition of an

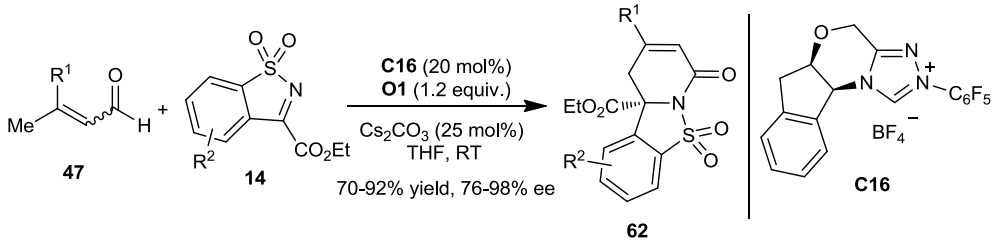
NHC to the β-methyl enals **41** generated the Breslow intermediate, which was oxidized by the bisquinone gave the α,β-unsaturated acyl azolium intermediate **55**. The dienolate **46** was readily generated through deprotonation of the acyl azolium intermediate **55** in the presense of K_2CO_3. The Lewis acid co-catalysts *i.e.* $Sc(OTf)_3$ and $Mg(OTf)_2$ were used to improve the enantioselectivities of the targeted lactones **48**. It was proposed that the Lewis acid plays a role in bringing the trifluoromethyl ketones into close proximity with the azolium dienolates.



Scheme 24 NHC-catalyzed oxidative [4+2] cycloaddition of enals with trifluoromethyl ketones

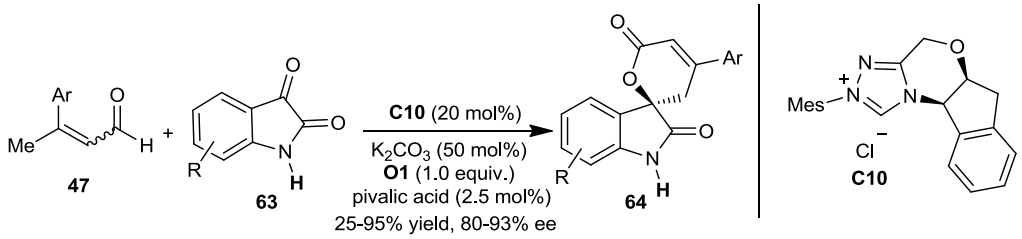
Later, the same group extended the NHC-catalyzed oxidative [4+2] cycloaddition of β-methyl enals from ketones to imines employing the same stratgy (Scheme 25).[40] The reaction worked well in the presence of a pre-catalyst **C16** and an oxidant **O1** to afford

the desired products **62** in moderate to good yields with moderate to excellent enantioselectivities. The authors disclosed that the concentration of the β-methyl enal had a great impact on the reaction rates, as a higher concentration of the β-methyl enals suppressed the combination of the NHC with the imines, leading to a faster reaction rate. The study of the mechanism revealed that the generation of the Breslow intermediate was the rate-determining step.



Scheme 25 NHC-catalyzed oxidative [4+2] cycloaddition of enals with imines

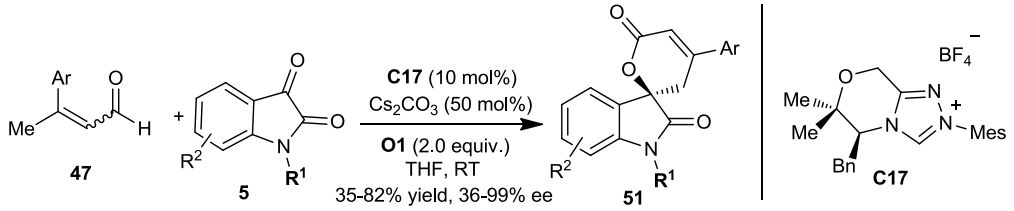
In 2015 Zhong and co-workers introduced non-protected isatins into the oxidative NHC catalyzed [4+2] cycloaddition reactions of β-methyl enals, and prepared a series of chiral unprotected spiro-indoline-δ-lactones in good to excellent yields with high enantioselectivities (Scheme 26).[41] Pivalic acid was added as co-catalyst. It was proposed that the aldol reaction of the azolium dienolates with the non-protected isatins can be promoted by binary hydrogen bonds of pivalic acid. Unfortunately, the N-protected isatins gave very low enantioselectivities of the spirooxindoles under the standard conditions.



Scheme 26 NHC-catalyzed oxidative [4+2] cycloaddition of enals with unprotected isatins

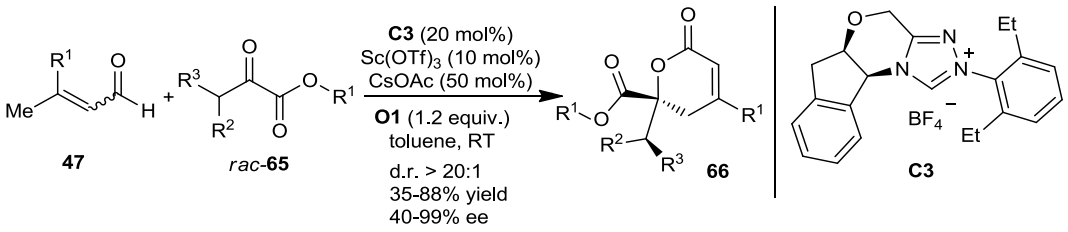
To further develop the oxidative generation of azolium dienolate species, Liu' group successfully accomplished the [4+2] cycloaddition of the enals **47** with the

N-protected isatins ultlizing NHC precursor **C17** (Scheme 27).[42] The corresponding products **51** could be obtained in good yield with high enantioselectivities without using any Lewis or Bronsted acids as the co-catalyst.

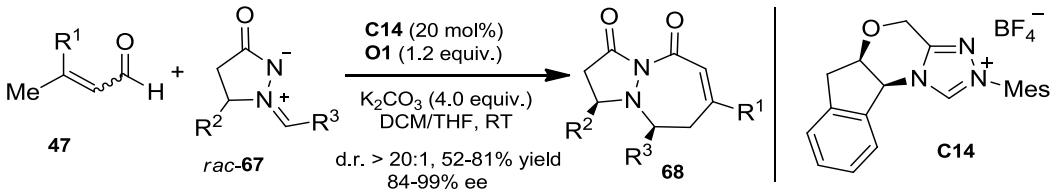


Scheme 27 NHC-catalyzed oxidative [4+2] cycloaddition of enals with N-protected isatins

Extension of the strategy to asymmetric NHC-catalyzed oxidative [4+2] cycloaddition using β-methyl enals with α-ketoesters was investigated by Wang and co-workers.[43] Chiral δ-lactones **66** with high diastereo- and enantioselectivities were obtained using NHC pre-catalyst **C3** and a Lewis acid $Sc(OTf)_3$ as co-catalyst. A simultaneous dynamic kinetic resolution of α-ketoesters was discoveried in this process. They proposed that the Lewis acid $Sc(OTf)_3$ contributed to bring the α-ketoesters into close proximity with the azolium dienolates.

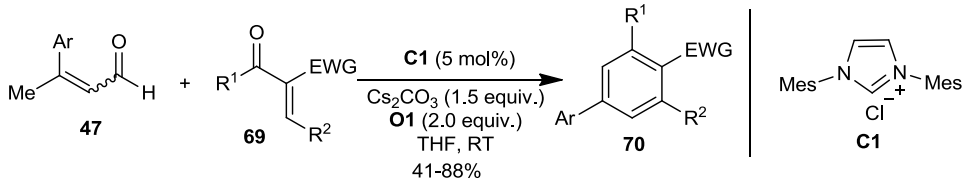


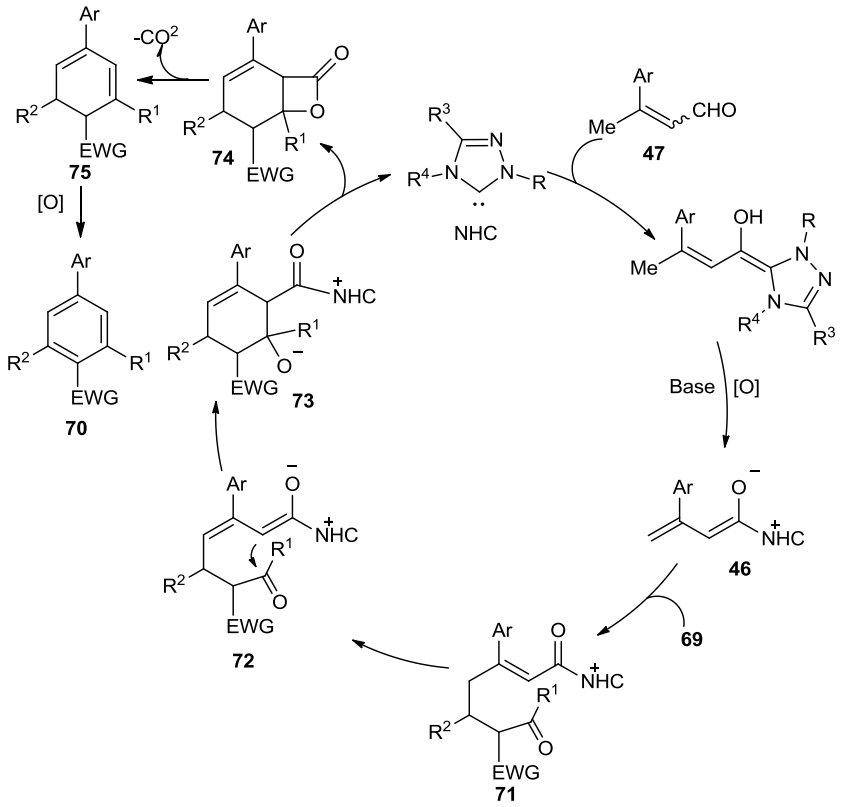
Scheme 28 NHC-catalyzed [4+2] cycloaddition with an intermolecular dynamic kinetic resolution of α-ketoesters



Scheme 29 NHC-catalyzed [4+3] cycloadditions of azolium dienolates with azomethine imines

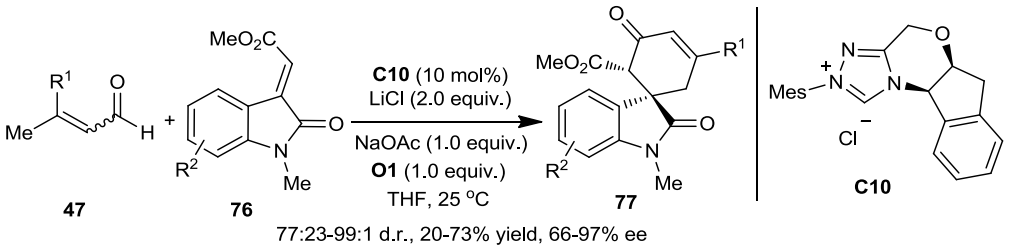
Azomethine imines have been widely used as efficient 1,3-dipolar reagents in lots of cycloaddition reactions. Recently, Chi and co-workers demonstrated that the oxidative NHC-catalyzed [4+3] cycloaddition of azomethine imines **67** with enals reacted well by employing the NHC precatalyst **C14** and oxidant **O1** to furnish the dinitrogen fused seven-membered heterocyclic compounds **68** in good yields with excellent asymmetric induction (Scheme 29).[44]



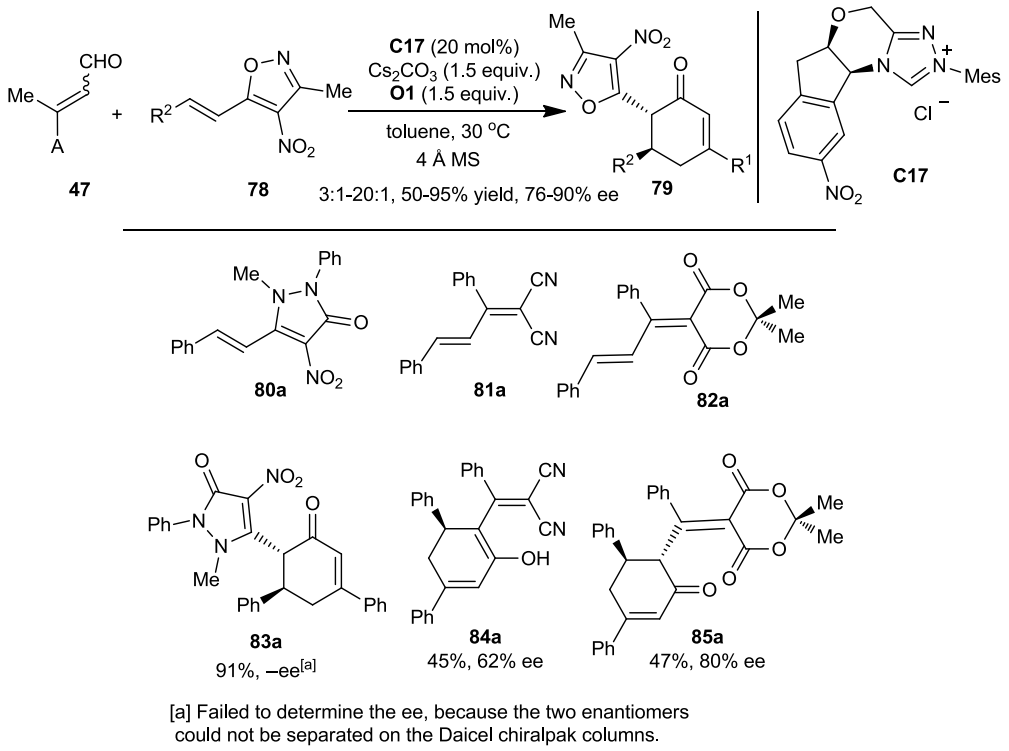


Scheme 30 Synthesis of multi-substituted benzene derivatives via the NHC-catalyzed [4+2] cycloaddition of enals with the Michael acceptors

Chi and co-workers successfully constructed multi-substituted benzene derivatives employing the NHC-generated azolium dienolate intermediates (Scheme 30).[45] The [4+2] cycloaddition of of enals **47** and the Michael acceptors **69** proceed smoothly to



Scheme 31 Diastereo- and enantioselective NHC-catalyzed [4+2] cycloaddition of 3 - alkylenyloxindoles with azoliumdienolates



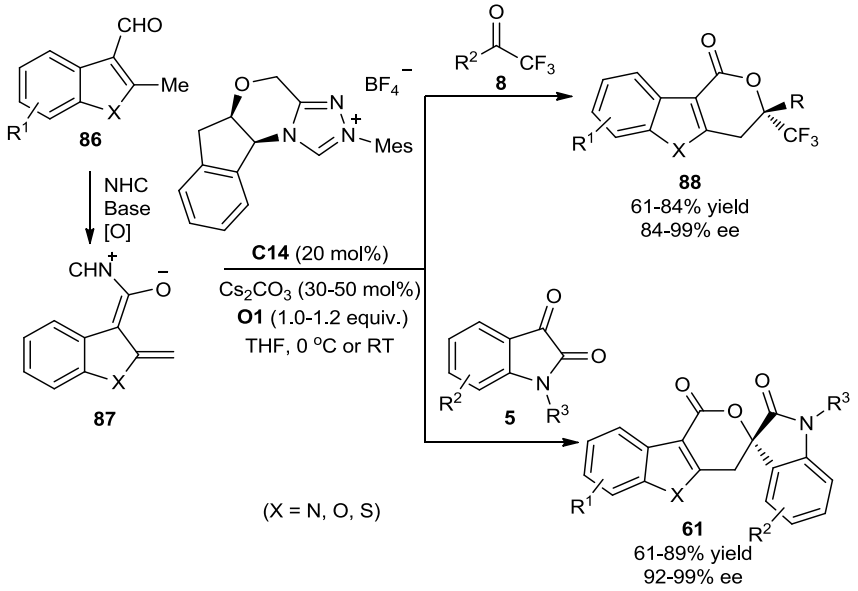
Scheme 32 Synthesis of diarylcyclohexenones via 1,6-addition of azolium dienolates to electron-deficient 2,4-dienes

deliver the corresponding product in moderate to very good yields ultlizing imidazolium salt **C1** as pre-catalyst and quinine **O1** as oxidant. The possible mechanism involved the generation of the azolium dienolate **46**, which underwent a nucleophilic Michael-type addition of to the enone **69** to afford the adduct **71**. The deprotonation of intermediate **71** gave **72**, then an intramolecular aldol reaction resulted in giving the intermediate **73**, which afforded the β-lactone **74** and returned the NHC. Finally, the subsequent decarboxylation and oxidative aromatization provided

the targeted products **70**.

Recently Liu and co-workers reported an enantioselective synthesis of the spiro-carbocyclic oxindoles **77** *via* the oxidative NHC-catalyzed [4+2] cycloaddition of the enals **47** and the 3-alkylenyloxindoles **76** (Scheme 31).[46] The transformation proceeded well in the presence of NHC pre-catalyst **C10** to give the desired spirocarbocyclicoxindoles **77** in moderate to good yields with high stereoselectivities.

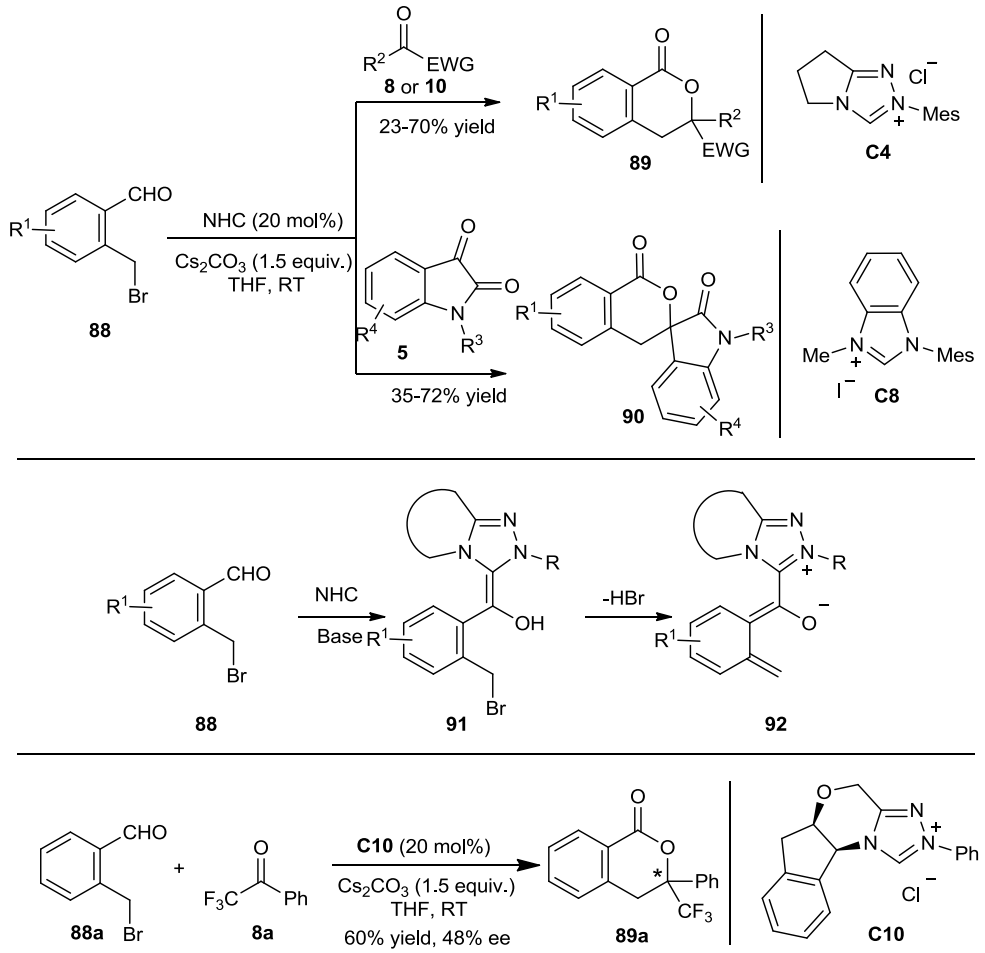
The asymmetric [4+2] cycloadditions of NHC-generated azolium dienolate intermediates with different kinds of dienophiles *via* the initial 1,2 and 1,4-Michael addition have been extensively explored, but the transformation involving the initial 1,6-addition is very limited.[47] In this regard, our group successfully accomplished an oxidative NHC-catalyzed asymmetric [4+2] cycloaddition of enals **47** with the different kinds of electron-deficient 2,4-dienes **78-82** employing a double vinylogous Michael-addition strategy (Scheme 32).[48] The reaction provided the targeted 3,5-diaryl cyclohexenones in good yields with high diastereo- and enantioselectivities.



Scheme 33 NHC-catalyzed [4+2] cycloadditions of α-branched benzofuran/ benzothiophene aldehydes/ indole 3-carboxaldehydes via ortho-quinodimethane intermediates

In 2013, Chi and co-workers extended the strategy from simple aryl aldehydes to heteroaryl aldehydes containing an indole, benzofuran or benzothiophene moiety.[49]

They found that the α-branched aryl aldehydes could generate the *o*-QDM azolium dienolates in the presence of a triazolium salt **C14** and an oxidant **O1** (Scheme 33). Trifluoromethyl ketones and isatins were choosen as suitable substrates to react with heteroaryl aldehydes via *o*-quinodimethane intermediates **87** furnishing the targeted products **88** and **61** in moderate to good yield with high enenatioselectivities. Unfortunately, the benzaldehyde analogues were not tolerated in the optimized conditions.

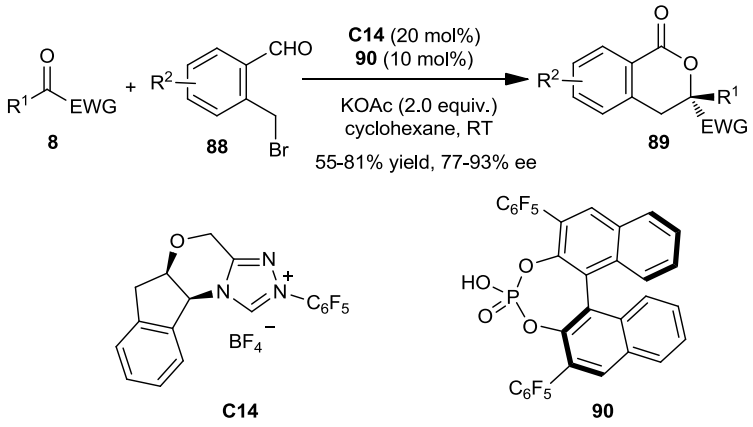


Scheme 34 NHC-catalyzed synthesis of 1 ‑isochromanones via o-quinodimethane intermediates

Recently Glorius and co-workers have successfully discovered that a leaving group at the *ortho*-benzylic position of aromatic aldehydes could generate the o-QDM intermediates **92** in the presence of NHC pre-catalyst and oxidant (Scheme 34).[50] The oxidative NHC-catalyzed [4+2] cycloadditon of 2-(bromomethyl)benzaldehyde with

activated ketones **8** and **10** or isatin derivatives **5** provided the corresponding 1-isochromanones **89** and **90** in moderate yields, respectively. It was proposed that the initial generation of the Breslow intermediate **91** and the subsequent HBr elimination are the key steps. The authors also tried the asymmetric version of 2-(bromomethyl)benzaldehyde with trifluoroacetophenone using chiral NHC pre-catalyst, but the reaction offered the desired product only with 48% ee value.

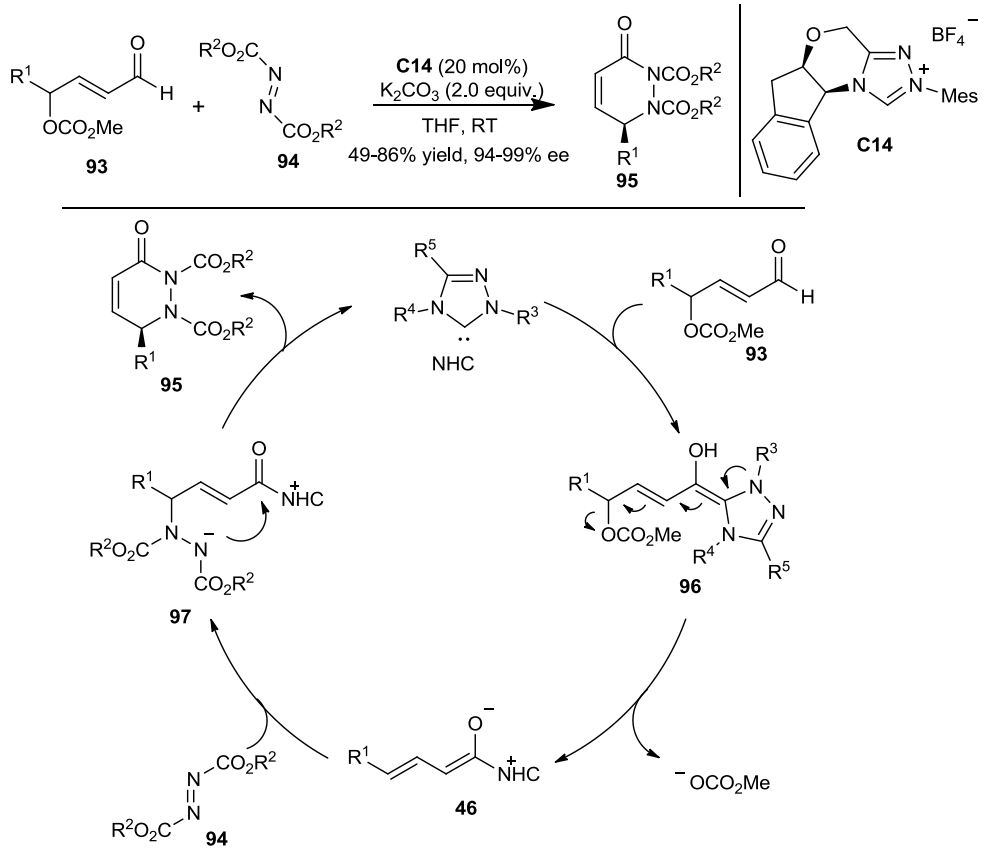
In 2017 Rovis's group successfully accomplished the higly enantioselective [4+2] cycloaddition of fluorinated ketones and 2-(bromomethyl)benzaldehyde via cooperative NHC and Brønsted acid catalysis (Scheme 35).[51] The transformation provided the targeted chromanones **89** in moderate to good yields with excellent asymmetric induction in the presence of the NHC precursor **C14** and a chiral phosphoric acid **90**.



Scheme 35 Asymmetric [4+2] cycloaddition of 2-(bromomethyl)benzaldehyde with activated ketones via NHC and chiral Brønsted acid co-catalysis

In 2013 Ye and co-workers demonstrated that acyl azolium dienolates could be generated *via* introducing a leaving group (-OCO_2Me) at the γ-position of enals.[52] A variety of enals reacted well with the azodicarboxylates **94** by employing **C14** as the pre-catalyst to afford the desired dihydropyridazinones **95** in 49-86% yields with 94-99% ee. The heterocyclic products **95** of this transformation served as precursors of the corresponding γ-amino acid derivatives. The proposed catalytic cycle involving the addition of the NHC to enals **93** afforded the Breslow intermediate **96**, which

underwent the elimination of the leaving group to form the azolium dienolate intermediate **46**. The followed cyclization of **46** with the azodicarboxylates **94** provided the azolium intermediate **97**, which gave the corresponding product **95** and returned the NHC catalyst (Scheme 36).

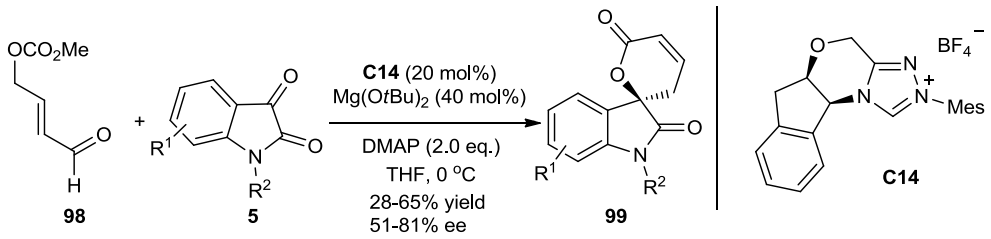


Scheme 36 NHC-catalyzed [4+2] cycloaddition of enals with azodicarboxylates

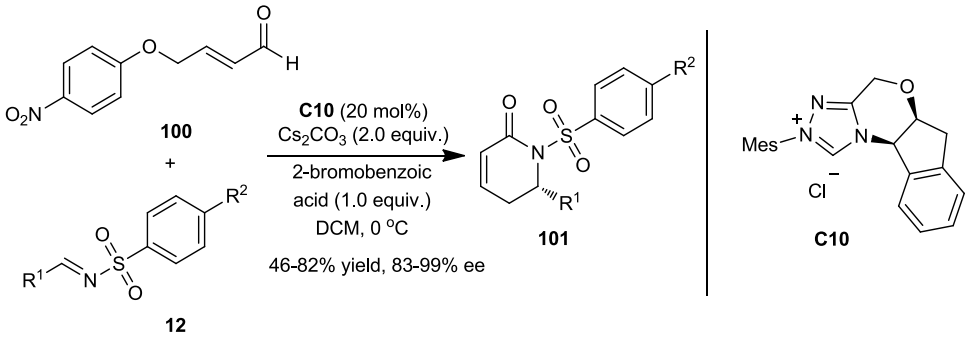
The simplest, unsubstituted acyl azolium dienolate could be generated *via* introducing a leaving group (-OCO_2Me) at the γ-position of enals. With this stragety, the [4+2] cycloaddition reactions of enal **98** and isatin derivatives were successfully developed by Ye' group (Scheme 37).[53] Using **C14** NHC precursor and $Mg(OtBu)_2$ as co-catalyst, the reaction proceed smooothly to furnish the spirocyclic oxindolodihydropyranones in moderate yields and enantioselectivities.

Employing the simplest, unsubstituted acyl azolium dienolate intermediate, Liu and co-workers developed the NHC catalyzed [4+2] cycloaddition of an enal **100** and the aldimines **12**.[54] This transformation furnished the desired δ-lactams **101** with high asymmetric induction in the presence of the pre-catalyst **C10**, cesium carbonate and

2-bromobenzoic acid (Scheme 38).



