Development of Novel Asymmetric Organocatalytic Reactions Based on Ketimines and *para*-Quinone Methides

vorgelegt von

Kun Zhao

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

vorgelegt von

M.Sc.

Kun Zhao

aus Qing Zhou,Shandong (V. R. China)

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

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Parts of this work have been published:

1. "Organocatalytic domino oxa-Michael/1,6-addition reactions: asymmetric synthesis of chromans bearing oxindole scaffolds", Kun Zhao, Ying Zhi, Tao Shu, Arto Valkonen, Kari Rissanen, Dieter Enders, *Angew. Chem. Int. Ed*. **2016**, *55*, 12104.

2. "Asymmetric organocatalytic synthesis of 3-diarylmethine-substituted oxindoles bearing a quaternary stereocenter *via* 1,6-conjugate addition to *para*-quinone methides", Kun Zhao, Ying Zhi, Ai Wang, Dieter Enders, *ACS Catal*. **2016**, *6*, 657.

3. "Asymmetric synthesis of 3,3'-pyrrolidinyl-dispirooxindoles *via* a one-pot organocatalytic Mannich/deprotection/aza-Michael sequence", Kun Zhao, Ying Zhi, Xinyi Li, Rakesh Puttreddy, Kari Rissanen, Dieter Enders, *Chem. Commun.* **2016**, *52*, 2249.

4. "An organocatalytic Minnich/Denitration reaction for the asymmetric synthesis of 3-ethylacetate-substitued 3-amino-2-oxindoles : formal synthesis of AG-041R", Kun Zhao, Tao Shu, Jiaqi Jia, Gerhard Raabe, Dieter Enders, *Chem. Eur. J.* **2015**, *21*, 3933.

Contributions to other projects:

5. "Asymmetric synthesis of functionalized trifluoromethyl-substituted pyrrolidines via an organocatalytic domino Michael/Mannich [3+2] cycloaddition", Ying Zhi**,** Kun Zhao, Qiang Liu, Ai Wang, Dieter Enders, *Chem. Commun.* **2016**, *52*, 14011.

6. "Synthesis of benzotriazepine derivatives *via* [4+3] cycloaddition of aza-*o*-quinone methide intermediates and azomethine imines", Ying Zhi, Kun Zhao, Tao Shu, Dieter Enders, *Synthesis* **2016**, *48*, 238.

7. "Asymmetric synthesis of cyclopentanes bearing four coutiguous stereocenters *via* an NHC-catalyzed Michael/Michael/esterification domino reaction", Tao Shu, Qijian Ni, Xiaoxiao Song, Kun Zhao, Tianyu Wu, Rakesh Puttreddy, Kari Rissanen, Dieter Enders, *Chem. Commun.* **2016**, *52*, 2609.

Meinen Eltern und Ying

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1. Introduction

1.1 Organocatalysis

Since the turn of the millennium, organocatalysis developed rapidly and have been considered as one of the most powerful tools in organic synthesis. Indeed, organocatalysis has become the third pillar of asymmetric catalysis besides metal and biocatalysis.[1] As demonstrated in Figure 1, the number of publications covering organocatalysis has markedly increased over the last sixteen years.