Scheme 37 NHC-catalyzed cycloaddition reaction of an unsubstituted azolium dienolate with isatins

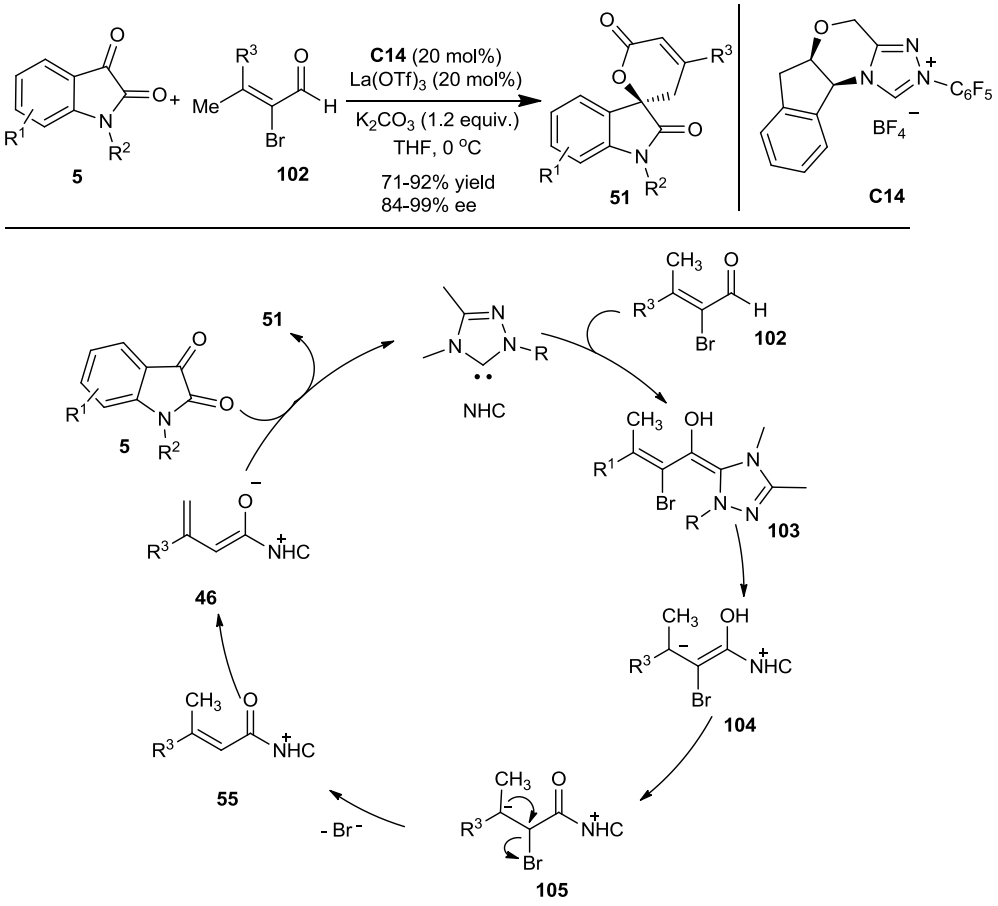


Scheme 38 [4+2] cycloaddition of an enal bearing a leaving group at the γ-position with aldimines

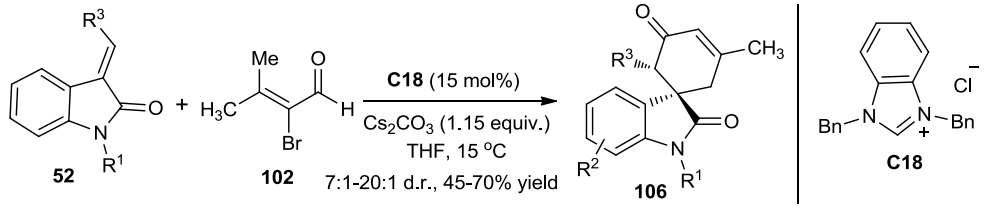
Yao and co-workers developed another method for the generation of azolium dienolates *via* employing α-bromo-β-methyl enals **102** as precursors. The combination of NHC precursor triazolium salt **C14** and a lanthanide based Lewis acid furnished the [4+2] cycloaddition very well, offering a variety of oxindole-lactones in 71-92% yields with 84-99% ee (Scheme 39).[55] The possible reaction mechanism including the addition of the NHC to 2-bromo-2-enal **102** afforded the Breslow intermediate **103**, which was transformed into **55** through tautomerization and debromination. The acyl azolium intermediate **55** was deprotonated at the γ-position to provide the azolium dienolates **46**. The [4+2] cycloaddition of azolium dienolates **46** and isatins **5** furnished the corresponding products **51** and regenerated the NHC-catalyst.

Ye and co-workers utilized the NHC-generated azolium dienolate intermediates from α-bromo-β-methyl enals to build spiro-carbocyclic oxindole compounds.[56] The [4+2] cycloaddition reaction of α-bromo-β-methyl enals **102** and 3-alkylenyloxindoles **52**

furnished the desired product **106** in moderate yields with good to excellent diastereoselectivities by using benzimidazole salt **C18** as NHC pre-catalyst (Scheme 40).

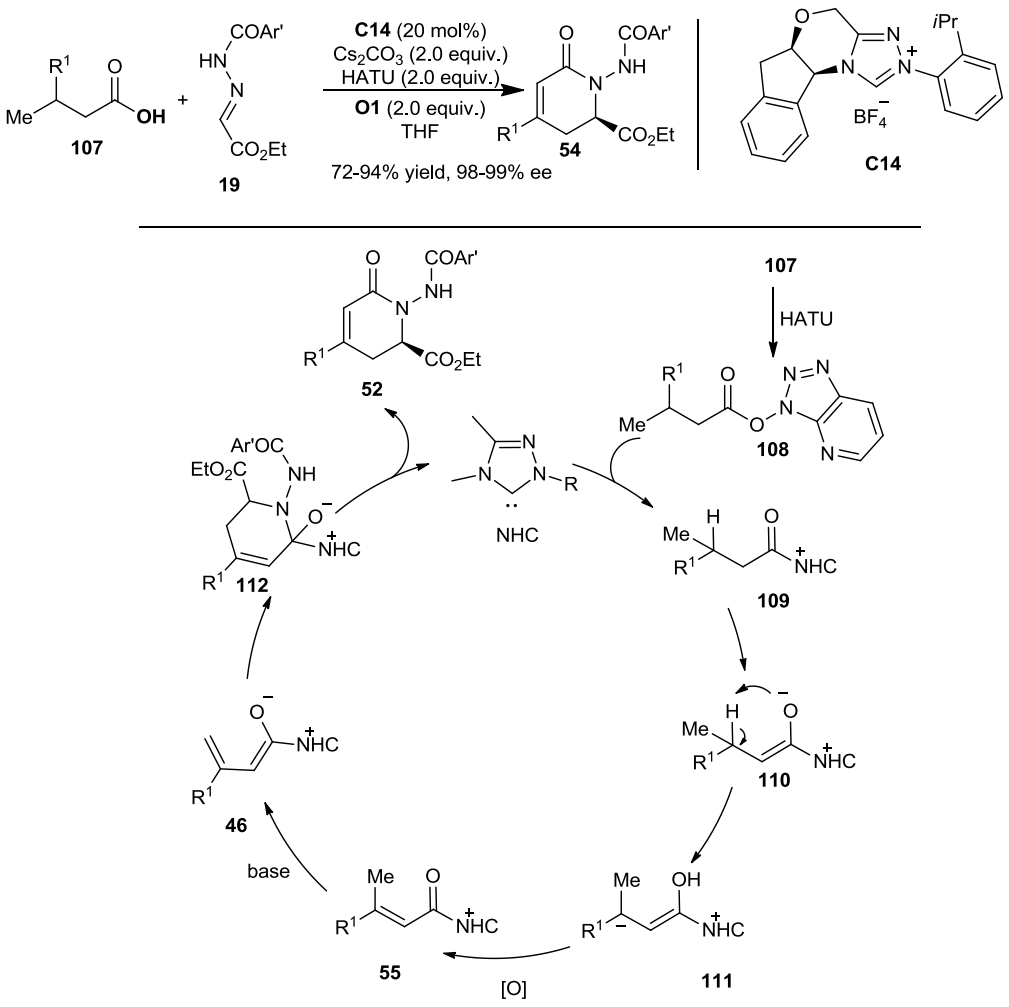


Scheme 39 NHC-catalyzed [4+2] cycloaddition of α-bromo-α,β-unsaturated aldehydes with isatin derivatives



Scheme 40 Diastereoselective NHC-catalyzed [4+2] cycloaddition of 3 - alkylenyloxindoles with azolium dienolates

1.3.3 Azolium Dienolates Generated from Saturated Carboxylic Acids.

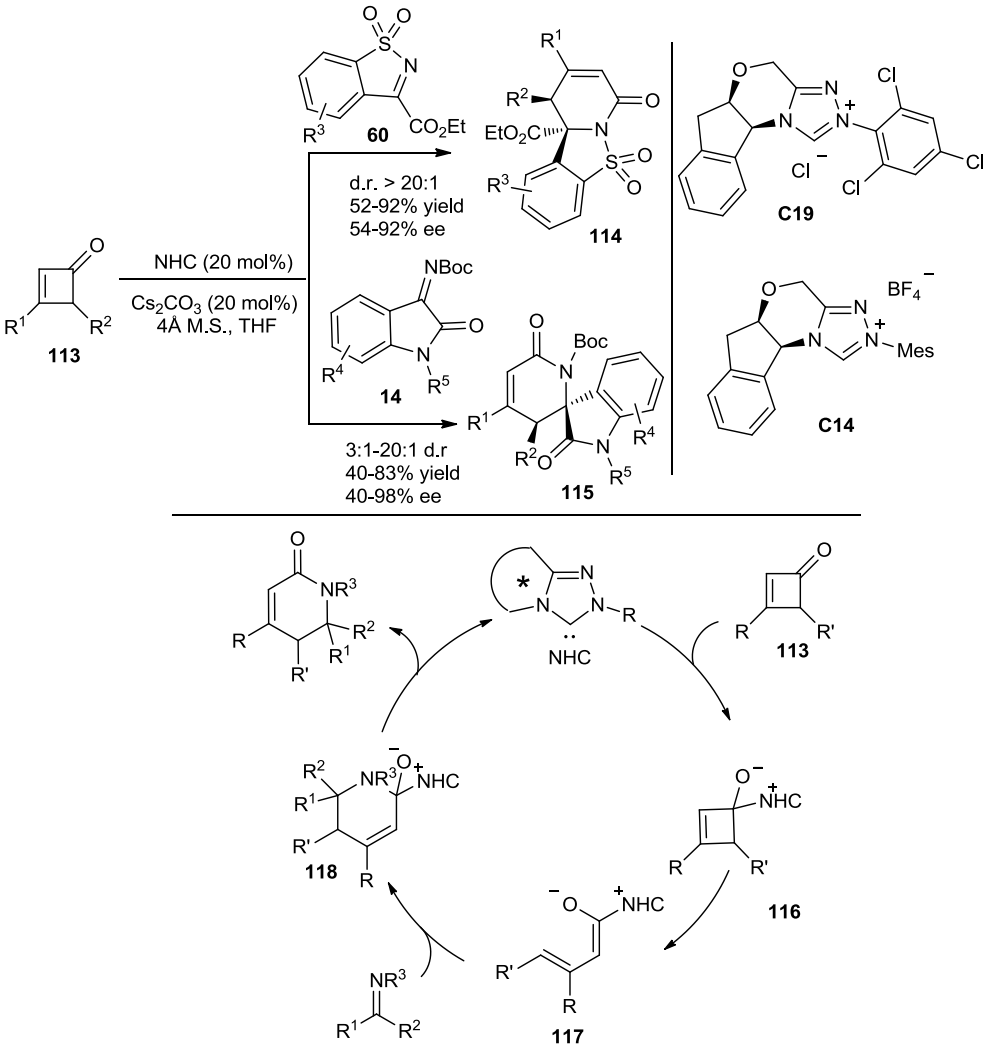


Scheme 41 NHC-catalyzed [4+2] cycloaddition of saturated α,β-unsaturated carboxylic acids with hydrazones

In 2015 Yao and co-workers demonstrated that saturated carboxylic acids could generate azolium dienolate intermediates under oxidative NHC catalysis.[57] The oxidative NHC-catalyzed [4+2] cycloaddition reactions of saturated carboxylic acids **107** and hydrazones proceeded smoothly by employing **C14** as the pre-catalyst and HATU as activator to furnish the desried δ-lactams **54** in good to excellent yield with excellent enantioselectivities (Scheme 41). The possible catalytic cycle involving the addition of the NHC to esters **108** delivered the Breslow intermediate **109** which was transformed into the enolate **110** with the aid of base. The enolate **110** underwent a β-sp^3-H shift to afford homoenolate intermediate **111**. The subsequent oxidation of **111** furnished α,β-unsaturated acyl azolium intermediate **55**, which was deprotonated at

the γ-position to afford the azolium dienolates **46**. The [4+2] cycloaddition of **46** and hydrazones delivered the targeted products **54** and regenerated the NHC pre-catalyst.

1.3.4 Azolium Dienolates Generated from Cyclobutenones



Scheme 42 NHC-catalyzed [4+2] cycloadditions of cyclobutenones with imines

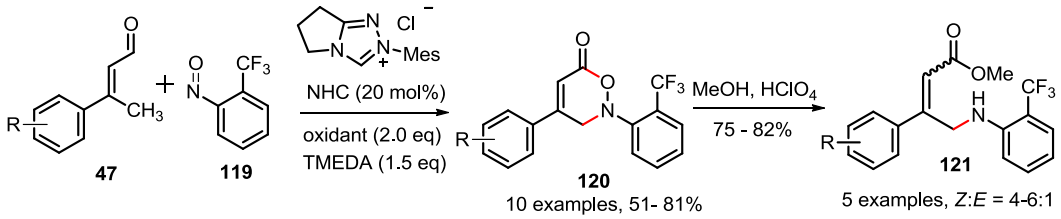
Cyclobutenones have been proved to be powerful reagents in organic synthesis owing to their distinct reactivity.[58] The transition metal catalyzed reactions of cyclobutenones have been widely investigated, but the enantioselective transformations of cyclobutenones still remained a challenge. In this regard, Chi and co-workers developed the asymmetric [4+2] cycloaddition reactions of cyclobutenones **113** with imines employing NHC catalysis.[59] The transformation proceeded smoothly in the

presence of NHC pre-catalyst **C19** or **C14** to furnish the targeted product in good yields with high enantioselectivies. Mechanistically this reaction involved the addition of NHC to the cyclobutenones **113** to give the intermediate **116**, which formed the azolium dienolate intermediates **117** *via* C–C bond breaking. The azolium dienolates **117** then reacted with the imines in a stepwise vinylogous addition followed by intramolecular cyclization or hetero-Diels-Alder reaction mode to afford the adduct **118**, which then delivered the corresponding product and returned the NHC catalyst (Scheme 42).

1.4 Overview of the doctoral work

In the past decades, N-heterocyclic carbene (NHC) catalysis has underwent a rapid development and became a powerful method in organic synthesis. Based on the widespread applications of NHC catalysis, this doctoral work focuses on the reactions of β-methyl enals and isatin-derived enals catalyzed by NHCs. There are three research projects covered in this thesis.

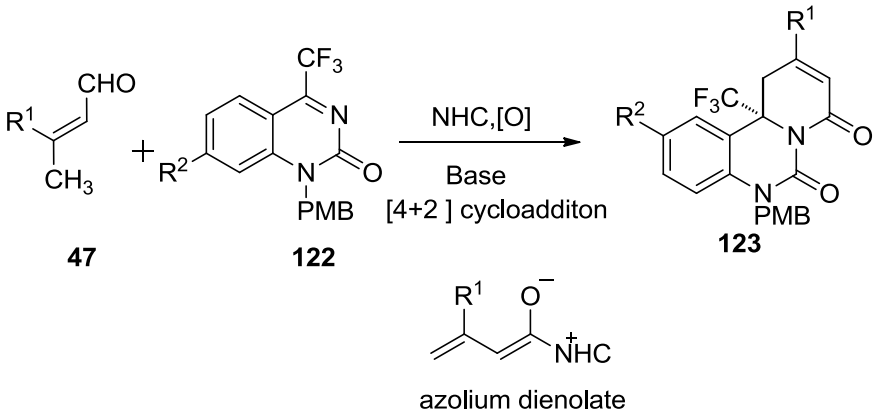
The first project focuses on the preparation of α,β-unsaturated γ-amino acid esters. In the reaction, β–methyl enals **47** were employed as precursors in the generation of the azolium dienolate intermediates. As shown in Scheme 43, the desired cycloadditon adducts **120** were obtained by reaction with nitroso compounds with the flexible variation of the substituents enals and could be transformed into the targeted γ-amino enoates by ring-opening with methanol under acidic conditions.



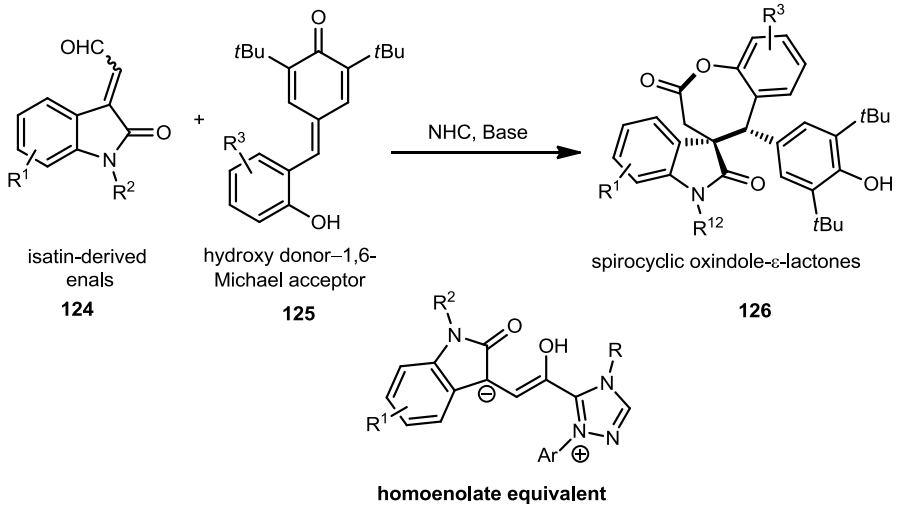
Scheme 43 Synthesis of α,β-unsaturated γ-amino acid esters via N-heterocyclic carbene-catalyzed [4+2] cycloaddition

Project 2 deals with the on the generation of azolium dienolate equivalents *via* β–methyl enals (Scheme 44). Cyclic trifluoromethyl ketimines were introduced as

electrophiles in the NHC-catalyzed [4+2] reactions with β–methyl enals, and a series of biologically interesting heterocyclic dihydroquinazolinone derivatives were prepared.



Scheme 44 N-heterocyclic carbene-catalyzed [4+2] cycloaddition of β–methyl enals and cyclic trifluoromethyl ketimines



Scheme 45 N-heterocyclic carbene-catalyzed [3+4] cycloaddition of isatin-derived enals

Project 3 focuses on the [3+4] annulation of isatin-derived enals *via* homoenolate equivalent intermediates (Scheme 45). The *ortho*-hydroxyphenyl-substituted para quinone methides as bifunctional reagents were applied to the asymmetric [3+4] annulation reactions affording the spirocyclic oxindole-ε-lactones in high yields and very good stereoselectivities.

2. Results and Discussion

2.1 Synthesis of α,β-unsaturated γ-amino acid esters via NHC-catalyzed [4+2] annulation reactions

2.1.1 Background and motivation

Developing novel catalytic methods to construct carbon-nitrogen (C-N) bond is always a central issue in organic synthesis though some classical general methods, including substitutions with amines, the hydroamination of alkenes and the aza-Michael addition, have been well explored. Recently, List[60] and Jørgensen[61] and their coworkers independently developed the proline catalyzed α-amination of carbonyl compounds and a series of other stereoselective C-N bond generation reactions were reported.[62]

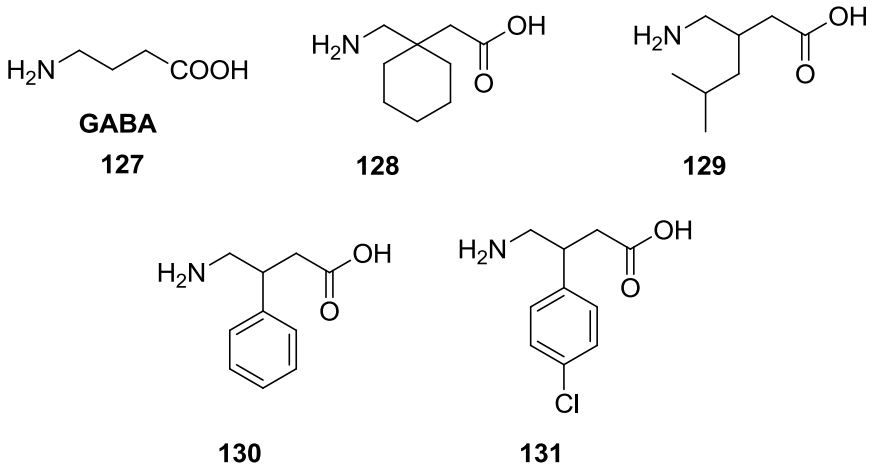
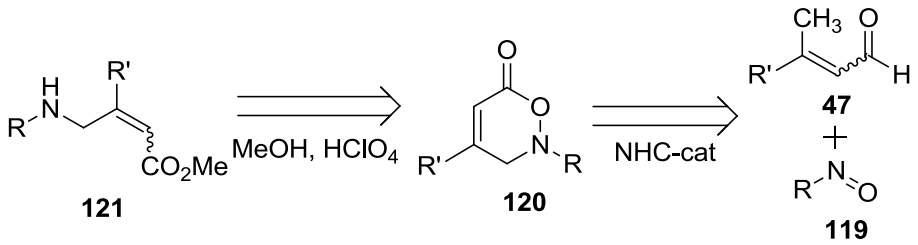


Figure 1 Typical examples of GABA derivatives

The synthesis of GABA derivatives has attracted more and more interest due to their enormous significance in medicine.[63] Compared with the well developed saturated GABA derivatives, the preparation of α,β-unsaturated GABA derivatives is far less explored.[64] Thus, exploring novel and efficient protocols to synthesize α, β-unsaturated γ-amino acid derivatives is very meaningful. γ-Amino butyric acid (GABA) derivatives draw more and more attentions owing to their biological activity

as chief inhibitory neurotransmitters in the adult mammalian central nervous system (CNS).[65] GABA analogues, such as gabapentin **128**,[66] pregabalin **129**,[67] phenibut **130**,[68] and bacolfen **131**[69] have played an important role in the treatment of CNS disorders (Figure 1).

N-Heterocyclic carbene (NHC) catalysis, as a significant subfield of Lewis base organocatalysis,[70] has been proved as an efficient strategy for the activation of the γ-carbon of carbonyl compounds.[71] Based on initial reports of Ye[31] and Chi[32] and their coworkers, we envisaged a new method for the synthesis of α,β-unsaturated γ-amino acid ester derivatives through an esterification under ring opening of 1,2-oxazin-6-ones, which can be efficiently furnished by NHC-catalyzed oxidative [4+2] cycloaddition of β-methyl enals and nitroso compounds (Scheme 46).



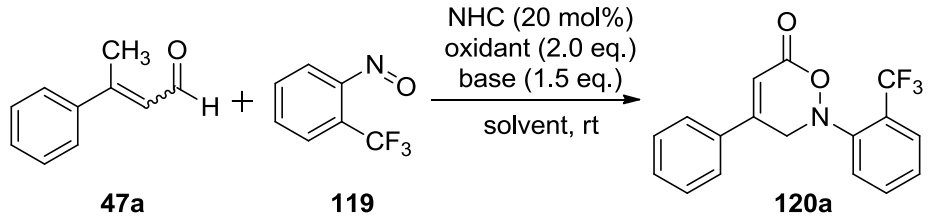
Scheme 46 Retrosynthetic analysis for the synthesis of α, β–unsaturated γ-amino acid esters

2.1.2 Optimization of the reaction conditions

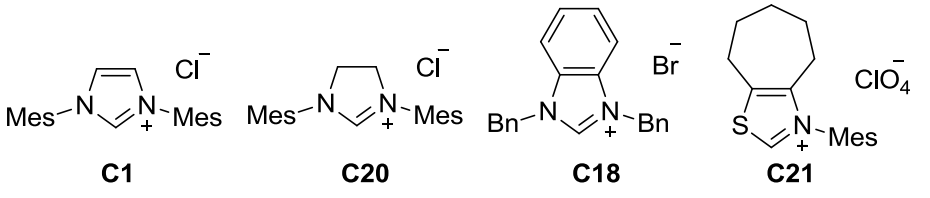
Initially, the readily available enals **47** and the aryl nitroso compound **119a** were choosen as model substrates to investigate the [4+2] cycloaddition reaction with various NHC catalysts. It turned out that very low yields or only traces of the corresponding products were observed when imidazolium salts **C1**, **C20** and **C18** were employed as the pre-catalyst (entries 1-3). The bicyclic thiazolium salt **C21** was also used to examine the [4+2] cycloaddition reaction and offered 8% yield (entry 4). Then we turned our attention to the triazolium salts **C22**, **C23**, **C4** and we were able with the triazolium salt **C4** to obtain the targeted 1, 2-oxazinone **120a** in 34% yield (entries 5-7). To further improve the method we screened various bases and solvents. The results indicated that TMEDA was the base of choice in toluene as solvent

(entries 7-14). Some increase of the yield was achieved when **119a** was slowly added and 4Å MS were used as additive (entries 15 and 16).

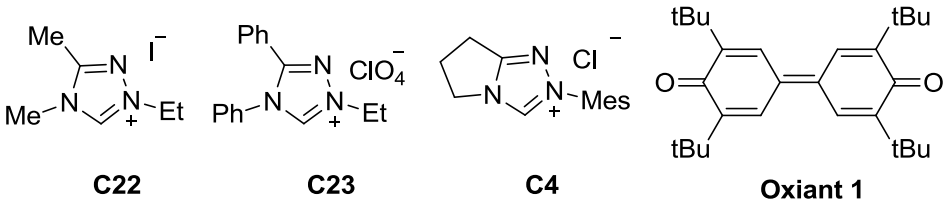
Table 1 Optimization of the reaction conditions[a]



47a **119** **120a**



C1 **C20** **C18** **C21**



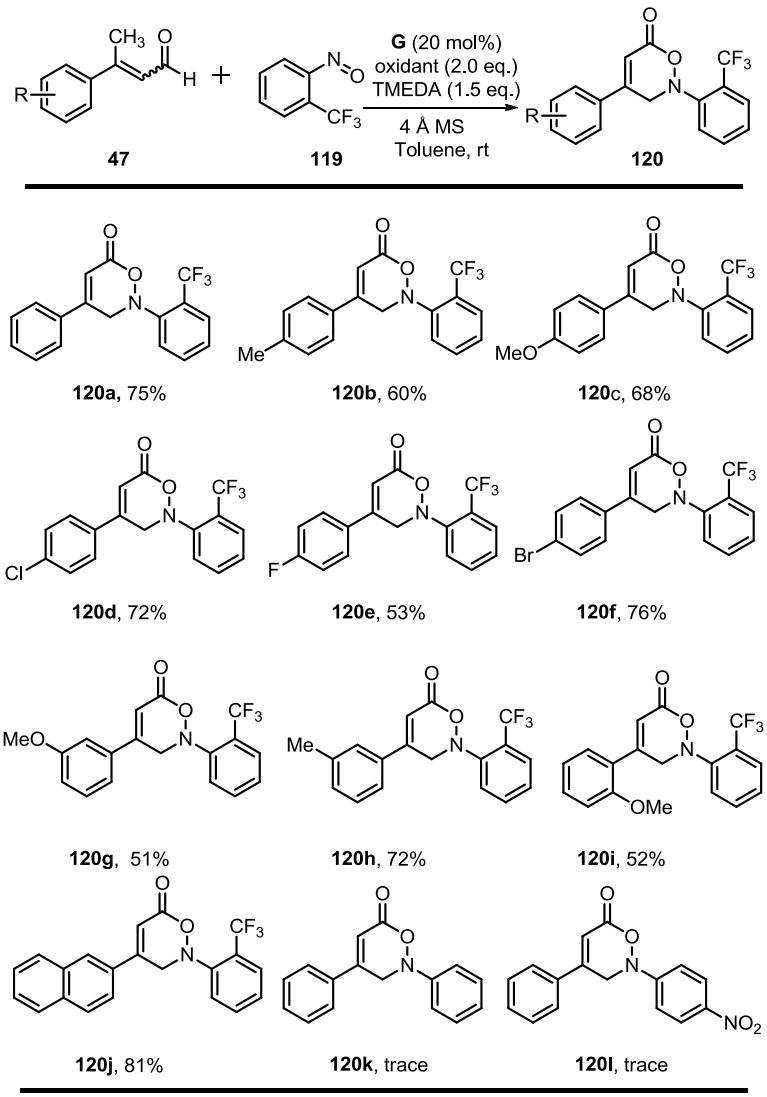
C22 **C23** **C4** **Oxiant 1**

Entry	Cat.	Solvent	Base	Yield (%)[b]
1	**C1**	Toluene	DIPEA	Trace
2	**C20**	Toluene	DIPEA	10
3	**C18**	Toluene	DIPEA	Trace
4	**C21**	Toluene	DIPEA	8
5	**C22**	Toluene	DIPEA	Trace
6	**C23**	Toluene	DIPEA	Trace
7	**C4**	Toluene	DIPEA	34
8	**C4**	Toluene	Cs2CO3	Trace
9	**C4**	Toluene	DABCO	39
10	**C4**	Toluene	NEt3	40
11	**C4**	Toluene	TMEDA	52
12	**C4**	DCM	TMEDA	36

13	**C4**	THF	TMEDA	48
14	**C4**	Dioxane	TMEDA	47
15[c]	**C4**	Toluene	TMEDA	58
16[d]	**C4**	**Toluene**	**TMEDA**	**75**

[a]All reactions were conducted with 0.40 mmol of **47a** (2.0 equiv), 0.2 mmol of **119** (1.0 equiv) and 20 mol% of catalyst in 2.0 mL solvent at room temperature for 12h. [b]Yield of isolated compound **120a** after chromatography. [c]The reaction was conducted with 4Å MS (50mg). [d]**119** in toluene (1.0 mL) was added within 1 hour.

Table 2 Substrate scope of the (NHC)-catalyzed [4+2] cycloaddition[a]



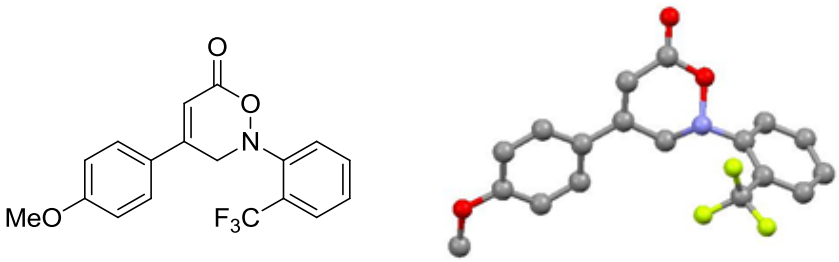
[a]Unless otherwise noted, the reactions were conducted with 0.40 mmol of **47** (1.0 equiv), 0.80 mmol of **119** (2.0 equiv) and 20 mol% of catalyst **C4** and 4Å MS (100

mg) in toluene (4.0 mL) for 12h at room temperature. Yields are those of the isolated products **120a-j** after column chromatography.

2.1.3 Investigation of the substrate scope

With the optimised reaction condition in hand, the substrate scope of the NHC-catalyzed [4+2] cycloaddition was then investigated and the results are shown in Table 2. It was found that both aromatic enals with an electron-withdrawing group (F, Cl, Br) and with an electron-donating group (Me, MeO) proceeded smoothly to afford the targeted products in very good yield (**120a-f**). The substituents at the *ortho*- and *meta*-position had no negative effect on the reaction (**120g-i**). It should be noted that (*E*)-3-(naphthalen-2-yl)but-2-enal also worked well and provided the corresponding product in 81% yield (**120j**). To increase the breadth of the reaction, different nitroso compounds, including nitrosobenzene and 1-nitro-4-nitrosobenzene, were also tried under the standard condition, but unfortunately only a trace of product was observed.

2.1.4 Determination of the absolute configuration



120c

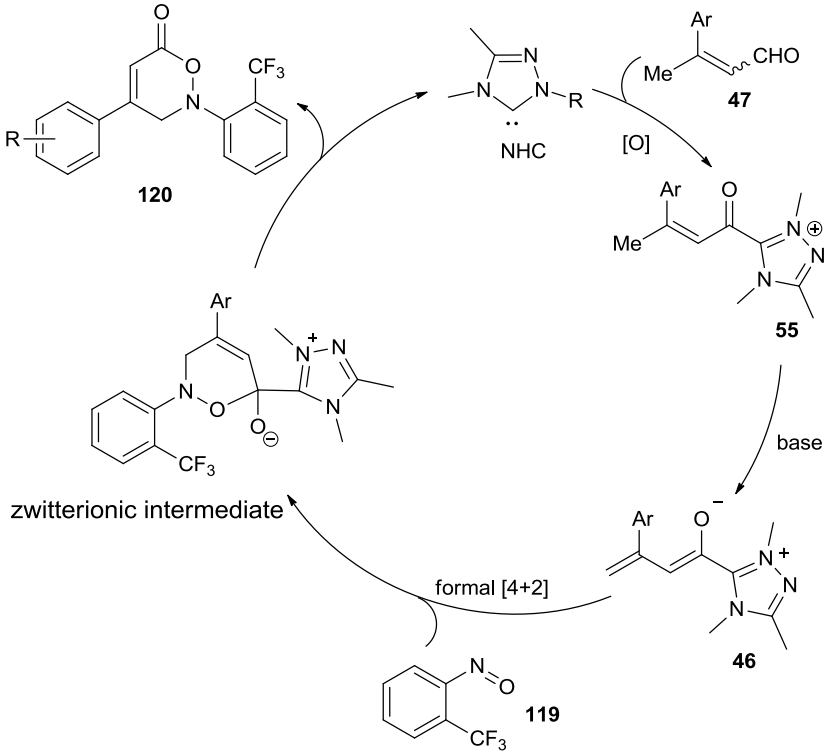
*Fig 2 X-ray crystal structure of **120c***

The structure of the cycloadduct **120c** was established by the X-ray analysis of a single crystal (Fig 2).

2.1.5 Possible mechanism

A plausible catalytic cycle is depicted in Scheme 47. First, the addition of the NHC to the enals **47** afforded the Breslow intermediate, which was oxidized by the bisquinone

to furnish the unsaturated acyl azolium intermediate **55**. The dienolate intermediate **46** was readily generated via γ-deprotonation of **55** with the assistance of base. Finally, the dienolate underwent a (4+2) cycloadditon with nitroso compound **119** to give the zwitterionic intermediate. The elimination of the NHC catalyst from the zwitterionic intermediate released **120** as the final product and returned the catalyst for further cycles.



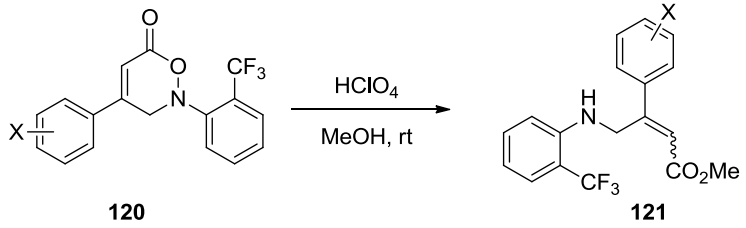
Scheme 47 Proposed mechanism of the NHC-catalyzed [4+2] cycloadditon

2.1.6 Synthesis of α,β–unsaturated γ-amino acid esters

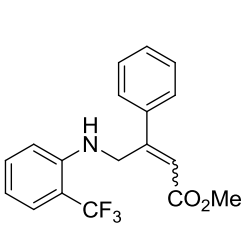
As designed, ring opening of the resulting 1,2-oxazin-6-one compounds **120** led to the formation of the N-*o*-trifluoromethylphenyl α,β–unsaturated γ-amino acid esters **121** which was turned out to be a very effective and simple strategy by employing acid-catalyzed esterification. As shows in Table 3, the substrates with electron-withdrawing (4-Cl and 4-Br) and electron-donating (3-Me) substituents were tolerable to offer the desired γ-amino methyl enoate in good yields, respectively. The 1-naphthyl substrate also worked well to give the γ-amino methyl enoate **121j** in 79%

yield and a 6:1 Z/E ratio

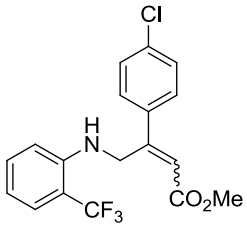
*Table 3 Preparation of α, β – unsaturated γ-amino acid esters **121***[a]



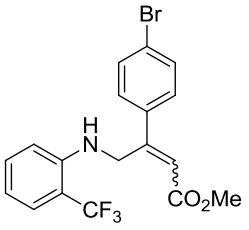
120 **121**



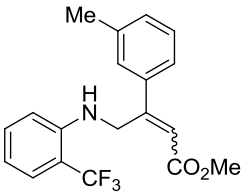
121a, 81%, *Z*/*E* = 5:1



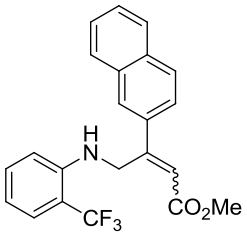
121d, 78%, *Z*/*E* = 4:1



121f, 75%, *Z*/*E*= 5:1



121h, 82%, *Z*/*E* = 5:1



121j, 79%, *Z*/*E* = 6:1

[a]Unless otherwise noted, the reactions were conducted with 0.20 mmol of **120** (1.0 equiv) and 3-5 drops $HClO_4$ in MeOH (2.0 mL) for 24h at room temperature. Yields are those of the isolated products after column chromatography.

2.2 N-Heterocyclic carbene-catalyzed [4+2] annulation of β-methyl enals and cyclic trifluoromethyl ketimines

2.2.1 Background and motivation

The enantioselective syntheses of molecules containing a trifluoromethyl group under mild conditions has become an extremely desirable methodology in medicinal and organic chemistry because of the extraordinary properties of trifluoromethylated compounds.[72] As an important class of heterocyclic compounds, dihydroquinazolinones exhibit a widespread range of beneficial biological activities,

as for instance the treatment of cardiovascular pain,[73] antiviral activities[74] and serving as potent inhibitors of Na^{+}/Ca^{2+} exchange (SM-15811, Figure 1).[75] Moreover, dihydroquinazolinone compounds containing a trifluoromethyl group containing tetrasubstituted carbon center, such as DPC 083 and DPC 961, have played an extremely significant role in the treatment of AIDS (Figure 3).[75]

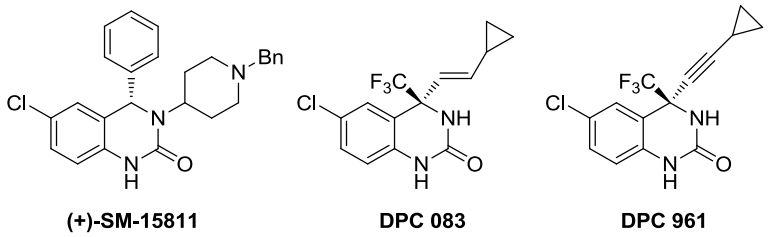
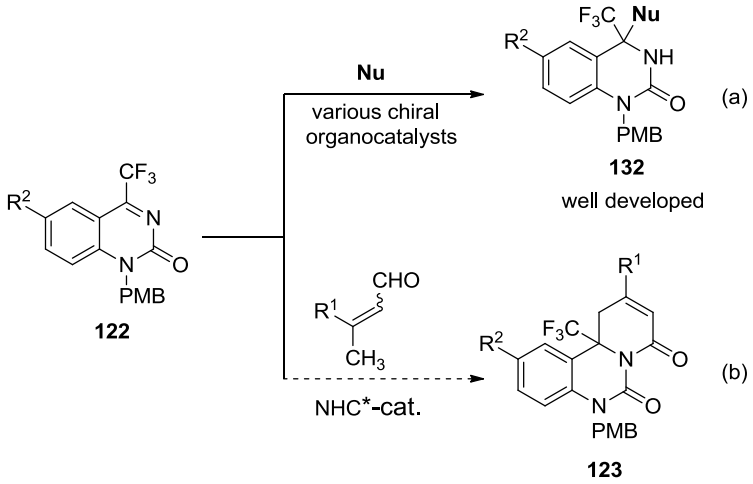


Figure 3 Typical biological compounds of dihydroquinazolinones



Scheme 48 Asymmetric transformations of trifluoromethyl 2(1H)-quinazolinones

On account of the synthetic and biological importance of chiral trifluoromethyl substituted 2(1H)-quinazolinones, great efforts have been dedicated to their enantioselective preparation. Various chiral organocatalysts have been investigated and applied in their transformations, for instance secondary amine catalysts,[76] cinchona alkaloid thiourea catalysts,[77] quinine-squaramide catalysts,[78] saccharide-derived amino-thiourea catalysts[79] and chiral phosphoric acid catalysts.[80] However, all of the research have devoted to the one-step reaction employing different nucleophilic reagents (Scheme 48a). In contrast, the organocatalyzed enantioselective cascade annulation reactions of trifluoromethyl 2(1H)-quinazolinones

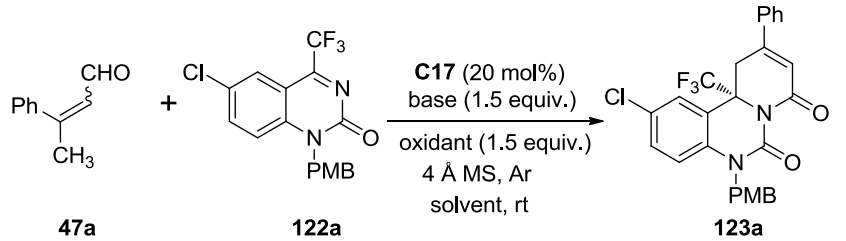
still remain a challenge and there are no reports in the literature involving such a potentially benificial transformation. Recently Shi and coworkers developed the Mannich/cyclization domino reaction of this cyclic trifluoromethyl ketimine with isocyanoacetate, but cinchona alkaloid squaramide and silver catalysts are both required in their catalytic system.[81] Thus, developing novel asymmetric domino reactions of trifluoromethyl 2(1H)-quinazolinones is still a significant goal.

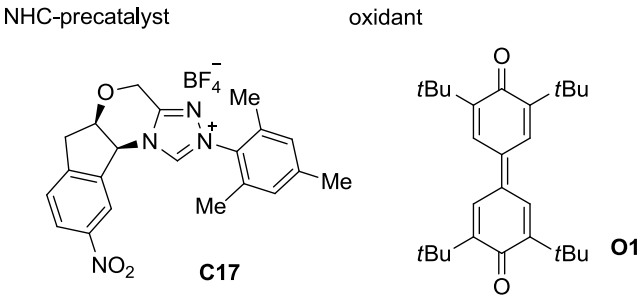
N-Heterocyclic carbene (NHC)-promoted cycloadditions have been proved as an efficient tool for the establishment of different chiral carbo- and heterocyclic structures from readily available substrates. Particularly, activation of the γ-carbon of carbonyl compounds employing NHC catalysis has drawn extensive interest since initial reports of Ye[31] and Chi[32] and their coworkers. However, in comparison with the well developed [4+2] annulation of activated ketones, the corresponding reactions with imines affording δ-lactam compounds with biological properties and great synthetic potential still remains a limitation. Herein we report an oxidative N-heterocyclic carbene-catalyzed [4+2] annulation of β-methyl enals and cyclic trifluoromethyl ketimines for the asymmetric preparation of biologically active dihydroquinazolinone derivatives (Scheme 48b).

2.2.2 Optimization of the reaction conditions

Initially, a model reaction of the isatin-derived enal **47a** with the cyclic trifluoromethyl ketimine **122a** was investigated under the catalysis of NHCs (Table 4). We were pleased to find that the (4+2) annulation catalyzed by the pre-catalyst, in the presence of Cs_2CO_3 as the base, furnished the desired product **123a** in 75% yield with 95:5 e.r. (entry 1). With this excellent result we explored a variety of alternative bases, such as the inorganic bases CsOAc, K_2CO_3, KOAc, Na_2CO_3, NaOAc, K_3PO_4 and the organic bases DIPEA, NEt_3, and demonstrated that CsOAc was the best choice (entries 2–9). Solvent screening revealed that the reactions worked as well in the presence of several other solvents but inferior yields and enantioselectivives were obtained as compared with tetrahydrofuran (THF) (entry 12).

Table 4 Optimization of the NHC-catalyzed [4+2] annulation





Entry	Base	Solvent	Yield [%][b]	e.r.[c]
1	Cs_2CO_3	toluene	75	95:5
2	CsOAc	toluene	75	95.5:4.5
3	K_2CO_3	toluene	70	94.5:5.5
4	KOAc	toluene	58	94.5:5.5
5	Na_2CO_3	toluene	56	92.5:7.5
6	NaOAc	toluene	42	96:4
7	K_3PO_4	toluene	40	95.5:4.5
8	DIPEA	toluene	35	77:23
9	NEt_3	toluene	40	94:6
10	CsOAc	DCM	74	95.5:4.5
11	CsOAc	DCE	70	95:5
12	CsOAc	THF	75	96.5:3.5
13	CsOAc	CH_3CN	65	95.5:4.5

[a] All reactions were conducted with 0.4 mmol of **47a** (2.0 equiv), 0.2 mmol of **122a** (1.0 equiv.), base (1.5 equiv.), oxidant 1 (1.5 equiv.), 20 mol% of **C17** and 4Å MS in 2.0 mL solvent under Ar atmosphere at room temperature for 24h. [b]Yield of isolated product 3a after chromatography. [c] Determined by HPLC using a chiral stationary phase.

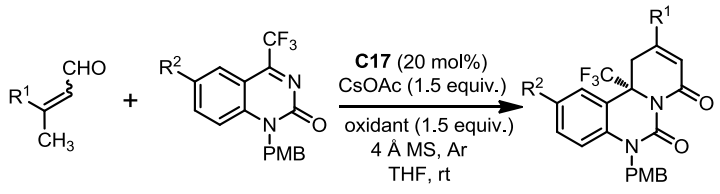
2.2.3 Investigation of the substrate scope

With the optimized conditions in hand, the reaction scope with respect to the cyclic trifluoromethyl ketimine and the enal substrates was examined (Table 5). The electronic properties and positions of the substituent on the phenyl of the enals had a slight influence on the reaction. For example, the 2-Me, 2-OMe, 3-Me and 3-OMe substituted enals worked as well and gave the desired products in very good yields with good to excellent enantiomeric ratios (**123b-e**). The reaction proceeded smoothly when the enals were substituted with electron-donating (4-$OMeC_6H_4$ and 4-MeC_6H_4) or electron-withdrawing (4-FC_6H_4, 4-ClC_6H_4 and 4-BrC_6H_4) groups, affording the desired products **123f–j** in good yields with a high enantiomeric ratio. Furthermore, the reaction of the enal bearing a 2-naphthyl group was also successful (**123k**). Notably, a β,β'-dialkyl enal (citral) delivered the corresponding product **123p** with 90:10 e.r. albeit in somewhat decreased yield and d.r. The scope of the cyclic trifluoromethylketimines was also examined. The reaction worked well when the cyclic trifluoromethylketimines were substituted with electron-donating (Me) or electron-withdrawing (F, Cl) groups, providing the dihydroquinazolinone derivatives in good yields and excellent e.r. (**123m** and **123n**). As expected, the reaction of these ketimines also were tolerable when different enals were used (**123l**, **3o** and **123q**).

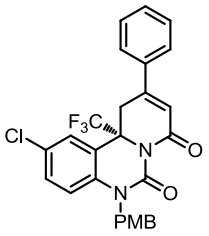
2.2.4 Determination of the absolute configuration

The absolute configuration of the dihydroquinazoline **3e** was determined to be (*R*) according to an X-ray crystallographic analysis while the other product configurations were assigned by analogy (Fig 4).

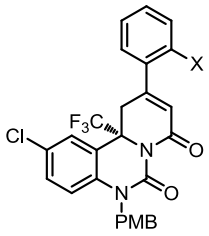
Table 5 Substrate scope of the NHC-catalyzed [4+2] annulations



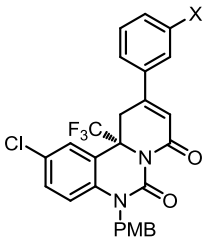
47 **122** **123**



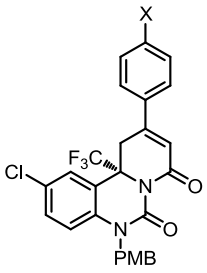
123a 75%, 96.5:3.5 e.r.



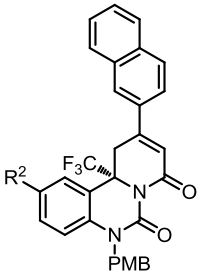
123b, X = Me, 60%, 97:3 e.r.
123c, X = OMe, 74%, 87:13 e.r.



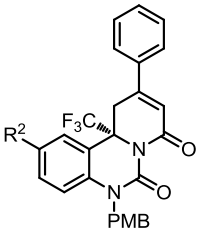
123d, X = Me, 85%, 98.5:1.5 e.r.
123e, X = OMe, 76%, 95:5 e.r.



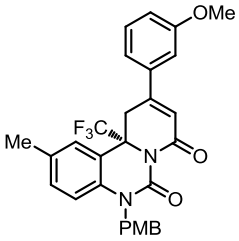
123f, X = Me, 65%, 97:3 e.r.
123g, X = OMe, 64%, 96:4 e.r.
123h, X = F, 67%, 95:5 e.r.
123i, X = Br, 65%, 97:3 e.r.
123j, X = Cl, 73%, 96.5:3.5 e.r.



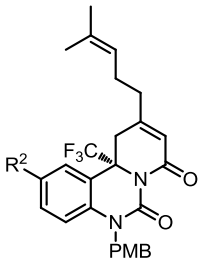
123k, R^2 = Cl 70%, 98.5:1.5 e.r.
123l, R^2 = F, 70%, 93:7 e.r.



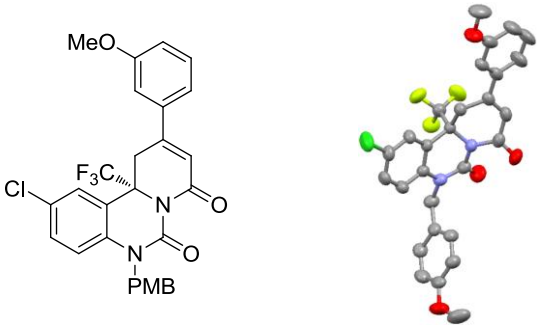
123m, R^2 = F, 78%, 97.5:2.5 e.r.
123n, R^2 = Me, 75%, 97:3 e.r.



123o, 72%, 97:3 e.r.



123p, R^2 = Cl, 46%, 90:10 e.r.
123q, R^2 = Me, 42%, 88:12 e.r.

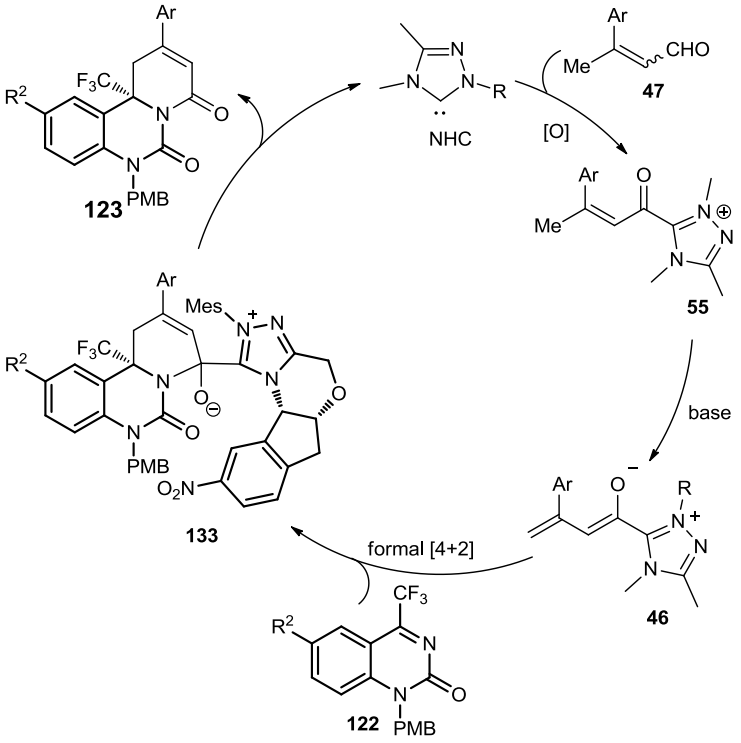


123e

*Fig 4 X-ray crystal structure of **123e***

2.2.5 Possible mechanism

A plausible catalytic cycle is depicted in Scheme 49. First, the addition of the NHC to the enals **47** furnishes the Breslow intermediate, which is oxidized by the bisquinone to give the unsaturated acyl azolium intermediate **55**. The reactive dienolate **46** is readily generated via γ-deprotonation of **55** in the presence of base. At last, the dienolate undergoes a Mannich-type addition with the cyclic trifluoromethyl **122** followed by lactamization to give the intermediate **133**. The elimination of the NHC catalyst from intermediate **133** releases **123** as the final product and returns the catalyst for further cycles.



Scheme 49 Proposed reaction mechanism of the NHC-catalyzed [4+2] annulations

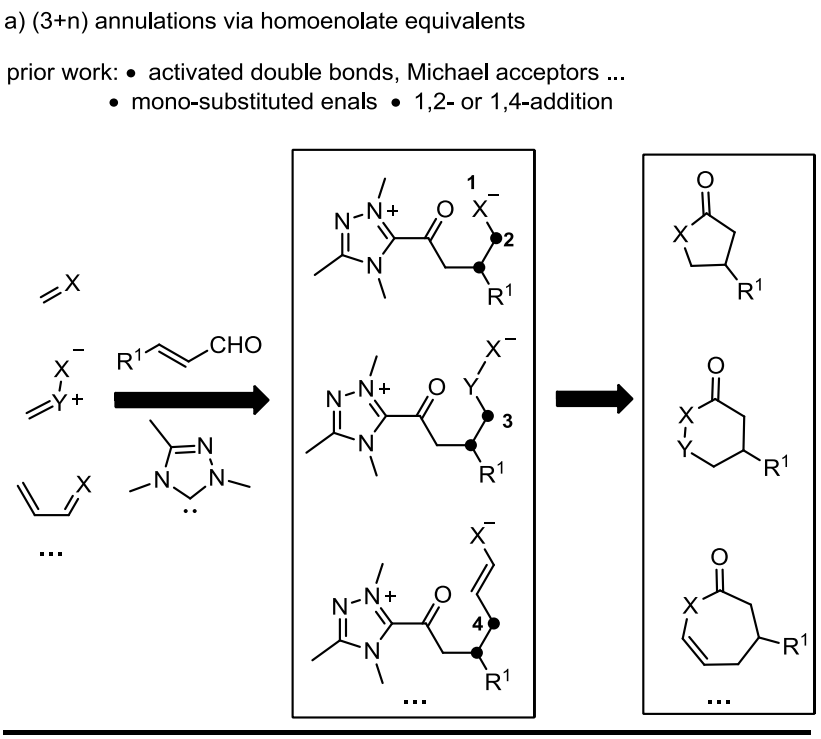
2.3 Asymmetric synthesis of spirooxindole ε-lactones through N-heterocyclic carbene catalysis

2.3.1 Background and motivation

The preparation of various diversified spirooxindole compounds has attracted

extensive attention due to their biological activities and great effects in the resistance of many neurodegenerative diseases and human cancers.[82] A lot of efforts have been dedicated to the synthesis of these molecules bearing three, four, five or six-membered rings fused at the C3 position. However, the construction of chiral seven or larger membered spirooxindoles is still a formidable challenge. Moreover, generating multiple stereocenters from the substituents present on the ring leads to another synthetic challenge. To our best knowledge, there are no reports in the literature involving the synthesis of spirocyclic oxindole-ε-lactones. Thus, developing novel efficient and stereoselective strategies for the preparation of these challenging spirooxindoles is highly desirable.

In the past decade, N-heterocyclic carbenes (NHCs) have developed rapidly and emerged as a significant class of organocatalysts. In particular, NHC-generated homoenolate equivalent intermediates from enals have been widely explored since the initial (3+2) cycloadditions of α,β-unsaturated aldehydes developed independently by the Glorius[13] and Bode[12] and their coworkers. Despite this rapid development, today three major issues still need to be solved: 1) the homoenolate precursors are usually generated from mono-substituted enals and only a few examples employing β,β-disubstituted substrates have been explored,[83] 2) the initial step is always restricted to the 1,2- and 1,4- addition, 3) the annulation partners are restricted to activated double bonds and Michael acceptors (Scheme 50a). Recently, Scheidt[84] and Ye[85] and their coworkers independently reported elegant NHC-catalyzed (3+4) annulations of enals and o-quinone methides for the preparation of benzo-ε-lactones. In 2016 our group successfully introduced isatin-derived enals as homoenolate precursors solving the first



Scheme 50 Motivation and Synthetic Strategy

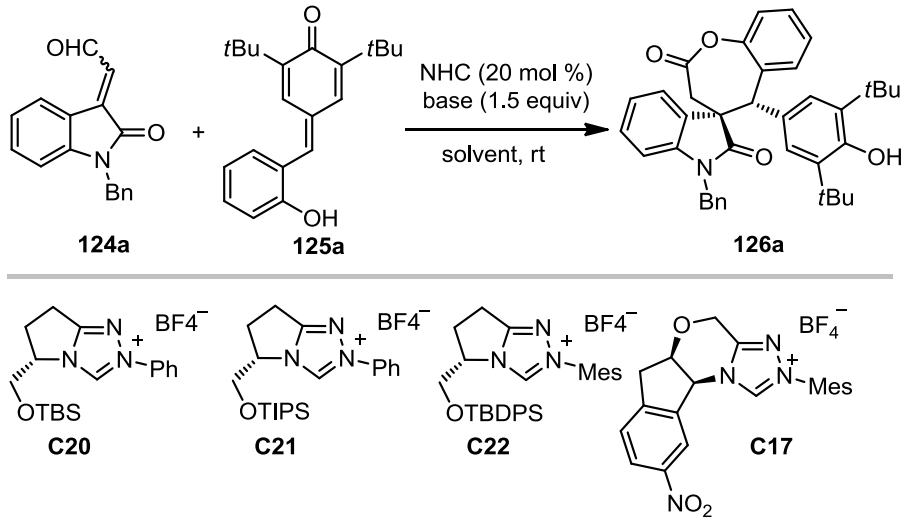
issue.[86] Recently we revealed that asymmetric annulations initiated by 1,6-addition of homoenolate equivalents are also feasible,[87] whereas Glorius and co-workers spread the annulation partners to in situ generated bifunctional reagents through 1,3-addition of the homoenolate equivalents via the cooperative catalysis of NHC and palladium.[88] Despite these advances, developing reactions of homoenolate equivalents with bifunctional reagents is still a challenge. The protonation of the β-carbon of the extended Breslow intermediates will result in the annulation reactions with the bifunctional reagents via azolium enolate intermediates.[89] Other competitive pathways could also emerge involving the extended Breslow intermediates. For instance the Stetter reaction,[90] the redox esterification[91] and the annulation with activated C-C double bonds (Scheme 50b).[87, 92] Even if these reactions had been successfully suppressed, the serious steric congestion of the β,β-disubstituted enals need to be overcome. As our ongoing interest in isatin-derived enals and 1,6-additions via NHC catalysis, the development of a novel NHC-catalyzed (3+4) annulation reaction of isatin-derived enals with 1,6-acceptor tethered oxygen nucleophiles for the asymmetric preparation of spirocyclic oxindole-ε-lactones is now described.

2.3.2 Optimization of the reaction conditions

The evaluation of the reaction conditions started with isatin-derived enal **124a** and ortho-hydroxyphenyl-substituted para-quinone methide **124a** as model substrates in the presence of *N*-mesityl-substituted triazolium salt **C20** as the pre-catalyst and NEt_3 as the base in DCM at room temperature (Table 6, entry 1). The desired spirocyclic oxindole-ε-lactone **126a** was generated in 85% yield with an enantiomeric ratio of 89.5:10.5 and 7:1 dr. Switching the catalyst to **C21** the product was afforded in 83% yield with 7:1 dr and slightly decreased er of 88:12 (entry 2). The pre-catalyst **C22** was also screened for the reaction and the desired ε-lactone was obtained with lower yield and asymmetric induction. The reaction proceeded well in the presence of pre-catalyst **C17**, delivering a slightly better er value (90:10 er) with low yield and diastereoselectivity (entry 4). Then various solvents were investigated and the results

revealed that $CHCl_3$ was the best choice as the reaction result was improved to 81% yield and 90.5:9.5 er value (entries 5–11). A variety of alternative bases, such as the organic bases DIPEA, TMEDA, DMAP, DABCO, and the inorganic bases KOAc, K_2CO_3, K_3PO_4, were all compatible with this reaction but inferior yields were obtained as compared with NEt_3 (entries 12–18). It was also found that the employment of 4Å molecular sieves as additive improved the enantiomeric ratio value (91:9 er, entry 19). Further improvement was achieved when the reaction was carried out at 0 ^oC (entry 20).