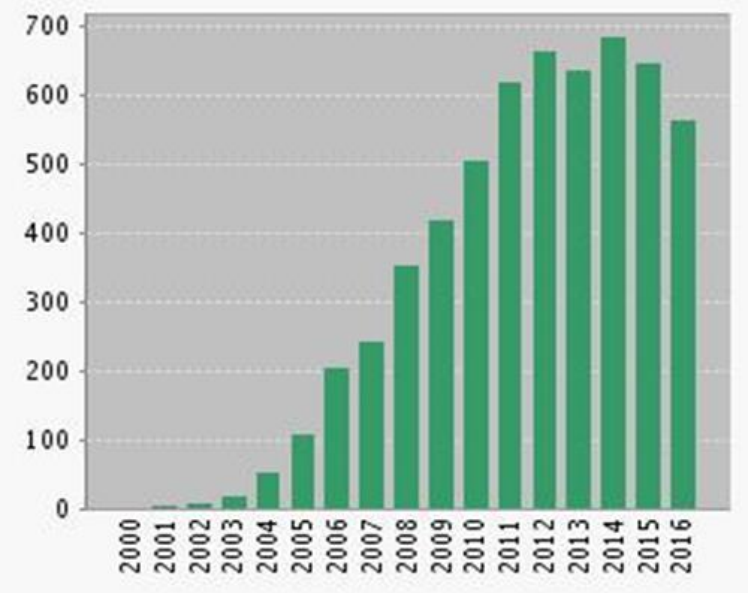


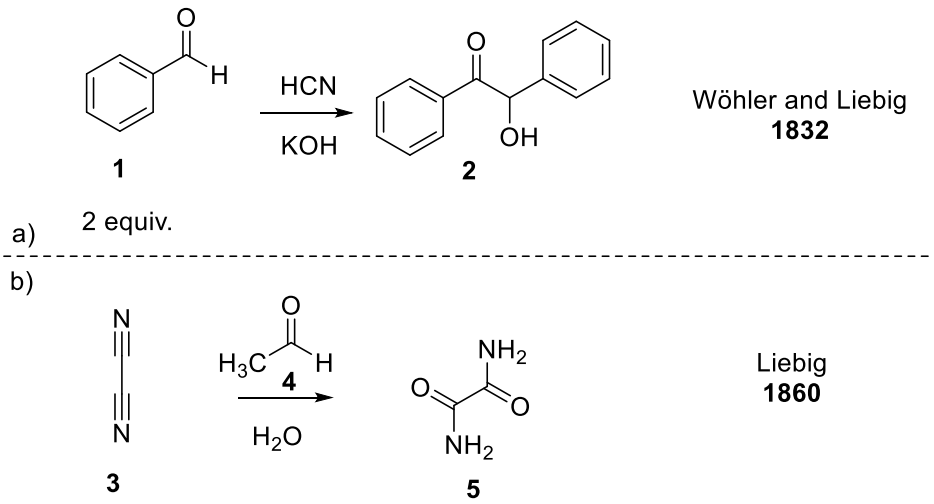
Figure 1. *Number of publications covering "organocatalysis".*[2]

Organocatalysis offers some advantages to researchers in industry and academia.[3] In organocatalysis, the catalysts are readily accessible small chiral organic molecules, and most of them are derived from nature's chiral pool such as amino acids or cinchona alkaloids. Furthermore, these catalysts are generally insensitive to moisture and oxygen, allowing the reactions to proceed easily and avoiding using stringent conditions such as degassing techniques.

1.1.1 Historical background

In this section, the pioneering investigations in the field of organocatalysis will be briefly introduced. More modern examples can be found in several excellent reviews and books on the topic of organocatalysis.[1]