Table 6 Optimization of the Reaction Conditions



entry	pre-cat.	base	solvent	yield (%)[a]	dr[b]	er[c]
1	**C20**	NEt_3	DCM	85	7:1	89.5:10.5
2	**C21**	NEt_3	DCM	83	7:1	88:12
3	**C22**	NEt_3	DCM	62	3:1	85:15
4	**C17**	NEt_3	DCM	52	2:1	-90:10
5	**C20**	NEt_3	DCE	60	6:1	87.5:12.5
6	**C20**	NEt_3	$CHCl_3$	81	7:1	90.5:9.5
7	**C20**	NEt_3	CCl_4	72	7:1	90:10

8	**C20**	NEt_3	THF	trace	–	–
9	**C20**	NEt_3	dioxane	trace	–	–
10	**C20**	NEt_3	DME	trace	–	–
11	**C20**	NEt_3	CH_3CN	trace	–	–
12	**C20**	DIPEA	$CHCl_3$	76	7:1	90:10
13	**C20**	TMEDA	$CHCl_3$	72	7:1	90:10
14	**C20**	DMAP	$CHCl_3$	66	7:1	91:9
15	**C20**	DABCO	$CHCl_3$	75	7:1	90:10
16	**C20**	KOAc	$CHCl_3$	66	6:1	90:10
17	**C20**	K_2CO_3	$CHCl_3$	68	6:1	90:10
18	**C20**	K_3PO4	$CHCl_3$	78	6:1	90:10
19[d]	**C20**	NEt_3	$CHCl_3$	85	7:1	91:9
20[d,e]	**C20**	NEt_3	$CHCl_3$	84	7:1	94:6

[a]Yield of isolated product **3a** after chromatography. [b]The dr values were determined by ^{1}H NMR analysis. [c]The er-values were determined by HPLC analysis of the purified product on a chiral stationary phase. [d]4Å molecular sieves were added. [e]The reaction was carried out at 0 ^oC.

2.3.3 Investigation of the substrate scope

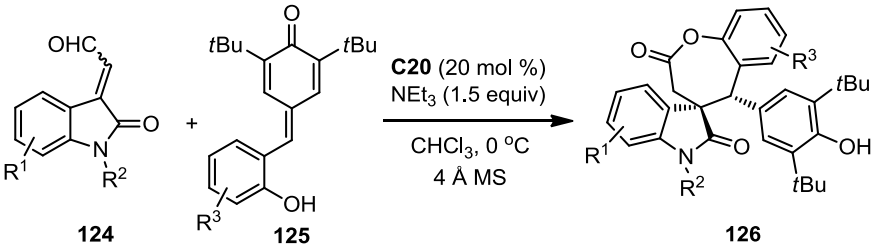
To demonstrate the generality of this NHC-mediated asymmetric [3+4] cycloaddition, the substrate scope of the *ortho*-hydroxyphenyl substituted *p*-QMs **125** was investigated, and the results as shows in Table 7. When the [3+4] cycloaddition between isatin-derived enal **124a** and *ortho*-hydroxyphenyl substituted *para*-quinone methide **125** was examined under the standard conditions, the corresponding

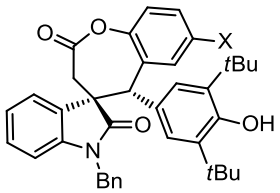
spirobenzoxopinones **126** were provided in very good yields with moderate to good diastereo- (3:1-10:1 dr) and very good enantiomeric ratios (88.5:11.5-94:6 er). Both electron-withdrawing (F, Cl, Br,) and electron-donating (Me, MeO, EtO) substituents on the ortho-hydroxyphenyl group of pQMs were tolerated. To further explore the scope of the NHC-catalyzed [4+3] cycloaddition, the enantioselective reactions between ortho-hydroxyphenyl substituted *p*-QM **125a** and a series of isatin-derived enals **124** were tested. Various substituents, including electron-withdrawing (F, Cl, Br) and electron-donating groups (Me) were tolerated on the aromatic ring of the isatin-derived enals component with only slight influence on the yields and asymmetric induction. For instance, the 5-Me, 5-F, 5-Cl and 5-Br substituted isatin derived enals proceeded smoothly to furnish the targeted products in excellent yields with good diastereomeric ratios and very good er values (**126j-m**). The 6-Cl substituted substrate showed a very good reactivity and stereoselectivity providing **3n** in 84% yield with 91.5:8.5 er and 6:1 dr values. A good yield and stereoselectivity was also achieved with the introduction of a substituent at position 7 of the isatin derived enal (**3o**). Furthermore, the isatin derived enals with varying nitrogen protecting groups were also tolerated under the optimized condition. The reactions of N-4-bromobenzyl, methyl and ethyl isatin derived enals **124p-r** worked well and furnished the desired products **126p-r** with good asymmetric induction. Gratifyingly, the N-aryl and allyl isatin derived enals were also found to furnish the corresponding products **3s-v** in good yields with very good stereoselectivities.

2.3.4 Determination of the absolute configuration

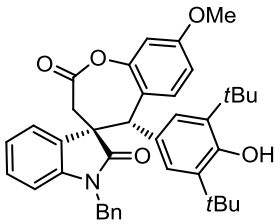
The absolute configuration of the spirocyclic oxindole-ε-lactone **126s** was determined by X-ray crystal structure analysis (Figure 5) and the configurations of all other products were assigned accordingly.

Table 7 Substrate scope

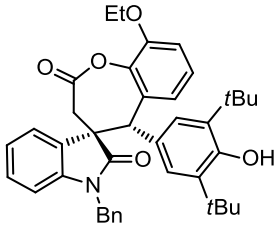




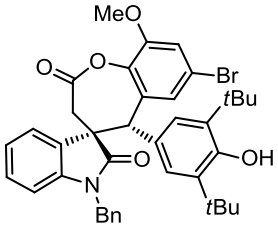
126a, X = H, 84% yield, 94:6 er, 7:1 dr
126b, X = MeO, 84% yield, 89:11 er, 6:1 dr
126c, X = Me, 90% yield, 88.5:11.5 er, 6:1 dr
126d, X = F, 73% yield, 89:11 er, 10:1 dr
126e, X = Cl, 80% yield, 94:6 er, 7:1 dr
126f, X = Br, 92% yield, 94:6 er, 3:1 dr



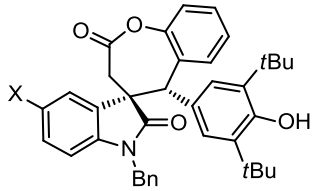
126g, 93% yield
93.5:6.5 er, 3:1 dr



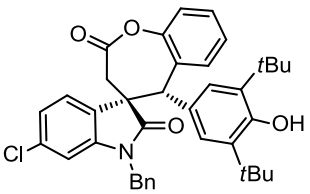
126h, 80% yield,
94:6 er, 7:1 dr



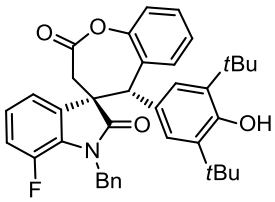
126i, 84% yield
93.5:6.5 er, 4:1 dr



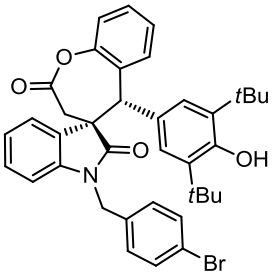
126j, X = Me, 88% yield, 91:9 er, 6:1 dr
126k, X = F, 93% yield, 97:3 er, 7:1 dr
126l, X = Cl, 90% yield, 92:8 er, 4:1 dr
126m, X = Br, 85% yield, 92:8 er, 4:1 dr



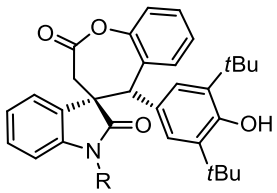
126n, 84% yield
91.5:8.5 er, 6:1 dr.



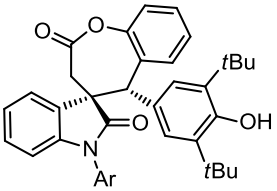
126o, 85% yield
93.5:6.5 er, 6:1 dr



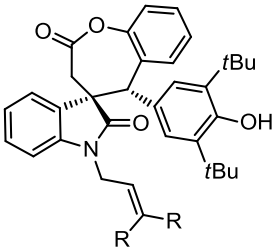
126p, 89% yield
91.5:8.5 er, 7:1 dr



126q, R = Me, 78% yield
95:5 er, 7:1 dr
126r, R = Et, 79% yield
92:8 er, 7:1 dr



126s, Ar = Ph, 75% yield
92:8 er, 5:1 dr
126t, Ar = PMP, 88% yield
91:9 er, 8:1 dr



126u, R = Me, 86% yield
91:9 er, 7:1 dr
126v, R = H, 79% yield
91:9 er, 7:1 dr

Yields of isolated products **126** after chromatography. The dr data were determined

by ^{1}H NMR analysis and the er data were determined by chiral stationary phase HPLC analysis of the purified products.

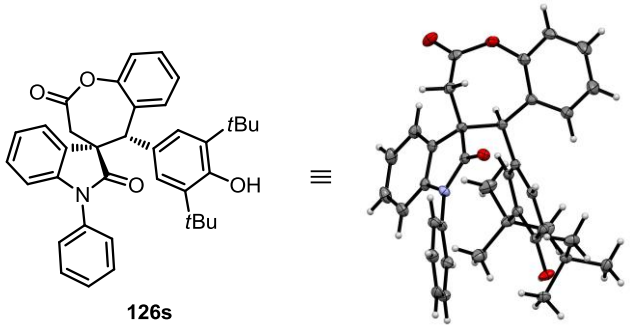
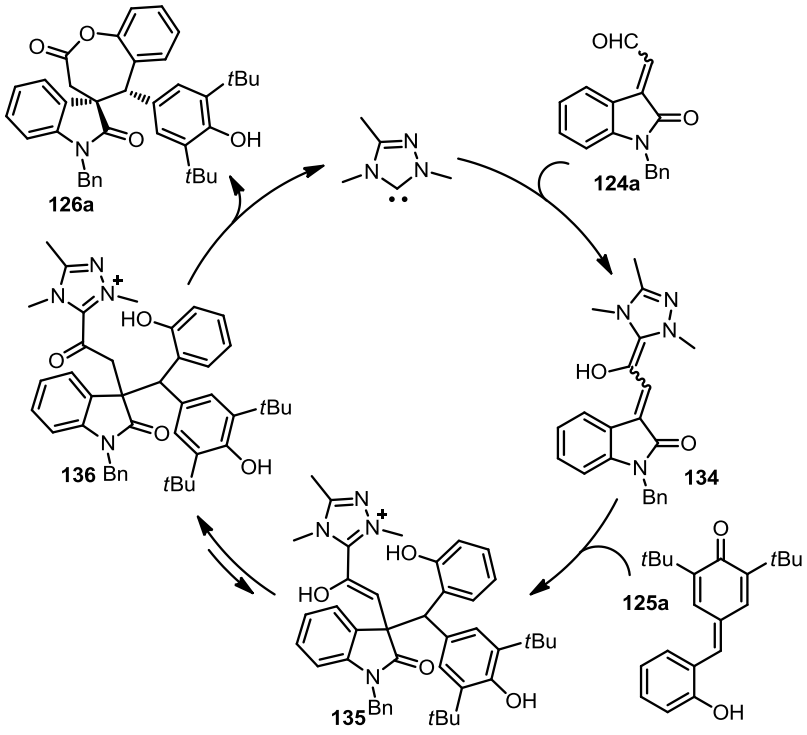


*Figure 5 X-ray crystal structure of **126s***



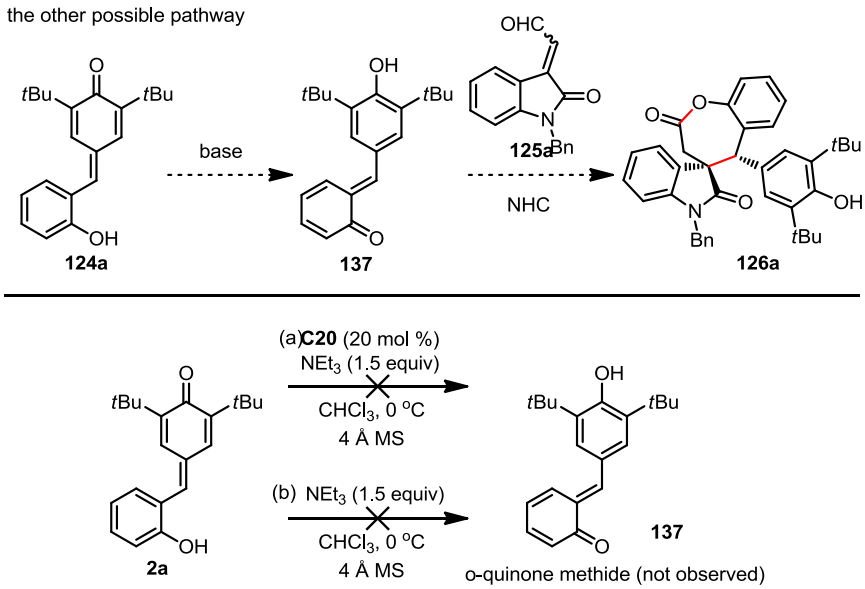
Scheme 51 Plausible catalytic cycle

2.3.5 Proposed mechanism

The proposal of the possible reaction mechanism is shown in Scheme 51. The addition of the NHC catalyst to the isatin-derived enal **124a** affords the Breslow intermediate **134**, which undergoes a 1,6-Michael addition to the *ortho*-hydroxyphenyl-substituted para-quinone methide **125a** furnishing the intermediate **135**. Tautomerization of **135** forms the acyl azolium intermediate **136**.

The final intramolecular lactonization of **136** provides the desired product **126a** and returns the NHC pre-catalyst.

An attractive possible pathway involving the generation of o-quinone methides under basic conditions followed by subsequent (4+3) annulation was ruled out by the control experiment in which no reaction was observed under the reaction conditions (Scheme 52).



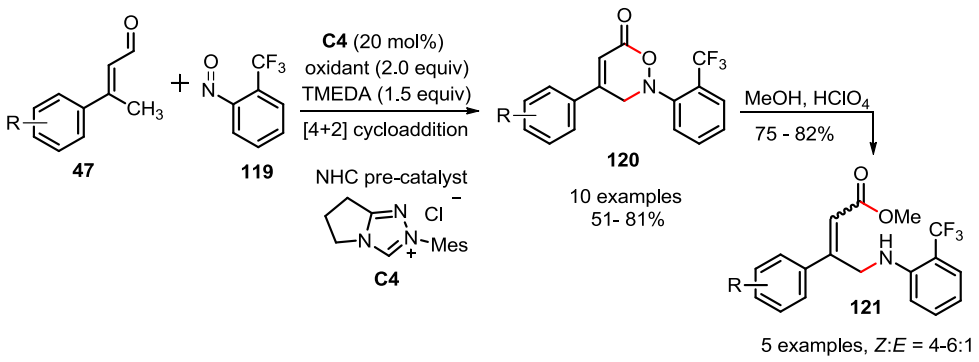
Scheme 52 Ruled out other pathway by control experiments

3. Research Summary and Outlook

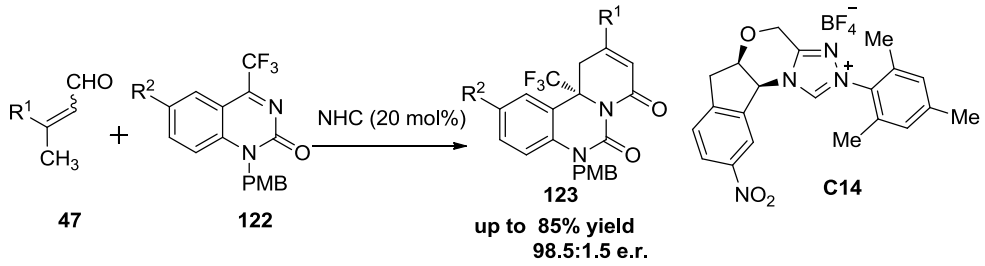
In this thesis, three *N*-heterocyclic carbene catalyzed organocatalytic methodologies *via* azolium dienolate equivalents and homoenolate equivalents are presented and parts of the research results were already published in peer-reviewed journals. The conclusion of these three projects will be briefly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

3.1 Synthesis of α,β-unsaturated γ-amino acid esters via NHC-catalyzed [4+2] annulation reactions

In this project, an efficient two step protocol for the preparation of α,β-unsaturated γ-amino acid esters was successfully developed employing the NHC-catalyzed oxidative [4+2] cycloaddition of β-methyl enals and aryl nitroso compounds. The resulting intermediates 1,2-oxazin-6-ones are prepared in good to very good yields and can be transformed to the title γ-amino enoates by ring-opening with methanol under acidic conditions.



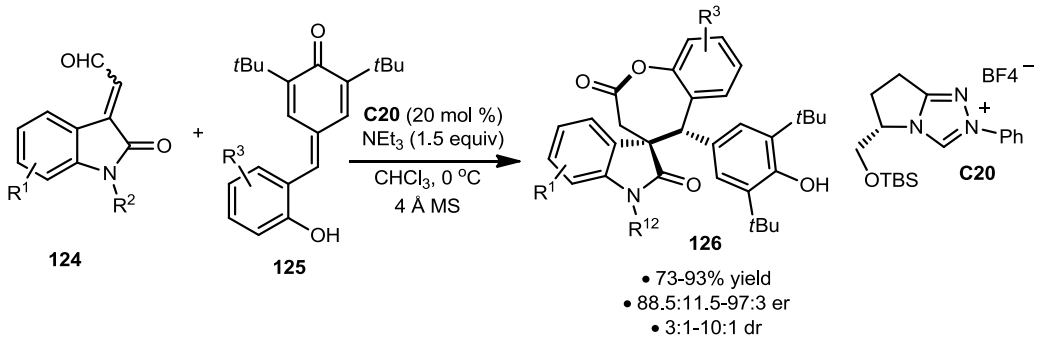
3.2 N-Heterocyclic carbene-catalyzed [4+2] annulation of β-methyl enals and cyclic trifluoromethyl ketimines



In this project, the asymmetric oxidative N-heterocyclic carbene-catalyzed [4+2] annulation reaction of β-methyl enals and cyclic trifluoromethyl ketimines has been successfully established. A variety of potentially useful dihydroquinazolinone derivatives bearing a trifluoromethyl group and a tetrasubstituted stereocenter were efficiently prepared with very good yields and excellent enantioselectivities.

3.3 Asymmetric synthesis of spirooxindole ε-lactones through N-heterocyclic carbene catalysis

In this project, an unprecedented N-heterocyclic carbene (NHC)-catalyzed (3+4) annulation of isatin-derived enals and *ortho*-hydroxyphenyl-substituted *para* quinone methides has been developed. The new methodology uses a 1,6-Michael addition of the homoenolate equivalent intermediates to the hydroxy donor-1,6-Michael acceptors followed by esterification and leads to spirocyclic oxindole-ε-lactones in high yields and very good stereoselectivities.



3.4 Perspective and outlook

The exploration of N-heterocyclic carbenes is undoubtedly one of the most important components in recent chemistry research. N-heterocyclic carbenes have had a deep

influence on the field of organic chemistry, usually permitting for the mild construction of complex compounds from simple starting substrates. The methodology of NHC-catalyzed reactions for the preparation of many biological and pharmaceutical frameworks was also extensively investigated. N-heterocyclic carbenes can be commercially prepared and are active and efficient on many kinds of organic synthesis. Designing and preparing efficient and novel N-heterocyclic carbenes that are more reactive and selective in the established reactivity still remains a major focus.

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}.

4.2.7 X-Ray crystal structure

The structure of **120c** and the absolute configuration of **123e** were established by the X-ray analysis of a single crystal by Prof. G. Raabe. The absolute configuration of **126s** was determined by X-ray crystal structure analysis by Prof. K. Rissanen.

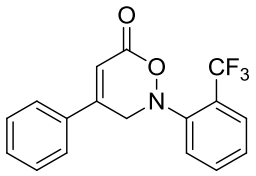
4.3 General procedure and analytical data

4.3.1 1,2-Oxazin-6-one synthesis

4.3.1.1 General procedure I (GP I)

A 10 mL glass tube equipped with a stirring bar was charged with the aldehyde **47** (0.8 mmol, 2.0 eq), oxidant (0.80 mmol, 2.0 equiv, 326 mg), TMEDA (0.3 mmol, 1.5 eq, 70 mg), 4Å MS (0.100 mg), NHC (0.08 mmol, 20 mol %, 18 mg) and anhydrous toluene (2.0 mL). The resulting solution was flushed with argon and stirred at room temperature for 30 minutes and then a solution of 1-nitroso-2-trifluoromethyl-benzene **119** (0.40 mmol, 1.0 equiv, 70 mg) in toluene (2.0 mL) was added protionwise over 45 minutes. The reaction mixture was stirred overnight and was directly purified by flash chromatography using hexane and ethyl acetate (12:1 to 8:1) as the eluent to provide the desired product **120**.

4.3.1.2 Analytical data of the synthesized compounds



120a

4-Phenyl-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120a)

The general procedure **I** was followed with aldehyde **47a** (0.8 mmol, 2.0 eq, 117 mg). The chromatographic purification afforded **120a** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 75% (96 mg).

Melting Point: 92-94 ^{o}C.

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

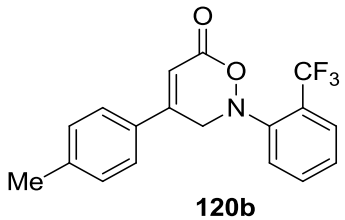
δ = 7.93 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.74 – 7.67 (m, 2H, Ar*H*), 7.57 – 7.41 (m, 6H, Ar*H*), 6.49 – 6.44 (m, 1H, C=C*H*), 4.28 (s, 2H, CH_2) ppm

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

δ = 165.8 (*C*=O), 154.9 (*C*=CH), 146.5 (C_{Ar}), 133.8 (C_{Ar}), 133.2 (C_{Ar}), 131.2 (C_{Ar}), 129.2 (2C) (C_{Ar}), 128.4 (C_{Ar}), 126.7 (q, *J* = 6.0 Hz) (C_{Ar}), 126.2 (2C) (C_{Ar}), 125.7 (q, *J* = 30.0 Hz) (C_{Ar}), 124.1(C_{Ar}), 123.2 (q, *J* = 271.5 Hz) (*C*F_3), 113.3 (C=*C*H), 57.1(*C*H_2) ppm

IR (ATR): 3380, 3067, 2927, 2330, 2090, 1709, 1610, 1456, 1279, 1132, 936, 756 cm^{-1}.

HRMS (ESI):*m/z* $[M+Na]^+$ calcd for $C_{17}H_{12}NO_2F_3Na^+$: 342.0712; found 342.0711.



120b

4-(p-Tolyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120b)

The general procedure **I** was followed with aldehyde **47b** (0.8 mmol, 2.0 eq, 128 mg).

The chromatographic purification afforded **120b** as a yellow solid.

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

Yield: 60% (81 mg)

Melting Point: 120-122 ^{o}C.

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

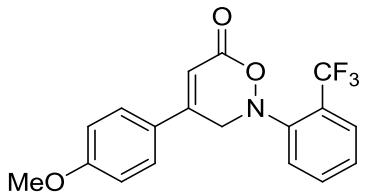
δ = 7.93 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.76 – 7.66 (m, 2H, Ar*H*), 7.48 – 7.46 (m, 1H, Ar*H*), 7.43 – 7.39 (m, 2H, Ar*H*), 7.27 – 7.25 (m, 2H, Ar*H*), 6.45 (m, 1H, C=C*H*), 4.26 (d, *J* = 1.2 Hz, 2H, CH_2), 2.40 (s, 3H, CH_3). ppm

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

δ = 166.0 (*C*=O), 154.7 (*C*=CH), 146.7 (C_{Ar}), 141.9 (C_{Ar}), 133.1 (C_{Ar}), 130.9 (C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.3 (C_{Ar}), 126.7 (q, *J* = 6.0 Hz, C_{Ar}), 126.3 (C_{Ar}), 126.2 (C_{Ar}), 125.7 (q, *J* = 30.0 Hz, C_{Ar}), 124.4 (C_{Ar}), 123.2 (q, *J* = 271.5 Hz, *C*F_3), 112.3 (C=*C*H), 57.1 (*C*H_2), 21.4 (*C*H_3) ppm

IR (ATR): 2921, 2324, 2091, 1914, 1707, 1606, 1454, 1269, 1121, 936, 769 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}NO_2F_3Na^+$: 356.0869; found 356.0866.



120c

4-(4-Methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120c)

The general procedure **I** was followed with aldehyde **47c** (0.8 mmol, 2.0 eq, 141 mg). The chromatographic purification afforded **120c** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 68% (95 mg).

Melting Point: 153-155 ^{o}C.

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

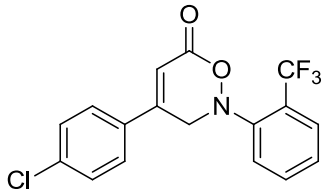
δ = 7.92 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.75 – 7.67 (m, 2H, Ar*H*), 7.50 – 7.44 (m, 3H, Ar*H*), 6.96 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.41 – 6.39 (m, 1H, C=C*H*), 4.25 (d, *J* = 1.2 Hz, 2H, CH_2), 3.85 (s, 3H, OCH_3).ppm

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

δ = 166.2 (*C*=O), 162.1 (C_{Ar}), 154.2 (*C*=CH), 146.7 (C_{Ar}), 133.2 (C_{Ar}), 128.2 (C_{Ar}), 127.9 (2C, C_{Ar}), 126.7 (q, *J* = 6.0 Hz, C_{Ar}), 125.9 (C_{Ar}), 125.7 (q, *J* = 30.0 Hz, C_{Ar}), 124.4 (C_{Ar}), 123.2 (q, *J* = 273 Hz, *C*F_3), 114.6 (2C, C_{Ar}), 111.0 (C=*C*H), 57.0 (*C*H_2), 55.5 (*C*H_3) ppm

IR (ATR): 2923, 1915, 1703, 1595, 1463, 1249, 1132, 785 cm^{-1}.

HRMS (ESI):*m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}NO_3F_3Na^+$: 372.0818; found 372.0817.



120d

4-(4-Chlorophenyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120d)

The general procedure **I** was followed with aldehyde **47d** (0.8 mmol, 2.0 eq, 144 mg). The chromatographic purification afforded **120d** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 72% (101 mg)

Melting Point: 93-95 ^{o}C.

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

δ = 7.90 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.74 – 7.65 (m, 2H, Ar*H*), 7.50 – 7.35 (m, 5H, Ar*H*), 6.45 (m, 1H, C=C*H*), 4.23 (d, *J* = 1.2 Hz, 2H, CH_2) ppm

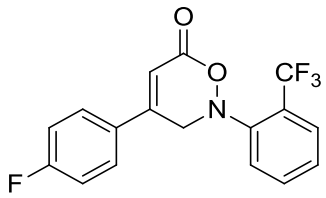
^{13}C NMR (100 MHz, $CDCl_3$):

δ = 165.3 (*C*=O), 153.3 (*C*=CH), 146.3 (C_{Ar}), 135.7 (C_{Ar}), 135.4 (C_{Ar}), 133.2 (C_{Ar}), 131.0 (C_{Ar}), 130.5 (C_{Ar}), 128.5 (C_{Ar}), 126.8 (q, *J* = 5.0 Hz, C_{Ar}), 126.3 (C_{Ar}), 125.8 (q,

J = 30.0 Hz, C_{Ar}), 124.4 (C_{Ar}), 124.3 (C_{Ar}), 123.1 (q, *J* = 271.0 Hz, CF_3), 114.6 (C=*C*H), 57.0 (CH_2) ppm

IR (ATR): 3073, 2918, 2099, 1906, 1707, 1601, 1452, 1284, 1112, 938, 761, 694 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{11}NO_2F_3ClNa^+$: 376.0323; found 376.0322.



120e

4-(4-Fluorophenyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120e)

The general procedure **I** was followed with aldehyde **47e** (0.8 mmol, 2.0 eq, 131 mg). The chromatographic purification afforded **120e** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 53% (72mg).

Melting Point: 103-105 °C.

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

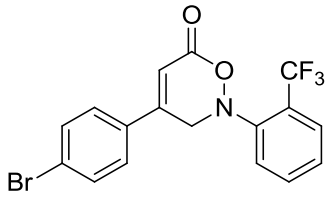
δ = 7.91 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.74 – 7.65 (m, 2H, Ar*H*), 7.54 – 7.42 (m, 3H, Ar*H*), 7.17 – 7.09 (m, 2H, Ar*H*), 6.42 – 6.40 (m, 1H, C=C*H*), 4.23 (d, *J* = 1.2 Hz, 2H, CH_2) ppm

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

δ = 165.6 (*C*=O), 165.3 (C_{Ar}), 163.6 (C_{Ar}), 153.6 (*C*=CH), 146.5 (C_{Ar}), 133.2 (C_{Ar}), 130 (q, *J* = 4.5Hz), 128.4 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (C_{Ar}), 126.8 (q, *J* = 6.0Hz, C_{Ar}), 124.4 (C_{Ar}), 123.2 (q, *J* = 271.5Hz, CF_3), 116.6 (C_{Ar}), 116.4 (C_{Ar}), 113.3 (C=*C*H), 57.2 (CH_2) ppm

IR (ATR): 3443, 2923, 2331, 2086, 1721, 1603, 1502, 1230, 1120, 932, 819 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{11}NO_2F_4Na^+$: 360.0618; found 360.0618.



120f

4-(4-Bromophenyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120f)

The general procedure **I** was followed with aldehyde **47f** (0.8 mmol, 2.0 eq, 178 mg). The chromatographic purification afforded **120f** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 76% (120 mg)

Melting Point: 131-133 ^{o}C.

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

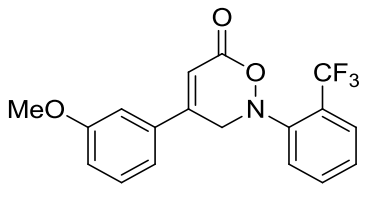
δ = 7.92 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.74 – 7.67 (m, 2H, Ar*H*), 7.59 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.48 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.37 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.50 – 6.44 (m, 1H, C=C*H*), 4.24 (d, *J* = 1.2 Hz, 2H, CH_2) ppm

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

δ = 165.5 (*C*=O), 153.6 (*C*=CH), 146.4 (C_{Ar}), 133.2 (C_{Ar}), 132.7 (C_{Ar}), 132.5 (2C, C_{Ar}), 128.5 (C_{Ar}), 127.7 (2C, C_{Ar}), 126.8 (q, *J* = 6.0 Hz, C_{Ar}), 125.8 (C_{Ar}), 125.7 (q, *J* = 31.5 Hz, C_{Ar}), 124.4 (C_{Ar}), 123.2 (q, *J* = 273.0 Hz, *C*F_3), 113.9 (C=*C*H), 57.0 (*C*H_2) ppm

IR (ATR): 3827, 3306, 2916, 2851, 2330, 2111, 1732, 1563, 1465, 1390, 1279, 1217, 1172, 1011, 1045, 994, 944, 857, 757, 667 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{11}NO_2F_3BrNa^+$: 419.9818; found 419.9819.



120g

4-(3-Methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120g)

The general procedure **I** was followed with aldehyde **47g** (0.8 mmol, 2.0 eq, 141 mg). The chromatographic purification afforded **120g** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 58% (81 mg).

Melting Point: 100-102 °C.

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

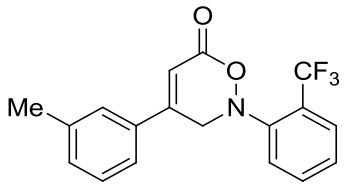
δ = 7.92 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.74 – 7.67 (m, 2H, Ar*H*), 7.47 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.39 – 7.34 (m, 1H, Ar*H*), 7.10 – 7.07 (m, 1H, Ar*H*), 7.04 – 6.99 (m, 2H, Ar*H*), 6.46 (m, 1H, C=C*H*), 4.25 (d, *J* = 1.2 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3) ppm

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

δ = 165.8 (*C*=O), 160.1 (C_{Ar}), 154.8 (*C*=CH), 146.5 (C_{Ar}), 135.2 (C_{Ar}), 133.2 (C_{Ar}), 130.3 (C_{Ar}), 128.4 (C_{Ar}), 126.7 (q, *J* = 6.0 Hz, C_{Ar}), 125.7 (q, *J* = 30.0 Hz, C_{Ar}), 124.4 (C_{Ar}), 123.2 (q, *J* = 271.5 Hz, *C*F_3), 118.6 (C_{Ar}), 116.6 (C_{Ar}), 113.6 (C_{Ar}), 111.8 (C=*C*H), 57.2 (*C*H_2), 55.4 (*C*H_3) ppm

IR (ATR): 2928, 1716, 1606, 1454, 1275, 1125, 890, 764 cm^{-1}.

HRMS (ESI):*m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}NO_3F_3Na^+$: 372.0818; found 372.0817.



120h

4-(m-Tolyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120h)

The general procedure **I** was followed with aldehyde **47h** (0.8 mmol, 2.0 eq, 128 mg). The chromatographic purification afforded **120h** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 72% (96 mg).

Melting Point: 114-116 °C.

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

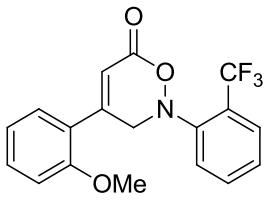
δ = 7.93 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.74 – 7.67 (m, 2H, Ar*H*), 7.47 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.36 – 7.27 (m, 4H, Ar*H*), 6.46 (m, 1H, C=C*H*), 4.27 (d, *J* = 1.2 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3) ppm

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

δ = 165.9 (*C*=O), 155.0 (*C*=CH), 146.6 (C_{Ar}), 139.0 (C_{Ar}), 133.8 (C_{Ar}), 133.2 (C_{Ar}), 132.0 (C_{Ar}), 129.1 (C_{Ar}), 128.3 (C_{Ar}), 126.9 (C_{Ar}), 126.7 (q, *J* = 6.0 Hz, C_{Ar}), 125.8 (q, *J* = 31.5 Hz, C_{Ar}), 124.4 (C_{Ar}), 123.4 (C_{Ar}), 123.2 (q, *J* = 271.5 Hz, *C*F_3), 113.2 (C=*C*H), 57.2 (*C*H_2), 21.4 (*C*H_3) ppm

IR (ATR): 2933, 1712, 1451, 1270, 1123, 924, 766 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}NO_2F_3Na^+$: 356.0869; found 356.0868.



120i

4-(2-Methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120i)

The general procedure **I** was followed with aldehyde **47i** (0.8 mmol, 2.0 eq, 141 mg). The chromatographic purification afforded **120i** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 52% (72 mg).

Melting Point: 1221-123 °C.

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

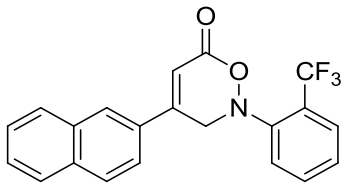
δ = 7.93 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.73 – 7.65 (m, 2H, Ar*H*), 7.48 – 7.32 (m, 3H, Ar*H*), 7.02 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.94 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.36 (s, 1H, C=C*H*), 4.28 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3)ppm

^{13}C NMR (100 MHz, $CDCl_3$):

δ = 165.9 (*C*=O), 157.2 (C_{Ar}), 155.7 (*C*=CH), 146.9 (C_{Ar}), 133.0 (C_{Ar}), 131.9 (C_{Ar}), 129.1 (C_{Ar}), 128.1 (C_{Ar}), 126.6 (q, *J* = 3.0 Hz, C_{Ar}), 125.8 (q, *J* = 20.0 Hz, C_{Ar}), 124.5 (C_{Ar}), 124.3 (C_{Ar}), 123.2 (q, *J* = 181.0 Hz, *C*F_3), 121.1 (C_{Ar}), 115.8 (C_{Ar}), 111.3 (C=*C*H), 58.6 (*C*H_2), 55.4 (*C*H_3) ppm

IR (ATR): 3309, 2929, 2088, 1714, 1603, 1456, 1249, 1128, 916, 755 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{18}H_{14}NO_3F_3Na^+$: 372.0818; found 372.0815.



120j

4-(Naphthalen-2-yl)-2-(2-(trifluoromethyl)phenyl)-2,3-dihydro-6H-1,2-oxazin-6-one (120j)

The general procedure **I** was followed with aldehyde **47j** (0.8 mmol, 2.0 eq, 157 mg). The chromatographic purification afforded **120j** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 81% (120 mg)

Melting Point: 138-140 °C.

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

δ = 8.01 – 7.78 (m, 6H, Ar*H*), 7.77 – 7.63 (m, 3H, Ar*H*), 7.61 – 7.45 (m, 3H, Ar*H*), 6.62 (s, 1H, C=C*H*), 4.41 (s, 2H, CH_2) ppm

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

δ = 165.9 (*C*=O), 154.5 (*C*=CH), 146.6 (C_{Ar}), 134.4 (C_{Ar}), 133.2 (C_{Ar}), 132.9 (C_{Ar}), 130.9 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.4 (C_{Ar}), 127.9 (C_{Ar}), 127.8 (C_{Ar}), 127.1 (C_{Ar}), 126.8 (q, *J* = 4.5 Hz, C_{Ar}), 126.6 (C_{Ar}), 125.8 (q, *J* = 30.0 Hz, C_{Ar}), 124.5 (C_{Ar}), 123.2 (q, *J* = 271.5 Hz, *C*F_3), 122.8 (C_{Ar}), 113.5 (C=*C*H), 57.1 (*C*H_2) ppm

IR (ATR): 2925, 2103, 1911, 1718, 1610, 1467, 1234, 1126, 764 cm^{-1}.

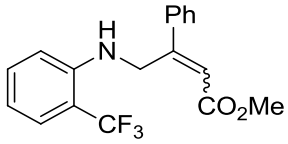
HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{14}NO_2F_3Na^+$: 392.0869; found 392.0865.

4.3.2 Synthesis of α,β-unsaturated γ-amino acid esters

4.3.2.1 General procedure II (GP II)

A 10 mL glass tube equipped with a stirring bar was charged with the compounds **120** (0.20 mmol, 1.0 equiv) and methanol (2.0 mL). To the resulting solution was added 3 drops perchloric acid and the reaction mixture was stired overnight . The solvent was removed in vacuo and the residue was diluted with CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL ×3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and then brine (10 mL), dried ($MgSO_4$), and concentrated. The pure product was obtained through flash silica gel column chromatography of the residue using hexane and ethyl acetate (4:1 to 2:1) as the eluents.

4.3.2.2 Analytical data of the synthesized compounds



121a

Methyl (*Z*)-3-phenyl-4-((2-(trifluoromethyl)phenyl)amino)but-2-enoate (121a)

The general procedure **II** was followed with **120a** (0.2 mmol, 1.0 eq, 64 mg). The chromatographic purification afforded **121a** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 2:1)

Yield: 81% (54mg)

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

δ = 7.52 (m, *J* = 6.6, 3.0 Hz, 2H, ArH), 7.49 – 7.40 (m, 4H, Ar*H*), 7.32 – 7.24 (m, 2H, Ar*H*), 7.13 (dd, *J* = 8.6, 2.8 Hz, 1H, Ar*H*), 6.54 (s, 1H, C=C*H*), 4.67 (s, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3) ppm

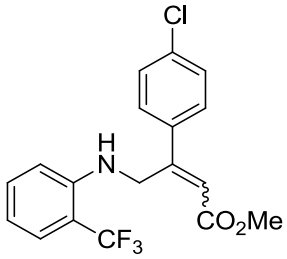
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 172.1 (CO_2CH_3), 159.3 (*C*=CH), 155.6 (C_{Ar}), 132.5 (C_{Ar}), 131.5 (C_{Ar}), 130.5 (C_{Ar}), 130.3 (C_{Ar}), 129.1 (2C, C_{Ar}), 128.5 (q, *J* = 1.5 Hz, C_{Ar}), 125.9 (2C, C_{Ar}), 123.1(q, *J* = 271.5 Hz, CF_3), 119.7 (C_{Ar}), 118.1 (C=*C*H), 113.1(q, *J* = 6.0 Hz, C_{Ar}), 56.4 (CH_2), 55.8 (CO_2CH_3) ppm

IR (ATR): 3072, 2924, 2853, 2078, 1692, 1611, 1504, 1448, 1328, 1241, 1116, 1031, 862, 762, 685 cm^{-1}.

MS (EI): *m/z* (%) = 335.2 (0.87) $[M]^+$, 302.2 (4.3) $[M\text{-}CH_3O]^+$.

Anal. Calcd for $C_{18}H_{16}NO_2F_3$: C, 64.47; H, 4.84; N, 4.18. Found: C, 64.39; H, 4.22; N, 4.12.



121d

Methyl (*Z*)-3-(4-chlorophenyl)-4-((2-(trifluoromethyl)phenyl)amino)but-2-enoate (121d)

The general procedure **II** was followed with **120d** (0.2 mmol, 1.0 eq, 71 mg). The chromatographic purification using hexane and ethyl acetate (4:1 to 2:1) afforded **121d** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 2:1).

Yield: 78% (58 mg).

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

δ = 7.49 – 7.46 (m, 1H, Ar*H*), 7.44 – 7.32 (m, 4H, Ar*H*), 7.30 – 7.25 (m, 2H, Ar*H*), 7.12 (dd, *J* = 8.4, 3.0 Hz, 1H, Ar*H*), 6.54 (s, 1H, C=C*H*), 4.64 (s, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3) ppm

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

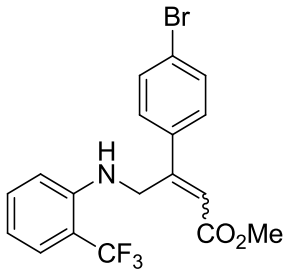
δ = 171.6 (CO_2CH_3), 159.4 (*C*=CH), 154.1 (C_{Ar}), 135.2 (C_{Ar}), 133.3 (C_{Ar}), 132.4 (C_{Ar}), 130.4 (2C, C_{Ar})), 130.1 (q, *J* = 45.0 Hz, C_{Ar}), 128.1 (q, *J* = 1.5 Hz, C_{Ar}), 125.9 (C_{Ar}),

124.0 (C_{Ar}), 123.1 (q, J = 273.0 Hz, CF_3), 120.9 (C_{Ar}), 118.1 (C=*C*H), 113.1(q, J = 4.5 Hz, C_{Ar}), 56.2 (CH_2), 55.8 (CO_2CH_3) ppm

IR (ATR):3079, 2926, 2852, 2068, 1693, 1616, 1506, 1430, 1314, 1236, 1129, 1037, 881, 788, 733, 677 cm^{-1}.

MS (EI): *m/z* (%) = 369.2 (40.34) $[M]^+$, 336.1 (6.11) $[M\text{-}CH_3O]^+$.

Anal. Calcd for $C_{18}H_{15}NO_2F_3Cl$: C, 58.47; H, 4.09; N, 3.798. Found: C, 58.28; H, 3.81; N, 3.66.



121f

Methyl (*Z*)-3-(4-bromophenyl)-4-((2-(trifluoromethyl)phenyl)amino)but-2-enoate (121f)

The general procedure **II** was followed with **120f** (0.2 mmol, 1.0 eq, 79 mg). The chromatographic purification afforded **121f** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 2:1).

Yield: 75% (62 mg)

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

δ = 7.57 (d, J = 9.0 Hz, 2H, Ar*H*), 7.41 – 7.36 (m, 3H, Ar*H*), 7.31 – 7.25 (m, 2H, Ar*H*), 7.12 (dd, J = 9.0, 3.0 Hz, 1H, Ar*H*), 6.54 – 6.53 (m, 1H, C=C*H*), 4.63 (d, J = 1.2 Hz, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3) ppm

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

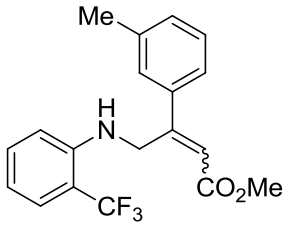
δ = 171.7 (CO_2CH_3), 159.4 (*C*=CH), 154.3 (C_{Ar}), 132.4 (C_{Ar}), 132.3 (2C, C_{Ar}), 130.5 (C_{Ar}), 130.4 (q, J = 31.5 Hz, C_{Ar}), 128.2 (q, J = 1.5 Hz, C_{Ar}), 127.3 (2C, C_{Ar}), 124.8 (C_{Ar}), 123.1 (q, J = 271.5 Hz, CF_3), 120.3 (C_{Ar}), 118.1 (C=*C*H), 113.1 (q, J = 6.0 Hz, C_{Ar}), 56.2 (CH_2), 55.8 (CO_2CH_3) ppm

IR (ATR): 3067, 2919, 2851, 2108, 1689, 1618, 1500, 1435, 1308, 1174, 1119, 1036,

1007, 976, 880, 755, 690 cm^{-1}.

MS (EI): *m/z* (%) = 413.1 (100.00) $[M]^+$, 380.1 (4.77) $[M\text{-}CH_3O]^+$.

Anal. Calcd for $C_{18}H_{15}NO_2F_3Br$: C, 52.19; H, 3.65; N, 3.38. Found: C, 52.83; H, 3.72; N, 3.10.



121h

Methyl (*Z*)-3-(m-tolyl)-4-((2-(trifluoromethyl)phenyl)amino)but-2-enoate (121h)

The general procedure was followed with **120h** (0.2 mmol, 1.0 eq, 67 mg). The chromatographic purification using afforded **121h** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 2:1).

Yield: 82% (57 mg).

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

δ = 7.35 – 7.23 (m, 7H, Ar*H*), 7.13 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H*), 6.51 (s, 1H, C=C*H*), 4.66 (s, 2H, CH_2), 3.86 (s, 3H, CO_2CH_3), 2.39 (s, 3H, ArCH_3)ppm

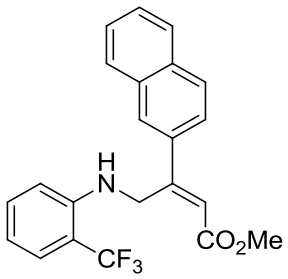
^{13}C NMR (150 MHz, $CDCl_3$)

δ = 172.2 (CO_2CH_3), 159.3 (*C*=CH), 155.9 (C_{Ar}), 138.8 (C_{Ar}), 132.5 (C_{Ar}), 131.5 (C_{Ar}), 131.3 (C_{Ar}), 130.4 (q, *J* = 31.5 Hz, C_{Ar}), 129.0 (C_{Ar}), 128.5 (q, *J* = 1.5 Hz, (C_{Ar}), 126.5 (C_{Ar}), 123.1 (q, *J* = 273.0 Hz, CF_3), 123.0 (C_{Ar}), 119.5 (C_{Ar}), 118.1 (C=*C*H), 113.1 (q, *J* = 4.5 Hz, C_{Ar}), 56.5 (CH_2), 55.8 (CO_2CH_3), 21.4 ppm

IR (ATR): 3086, 2924, 2854, 2037, 1684, 1611, 1504, 1424, 1324, 1238, 1171, 1120, 1034, 858, 796, 734, 683 cm^{-1}.

MS (CI): *m/z* (%) = 339.1 (0.58) $[M]^+$, 160.1 (2.08) $[M\text{-}C_{12}H_{13}O_2]^+$.

Anal. Calcd for $C_{19}H_{18}F_3NO_2F_3$: C, 65.32; H, 5.19; N, 4.01. Found: C, 64.02; H, 4.75; N, 3.90.



121j

Methyl (*Z*)-3-(naphthalen-2-yl)-4-((2-(trifluoromethyl)phenyl)amino)but-2–enoate (121j)

The general procedure **II** was followed with aldehyde **120j** (0.2 mmol, 1.0 eq, 74 mg). The chromatographic purification afforded **121j** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 2:1).

Yield: 79% (61 mg)

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

δ = 7.92 – 7.82 (m, 5H, Ar*H*), 7.66 (dd, *J* = 8.4, 1.2 Hz, 1H, Ar*H*), 7.56 – 7.51 (m, 2H, Ar*H*), 7.33 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.29 (d, *J* = 3.0 Hz, 1H, Ar*H*), 7.14 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H*), 6.65 (s, 1H, C=C*H*), 4.80 (s, 2H, CH_2), 3.87 (s, 3H, CO_2CH_3) ppm

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

δ = 172.1 (CO_2CH_3), 159.3 (*C*=CH), 155.5 (C_{Ar}), 134.1 (C_{Ar}), 133.1 (C_{Ar}), 132.5 (C_{Ar}), 130.5 (q, *J* = 31.5 Hz, C_{Ar}), 128.9 (C_{Ar}), 128.9 (C_{Ar}), 128.5 (C_{Ar}), 128.5 (q, *J* = 1.5 Hz, C_{Ar}), 127.8 (C_{Ar}), 127.4 (C_{Ar}), 127.0 (C_{Ar}), 125.4 (C_{Ar}), 123.2 (q, *J* = 271.5 Hz, CF_3), 123.2 (C_{Ar}), 120.0 (C_{Ar}), 118.1 (C=*C*H), 113.1(q, *J* = 4.5 Hz, C_{Ar}), 56.5 (CH_2), 55.8 (CO_2CH_3) ppm

IR (ATR): 3060, 2925, 2854, 2105, 1688, 1614, 1506, 1432, 1382, 1313, 1236, 1128, 1037, 976, 853, 816, 731, 672 cm^{-1}.

MS (EI): *m/z* (%) = 385.0 (1.39) $[M]^+$, 352.2 (0.74) $[M\text{-}CH_3O]^+$.

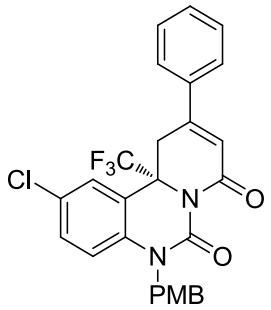
Anal. Calcd for $C_{22}H_{18}NO_2F_3$: C, 68.57; H, 4.71; N, 3.63. Found: C, 68.53; H, 5.07; N, 3.43.

4.3.3 Synthesis of dihydroquinazolinone derivatives

4.3.3.1 General procedure III (GP III)

A 10 mL glass tube equipped with a stirring bar was charged with aldehyde **47** (0.4 mmol, 2.0 equiv.), oxidant (0.3 mmol, 1.5 equiv., 124 mg), the substrate **122** (0.2 mmol, 1.0 equiv.), CsOAc (0.3 mmol, 1.5 equiv., 58 mg), 4Å MS (100 mg), **C14** (0.04 mmol, 20 mol%, 19 mg) and anhydrous THF (2.0 mL). The resulting solution was flushed with argon and stirred at room temperature for 24 h and was directly purified by flash chromatography using *n*-hexane and ethyl acetate as the eluent to provide the desired product **123**.

4.3.3.2 Analytical data of the synthesized compounds



123a

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-phenyl-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123a)

Prepared according to the general procedure **III** by using **47a** (58 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (18.6 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123a** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 75% (77mg).

Melting Point: 159-161 ^{o}C.

$[\alpha]_D^{25}$ = -14.8 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 12.85 min (minor), 17.13 min (major).

er: 96.5:3.5.

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

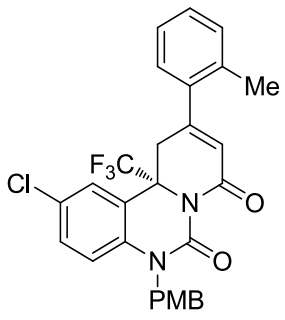
δ = 7.59 – 7.55 (m, 2H, Ar*H*), 7.52 – 7.47 (m, 3H, Ar*H*), 7.38 (d, *J* = 2.4 Hz, 1H, Ar*H*), 7.30 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar*H*), 7.26 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.86 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.51 (d, *J* = 3.0 Hz, 1H, C=C*H*), 5.33 (d, *J* = 10.2 Hz, 1H, C*H*HNC=O), 5.00 (d, *J* = 10.2 Hz, 1H, CH*H*NC=O), 3.82 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.78 (s, 3H, OCH_3), 3.42 (dd, *J* = 18.0, 1.8 Hz, 1H, CH*H*C=CH) ppm

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

δ = 162.1 (C=CH*C*=O), 159.1 (C_{Ar}), 148.3 (*C*=CHC=O), 145.6 (N*C*=ON), 136.5 (C_{Ar}), 135.7 (C_{Ar}), 130.9 (C_{Ar}), 130.7 (C_{Ar}), 129.2 (2C, C_{Ar}), 128.8 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.6 (C_{Ar}), 126.1 (C_{Ar}), 126.0 (2C, C_{Ar}), 124.1 (C_{Ar}), 122.7 (C_{Ar}), 119.7 (q, *J* = 3.0 Hz, *C*F_3), 117.0 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3*C*), 55.3 (*C*H_3O), 47.8 (*C*H_2N), 32.9 (*C*H_2C=CH) ppm

IR (ATR): 2962, 2263, 1729, 1597, 1505, 1434, 1371, 1310, 1203, 1112, 1024, 911, 858, 809, 731 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{20}N_2O_3F_3ClNa^+$: 535.1007; found 535.0990.



123b

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(o-tolyl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123b)

Prepared according to the general procedure **III** by using **47b** (64 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h

at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123b** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 60% (63mg).

$[\alpha]_D^{25}$= -19.1 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^oC, retention time: 10.91 min (minor), 11.86 min (major).

er: 96.5:3.5.

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

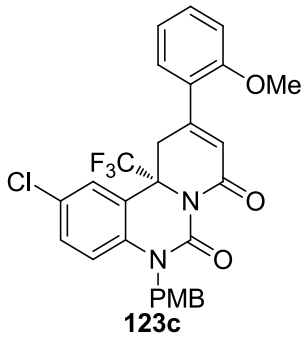
δ = 7.33 – 7.25 (m, 7H, Ar*H*), 7.18 (d, *J* = 7.2 Hz, 1H, Ar*H*), 6.96 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.86 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.18 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.34 (d, *J* = 15.6 Hz, 1H, C*H*HNC=O), 4.99 (d, *J* = 15.6 Hz, 1H, CH*H*NC=O), 3.78 (s, 3H, OCH_3), 3.56 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.44 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH), 2.39 (s, 3H, ArCH_3) ppm

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

δ = 161.8 (C=CH*C*=O), 159.1 (C_{Ar}), 148.5 (*C*=CHC=O), 147.8 (N*C*=ON), 137.1 (C_{Ar}), 136.4 (C_{Ar}), 134.8 (C_{Ar}), 131.2 (C_{Ar}), 130.9 (C_{Ar}), 129.4 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (2C, C_{Ar}), 127.6 (C_{Ar}), 127.3 (C_{Ar}), 126.4 (C_{Ar}), 126.2 (C_{Ar}), 124.2 (C_{Ar}), 123.2 (q, *J* = 4.5 Hz, *C*F_3), 122.7 (C_{Ar}), 116.7 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3*C*), 55.3 (*C*H_3O), 47.8 (*C*H_2N), 35.5 (*C*H_2C=CH), 20.0 (Ar*C*H_3) ppm

IR (ATR): 2927, 2254, 1733, 1608, 1500, 1437, 1368, 1253, 1176, 1026, 908, 818, 730 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_3F_3ClNa^+$: 549.1163; found 549.1162.



123c

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(2-methoxyphenyl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123c)

Prepared according to the general procedure **III** by using **47c** (70 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **3c** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 74% (80mg).

Melting Point: 144-146 ^{o}C.

$[\alpha]_D^{25}$= -10.6 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 14.52 min (minor), 16.32 min (major).

er: 87:13.

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

δ = 7.45 – 7.40 (m, 1H, Ar*H*), 7.30 – 7.24 (m, 5H, Ar*H*), 7.04 – 6.92 (m, 3H, Ar*H*), 6.86 (dd, *J* = 8.4 1.8 Hz, 2H, Ar*H*), 6.29 (s, 1H, C=C*H*), 5.33 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.98 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.97 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.90 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.36 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH) ppm

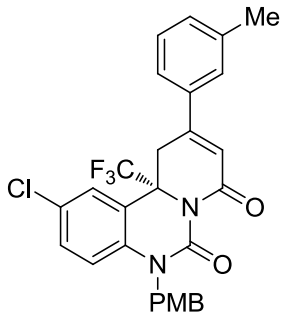
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 162.2 (C=CH*C*=O), 159.0 (C_{Ar}), 157.0 (C_{Ar}), 148.6(*C*=CHC=O), 147.4 (N*C*=ON), 136.6 (C_{Ar}), 131.5 (C_{Ar}), 130.7 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (2C, C_{Ar}), 127.7 (C_{Ar}), 126.3 (C_{Ar}), 126.1 (C_{Ar}), 124.2 (C_{Ar}), 123.1 (CF_3), 122.1 (C_{Ar}), 121.2 (C_{Ar}),

116.9 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 111.3 (C_{Ar}), 62.5 (*J* = 28.5 Hz, CF_3C), 55.6 (CH_3O), 55.3 (CH_3O), 47.8 (CH_2N), 33.8 (CH_2C=CH) ppm

IR (ATR): 2923, 2291, 1725, 1651, 1586, 1500, 1367, 1301, 1252, 1171, 1020, 919, 821, 749 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_4F_3ClNa^+$: 565.1112; found 565.1098.



123d

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(m-tolyl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123d)

Prepared according to the general **III** procedure by using **47d** (64 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123d** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 85% (89mg).

Melting Point: 153-155 ^oC.

$[\alpha]_D^{25}$ = -23.2 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC; *n*-heptane/iPrOH = 7/3; flow rate 0.7 mL/min; T= 30 ^oC; retention time: 13.11 min (minor), 15.76 min (major).

er: 98.5:1.5.

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

δ = 7.40 –7.35 (m, 4H, Ar*H*), 7.33 – 7.23 (m, 4H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.86 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.49 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.32 (d, *J* = 16.2 Hz,

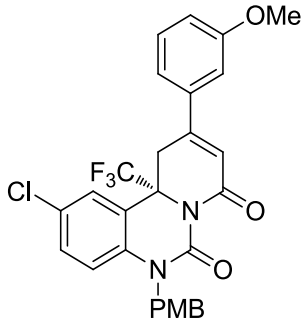
1H, C*H*HNC=O), 5.00 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.81 (d, *J* = 17.4 Hz, 1H, C*H*HC=CH), 3.77 (s, 3H, OCH_3), 3.40 (d, *J* = 17.4 Hz, 1H, CH*H*C=CH), 2.44 (s, 3H, ArCH_3) ppm

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

δ = 162.2 (C=CH*C*=O), 159.1 (C_{Ar}), 148.5(*C*=CHC=O), 145.8 (N*C*=ON), 139.0 (C_{Ar}), 136.5 (C_{Ar}), 135.7 (C_{Ar}), 131.5 (C_{Ar}), 130.9 (C_{Ar}), 129.1 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.6 (C_{Ar}), 126.6 (C_{Ar}), 126.2 (C_{Ar}), 126.0 (C_{Ar}), 123.2 (*C*F_3), 122.7 (C_{Ar}), 119.5 (C_{Ar}), 117.0 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 30.0 Hz, CF_3*C*), 55.3 (*C*H_3O), 47.8 (*C*H_2N), 32.8 (*C*H_2C=CH), 21.5 (Ar*C*H_3) ppm

IR (ATR): 2924, 2292, 1727, 1651, 1595, 1502, 1430, 1367, 1301, 1254, 1173, 1028, 910, 865, 790, 740, 690 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_3F_3ClNa^+$: 549.1163; found 549.1168.



123e

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(3-methoxyphenyl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123e)

Prepared according to the general procedure **III** by using **47e** (70 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123e** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 76% (82mg).

Melting Point: 180-182 ^{o}C.

$[\alpha]_D^{25}$ = -14.1 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 °C, retention time: 14.98 min (minor), 18.65 min (major).

er: 95.5:4.5.

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

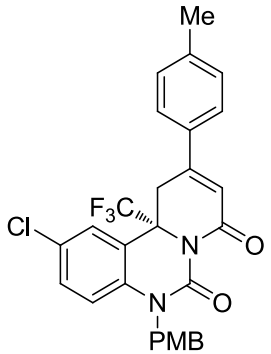
δ= 7.43 – 7.36 (m, 2H, Ar*H*), 7.31 – 7.25 (m, 3H, Ar*H*), 7.16 – 7.13 (m, 1H, Ar*H*), 7.08 – 7.01 (m, 2H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.86 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.50 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.31 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.99 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.87 (s, 3H, OCH_3), 3.82 – 3.76 (m, 4H, C*H*HC=CH, OCH_3), 3.40 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH) ppm

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

δ = 162.1 (C=CH*C*=O), 160.1 (C_{Ar}), 159.1 (C_{Ar}), 148.4 (*C*=CHC=O), 145.5 (N*C*=ON), 137.1 (C_{Ar}), 136.5 (C_{Ar}), 130.9 (C_{Ar}), 130.3 (C_{Ar}), 128.8 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.6 (C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 124.1 (C_{Ar}), 122.7 (*C*F_3), 119.8 (C_{Ar}), 118.4 (C_{Ar}), 117.0 (C=*C*HC=O), 115.9 (C_{Ar}), 114.3 (2C, C_{Ar}), 111.9 (C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3*C*), 55.5 (*C*H_3O), 47.8 (*C*H_2N), 32.9 (*C*H_2C=CH) ppm

IR (ATR): 2933, 2290, 1728, 1656, 1594, 1501, 1431, 1368, 1302, 1256, 1178, 1027, 905, 846, 796, 741, 691 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_4F_3ClNa^+$: 565.1112; found 565.1102.



123f

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(p-tolyl)-11a-(trifluoromethyl)-11,11a-dihy

dro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123f)

Prepared according to the general procedure **III** by using **47f** (64 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123f** as a yellow solid. (68.4 mg, 65% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 65% (68mg).