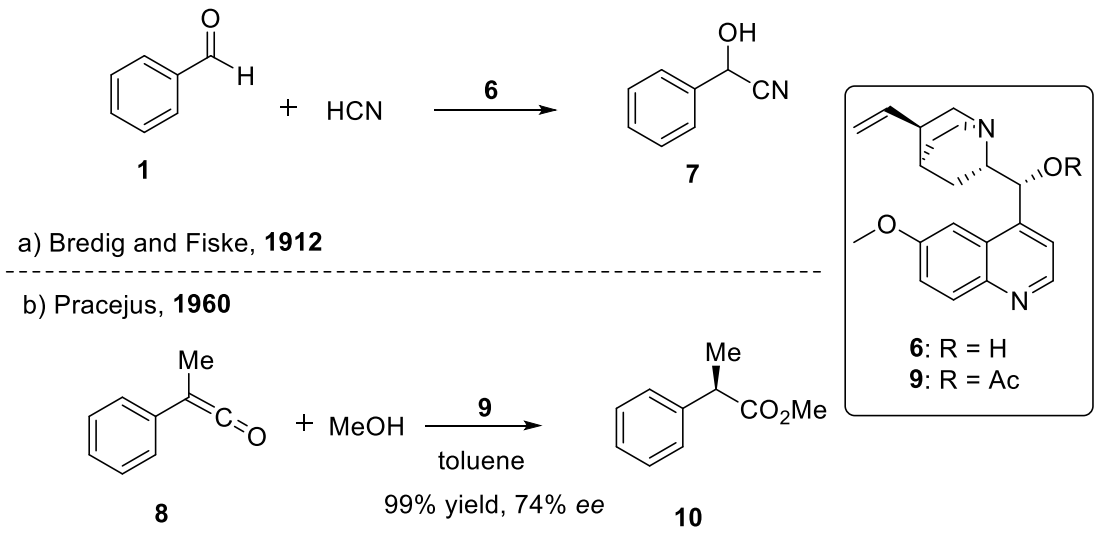
The history of organocatalysis began in 1832, when Friedrich Wöhler and Justus von Liebig discovered the first organocatalyzed benzoin condensation reaction, where two equivalents of benzaldehyde **1** reacted to yield compound **2** in the presence of cyanide (Scheme 1a).[4] About 40 years later, another reaction was disclosed by Liebig, and in the presence of the acetaldehyde catalyst the oxamide **5** could be synthesized from substrates **3** and water (Scheme 1b).[5] After these pioneering examples, several other researchers, including Knoevengel, Bölsing and Verley, and Dajin, made important contributions to this field.[6]



Scheme 1. *Pioneering cases of organocatalytic reactions.*

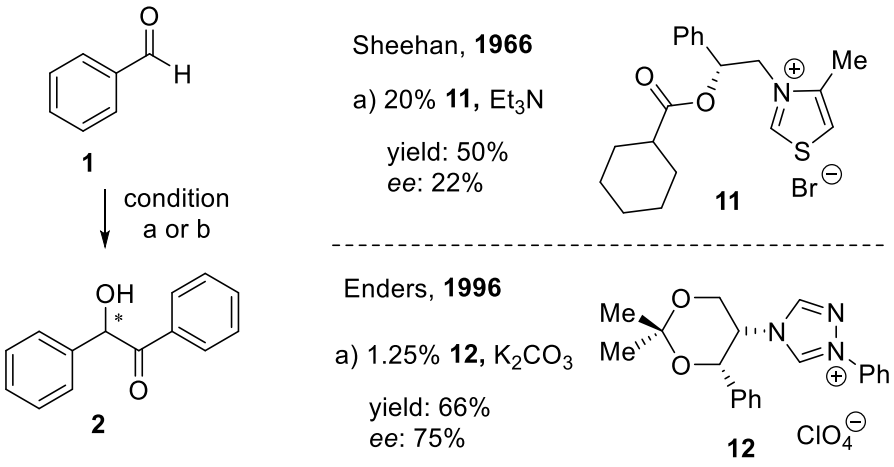
In 1912, the first asymmetric organocatalytic reaction was discovered by Bredig and Fiske (Scheme 2a).[7] They disclosed the addition of HCN to benzaldehyde employing a cinchona alkaloid catalyst **6**, albeit with very low enantioselectivities (<10%). About 50 years later, Pracejus reported the addition of methanol to ketene using *O*-acetyl

quinine **9** with 74% enantioselectivity (Scheme 2b).[8]