Melting Point: 188-190 ^{o}C.

$[\alpha]_D^{25}$= -29.0 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 13.97 min (minor), 20.01 min (major).

er: 97:3.

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

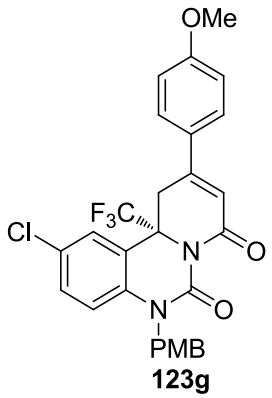
δ = 7.48 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.41 – 7.37 (m, 1H, Ar*H*), 7.32 – 7.23 (m, 5H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.85 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.49 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.31 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.99 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.85 – 3.74 (m, 4H, C*H*HC=CH, OCH_3), 3.39 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH), 2.41 (s, 3H, ArCH_3) ppm

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

δ = 162.3 (C=CH*C*=O), 159.1 (C_{Ar}), 148.5 (*C*=CHC=O), 145.5 (N*C*=ON), 141.3 (C_{Ar}), 136.5 (C_{Ar}), 132.7 (C_{Ar}), 130.9 (C_{Ar}), 129.9 (2C, C_{Ar}), 128.7 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.6 (C_{Ar}), 126.2 (C_{Ar}), 125.9 (2C, C_{Ar}), 124.1 (C_{Ar}), 122.8 (*C*F_3), 118.7 (C_{Ar}), 117.0 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3*C*), 55.3 (*C*H_3O), 47.7 (*C*H_2N), 32.7 (*C*H_2C=CH), 21.4 (Ar*C*H_3) ppm

IR (ATR): 2945, 2259, 1731, 1653, 1595, 1506, 1426, 1368, 1184, 1023, 914, 814, 735 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_3F_3ClNa^+$: 549.1163; found 549.1163.



123g

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(4-methoxyphenyl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123g)

Prepared according to the general procedure **III** by using **47g** (70 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123g** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 64% (69 mg).

Melting Point: 230-232 ^{o}C.

$[\alpha]_D^{25}$= -18.7 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 17.76 min (minor), 24.45 min (major).

er: 96:4.

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

δ = 7.54 (d, *J* = 8.8 Hz, 2H, Ar*H*), 7.41 – 7.36 (m, 1H, Ar*H*), 7.31 – 7.23 (m, 3H, Ar*H*), 6.97 (dd, *J* = 25.5, 8.8 Hz, 3H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.44 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.30 (d, *J* = 16.1 Hz, 1H, C*H*HNC=O), 4.99 (d, *J* = 16.1 Hz, 1H, CH*H*NC=O), 3.92 – 3.73 (m, 7H, , C*H*HC=CH, OCH_3, OCH_3), 3.36 (d, *J* = 17.6 Hz, 1H, CH*H*C=CH) ppm

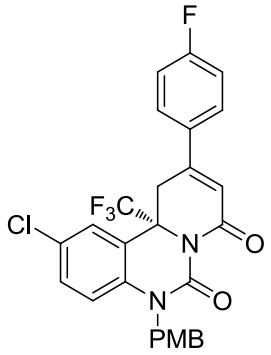
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 162.4 (C=CH*C*=O), 161.8 (C_{Ar}), 159.0 (C_{Ar}), 148.5 (*C*=CHC=O), 145.1 (N*C*=ON), 136.5 (C_{Ar}), 130.9 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.6

(2C, C_{Ar}), 126.1 (C_{Ar}), 124.1 (C_{Ar}), 122.8 (CF_3), 117.5 (C_{Ar}), 117.0 (C=*C*HC=O), 114.6 (2C, C_{Ar}), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3C), 55.5 (CH_3O), 55.3 (CH_3O), 47.7 (CH_2N), 32.6 (CH_2C=CH) ppm

IR (ATR): 2927, 2288, 1732, 1669, 1599, 1506, 1425, 1370, 1227, 1173, 1067, 1018, 884, 816, 738 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{28}H_{22}N_2O_4F_3ClNa^+$: 565.1112; found 565.1087.



123h

(*R*)-2-Chloro-10-(4-fluorophenyl)-5-(4-methoxybenzyl)-11a-(trifluoromethyl)-11, 11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123h)

Prepared according to the general procedure **III** by using **47h** (66 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123h** as a yellow wax.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 67% (71 mg).

$[\alpha]_D^{25}$ = -12.9 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^oC, retention time: 11.70 min (minor), 16.05 min (major).

er: 94.5:5.5.

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

δ = 7.58 – 7.52 (m, 2H, Ar*H*), 7.37 – 7.13 (m, 6H, Ar*H*), 6.95 (d, *J* = 8.8 Hz, 1H, Ar*H*),

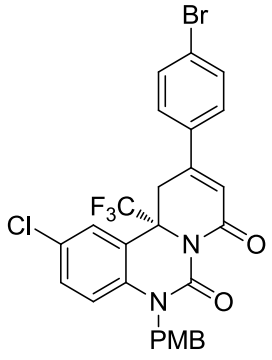
6.84 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.45 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.30 (d, *J* = 16.0 Hz, 1H, C*H*HNC=O), 4.97 (d, *J* = 16.0 Hz, 1H, CH*H*NC=O), 3.83 – 3.67 (m, 4H, C*H*HC=CH, OCH_3), 3.39 (d, *J* = 18.4 Hz, 1H, CH*H*C=CH) ppm

^{13}C NMR (100 MHz, $CDCl_3$):

δ = 161.9 (C=CH*C*=O), 159.1 (C_{Ar}), 148.3 (*C*=CHC=O), 144.4 (N*C*=ON), 136.5 (C_{Ar}), 131.8 (C_{Ar}), 131.0 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (2C, C_{Ar}), 128.1 (C_{Ar}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 126.1 (C_{Ar}), 122.5 (C_{Ar}), 124.2 (C_{Ar}), 123.6 (*C*F_3), 119.5 (C_{Ar}), 117.0 (C=*C*HC=O), 116.5 (C_{Ar}), 116.3 (C_{Ar}), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.0 Hz, CF_3*C*), 55.2 (*C*H_3O), 47.8 (*C*H_2N), 32.9 (*C*H_2C=CH) ppm

IR (ATR): 2923, 2257, 1721, 1600, 1507, 1427, 1373, 1215, 1171, 1068, 1022, 908, 828, 730 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{19}N_2O_3F_4ClNa^+$: 553.0913; found 553.0887.



123i

(*R*)-10-(4-Bromophenyl)-2-chloro-5-(4-methoxybenzyl)-11a-(trifluoromethyl)-11, 11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123i)

Prepared according to the general procedure **III** by using **47i** (89 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123i** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 65% (77 mg).

Melting Point: 212-214 °C.

$[\alpha]_D^{25}$= -28.5 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 °C, retention time: 12.91 min (minor), 17.88 min (major).

er: 97:3.

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

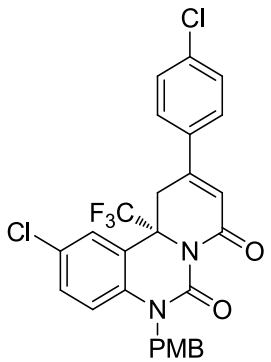
δ = 7.62 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.44 (d, *J* = 8.4 Hz, 2H, Ar*H*), 7.37 (d, *J* = 2.4 Hz, 1H, Ar*H*), 7.30 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H*), 7.27 – 7.23 (m, 2H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.85 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.49 (d, *J* = 3.0 Hz, 1H, C=C*H*), 5.31 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.99 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.76 - 3.78(m, 4H, C*H*HC=CH, OCH_3), 3.41 (d, *J* = 17.4 Hz, 1H, CH*H*C=CH) ppm

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

δ = 161.8 (C=CH*C*=O), 159.1 (C_{Ar}), 148.3 (*C*=CHC=O), 144.4 (N*C*=ON), 136.5 (C_{Ar}), 134.5 (C_{Ar}), 132.5 (2C, C_{Ar}), 131.0 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (2C, C_{Ar}), 127.5 (2C, C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 125.3 (C_{Ar}), 124.0 (C_{Ar}), 122.5 (*C*F_3), 120.0 (C_{Ar}), 117.1 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3*C*), 55.3 (*C*H_3O), 47.8 (*C*H_2N), 32.6 (*C*H_2C=CH) ppm

IR (ATR): 2933, 2291, 1730, 1591, 1502, 1425, 1369, 1178, 1072, 1011, 819, 743, 693 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{27}H_{19}N_2O_3F_3ClBrNa^+$: 613.0112; found 613.0095.



123j

(*R*)-2-Chloro-10-(4-chlorophenyl)-5-(4-methoxybenzyl)-11a-(trifluoromethyl)-11, 11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123j)

Prepared according to the general procedure **III** by using **47j** (61 mg, 0.4 mmol) , **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 ; 1) as the eluent afforded **123j** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 73% (80 mg).

Melting Point: 193-195 ^{o}C.

$\mathbf{[\alpha]_D^{25}}$ = -28.0 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC; *n*-heptane/iPrOH = 7/3; flow rate 0.7 mL/min; T= 30 ^{o}C; retention time: 12.16 min (minor), 16.88 min (major), e.r.: 96.5:3.5

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

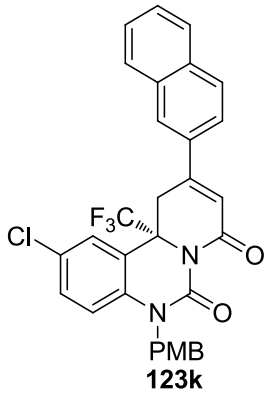
δ = 7.54 – 7.44 (m, 4H, Ar*H*), 7.36 (s, 1H, Ar*H*), 7.32 – 7.22 (m, 3H, Ar*H*), 6.96 (d, *J* = 9.0 Hz, 1H, Ar*H*), 6.86 (d, *J* = 7.8 Hz, 2H, Ar*H*), 6.49 (s, 1H, C=C*H*), 5.32 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.99 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.82 – 3.71 (m, 4H, C*H*HC=CH, OCH_3), 3.41 (d, *J* = 17.4 Hz, 1H, CH*H*C=CH) ppm

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

δ = 161.8 (C=CH*C*=O), 159.1 (C_{Ar}), 148.3 (*C*=CHC=O), 144.3 (N*C*=ON), 137.0 (C_{Ar}), 136.5 (C_{Ar}), 134.1 (C_{Ar}), 131.0 (C_{Ar}), 129.5 (2C, C_{Ar}), 128.8 (C_{Ar}), 128.2 (2C, C_{Ar}), 127.5 (C_{Ar}), 127.3 (2C, C_{Ar}), 126.1 (C_{Ar}), 124.0 (C_{Ar}), 122.5 (*C*F_3), 120.0 (C_{Ar}), 117.1 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3C), 55.3 (CH_3O), 47.8 (CH_2N), 32.7 (CH_2C=CH) ppm

IR (ATR): 2926, 2095, 1727, 1603, 1501, 1428, 1375, 1184, 1097, 1019, 817, 747 cm^{-1}.

MS (ESI): m/z = 569.1 $[M+Na]^+$.



123k

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(naphthalen-2-yl)-11a-(trifluoromethyl)-11 ,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123k)

Prepared according to the general procedure **III** by using **47k** (78 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123k** as a yellow solid. (78.7 mg, 70% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 70% (79 mg).

Melting Point: 209-211 ^{o}C.

$[\alpha]_D^{25}$= -65.0 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 15.78 min (minor), 20.65 min (major).

er: 98.5:1.5.

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

δ = 8.03 (s, 1H, Ar*H*), 7.97 – 7.90 (m, 2H, Ar*H*), 7.89 – 7.85 (m, 1H, Ar*H*), 7.66 (dd, *J* = 9.0, 1.2 Hz, 1H, Ar*H*), 7.59 – 7.55 (m, 2H, Ar*H*), 7.47 – 7.45 (d, *J* = 1.2 Hz, 1H, Ar*H*), 7.33 – 7.26 (m, 3H, Ar*H*), 6.98 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.87 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.65 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.33 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 5.01 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.96 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.78 (s, 3H, OCH_3), 3.47 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH) ppm

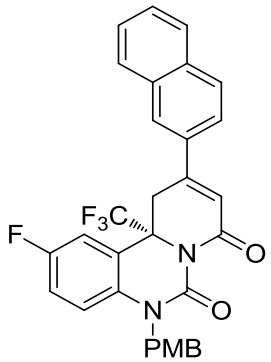
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 162.1 (C=CH*C*=O), 159.1 (C_{Ar}), 148.5 (*C*=CHC=O), 145.3 (N*C*=ON), 136.5 (C_{Ar}),

134.2 (C_{Ar}), 133.0 (C_{Ar}), 132.7 (C_{Ar}), 131.0 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.2 (C_{Ar}), 126.2 (C_{Ar}), 126.1 (C_{Ar}), 124.1 (C_{Ar}), 122.9 (CF_3), 122.7 (C_{Ar}), 119.8 (C_{Ar}), 117.0 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.5 (q, J = 28.5 Hz, CF_3C), 55.3 (CH_3O), 47.8 (CH_2N), 32.6 (CH_2C=CH) ppm

IR (ATR): 2944, 2288, 1743, 1602, 1504, 1217, 1023, 910, 861, 810, 736 cm^{-1}.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{31}H_{22}N_2O_3F_3ClNa^+$: 585.1163; found 585.1148.



123l

(*R*)-2-Fluoro-5-(4-methoxybenzyl)-10-(naphthalen-2-yl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123l)

Prepared according to the general procedure **III** by using **47l** (78 mg, 0.4 mmol), **122b** (70 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 ; 1) as the eluent afforded **123l** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 70% (76 mg).

Melting Point: 198-200 ^oC.

$[\alpha]_D^{25}$= -59.6 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC; *n*-heptane/iPrOH = 7/3; flow rate 0.7 mL/min; T= 30 ^oC; retention time: 15.99 min (minor), 19.88 min (major), e.r.: 93.5:6.5.

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

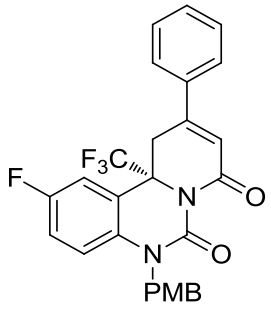
δ = 8.04 – 8.00 (m, 1H, Ar*H*), 7.96 – 7.93 (m, 2H, Ar*H*), 7.81 – 7.91 (m, 1H, Ar*H*), 7.67 (dd, *J* = 9.0, 1.8 Hz, 1H, Ar*H*), 7.61 – 7.56 (m, 2H, Ar*H*), 7.29 (d, *J* = 9.0 Hz, 2H, Ar*H*), 7.23 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar*H*), 7.10 – 7.05 (m, 1H, Ar*H*), 7.01 (dd, *J* = 9.0, 4.2 Hz, 1H, Ar*H*), 6.88 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.67 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.38 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.97 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.95 (d, *J* = 17.4 Hz, 1H, C*H*HC=CH), 3.79 (s, 3H, OCH_3), 3.52 (d, *J* = 17.4 Hz, 1H, CH*H*C=CH) ppm

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

δ = 162.2 (C=CH*C*=O), 159.3 (C_{Ar}), 159.1 (C_{Ar}), 157.6 (C_{Ar}), 148.5 (*C*=CHC=O), 145.1 (N*C*=ON), 134.3 (C_{Ar}), 134.2 (C_{Ar}), 133.0 (C_{Ar}), 132.8 (C_{Ar}), 129.2 (C_{Ar}), 128.7 (C_{Ar}), 128.3 (2C, C_{Ar}), 127.8 (C_{Ar}), 127. (C_{Ar}), 127.7 (C_{Ar}), 126.1 (C_{Ar}), 126.0 (C_{Ar}), 124.2 (*C*F_3), 122.8 (C_{Ar}), 120.0 (C=*C*HC=O), 117.8 (d, *J* = 21.0 Hz, C_{Ar}), 117.2 (d, *J* = 7.5 Hz, C_{Ar}), 114.3 (2C, C_{Ar}), 113.4 (d, *J* = 25.5 Hz, C_{Ar}), 62.4 (d, *J* = 28.5 Hz, CF_3*C*), 55.3 (*C*H_3O), 48.0 (*C*H_2N), 32.7 (*C*H_2C=CH) ppm

IR (ATR): 2957, 2228, 1723, 1508, 1447, 1375, 1190, 1018, 903, 821, 732 cm^{-1}.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{31}H_{23}N_2O_3F_4^+$: 547.1639; found 547.1625.



123m

(*R*)-2-Fluoro-5-(4-methoxybenzyl)-10-phenyl-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (3m)

Prepared according to the above general procedure **III** by using **47a** (59 mg, 0.4 mmol), **122b** (70 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123m** as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 78% (77mg).

Melting Point: 116-118 ^{o}C.

$[\alpha]_D^{25}$ = -13.5 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 14.40 min (minor), 19.68 min (major).

er: 97.5:2.5.

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

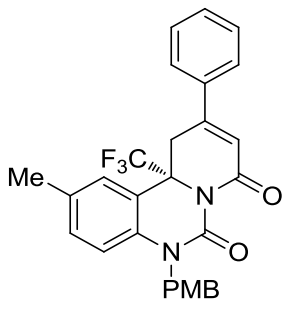
δ = 7.59 – 7.51 (m, 2H, Ar*H*), 7.52 – 7.46 (m, 3H, Ar*H*), 7.30 – 7.25 (m, 2H, Ar*H*), 7.15 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar*H*), 7.08 – 6.96 (m, 2H, Ar*H*), 6.86 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.50 (d, *J* = 2.4 Hz, 1H, C=C*H*), 5.35 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.95 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.83 – 3.75 (m, 4H, C*H*HC=CH, OCH_3), 3.42 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH) ppm

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

δ = 162.2 (C=CH*C*=O), 159.2 (C_{Ar}), 159.0 (C_{Ar}), 157.6 (C_{Ar}), 148.5 (*C*=CHC=O), 145.5 (N*C*=ON), 135.7 (C_{Ar}), 134.3 (C_{Ar}), 130.7 (C_{Ar}), 129.2 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 127.8 (C_{Ar}), 126.0 (2C, C_{Ar}), 124.1 (*C*F_3), 119.7 (C=*C*HC=O), 117.8 (d, *J* = 21.0 Hz, C_{Ar}), 117.2 (d, *J* = 7.5 Hz, C_{Ar}), 114.3 (2C, C_{Ar}), 113.4 (d, *J* = 25.5 Hz, C_{Ar}), 62.4 (q, *J* = 28.5 Hz, CF_3*C*), 55.3 (*C*H_3O), 48.0 (*C*H_2N), 32.8 (*C*H_2C=CH) ppm

IR (ATR): 2936, 2288, 1722, 1662, 1612, 1512, 1441, 1377, 1256, 1184, 1021, 911, 858, 810, 731 cm^{-1}.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{21}N_2O_3F_4^+$: 497.1482; found 497.1463.



123n

(*R*)-5-(4-Methoxybenzyl)-2-methyl-10-phenyl-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123n)

Prepared according to the general procedure **III** by using **47a** (59 mg, 0.4 mmol), **122c** (70 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123n** as a yellow wax. (73.8 mg, 75% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 75% (74 mg).

$[\alpha]_D^{25}$ = -18.2 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^oC, retention time: 12.55 min (minor), 16.54 min (major).

er: 97:3.

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

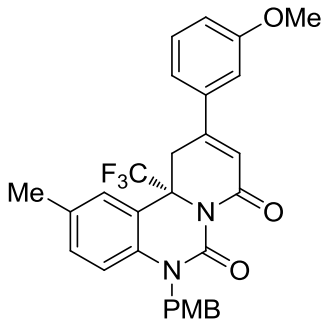
δ = 7.61 – 7.41 (m, 5H, Ar*H*), 7.31 – 7.10 (m, 4H, Ar*H*), 6.94 – 6.79 (m, 3H, Ar*H*), 6.49 (s, 1H, C=C*H*), 5.32 (d, *J* = 15.6 Hz, 1H, C*H*HNC=O), 4.98 (d, *J* = 15.6 Hz, 1H, CH*H*NC=O), 3.86 (d, *J* = 17.4 Hz, 1H, C*H*HC=CH), 3.76 (s, 3H, OCH_3), 3.42 (d, *J* = 17.4 Hz, 1H, CH*H*C=CH), 2.34 (s, 3H, ArCH_3) ppm

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

δ = 162.5 (C=CH*C*=O), 158.9 (C_{Ar}), 148.8 (*C*=CHC=O), 145.7 (N*C*=ON), 136.0 (C_{Ar}), 135.4 (C_{Ar}), 133.2 (C_{Ar}), 131.5 (C_{Ar}), 130.6 (C_{Ar}), 129.2 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 128.3 (C_{Ar}), 126.4 (C_{Ar}), 126.0 (2C, C_{Ar}), 124.4 (C_{Ar}), 121.2 (CF_3), 119.8 (C_{Ar}), 115.6 (C=*C*HC=O), 114.2 (2C, C_{Ar}), 62.6 (q, *J* = 28.5 Hz, CF_3C), 55.3 (CH_3O), 47.7 (CH_2N), 33.0 (CH_2C=CH), 20.8 (ArCH_3) ppm

IR (ATR): 2930, 2244, 1724, 1662, 1612, 1508, 1442, 1380, 1311, 1235, 1175, 1028, 902, 863, 817, 728 cm^{-1}.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{24}N_2O_3F_3^+$: 493.1734; found 493.1713.



123o

(*R*)-5-(4-Methoxybenzyl)-10-(3-methoxyphenyl)-2-methyl-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123o)

Prepared according to the general procedure **III** by using **47e** (70 mg, 0.4 mmol), **122c** (70 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123o** as a yellow solid. (75.2 mg, 72% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 72% (75 mg).

Melting Point: 205-207 ^{o}C.

$[\alpha]_D^{25}$= -20.2 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^{o}C, retention time: 16.75 min (minor), 21.70 min (major).

er: 97:3.

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

δ = 7.40 (t, *J* = 8.4 Hz, 1H, Ar*H*), 7.29 – 7.25 (m, 2H, Ar*H*), 7.20 – 7.11 (m, 3H, Ar*H*), 7.09 – 7.06 (m, 1H, Ar*H*), 7.01 (dd, *J* = 8.2, 2.4 Hz, 1H, Ar*H*), 6.91 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.85 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.49 (d, *J* = 3.0 Hz, 1H, C=C*H*), 5.32 (d, *J* = 16.2 Hz, 1H, C*H*HNC=O), 4.98 (d, *J* = 16.2 Hz, 1H, CH*H*NC=O), 3.87 (s, 3H, OCH_3), 3.83 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.77 (s, 3H, OCH_3), 3.40 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH), 2.34 (s, 3H, ArCH_3) ppm

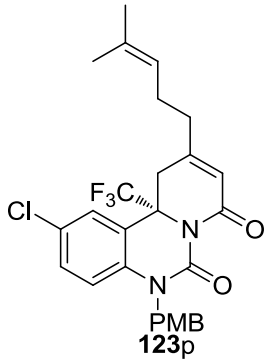
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 162.5 (C=CH*C*=O), 160.0 (C_{Ar}), 158.9 (C_{Ar}), 148.8 (*C*=CHC=O), 145.5 (N*C*=ON), 137.4 (C_{Ar}), 135.4 (C_{Ar}), 133.2 (C_{Ar}), 131.5 (C_{Ar}), 130.2 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.3

(C_{Ar}), 126.4 (C_{Ar}), 124.3 (C_{Ar}), 121.1 (C_{Ar}), 119.9 (q, *J* = 6.0 Hz, *C*F_3), 118.4 (C=*C*HC=O), 115.6 (2C, C_{Ar}), 114.2 (2C, C_{Ar}), 112.0 (C_{Ar}), 62.5 (q, *J* = 28.5 Hz, CF_3*C*), 55.5 (*C*H_3O), 55.2 (*C*H_3O), 47.7 (*C*H_2N), 33.0 (*C*H_2C=CH), 20.8 (Ar*C*H_3) ppm

IR (ATR): 2926, 2325, 1730, 1666, 1606, 1511, 1439, 1375, 1257, 1173, 1034, 956, 863, 814, 736, 691 cm^{-1}.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{26}N_2O_4F_3^+$: 523.1839; found 523.1816.



123p

(*R*)-2-Chloro-5-(4-methoxybenzyl)-10-(4-methylpent-3-en-1-yl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123p)

Prepared according to the general procedure **III** by using **47l** (61 mg, 0.4 mmol), **122a** (74 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123p** as a yellow wax. (45.6 mg, 44% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 44% (46 mg).

$[\alpha]_D^{25}$= +26.4 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC, *n*-heptane/iPrOH = 7/3, flow rate 0.7 mL/min, T= 30 ^oC, retention time: 10.24 min (minor), 11.70 min (major).

er: 90:10.

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

δ = 7.28 – 7.21 (m, 4H, Ar*H*), 6.92 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.85 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.01 (s, 1H, C=C*H*), 5.29 (d, *J* = 16.2 Hz, 1H, CC*H*HNC=O), 5.08 (t, *J* = 6.0

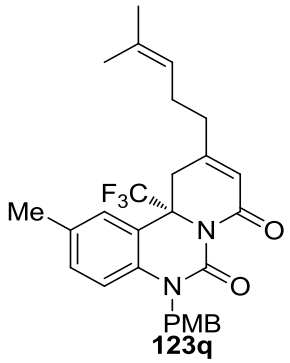
Hz, 1H, $(CH_3)_2C=CH$), 4.95 (d, *J* = 16.2 Hz, 1H, CCH*H*NC=O), 3.77 (s, 3H, OCH_3), 3.23 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.03 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH), 2.35 – 2.22 (m, 4H, C=CHCH_2CH_2), 1.70 (s, 3H, $(CH_3)_2C=CH$)), 1.64 (s, 3H, $(CH_3)_2C=CH$)) ppm

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

δ = 161.8 (C=CH*C*=O), 159.0 (C_{Ar}), 150.2 (*C*=CHC=O), 148.6 (N*C*=ON), 136.5 (C_{Ar}), 133.7 (C_{Ar}), 130.8 ($(CH_3)_2C$=CH), 128.6 (C_{Ar}), 128.2 (2C, C_{Ar}), 127.7 (C_{Ar}), 126.1 (C_{Ar}), 124.1 ($(CH_3)_2C=CH$), 122.9 (CF_3), 121.9 (C_{Ar}), 120.1 (C_{Ar}), 116.9 (C=*C*HC=O), 114.3 (2C, C_{Ar}), 62.2 (q, *J* = 28.5 Hz, CF_3C), 55.3 (CH_3O), 47.7 (CH_2N), 36.2 (CCH_2C=CH), 34.3 ($(CH_3)_2C=CHCH_2CH_2$), 25.7($(CH_3)_2C=CHCH_2CH_2$), 24.9($(CH_3)_2C$=CH), 17.9 ($(CH_3)_2C$=CH) ppm

IR (ATR): 2926, 2253, 1733, 1676, 1603, 1503, 1428, 1369, 1303, 1254, 1216, 1172, 1116, 1028, 908, 815, 733 cm^{-1}.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_3F_3Cl^+$: 519.1657; found 519.1634.



123q

(*R*)-5-(4-Methoxybenzyl)-2-methyl-10-(4-methylpent-3-en-1-yl)-11a-(trifluoromethyl)-11,11a-dihydro-6H-pyrido[1,2-c]quinazoline-6,8(5H)-dione (123q)

Prepared according to the general procedure **III** by using **47l** (61 mg, 0.4 mmol), **122b** (70 mg, 0.2 mmol) and pre-catalyst **C14** (19 mg, 0.04 mmol) in THF (2.0 mL) for 24 h at room temperature. The chromatographic purification using *n*-hexane and ethyl acetate (4 : 1) as the eluent afforded **123q** as a yellow wax. (41.8 mg, 42% yield).

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 42% (42 mg).

$[\alpha]_D^{25}$= +21.2 (c = 1.0, $CHCl_2$).

HPLC: CHIRALPAK IC; *n*-heptane/iPrOH = 7/3; flow rate 0.7 mL/min; T= 30 ^oC; retention time: 11.86 min (minor), 13.84 min (major),.

er: 88:12.

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

δ = 7.23 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.11 – 7.01 (m, 2H, Ar*H*), 6.89 – 6.79 (m, 3H, Ar*H*), 5.98 (s, 1H, C=C*H*), 5.28 (d, *J* = 16.0 Hz, 1H, C*H*HNC=O), 5.10 – 5.03 (m, 1H, $(CH_3)_2C$=C*H*), 4.92 (d, *J* = 16.0 Hz, 1H, CH*H*NC=O), 3.75 (s, 3H, OCH_3), 3.24 (d, *J* = 18.0 Hz, 1H, C*H*HC=CH), 3.02 (d, *J* = 18.0 Hz, 1H, CH*H*C=CH), 2.34 – 2.20 (m, 7H, ArCH_3, C=CHCH_2CH_2), 1.68 (s, 3H, $(CH_3)_2$C=CH)), 1.62 (s, 3H, $(CH_3)_2$C=CH) ppm

^{13}C NMR (100 MHz, $CDCl_3$):

δ = 162.2 (C=CH*C*=O), 158.8 (C_{Ar}), 150.1 (*C*=CHC=O), 148.9 (N*C*=ON), 135.4 (C_{Ar}), 133.5 (C_{Ar}), 133.0 (C_{Ar}), 131.3 ($(CH_3)_2C$=CH), 128.3 (C_{Ar}), 128.2 (2C, C_{Ar}), 126.3 (C_{Ar}), 124.1 ($(CH_3)_2$C=*C*H), 122.0 (*C*F_3), 121.3 (C_{Ar}), 120.1 (C_{Ar}), 115.5 (C=*C*HC=O), 114.1 (2C, C_{Ar}), 64.5 (CF_3C), 55.2 (*C*H_3O), 47.6 (*C*H_2N), 36.2 (*C*H2C=CH), 34.4 ($(CH_3)_2$C=CHCH_2CH_2)), 25.6 ($(CH_3)_2$C=CH*C*H_2CH_2), 24.9 ($(CH_3)_2$C=CH), 20.8 (Ar*C*H_3), 17.8 ($(CH_3)_2$C=CH) ppm

IR (ATR): 2962, 2250, 1735, 1610, 1511, 1442, 1367, 1217, 1027, 903, 812, 745, 666 cm^{-1}.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{30}N_2O_3F_3^+$: 499.2203; found 499.2184.

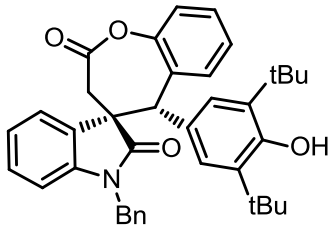
4.3.4 Synthesis of spirooxindole ε-lactones

4.3.4.1 General procedure IV (GP IV)

To a solution of isatin-derived enal **124** (0.3 mmol, 1.5 equiv) in $CHCl_3$ (2 mL), was added the substrates **125** (0.2 mmol, 1.0 equiv), NHC precursor **C20** (0.04 mmol, 0.2 equiv), Et_3N (0.3 mmol, 1.5 equiv) and 4 Å molecular sieves. The resulting mixture was stirred at 0 ^oC for 24 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (pentane/EtOAc

as the eluent, typically 20:1-10:1) to furnish the corresponding products.

4.3.4.2 Analytical data of the synthesized compounds



126a

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126a)

Compound **126a** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 84% (96mg)

dr: 7:1

Melting Point: 205-207 ^{o}C.

$[\alpha]_D^{21}$ = +167.5 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 6.60 min, $t_{r\ maj}$ = 27.23 min, T= 30 ^{o}C.

er: 96:4.

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

δ = 7.58 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.52 – 7.47 (m, 1H, Ar*H*), 7.36 (t, *J* = 7.2 Hz, 1H, Ar*H*), 7.29 – 7.19 (m, 5H, Ar*H*), 7.11 – 7.01 (m, 4H, Ar*H*), 6.98 (s, 2H, Ar*H*), 6.43 (d, *J* = 6.0 Hz, 1H, Ar*H*), 5.28 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.08 (s, 1H, O*H*), 4.75 (s, 1H, ArC*H*), 4.15 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.45 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.36 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.31 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

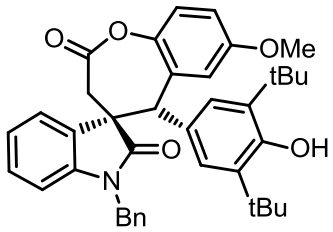
^{13}C NMR (151 MHz, $CDCl_3$):

δ = 176.0 (N*C*=O), 168.8 (O*C*=O), 153.0 (C_{Ar}), 151.0 (C_{Ar}), 141.1 (C_{Ar}), 135.2 (2C, C_{Ar}), 135.2 (C_{Ar}), 130.7 (C_{Ar}), 129.9, 129.6, 128.8 (2C, C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}),

127.7 (C_{Ar}), 127.2 (2C, C_{Ar}), 127.1 (2C, C_{Ar}), 126.0 (C_{Ar}), 124.7 (C_{Ar}), 123.4 (C_{Ar}), 122.8 (C_{Ar}), 119.6 (C_{Ar}), 109.1 (C_{Ar}), 56.5 (CH_2CCH), 51.2 ($PhCH_2$), 43.8 (CH_2CCH), 39.9 (CH_2CCH), 34.2 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

IR (KBr) 3450, 2955, 2328, 2178, 1973, 1750, 1700, 1610, 1450, 1375, 1286, 1188, 1019, 919, 840, 751, 704 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{39}NO_4Na$ $[M + Na]^+$: 596.2771, found 596.2766.



126b

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-7-methoxy-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126b)

Compound **126b** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 84% (101mg)

dr: 6:1

Melting Point:133-135 ^oC.

$[\alpha]_D^{21}$ = +113.2 (*c* = 1.0, CH_2Cl_2).

HPLC : Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min) $t_{r\ min}$ = 8.58 min, $t_{r\ maj}$ = 13.69 min, T= 30 ^oC.

er: 89:11.

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

δ = 7.52 – 7.47 (m, 1H, Ar*H*), 7.25 – 7.18 (m, 3H, Ar*H*), 7.17 – 7.13 (m, 2H, Ar*H*), 7.08 – 7.01 (m, 4H, Ar*H*), 6.99 (s, 2H, Ar*H*), 6.85 (dd, *J* = 9.0, 3.0 Hz, 1H, Ar*H*), 6.40 (d, *J* = 7.2 Hz, 1H, Ar*H*), 5.24 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.08 (s, 1H, O*H*), 4.68 (s, 1H, ArC*H*), 4.16 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.76 (s, 3H, CH_3O), 3.47 (d, *J* = 12.6 Hz,

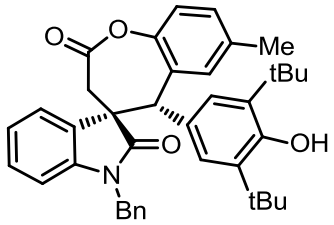
1H, C*H*HCO$_2$), 2.33 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.31 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 176.0 (N*C*=O), 169.3 (O*C*=O), 157.0 (*C*$_{Ar}$), 153.0 (*C*$_{Ar}$), 144.8 (*C*$_{Ar}$), 141.2 (*C*$_{Ar}$), 135.2 (2C, *C*$_{Ar}$), 135.1 (*C*$_{Ar}$), 130.8 (*C*$_{Ar}$), 130.5 (*C*$_{Ar}$), 128.8 (2C, *C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.7 (*C*$_{Ar}$), 127.2 (2C, *C*$_{Ar}$), 127.1 (2C, *C*$_{Ar}$), 124.6 (*C*$_{Ar}$), 123.4 (*C*$_{Ar}$), 122.8 (*C*$_{Ar}$), 120.3 (*C*$_{Ar}$), 115.4 (*C*$_{Ar}$), 113.5 (*C*$_{Ar}$), 109.1 (*C*$_{Ar}$), 56.5 (CH$_2$*C*CH), 55.4 (O*C*H$_3$), 51.4 (PhCH$_2$), 43.8 (CH$_2$C*C*H), 39.6 (*C*H$_2$CCH), 34.3 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3751, 3629, 3418, 3213, 2954, 2866, 2605, 2309, 2195, 2081, 2051, 2006, 1935, 1867, 1759, 1708, 1609, 1486, 1436, 1363, 1312, 1231, 1181, 1140, 1039, 973, 913, 886, 849, 820, 748, 697 cm^{-1}

HRMS (ESI) calcd for $C_{39}H_{41}NO_5Na$ [M + Na]$^+$: 626.2877, found 626.2873.



126c

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-7-methyl-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126c)

Compound **126c** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R$_f$ = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 90% (106mg).

dr: 6:1.

Melting Point:199-201 ^{o}C.

[α]$_D^{21}$ = +171.4 (*c* = 1.0, CH$_2$Cl$_2$).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 6.90 min, $t_{r\ maj}$ = 9.51

min, T= 30 ^{o}C.

er: 88.5:11.5.

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

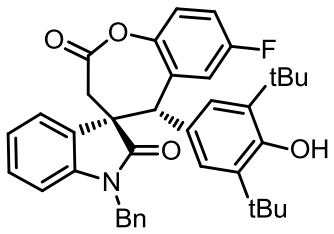
δ = 7.50 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.44 – 7.40 (m, 1H, Ar*H*), 7.25 – 7.18 (m, 3H, Ar*H*), 7.17 – 7.10 (m, 2H, Ar*H*), 7.07 – 7.01 (m, 4H, Ar*H*), 6.99 (s, 2H, Ar*H*), 6.40 (d, *J* = 7.2 Hz, 1H, Ar*H*), 5.23 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.09 (s, 1H, O*H*), 4.70 (s, 1H, ArC*H*), 4.16 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.46 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.37 – 2.31 (m, 4H, C*H*HCO$_2$, ArC*H*$_3$), 1.32 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 176.0 (N*C*=O), 169.1 (O*C*=O), 152.9 (*C*$_{Ar}$), 149.0 (*C*$_{Ar}$), 141.2 (*C*$_{Ar}$), 135.3 (*C*$_{Ar}$), 135.2 (*C*$_{Ar}$), 135.1 (2C, *C*$_{Ar}$), 130.8 (*C*$_{Ar}$), 130.5 (*C*$_{Ar}$), 129.1 (*C*$_{Ar}$), 128.9 (*C*$_{Ar}$), 128.8 (2C, *C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.7 (*C*$_{Ar}$), 127.4 (2C, *C*$_{Ar}$), 127.1 (2C, *C*$_{Ar}$), 124.6 (*C*$_{Ar}$), 123.4 (*C*$_{Ar}$), 122.8 (*C*$_{Ar}$), 119.3 (*C*$_{Ar}$), 109.1 (*C*$_{Ar}$), 56.7 (CH$_2$*C*CH), 51.2 (Ph*C*H$_2$), 43.8 (CH$_2$C*C*H), 39.6 (*C*H$_2$CCH), 34.3 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C), 21.4 (Ar*C*H$_3$) ppm.

IR (KBr) 3627, 3207, 2953, 2308, 2143, 2105, 2019, 1956, 1760, 1709, 1609, 1483, 1440, 1364, 1313, 1232, 1183, 1141, 1108, 1017, 913, 822, 748, 695 cm^{-1}.

HRMS (ESI) calcd for $C_{39}H_{41}NO_4Na$ [M + Na]$^{+}$: 610.2928, found 610.2919.



126d

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-7-fluoro-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126d)

Compound **126d** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R$_f$ = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 73% (86mg).

dr: 10:1.

Melting Point:246-248 ^{o}C.

$[\alpha]_D^{21}$ = +131.4 (*c* = 1.0, CH_2Cl_2).

HPLC (Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min) $t_{r\ min}$ = 7.00 min, $t_{r\ maj}$= 8.46 min, T= 30 ^{o}C.

er: 89:11.

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

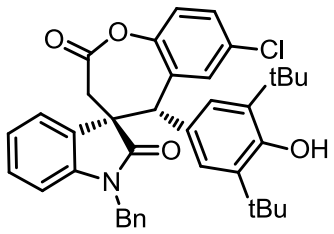
δ = 7.50 – 7.46 (m, 1H, Ar*H*), 7.30 (dd, *J* = 9.6, 3.0 Hz, 1H, Ar*H*), 7.26 – 7.17 (m, 4H, Ar*H*), 7.08 – 7.02 (m, 5H, Ar*H*), 6.96 (s, 2H), 6.44 – 6.40 (m, 1H, Ar*H*), 5.26 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.11 (s, 1H, O*H*), 4.69 (s, 1H, ArC*H*), 4.16 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.45 (d, *J* = 12.6 Hz, 1H, C*H*HCO_2), 2.37 (d, *J* = 12.6 Hz, 1H, CH*H*CO_2), 1.31 (s, 18H, (CH_3)$_3$C, (CH_3)$_3$C) ppm.

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

δ = 175.8 (N*C*=O), 168.5 (O*C*=O), 160.8 ($J_{C\text{-}F}$ = 244.8 Hz, C_{Ar}), 153.2 (C_{Ar}), 146.9 (C_{Ar}), 141.2 (C_{Ar}), 135.5 (2C, C_{Ar}), 135.0 (C_{Ar}), 131.8 ($J_{C\text{-}F}$ = 8.0 Hz, C_{Ar}), 130.4 (C_{Ar}), 128.8 (2C, C_{Ar}), 128.6 (C_{Ar}), 127.7 (C_{Ar}), 127.1 (2C, C_{Ar}), 127.0 (2C, C_{Ar}), 124.1 (C_{Ar}), 123.4 (C_{Ar}), 122.9 (C_{Ar}), 120.9 ($J_{C\text{-}F}$ = 8.6 Hz, C_{Ar}), 117.3 ($J_{C\text{-}F}$ = 25.7 Hz, C_{Ar}), 115.3 ($J_{C\text{-}F}$ = 23.7 Hz, C_{Ar}), 109.2 (C_{Ar}), 56.4 (CH_2*C*CH), 51.2 (Ph*C*H_2), 43.8 (CH_2C*C*H), 39.6 (*C*H_2CCH), 34.3 (2C, (CH_3)$_3$*C*, (CH_3)$_3$*C*), 30.3 (6C, (*C*H_3)$_3$C, (*C*H_3)$_3$C) ppm.

IR (KBr) 3730, 3643, 2959, 2872, 2616, 2285, 2221, 2183, 2084, 2032, 2008, 1969, 1913, 1762, 1710, 1612, 1478, 1437, 1363, 1315, 1267, 1233, 1177, 1139, 1023, 977, 914, 848, 753, 728, 695 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4FNa$ $[M + Na]^+$: 614.2677, found 614.2676.



126e

(*4S,5S*)-1'-Benzyl-7-chloro-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo [b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126e)

Compound **126e** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 80% (97mg).

dr: 7:1.

Melting Point:186-188 ^{o}C.

$[\alpha]_D^{21}$ = +122.2 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 7.12 min, $t_{r\ maj}$ = 8.88 min, T= 30 ^{o}C

er: 94:6.

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

δ = 7.60 (d, *J* = 2.4 Hz, 1H, Ar*H*), 7.50 – 7.46 (m, 1H, Ar*H*), 7.32 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar*H*), 7.25 – 7.19 (m, 3H, Ar*H*), 7.17 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.07 – 7.02 (m, 4H, Ar*H*), 6.96 (s, 2H, Ar*H*), 6.44 – 6.39 (m, 1H, Ar*H*), 5.23 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.12 (s, 1H, O*H*), 4.68 (s, 1H, ArC*H*), 4.17 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.45 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.38 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.31 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

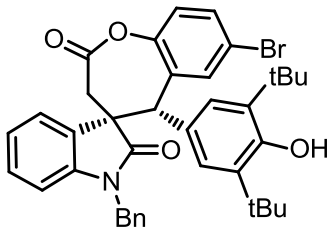
^{13}C NMR (151 MHz, $CDCl_3$):

δ = 175.7 (N*C*=O), 168.2 (O*C*=O), 153.2 (*C*$_{Ar}$), 149.5 (*C*$_{Ar}$), 141.2 (*C*$_{Ar}$), 135.4 (2C, *C*$_{Ar}$), 135.0 (*C*$_{Ar}$), 131.4 (*C*$_{Ar}$), 130.4 (*C*$_{Ar}$), 130.3 (*C*$_{Ar}$), 128.8 (2C, *C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 127.7 (*C*$_{Ar}$), 127.2 (2C, *C*$_{Ar}$), 127.1 (2C, *C*$_{Ar}$), 123.9 (*C*$_{Ar}$), 123.4 (*C*$_{Ar}$), 122.9 (*C*$_{Ar}$), 120.9 (*C*$_{Ar}$), 115.0 (*C*$_{Ar}$), 109.2 (*C*$_{Ar}$), 56.5 (CH$_2$*C*CH), 51.1 (Ph*C*H$_2$), 43.8

(CH_2CCH), 39.6 (CH_2CCH), 34.3 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

IR (KBr) 3862, 3625, 2953, 2441, 2285, 2211, 2107, 2050, 2007, 1905, 1764, 1708, 1610, 1471, 1366, 1222, 1177, 1109, 1018, 901, 822, 740 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4ClNa$ $[M + Na]^+$: 630.2382, found 630.2374.



126f

(*4S,5S*)-1'-Benzyl-7-bromo-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126f)

Compound **126f** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 92% (120mg).

dr: 3:1.

Melting Point: 186-188 ^oC.

$[\alpha]_D^{21}$ = +98.1 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 7.47 min, $t_{r\ maj}$ = 9.41 min, T= 30 ^oC.

er: 94:6.

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

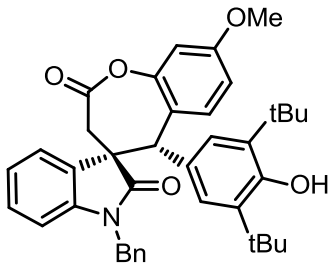
δ = 7.78 – 7.75 (m, 1H, Ar*H*), 7.51 – 7.45 (m, 2H, Ar*H*), 7.25 – 7.18 (m, 3H, Ar*H*), 7.11 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.08 – 7.01 (m, 4H, Ar*H*), 6.96 (s, 2H, Ar*H*), 6.43 – 6.38 (m, 1H, Ar*H*), 5.22 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.13 (s, 1H, O*H*), 4.68 (s, 1H, ArC*H*), 4.18 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.46 (d, *J* = 12.6 Hz, 1H, C*H*HCO_2), 2.38 (d, *J* = 12.6 Hz, 1H, CH*H*CO_2), 1.32 (s, 18H, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

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

δ = 175.7 (N*C*=O), 168.1 (O*C*=O), 153.2 (C_{Ar}), 150.1 (C_{Ar}), 141.2 (C_{Ar}), 135.4 (2C, C_{Ar}), 135.0 (C_{Ar}), 133.3 (C_{Ar}), 131.7 (C_{Ar}), 131.6 (C_{Ar}), 130.4 (C_{Ar}), 128.8 (2C, C_{Ar}), 128.6 (C_{Ar}), 127.7 (C_{Ar}), 127.2 (2C, C_{Ar}), 127.1 (2C, C_{Ar}), 123.8 (C_{Ar}), 123.4 (C_{Ar}), 122.9 (C_{Ar}), 121.3 (C_{Ar}), 119.2 (C_{Ar}), 109.2, 56.5 (CH_2CCH), 51.1 ($PhCH_2$), 43.8 (CH_2CCH), 39.6 (CH_2CCH), 34.3 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

IR (KBr) 3858, 3624, 2651, 2289, 2179, 2105, 2059, 1977, 1886, 1765, 1709, 1610, 1467, 1366, 1219, 1175, 1017, 899, 817, 745 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4BrNa$ $[M + Na]^+$: 674.1876, found 674.1876.



126g

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-8-methoxy-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126g)

Compound **126g** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 93% (112mg).

dr: 3:1.

Melting Point: 249-251 ^oC.

$[\alpha]_D^{21}$ = +76.0 (c = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 7.71 min, $t_{r\ maj}$ = 17.45 min, T= 30 ^oC.

er: 93.5:6.5.

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

δ = 7.50 – 7.44 (m, 2H, Ar*H*), 7.25 – 7.18 (m, 3H, Ar*H*), 7.06 (d, *J* = 7.2 Hz, 2, Ar*H*),

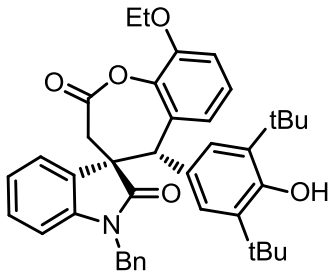
7.05 – 7.00 (m, 2H, Ar*H*), 6.96 (s, 2H, Ar*H*), 6.83 – 6.77 (m, 2H, Ar*H*), 6.43 – 6.39 (m, 1H, Ar*H*), 5.27 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.07 (s, 1H, O*H*), 4.67 (s, 1H, ArC*H*), 4.14 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.83 (s, 3H, CH_3O), 3.45 (d, *J* = 12.6 Hz, 1H, C*H*HCO_2), 2.35 (d, *J* = 12.6 Hz, 1H, CH*H*CO_2), 1.31 (s, 18H, (CH_3)$_3$C, (CH_3)$_3$C) ppm.

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

δ = 176.0 (N*C*=O), 168.9 (O*C*=O), 152.9 (C_{Ar}), 151.6 (C_{Ar}), 141.1 (C_{Ar}), 135.2 (C_{Ar}), 135.2 (2C, C_{Ar}), 130.8 (C_{Ar}), 130.4 (C_{Ar}), 128.8 (2C, C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 127.2 (2C, C_{Ar}), 127.1 (2C, C_{Ar}), 124.9 (C_{Ar}), 123.4 (C_{Ar}), 122.8 (C_{Ar}), 121.4 (C_{Ar}), 111.2 (C_{Ar}), 109.0 (C_{Ar}), 105.7 (C_{Ar}), 56.8 (CH$_2$*C*CH), 55.6 (O*C*H$_3$), 50.9 (Ph*C*H$_2$), 43.8 (CH$_2$C*C*H), 39.9 (*C*H$_2$CCH), 34.2 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3641, 2959, 2254, 1972, 1713, 1613, 1494, 1439, 1360, 1279, 1234, 1178, 1105, 1031, 971, 909, 855, 801, 727 cm^{-1}

HRMS (ESI) calcd for $C_{39}H_{41}NO_5Na$ $[M + Na]^+$: 626.2877, found 626.2875.



126h

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-9-ethoxy-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126h)

Compound **126h** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 80% (99mg).

dr: 4:1.

Melting Point: 240-242 °C.

[α]$_D^{21}$ = +152.3 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IB, 97:3 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 7.93 min, $t_{r\ maj}$ = 8.63 min, T= 30 ^{o}C.

er: 94:6 er.

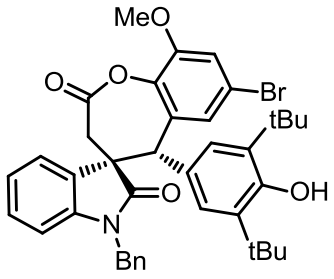
^{1}H NMR (600 MHz, $CDCl_3$):

δ = 7.51 – 7.47 (m, 1H, Ar*H*), 7.25 – 7.18 (m, 3H, Ar*H*), 7.16 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.12 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.08 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.06 – 7.00 (m, 2H, Ar*H*), 6.99 – 6.94 (m, 3H, Ar*H*), 6.47 – 6.39 (m, 1H, Ar*H*), 5.30 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.06 (s, 1H, O*H*), 4.75 (s, 1H, ArC*H*), 4.17 – 4.11 (m, 3H, PhC*H*H, CH_3CH_2), 3.46 (d, *J* = 12.6 Hz, 1H, C*H*HCO_2), 2.34 (d, *J* = 12.6 Hz, 1H, CH*H*CO_2), 1.47 (t, *J* = 7.2 Hz, 3H), 1.31 (s, 18H, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

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

δ = 176.0 (N*C*=O), 168.7 (O*C*=O), 152.9 (C_{Ar}), 149.0 (C_{Ar}), 141.1 (C_{Ar}), 140.2 (C_{Ar}), 135.3 (C_{Ar}), 135.2 (2C, C_{Ar}), 131.0 (C_{Ar}), 130.8 (C_{Ar}), 128.8 (2C, C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 127.2 (2C, C_{Ar}), 127.1 (2C, C_{Ar}), 125.8 (C_{Ar}), 125.0 (C_{Ar}), 123.5 (C_{Ar}), 122.8 (C_{Ar}), 121.3 (C_{Ar}), 113.0 (C_{Ar}), 109.0 (C_{Ar}), 64.8 (CH_3CH_2O), 56.4 (CH_2CCH), 51.2 ($PhCH_2$), 43.8 (CH_2CCH), 40.0 (CH_2CCH), 34.2 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$), 14.9 (CH_3CH_2O) ppm.

IR (KBr) 3604, 3419, 3068, 2961, 2553, 2284, 2183, 2106, 2055, 1974, 1898, 1761, 1714, 1606, 1461, 1360, 1279, 1179, 1232, 1069, 1020, 923, 849, 743, 668 cm^{-1}; **HRMS (ESI)** calcd for $C_{40}H_{43}NO_5Na$ $[M + Na]^+$: 640.3033, found 640.3035.



126i

(4S,5R)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-9-ethoxy-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126i)

Compound **126i** was prepared according to **GP IV** and isolated after flash

chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 84% (115mg).

dr: 4:1.

Melting Point: 277-279 ^{o}C.

$[\alpha]_D^{21}$ = +123.5 (*c* = 1.0, CH_2Cl_2).

HPLC Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 7.46 min, $t_{r\ maj}$ = 11.46 min, T= 30 ^{o}C.

er: 93.5:6.5

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

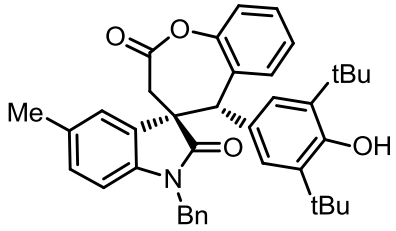
δ = 7.50 – 7.46 (m, 1H, Ar*H*), 7.35 – 7.31 (m, 1H, Ar*H*), 7.25 – 7.18 (m, 3H, Ar*H*), 7.12 – 7.08 (m, 1H, Ar*H*), 7.07 – 7.00 (m, 4H, Ar*H*), 6.94 (s, 2H, Ar*H*), 6.43 – 6.38 (m, 1H, Ar*H*), 5.24 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.11 (s, 1H, O*H*), 4.69 (s, 1H, ArC*H*), 4.16 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.91 (s, 3H, CH_3O), 3.46 (d, *J* = 12.6 Hz, 1H, C*H*HCO_2), 2.36 (d, *J* = 12.6 Hz, 1H, CH*H*CO_2), 1.31 (s, 18H, (CH_3)$_3$C, (CH_3)$_3$C) ppm.

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

δ = 175.7 (N*C*=O), 167.9 (O*C*=O), 153.1 (C_{Ar}), 150.3 (C_{Ar}), 141.1 (C_{Ar}), 139.1 (C_{Ar}), 135.3 (2C, C_{Ar}), 135.1 (C_{Ar}), 132.4 (C_{Ar}), 130.4 (C_{Ar}), 128.8 (2C, C_{Ar}), 128.5 (C_{Ar}), 127.7 (C_{Ar}), 127.2 (2C, C_{Ar}), 127.1 (2C, C_{Ar}), 124.6 (C_{Ar}), 124.1 (C_{Ar}), 123.4 (C_{Ar}), 122.9 (C_{Ar}), 118.9 (C_{Ar}), 115.1 (C_{Ar}), 109.1 (C_{Ar}), 56.5 (CH_2*C*CH), 56.4, 51.0 (Ph*C*H_2), 43.8 (CH_2C*C*H), 39.6 (*C*H_2CCH), 34.3 (2C, $(CH_3)_3$*C*, $(CH_3)_3$*C*), 30.3 (6C, (*C*H_3)$_3$C, (*C*H_3)$_3$C) ppm.

IR (KBr) 3605, 3081, 2954, 2323, 2163, 1974, 1760, 1701, 1604, 1438, 1370, 1296, 1175, 1123, 1014, 905, 845, 736, 695 cm^{-1}.

HRMS (ESI) calcd for $C_{39}H_{40}NO_5BrNa$ $[M + Na]^+$: 704.1982, found 704.1981.



126j

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-methyl-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126j)

Compound **126j** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 88% (103mg).

dr: 6:1.

Melting Point: 234-236 ^{o}C.

[α]$_D^{21}$ = +111.6 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 5.71 min, $t_{r\ maj}$ = 12.51 min, T= 30 ^{o}C.

er:91:9.

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

δ = 7.59 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.39 – 7.33 (m, 1H, Ar*H*), 7.31 (s, 1H, Ar*H*), 7.28 – 7.18 (m, 5H, Ar*H*), 7.07 (d, *J* = 7.2 Hz, 2H, Ar*H*), 6.98 (s, 2H, Ar*H*), 6.83 (d, *J* = 7.8 Hz, 1H, Ar*H*), 6.30 (d, *J* = 7.8 Hz, 1H, Ar*H*), 5.28 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.08 (s, 1H, O*H*), 4.74 (s, 1H, ArC*H*), 4.10 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.44 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.36 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 2.32 (s, 3H), 1.32 (s, 18H, (CH_3)$_3$C, (CH_3)$_3$C) ppm.

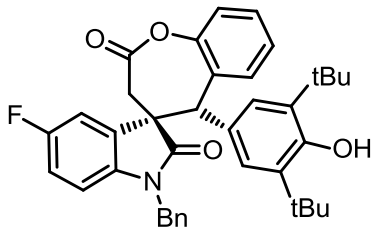
^{13}C NMR (151 MHz, $CDCl_3$):

δ = 175.9 (N*C*=O), 168.9 (O*C*=O), 152.9 (C_{Ar}), 151.0 (C_{Ar}), 138.8 (C_{Ar}), 135.3 (C_{Ar}), 135.2 (2C, C_{Ar}), 132.4 (C_{Ar}), 130.7 (C_{Ar}), 129.8 (C_{Ar}), 129.6 (C_{Ar}), 128.7 (2C, C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 127.6 (C_{Ar}), 127.2 (4C, C_{Ar}), 125.9 (C_{Ar}), 124.8 (C_{Ar}), 124.2 (C_{Ar}), 119.6 (C_{Ar}), 108.8 (C_{Ar}), 56.6 (CH$_2$*C*CH), 51.2 (Ph*C*H$_2$), 43.8 (CH$_2$C*C*H), 39.9

(CH_2CCH), 34.2 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$), 21.1 ppm.

IR (KBr) 3616, 3403, 2958, 2916, 2650, 2321, 2170, 2082, 2050, 1978, 1925, 1759, 1704, 1603, 1493, 1439,1364, 1316, 1284, 1217, 1170, 1098, 1016, 903, 813, 730, 703 cm^{-1}.

HRMS (ESI) calcd for $C_{39}H_{41}NO_4Na$ $[M + Na]^+$: 610.2928, found 610.2929.



126k

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-fluoro-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126k)

Compound **126k** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 83% (98mg).

dr: 7:1.

Melting Point: 251-253 ^oC.

$[\alpha]_D^{21}$ = +141.4 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 6.32 min, $t_{r\ maj}$ = 12.40 min, T= 30 ^oC.

er: 94:6.

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

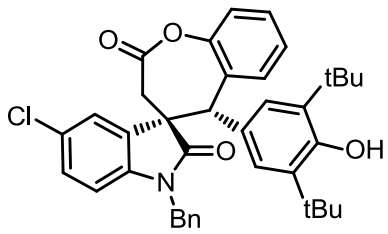
δ = 7.55 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.40 – 7.34 (m, 1H, Ar*H*), 7.30 – 7.20 (m, 6H, Ar*H*), 7.05 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.00 (s, 2H, Ar*H*), 6.78 – 6.71 (m, 1H, Ar*H*), 6.34 (dd, *J* = 9.0, 4.2 Hz, 1H, Ar*H*), 5.31 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.12 (s, 1H, O*H*), 4.70 (s, 1H, ArC*H*), 4.11 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.45 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.37 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.33 (s, 18H, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

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

δ = 175.7 (N*C*=O), 168.5 (O*C*=O), 160.1 ($J_{C\text{-}F}$ = 243.1 Hz, C_{Ar}), 158.5 (C_{Ar}), 153.1 (C_{Ar}), 150.9 (C_{Ar}), 137.1 ($J_{C\text{-}F}$ = 1.8 Hz, C_{Ar}), 135.4 (2C, C_{Ar}), 134.8 (C_{Ar}), 132.4 ($J_{C\text{-}F}$ = 7.9 Hz, C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (2C, C_{Ar}), 128.8 (C_{Ar}), 127.9 (C_{Ar}), 127.1 (2C, C_{Ar}), 127.0 (C_{Ar}), 126.0 (C_{Ar}), 124.4 (C_{Ar}), 119.6 (C_{Ar}), 114.8 ($J_{C\text{-}F}$ = 24.0 Hz, C_{Ar}), 111.8 ($J_{C\text{-}F}$ = 25.2 Hz, C_{Ar}), 109.7 ($J_{C\text{-}F}$ = 7.9 Hz, C_{Ar}), 56.8 (CH_2CCH), 51.2 ($PhCH_2$), 43.9 (CH_2CCH), 39.8 (CH_2CCH), 34.3 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

IR (KBr) 3592, 3081, 2964, 2298, 2202, 2052, 1921, 1758, 1706, 1621, 1489, 1440, 1363, 1342, 1285, 1258, 1238, 1209, 1174, 1124, 1097, 1012, 971, 926, 895, 870, 811, 750, 700, 655 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4FNa$ $[M + Na]^+$: 614.2677, found 614.2676.