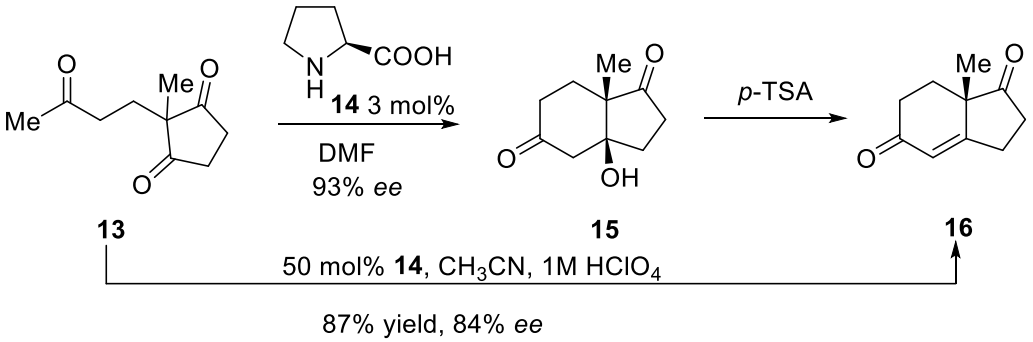
Scheme 2. *Pioneering asymmetric examples.*

In 1966, the first asymmetric benzoin condensation reaction was reported by Sheehan *et al.* (Scheme 3a).[9] The chiral thiazolium salt **11** was used as the precatalyst and the product **2** was formed with low *ee*. In the late eighties our group developed first enantioselective Stetter reactions[10a] and synthesized the triazolium type catalyst **12**, which was used for the Bemzoin transformation, giving better yield and higher enantioselectivity (75% *ee*) (Scheme 3b).[10b] The importance of these reports are groundbreaking in the area of N-heterocyclic carbene catalysis.



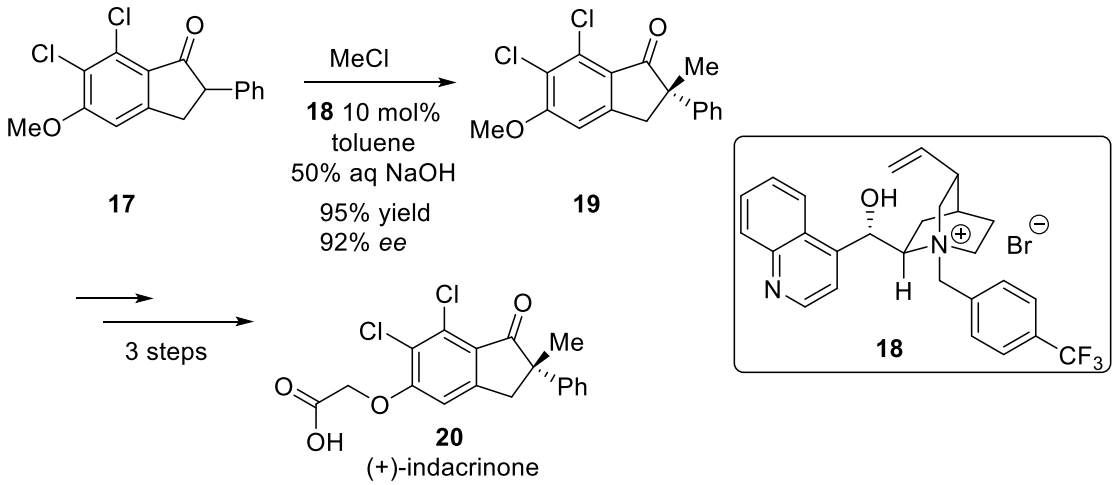
Scheme 3. *NHC-catalyzed asymmetric benzoin condensation reaction.*

During the early 1970s, another breakthrough in organocatalysis appeared. Several researchers used *L*-proline to catalyze an intramolecular aldol reaction, which is known as Hajos-Parrish-Eder-Sauer-Wiechert reaction.[11] This reaction yields the bicyclic product **16** (Wieland-Miescher ketone), which is a key building block for the synthesis of steroids (Scheme 4).