126l

(4S,5R)-1'-Benzyl-5'-chloro-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126l)

Compound **126l** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 90% (109mg).

dr: 4:1.

Melting Point: 228-230 °C.

$[\alpha]_D^{21}$ = +92.1 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 6.28 min, $t_{r\ maj}$ = 12.48 min, T= 30 °C.

er: 92:8.

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

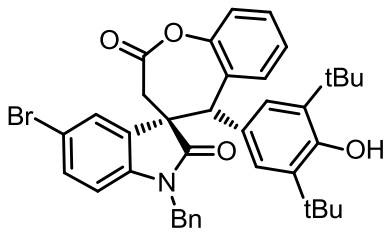
δ = 7.58 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.50 – 7.46 (m, 1H, Ar*H*), 7.38 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.29 – 7.19 (m, 5H, Ar*H*), 7.05 (d, *J* = 6.6 Hz, 2H, Ar*H*), 7.03 – 6.94 (m, 3H, Ar*H*), 6.32 (d, *J* = 8.4 Hz, 1H, Ar*H*), 5.31 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.12 (s, 1H, O*H*), 4.70 (s, 1H, ArC*H*), 4.07 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.45 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.38 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.34 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 175.5 (N*C*=O), 168.5 (O*C*=O), 153.1 (*C*$_{Ar}$), 150.9 (*C*$_{Ar}$), 139.7 (*C*$_{Ar}$), 135.4 (2C, *C*$_{Ar}$), 134.7 (*C*$_{Ar}$), 132.4 (*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 129.0 (*C*$_{Ar}$), 128.9 (2C, *C*$_{Ar}$), 128.8 (*C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 127.1 (2C, *C*$_{Ar}$), 127.1 (2C, *C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 124.3 (*C*$_{Ar}$), 124.1 (*C*$_{Ar}$), 119.6 (*C*$_{Ar}$), 110.0 (*C*$_{Ar}$), 56.8 (CH$_2$*C*CH), 51.4 (Ph*C*H$_2$), 43.9 (CH$_2$C*C*H), 39.6 (*C*H$_2$CCH), 34.3 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3621, 3412, 2956, 2324, 2062, 1989, 1934, 1756, 1707, 1605, 1480, 1441, 1357, 1216, 1167, 1097, 922, 815, 745, 700 cm^{-1}

HRMS (ESI) calcd for $C_{38}H_{38}NO_4ClNa$ [M + Na]$^+$: 630.2382, found 630.2377.



126m

(*4S,5S*)-1'-Benzyl-5'-bromo-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126m)

Compound **126m** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 85% (111mg).

dr: 4:1.

Melting Point: 236-238 ^{o}C.

$[\alpha]_D^{21}$ = +56.6 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 6.36 min, $t_{r\ maj}$ = 13.28 min, T= 30 ^{o}C.

er: 92:8.

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

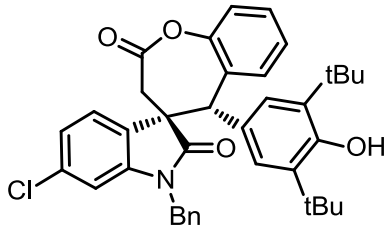
δ = 7.63 – 7.60 (m, 1H, Ar*H*), 7.59 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.38 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.30 – 7.20 (m, 5H, Ar*H*), 7.15 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar*H*), 7.04 (d, *J* = 7.1 Hz, 2H, Ar*H*), 6.98 (s, 2H, Ar*H*), 6.27 (d, *J* = 8.4 Hz, 1H, Ar*H*), 5.31 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.11 (s, 1H, O*H*), 4.69 (s, 1H, ArC*H*), 4.05 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.44 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.38 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.34 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 175.4 (N*C*=O), 168.5 (O*C*=O), 153.1 (*C*$_{Ar}$), 150.9 (*C*$_{Ar}$), 140.2 (*C*$_{Ar}$), 135.4 (2C, *C*$_{Ar}$), 134.7 (*C*$_{Ar}$), 132.8 (*C*$_{Ar}$), 131.3 (*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 128.9 (*C*$_{Ar}$), 128.9 (2C, *C*$_{Ar}$), 128.9 (*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 127.1 (4C, *C*$_{Ar}$), 126.8 (*C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 124.2 (*C*$_{Ar}$), 119.7 (*C*$_{Ar}$), 115.7 (*C*$_{Ar}$), 110.4 (*C*$_{Ar}$), 56.7 (CH$_2$*C*CH), 51.4 (Ph*C*H$_2$), 43.9 (CH$_2$C*C*H), 39.5 (*C*H$_2$CCH), 34.3 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3621, 3207, 2957, 2333, 2178, 2120, 2062, 2006, 1759, 1709, 1603, 1443, 1354, 1170, 1015, 914, 811, 739 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4BrNa$ [M + Na]$^{+}$: 674.1876, found 674.1875.



126n

(*4S,5S*)-1'-Benzyl-6'-chloro-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benz

o[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126n)

Compound **126n** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 90% (102mg).

dr: 6:1.

Melting Point: 176-178 ^{o}C.

$[\alpha]_D^{21}$ = +103.6 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min., $t_{r\ min}$ = 6.09 min, $t_{r\ maj}$ = 15.9 min, T= 30 ^{o}C.

er: 91.5:8.5.

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

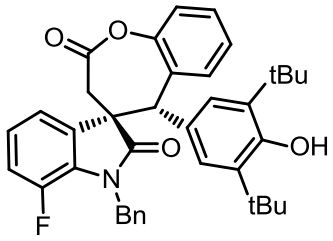
δ = 7.55 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.41 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.37 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.28 – 7.20 (m, 5H, Ar*H*), 7.07 (d, *J* = 7.2 Hz,, 2H, Ar*H*), 7.03 (dd, *J* = 7.8, 1.2 Hz, 1H, Ar*H*), 6.96 (s, 2H, Ar*H*), 6.42 (d, *J* = 1.2 Hz, 1H, Ar*H*), 5.29 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.12 (s, 1H, O*H*), 4.69 (s, 1H, ArC*H*), 4.06 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.43 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.33 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.34 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 175.9 (N*C*=O), 168.6 (O*C*=O), 153.1 (*C*$_{Ar}$), 150.9 (*C*$_{Ar}$), 142.4 (*C*$_{Ar}$), 135.4 (2C, *C*$_{Ar}$), 134.6 (*C*$_{Ar}$), 134.3 (*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 129.2 (2C, *C*$_{Ar}$), 129.0 (2C, *C*$_{Ar}$), 128.8 (*C*$_{Ar}$), 128.0 (*C*$_{Ar}$), 127.1 (2C, *C*$_{Ar}$), 127.0 (2C, *C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 124.4 (*C*$_{Ar}$), 124.3 (*C*$_{Ar}$), 122.7 (*C*$_{Ar}$), 119.6 (*C*$_{Ar}$), 109.6 (*C*$_{Ar}$), 56.3 (CH$_2$*C*CH), 51.2 (Ph*C*H$_2$), 43.9 (CH$_2$C*C*H), 39.8 (*C*H$_2$CCH), 34.3 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3607, 2957, 2664, 2067, 1902, 1722, 1604, 1443, 1370, 1338, 1145, 928, 870, 806, 742, 663 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4ClNa$ $[M + Na]^+$: 630.2382, found 630.2364.



126o

(*4S,5S*)-1'-Benzyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-7'-fluoro-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126o)

Compound **126o** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 85% (101mg).

dr: 6:1.

Melting Point: 237-239 ^{o}C.

$[\alpha]_D^{21}$ = +137.3 (*c* = 0.5, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 5.87 min, $t_{r\ maj}$ = 10.43 min, T= 30 ^{o}C.

er: 93.5:6.5.

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

δ = 7.54 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.39 – 7.34 (m, 1H, Ar*H*), 7.27 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.25 – 7.19 (m, 4H, Ar*H*), 7.19 – 7.14 (m, 2H, Ar*H*), 7.02 – 6.98 (m, 1H, Ar*H*), 6.96 (s, 2H, Ar*H*), 6.83 (dd, *J* = 11.4, 8.4 Hz, 1H, Ar*H*), 5.32 (d, *J* = 15.6 Hz, 1H, PhC*H*H), 5.11 (s, 1H, O*H*), 4.71 (s, 1H, ArC*H*), 4.44 (d, *J* = 15.6 Hz, 1H, PhCH*H*), 3.40 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.32 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.33 (s, 18H, (CH_3)$_3$C, (CH_3)$_3$C) ppm.

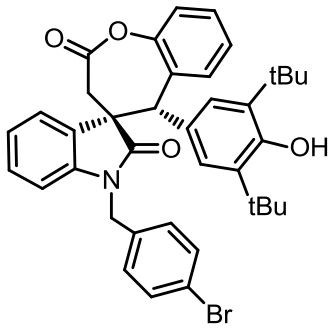
^{13}C NMR (151 MHz, $CDCl_3$):

δ = 175.8 (N*C*=O), 168.5 (O*C*=O), 153.1 (C_{Ar}), 150.9 (C_{Ar}), 148.0 ($J_{C\text{-}F}$ = 244.6 Hz, C_{Ar}), 136.5 (C_{Ar}), 135.4 (2C, C_{Ar}), 133.7 ($J_{C\text{-}F}$ = 2.9 Hz, C_{Ar}), 129.9 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (2C, C_{Ar}), 127.9 ($J_{C\text{-}F}$ = 8.6 Hz, C_{Ar}), 127.7 (C_{Ar}), 127.4 (2C, C_{Ar}), 126.8 (C_{Ar}), 126.0 (C_{Ar}), 124.4 (C_{Ar}), 123.6 ($J_{C\text{-}F}$ = 6.5 Hz, C_{Ar}), 119.6 (2C, C_{Ar}), 119.4

($J_{C\text{-}F}$ = 2.9 Hz, C_{Ar}), 116.6 ($J_{C\text{-}F}$ = 19.5 Hz, C_{Ar}), 56.8 (CH_2CCH), 51.4 ($PhCH_2$), 45.4 (CH_2CCH), 40.0 (CH_2CCH), 34.3 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.3 (6C, $(CH_3)_3C$, $(CH_3)_3C$) ppm.

IR (KBr) 3597, 2962, 2322, 1979, 1761, 1708, 1632, 1480, 1439, 1355, 1312, 1288, 1240, 1212, 1170, 1145, 1096, 1032, 925, 897, 840, 758, 732, 702 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4FNa$ $[M + Na]^+$: 614.2677, found 614.2675.



126p

(*4S,5S*)-1'-(4-Bromobenzyl)-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126p)

Compound **126p** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 5:1).

Yield: 89% (116mg).

dr: 7:1.

Melting Point: 121-123 ^oC.

$[\alpha]_D^{21}$ = +127.1 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 6.66 min, $t_{r\ maj}$ = 17.42 min, T= 30 ^oC.

er: 91.5:8.5.

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

δ = 7.58 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.53 – 7.48 (m, 1H, Ar*H*), 7.39 – 7.33 (m, 3H, Ar*H*), 7.28 – 7.22 (m, 2H, Ar*H*), 7.10 – 7.02 (m, 2H, Ar*H*), 6.97 (s, 2H, Ar*H*), 6.93 (d, *J* = 8.4

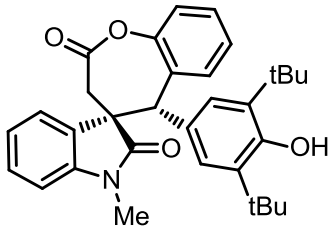
Hz, 2H, Ar*H*), 6.42 – 6.36 (m, 1H, Ar*H*), 5.17 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 5.08 (s, 1H, O*H*), 4.74 (s, 1H, ArC*H*), 4.14 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 3.43 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.33 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.30 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 176.0 (N*C*=O), 168.6 (O*C*=O), 153.0 (*C*$_{Ar}$), 151.0 (*C*$_{Ar}$), 140.8 (*C*$_{Ar}$), 135.2 (2C, *C*$_{Ar}$), 134.2 (*C*$_{Ar}$), 131.9 (2C, *C*$_{Ar}$), 130.7 (*C*$_{Ar}$), 129.8 (*C*$_{Ar}$), 129.4 (*C*$_{Ar}$), 128.9 (2C, *C*$_{Ar}$), 128.7 (*C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 127.2 (*C*$_{Ar}$), 126.0 (*C*$_{Ar}$), 124.6 (*C*$_{Ar}$), 123.6 (*C*$_{Ar}$), 123.0 (*C*$_{Ar}$), 121.7 (*C*$_{Ar}$), 119.7 (*C*$_{Ar}$), 108.9 (*C*$_{Ar}$), 56.6 (CH$_2$*C*CH), 51.3 (Ph*C*H$_2$), 43.3 (CH$_2$C*C*H), 39.8 (*C*H$_2$CCH), 34.2 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3624, 3066, 2955, 2658, 2324, 2066, 1911, 1758, 1707, 1608, 1480, 1440, 1364, 1303, 1217, 1176, 1139, 1011, 910, 734 cm^{-1}.

HRMS (ESI) calcd for $C_{38}H_{38}NO_4BrNa$ [M + Na]$^+$: 674.1876, found 674.1878.



126q

(*4S,5S*)-5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1'-methyl-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126q)

Compound **126q** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R$_f$ = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 78% (78mg).

dr: 7:1.

Melting Point: 235-237 °C.

[α]$_D^{21}$ = +158.2 (*c* = 1.0, CH$_2$Cl$_2$).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\,min}$ = 7.09 min, $t_{r\,maj}$ = 9.28

min, T= 30 ^{o}C.

er: 95:5.

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

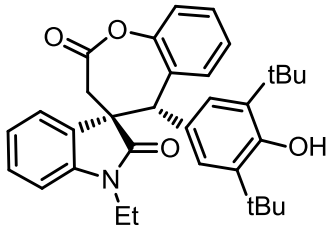
δ = 7.54 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.49 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.35 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.25 – 7.19 (m, 2H, Ar*H*), 7.17 – 7.12 (m, 1H, Ar*H*), 7.08 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.91 (s, 2H, Ar*H*), 6.52 (d, *J* = 7.8 Hz, 1H, Ar*H*), 5.03 (s, 1H, O*H*), 4.68 (s, 1H, ArC*H*), 3.37 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 3.03 (s, 3H, C*H*$_3$N), 2.34 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.29 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 175.6 (N*C*=O), 169.1 (O*C*=O), 152.9 (*C*$_{Ar}$), 150.9 (*C*$_{Ar}$), 142.1 (*C*$_{Ar}$), 135.1 (2C, *C*$_{Ar}$), 130.8 (*C*$_{Ar}$), 129.8 (2C, *C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 127.0 (2C, *C*$_{Ar}$), 125.9 (*C*$_{Ar}$), 124.5 (*C*$_{Ar}$), 123.3 (*C*$_{Ar}$), 122.8 (*C*$_{Ar}$), 119.5 (*C*$_{Ar}$), 107.7 (*C*$_{Ar}$), 56.6 (CH$_2$*C*CH), 51.6, 39.4 (*C*H$_2$CCH), 34.2 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C), 26.3 (N*C*H$_3$) ppm.

IR (KBr) 3573, 2948, 2660, 2065, 1921, 1753, 1707, 1606, 1441, 1357, 1282, 1214, 1132, 1026, 929, 845, 747, 661 cm^{-1}.

HRMS (ESI) calcd for $C_{32}H_{35}NO_4Na$ [M + Na]$^{+}$: 520.2458, found 520.2446.



126r

(*4S,5S*)-5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1'-ethyl-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126r)

Compound **126r** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 79% (81mg).

dr: 7:1.

Melting Point: 194-196 ^{o}C.

$[\alpha]_D^{21}$ = +106.3 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 5.45 min, $t_{r\ maj}$ = 7.62 min, T= 30 ^{o}C.

er: 92:8.

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

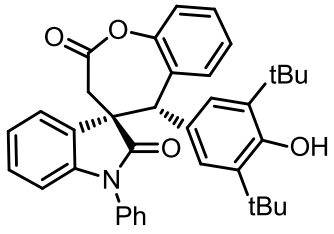
δ = 7.55 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.49 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.34 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.25 – 7.19 (m, 2H, Ar*H*), 7.14 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.07 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.92 (s, 2H, Ar*H*), 6.57 (d, *J* = 7.2 Hz, 1H, Ar*H*), 5.02 (s, 1H, O*H*), 4.69 (s, 1H, ArC*H*), 3.93 (dq, *J* = 21.6, 7.2 Hz, 1H, CH_3CHH), 3.36 (d, *J* = 12.6 Hz, 1H, $CHHCO_2$), 3.22 (dq, *J* = 21.6, 7.2 Hz, 1H, CH_3CHH), 2.30 (d, *J* = 12.6 Hz, 1H, $CHHCO_2$), 1.29 (s, 18H, $(CH_3)_3C$, $(CH_3)_3C$), 1.13 (t, *J* = 7.2 Hz, 3H, CH_3CH_2) ppm.

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

δ = 175.3 (N*C*=O), 169.0 (O*C*=O), 152.9 (C_{Ar}), 151.0 (C_{Ar}), 141.2 (C_{Ar}), 135.1 (C_{Ar}), 131.0 (C_{Ar}), 129.8 (2C, C_{Ar}), 129.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 127.1 (2C, C_{Ar}), 125.9 (C_{Ar}), 124.6 (C_{Ar}), 123.5 (C_{Ar}), 122.6 (C_{Ar}), 119.5 (C_{Ar}), 108.0 (C_{Ar}), 56.4 (CH_2CCH), 51.2 (CH_2CCH), 39.8 (CH_2CCH), 34.8 (CH_3CH_2), 34.3 (2C, $(CH_3)_3C$, $(CH_3)_3C$), 30.2 (6C, $(CH_3)_3C$, $(CH_3)_3C$), 12.6 (CH_3CH_2) ppm.

IR (KBr) 3537, 2954, 2325, 2071, 1907, 1755, 1694, 1609, 1440, 1374, 1284, 1209, 1136, 1021, 910, 744 cm^{-1}.

HRMS (ESI) calcd for $C_{33}H_{37}NO_4Na$ $[M + Na]^+$: 534.2615, found 534.2598.



126s

(*4S,5S*)-5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1'-phenyl-5H-spiro[benzo[b]oxepi

ne-4,3'-indoline]-2,2'(3H)-dione (126s)

Compound **126s** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 75% (84mg).

dr: 7:1.

Melting Point: 214-216 ^{o}C.

$[\alpha]_D^{21}$ = +158.9 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 5.62 min, $t_{r\ maj}$ = 6.03 min, T= 30 ^{o}C.

er: 92:8.

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

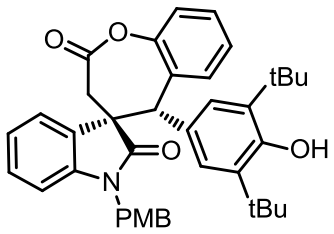
δ = 7.62 – 7.55 (m, 2H, Ar*H*), 7.44 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.35 (dd, *J* = 13.8, 7.2 Hz, 2H, Ar*H*), 7.25 – 7.19 (m, 2H, Ar*H*), 7.19 – 7.09 (m, 4H, Ar*H*), 7.00 (s, 2H, Ar*H*), 6.65 (d, *J* = 7.2 Hz, 1H, Ar*H*), 5.09 (s, 1H, O*H*), 4.78 (s, 1H, ArC*H*), 3.47 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.48 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.24 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 174.9 (N*C*=O), 168.8 (O*C*=O), 153.1 (*C*$_{Ar}$), 151.0 (*C*$_{Ar}$), 141.8 (*C*$_{Ar}$), 135.3 (2C, *C*$_{Ar}$), 133.8 (*C*$_{Ar}$), 130.6 (*C*$_{Ar}$), 129.9 (*C*$_{Ar}$), 129.4 (*C*$_{Ar}$), 129.3 (2C, *C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.8 (*C*$_{Ar}$), 127.4 (*C*$_{Ar}$), 125.9 (4C, *C*$_{Ar}$), 124.5 (*C*$_{Ar}$), 123.6 (*C*$_{Ar}$), 123.3 (*C*$_{Ar}$), 119.6 (*C*$_{Ar}$), 109.4 (*C*$_{Ar}$), 56.6 (CH$_2$*C*CH), 51.5 (CH$_2$C*C*H), 40.1 (*C*H$_2$CCH), 34.2 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.2 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3597, 3058, 2964, 2875, 2324, 2174, 2014, 1924, 1750, 1719, 1604, 1441, 1370, 1319, 1285, 1182, 1144, 1099, 1030, 908, 838, 796, 748, 697 cm^{-1}.

HRMS (ESI) calcd for $C_{37}H_{37}NO_4Na$ $[M + Na]^+$: 582.2615, found 582.2605.



126t

(*4S,5S*)-5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1'-(4-methoxybenzyl)-5H-spiro[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126t)

Compound **126t** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 4:1).

Yield: 88% (106mg).

dr: 8:1.

Melting Point: 124-126 ^{o}C.

$[\alpha]_D^{21}$ = +143.8 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\,mn}$ = 6.53 min, $t_{r\,maj}$ = 26.83 min, T= 30 ^{o}C.

er: 91: 9.

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

δ = 7.57 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.49 – 7.45 (m, 1H, Ar*H*), 7.38 – 7.33 (m, 1H, Ar*H*), 7.24 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.06 – 7.02 (m, 2H, Ar*H*), 7.01 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.97 (s, 2H, Ar*H*), 6.75 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.47 – 6.43 (m, 1H, Ar*H*), 5.22 (d, *J* = 15.6 Hz, 1H, ArC*H*H), 5.07 (s, 1H, O*H*), 4.74 (s, 1H, ArC*H*), 4.08 (d, *J* = 15.6 Hz, 1H, ArCH*H*), 3.73 (s, 3H, CH_3O), 3.42 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.32 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.31 (s, 18H, (CH_3)$_3$C, (CH_3)$_3$C) ppm.

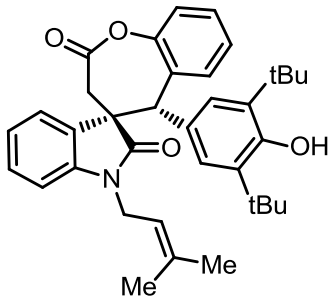
^{13}C NMR (151 MHz, $CDCl_3$):

δ = 175.9 (N*C*=O), 168.8 (O*C*=O), 159.0 (C_{Ar}), 152.9 (C_{Ar}), 151.0 (C_{Ar}), 141.2 (C_{Ar}), 135.2 (2C, C_{Ar}), 130.7 (C_{Ar}), 129.9 (C_{Ar}), 129.6 (C_{Ar}), 128.6 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.4 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (2C, C_{Ar}), 125.9 (C_{Ar}), 124.7 (C_{Ar}), 123.4 (C_{Ar}), 122.8 (C_{Ar}), 119.6 (C_{Ar}), 114.1 (2C, C_{Ar}), 109.1 (C_{Ar}), 56.5 (CH$_2$*C*CH), 55.2 (*C*H$_3$O), 51.2

(Ph*C*H_2), 43.3 (CH_2C*C*H), 39.9 (*C*H_2CCH), 34.2 (2C, $(CH_3)_3$*C*, $(CH_3)_3$*C*), 30.3 (6C, $(CH_3)_3$C, $(CH_3)_3$C) ppm.

IR (KBr) 3625, 2956, 2323, 2065, 1904, 1759, 1705, 1610, 1443, 1364, 1291, 1239, 1175, 1138, 1027, 911, 833, 734 cm^{-1}.

HRMS (ESI) calcd for $C_{39}H_{41}NO_5Na$ $[M + Na]^+$: 626.2877, found 626.2880.



126u

(*4S,5S*)-5-(3,5-Di-tert-butyl-4-hydroxyphenyl)-1'-(3-methylbut-2-en-1-yl)-5H-spiro-[benzo[b]oxepine-4,3'-indoline]-2,2'(3H)-dione (126u)

Compound **126u** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 86% (95mg).

dr: 7:1.

Melting Point: 171-173 ^oC.

$[\alpha]_D^{21}$ = +140.2 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 5.26 min, $t_{r\ maj}$ = 7.61 min, T= 30 ^oC.

er: 91:9.

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

δ = 7.55 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.48 (d, *J* = 7.2 Hz, 1H, Ar*H*), 7.34 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.25 – 7.19 (m, 2H, Ar*H*), 7.12 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.06 (t, *J* = 7.8 Hz, 1H, Ar*H*), 6.93 (s, 2H, Ar*H*), 6.52 (d, *J* = 7.2 Hz, 1H, Ar*H*), 5.04 (s, 1H, O*H*), 4.92 (t, *J* = 6.6

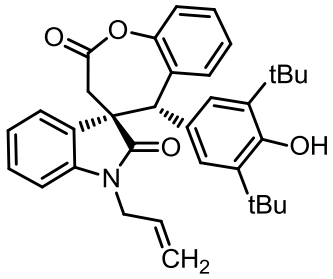
Hz, 1H, C=C*H*CH_2), 4.69 (s, 1H, ArC*H*), 4.47 (dd, *J* = 15.6, 6.6 Hz, 1H, C=CHC*H*H), 3.78 (dd, *J* = 15.6, 6.6 Hz, 1H, C=CHCH*H*), 3.36 (d, *J* = 12.6 Hz, 1H, C*H*HCO_2), 2.31 (d, *J* = 12.6 Hz, 1H, CH*H*CO_2), 1.73 (s, 3H, C*H*$_3$CCH_3), 1.66 (s, 3H, CH_3CC*H*$_3$), 1.30 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 175.2 (N*C*=O), 169.0 (O*C*=O), 152.9 (*C*$_{Ar}$), 151.0 (*C*$_{Ar}$), 141.5 (*C*$_{Ar}$), 136.8 (*C*$_{Ar}$), 135.1 (2C, *C*$_{Ar}$), 130.9 (CH2CH=*C*), 129.8 (2C, *C*$_{Ar}$), 129.6 (*C*$_{Ar}$), 128.5 (*C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 125.9 (*C*$_{Ar}$), 124.6 (*C*$_{Ar}$), 123.3 (*C*$_{Ar}$), 122.6 (*C*$_{Ar}$), 119.5 (CH2*C*H=C), 118.0 (*C*$_{Ar}$), 108.7 (*C*$_{Ar}$), 56.5 (CH_2*C*CH), 51.2 (CH_2C*C*H), 39.7 (*C*H_2CCH), 38.2 (N*C*H_2), 34.2 (2C, (CH_3)$_3$*C*, (CH_3)$_3$*C*), 30.3 (6C, (*C*H_3)$_3$C, (*C*H_3)$_3$C), 25.5 (CH_3C*C*H_3), 18.1 (*C*H_3CCH_3) ppm.

IR (KBr) 3621, 2961, 2324, 2056, 1902, 1759, 1704, 1609, 1483, 1437, 1366, 1315, 1292, 1213, 1174, 1142, 1100, 1044, 973, 908, 836, 734 cm^{-1}.

HRMS (ESI) calcd for $C_{36}H_{41}NO_4Na$ [M + Na]$^+$: 574.2928, found 574.2926.



126v

(*4S,5S*)-1'-Allyl-5-(3,5-di-tert-butyl-4-hydroxyphenyl)-5H-spiro[benzo[b]oxepine -4,3'-indoline]-2,2'(3H)-dione (126v)

Compound **126v** was prepared according to **GP IV** and isolated after flash chromatography as a white solid.

TLC: R_f = 0.50 (*n*-pentane:EtOAc = 6:1).

Yield: 79% (83mg).

dr: 7:1.

Melting Point: 115-117 ^{o}C.

[α]$_D^{21}$ = +124.5 (*c* = 1.0, CH_2Cl_2).

HPLC: Chiralcel IA, 9:1 *n*-heptane/iPrOH, 1.0 mL/min, $t_{r\ min}$ = 5.85 min, $t_{r\ maj}$ = 7.19 min, T= 30 ^{o}C.

er: 91:9.

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

δ = 7.56 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.26 – 7.20 (m, 2H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.94 (s, 2H), 6.56 (d, *J* = 7.2 Hz, 1H), 5.68 – 5.59 (m, 1H, C*H*H=CHCH$_2$), 5.12 (d, *J* = 10.2 Hz, 1H, CH*H*=CHCH$_2$), 5.04 (s, 1H, O*H*), 5.01 (d, *J* = 16.2 Hz, 1H, CH$_2$=CHC*H*H), 4.71 (s, 1H, ArC*H*), 4.52 – 4.45 (m, 1H, CH$_2$=C*H*CH$_2$), 3.83 (dd, *J* = 16.2, 5.4 Hz, 1H, CH$_2$=CHCH*H*), 3.38 (d, *J* = 12.6 Hz, 1H, C*H*HCO$_2$), 2.32 (d, *J* = 12.6 Hz, 1H, CH*H*CO$_2$), 1.29 (s, 18H, (C*H*$_3$)$_3$C, (C*H*$_3$)$_3$C) ppm.

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

δ = 175.4 (N*C*=O), 168.8 (O*C*=O), 152.9 (*C*$_{Ar}$), 151.0 (*C*$_{Ar}$), 141.3 (*C*$_{Ar}$), 135.2 (*C*$_{Ar}$), 130.9 (2C, *C*$_{Ar}$), 130.7 (CH$_2$*C*H=*C*H$_2$), 129.8 (2C, *C*$_{Ar}$), 129.5 (*C*$_{Ar}$), 128.6 (*C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 127.1 (*C*$_{Ar}$), 125.9 (*C*$_{Ar}$), 124.6 (*C*$_{Ar}$), 123.4 (*C*$_{Ar}$), 122.8 (*C*$_{Ar}$), 119.6 (*C*$_{Ar}$), 117.9 (CH$_2$CH=*C*H$_2$), 109.0 (*C*$_{Ar}$), 56.5 (CH$_2$*C*CH), 51.2 (CH$_2$C*C*H), 42.3 (*C*H$_2$CCH), 39.9 (N*C*H$_2$), 34.2 (2C, (CH$_3$)$_3$*C*, (CH$_3$)$_3$*C*), 30.3 (6C, (*C*H$_3$)$_3$C, (*C*H$_3$)$_3$C) ppm.

IR (KBr) 3634, 3065, 2958, 2253, 1994, 1758, 1704, 1611, 1484, 1437, 1365, 1315, 1287, 1215, 1187, 1140, 1101, 1014, 975, 910, 840, 730, 676 cm^{-1}.

HRMS (ESI) calcd for $C_{34}H_{37}NO_4Na$ [M + Na]$^{+}$: 546.2615, found 546.12613.

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6. Abbreviation

Å	Ångström
Ac	acetyl
Ar-	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
cat.	catalyst
Cy	cyclohexyl
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	p-methoxyphenyl
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

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