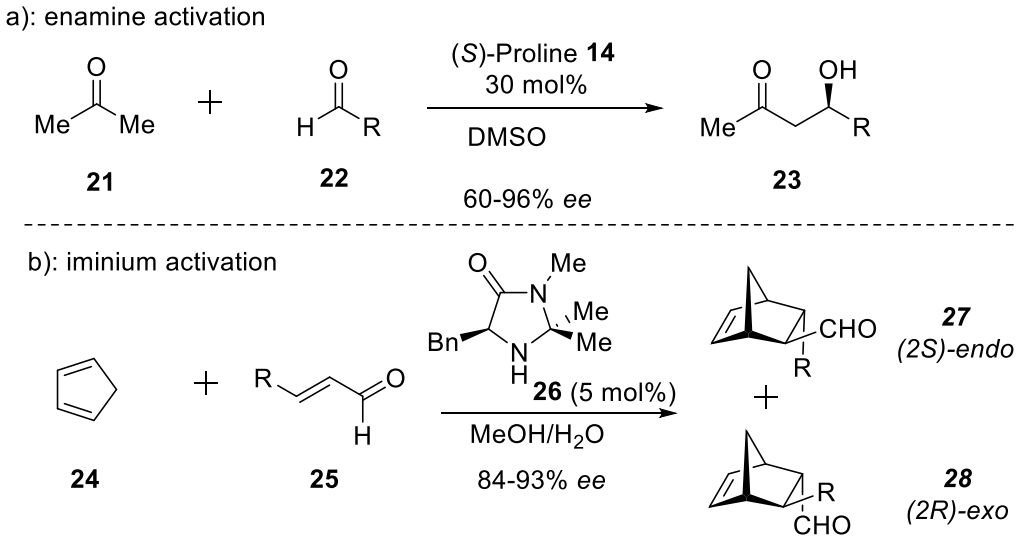
Scheme 4. *Proline-catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction.*

In 1984, researchers of the Merck Company reported the first asymmetric transformation in the field of phase-transfer catalysis. Dolling *et al*. used a cinchonine derivative **18** as the catalyst for the methylation of compound **17**, and the desired alkylated product **19** could be obtained in 95% yield and 92% *ee*. After three additional steps, the asymmetric synthesis of (+)-indacrinone (**20**) was achieved (Scheme 5).[12]



Scheme 5. *Asymmetric synthesis of (+)-indacrinone.*

In 2000, we witnessed another breakthrough in the field of organocatalysis. List and Barbas reported the first proline-catalyzed cross-aldol reaction between acetone **21** and different aldehydes **22** to generate compound **23** with 60-90% ee. The author thought this aldol reaction proceeded via an enamine intermediate (Scheme 6a).[13] Almost at the same time, the MacMillan group developed another activation mode known as iminium activation and they reported the first organocatalytic asymmetric Diels-Alder reaction between cyclopentadiene **24** and enals **25**, which was activated by the chiral imidazolinone **26** (Scheme 6b).[14]



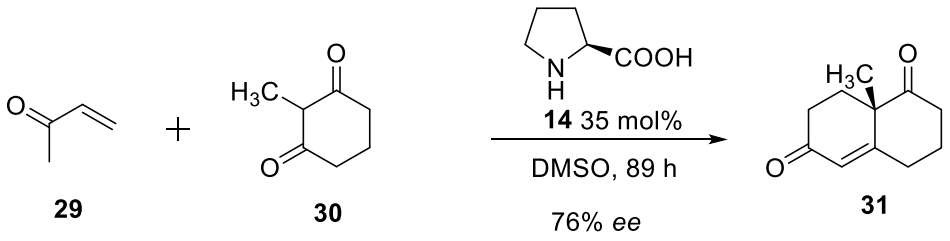
Scheme 6. *Pioneering reports of enamine and iminium activation.*

1.1.2 Organocatalytic domino reactions

Organocatalytic domino reactions have been demonstrated to be powerful synthetic tools in the hands of modern organic chemists, which can provide access to structurally complex compounds with very simple procedures from simple precursors.[15] In this section, two representative examples will be discussed.

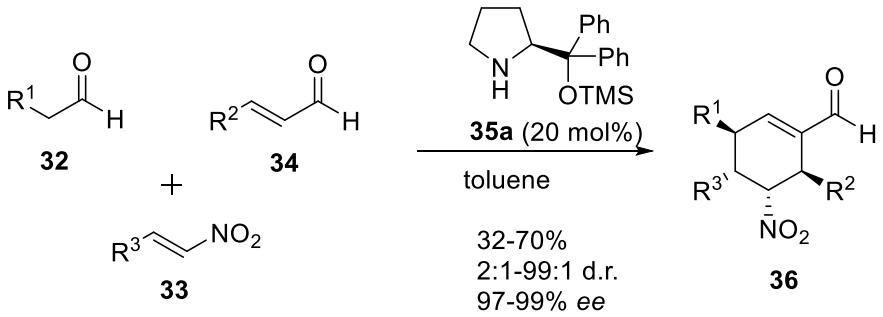
In 2000, Barbas and co-workers reported a proline-catalyzed asymmetric Robinson annulation reaction. In this reaction, in the presence (*S*)-proline as the catalyst, methyl

vinyl ketone **29** reacted with the diketone **30** to yield the Wieland-Miescher ketone **31** in 49% yield and 76% *ee* (Scheme 7). The first stereogenic Michael reaction was catalyzed by catalyst **14**, followed by an aldol condensation, to afford the adduct **31**.[16]



Scheme 7. *Proline-catalyzed asymmetric Robinson annulation reaction.*

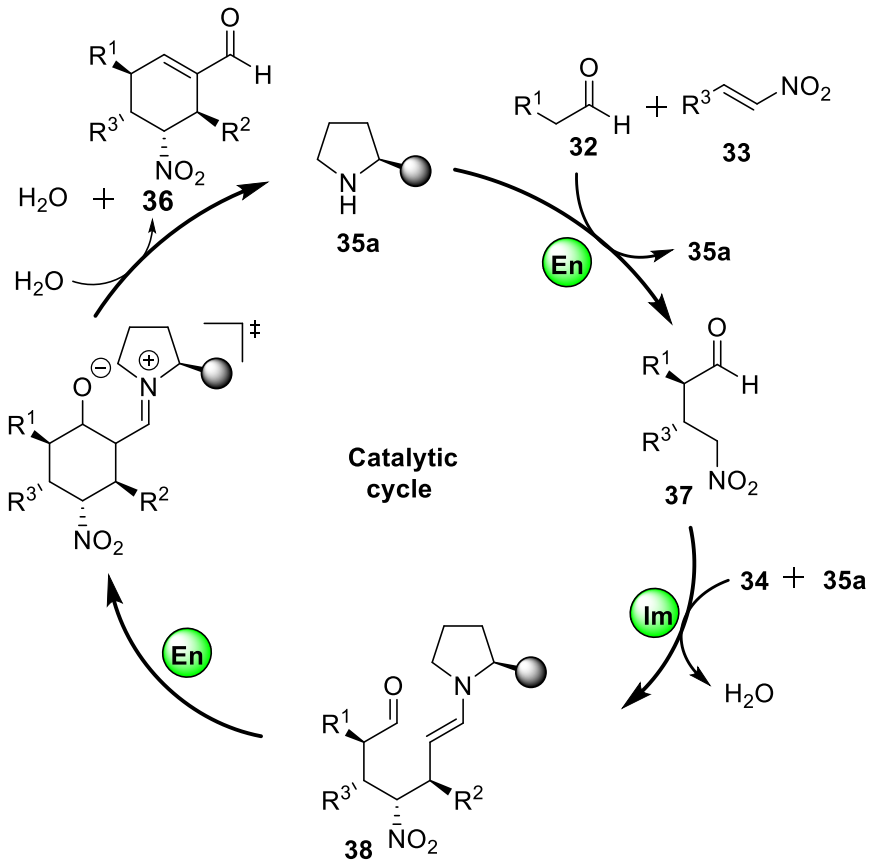
In 2006, Enders *et al*. reported the first three-component triple domino reaction for the synthesis of densely functionalized cyclohexene derivatives **36**. From three simple precursors **32-34**, in the presence of 20 mol% of **35a** this domino reaction proceeded through a Michael/Michael/aldol condensation process, yielding the desired products **36** in 32-70% yields and good to excellent stereoselectivities (Scheme 8).[17]



Scheme 8. *Organocatalytic asymmetric synthesis of cyclohexene derivatives via a triple domino reaction.*

The catalytic cycle is shown in Scheme 9. First, the catalyst **35a** reacts with aldehyde **32** to generate the enamine species, which add to the substrate **33** through a Michael reaction. Next, **35a** reacts with the enal **34** to form an iminium ion**,** which can be attacked by compound **37** in the second Michael reaction to deliver the enamine

intermediate **38**. Then an intramolecular aldol condensation occurred to afford the final products **36** and regenerate the catalyst **35a** (Scheme 9).



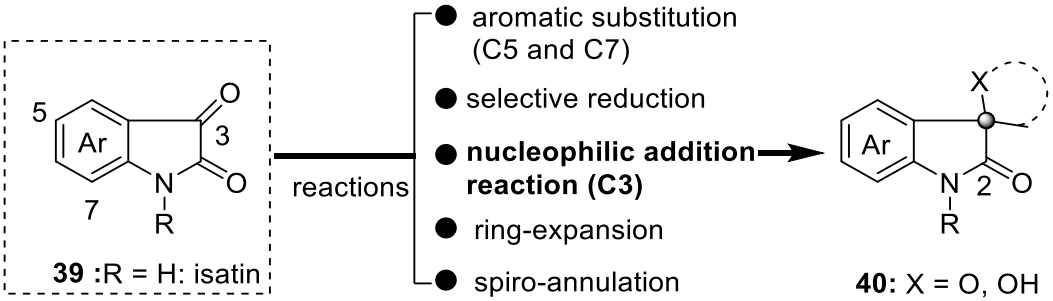
Scheme 9. *Catalytic cycle for this organocatalytic triple domino reaction.*

In addition, organocatalytic domino reactions are not only restricted to the field of amine catalysis. More and more domino reactions have been developed in other branches of organocatalysis, such as hydrogen-bonding catalysis, Brønsted-acid catalysis and NHC-catalysis.[18]

1.2 Ketimines derived from isatins: a new player in synthesis

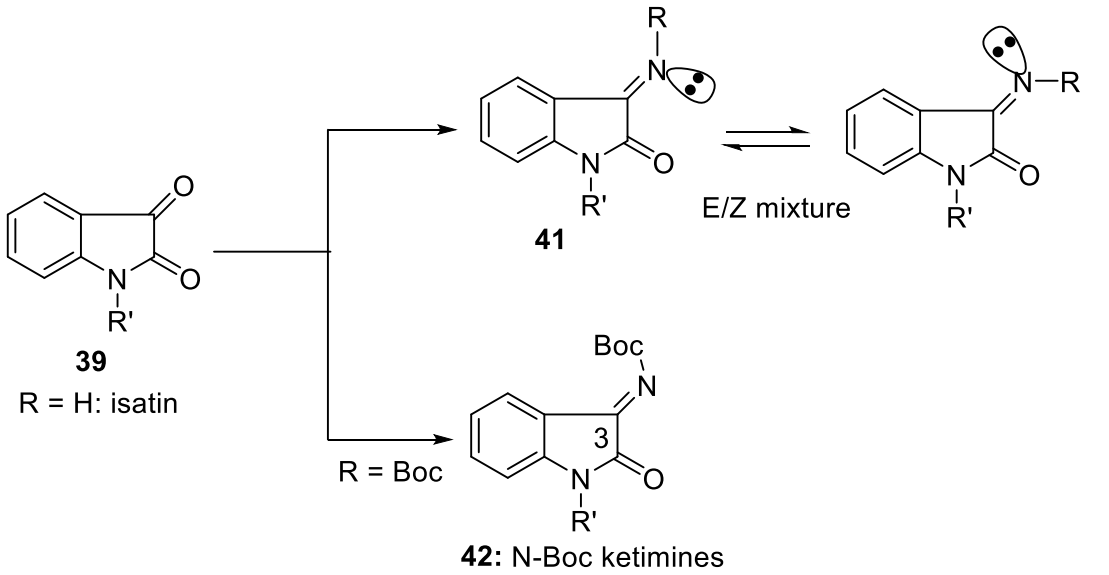
1.2.1 Background of isatins and isatin-derived ketimines

Indoline-2,3-dione (Scheme 10, left), usually known as isatin (**39**), has been known for more than one and a half century in organic synthesis. In 1841 Erdman and Laurent first synthesized it through oxidation of indigo using chromic and nitric acids. The isatin skeleton widely exists in nature from several plants such as *Isatis tinctoria* to the parotid gland secretions of *Bufo* frogs. Structurally, it bears an indole motif with a ketone and a γ-lactam unit. Synthetically, isatins have been considered as versatile molecules and can undergo several reactions including electrophilic aromatic substitution at C-5 or C-7 positions of the aromatic ring, selective reductions, nucleophilic addition reactions on the C-3 carbonyl group and spiro-annulations (Scheme 10, middle).[19] Among them, the addition reactions onto the C-3 carbonyl group, which is a prochiral center, have received extensive attention among researches, providing 2-oxindole derivatives **40** (Scheme 10, right).



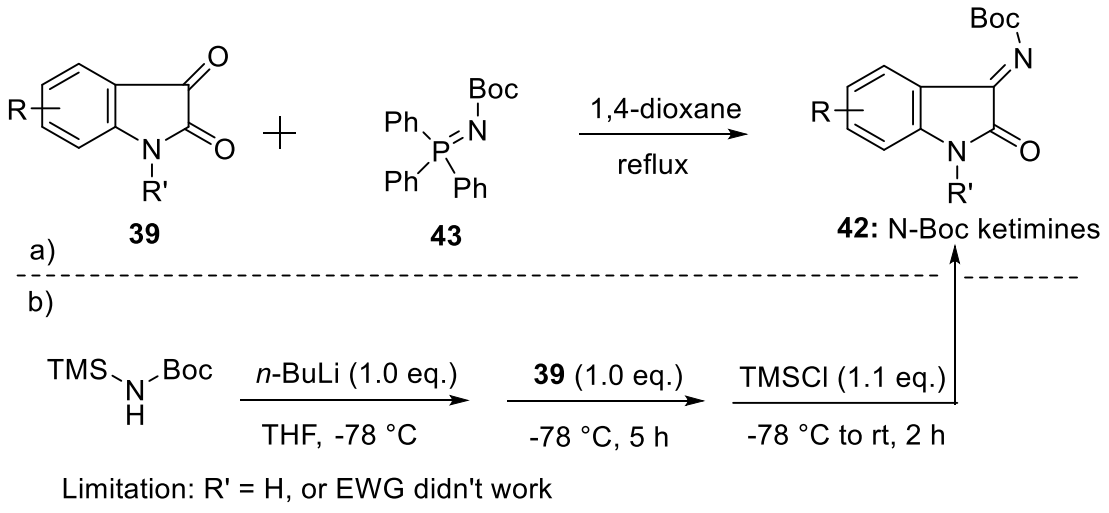
***Scheme 10**. The structure of isatin and general reactions based on it.*

The past several years have witnessed the emergence of ketimines derived from isatins. Several research groups found that compounds **41** exist as mixture of E/Z isomers and the ratio of these isomers is dependent on the solvent. This problem to some extent limits their use in synthesis.[20] If the electron-withdrawing group, such as the Boc group, is introduced, there is only one isomer.



Scheme 11. *The structure of ketimines derived from isatins.*

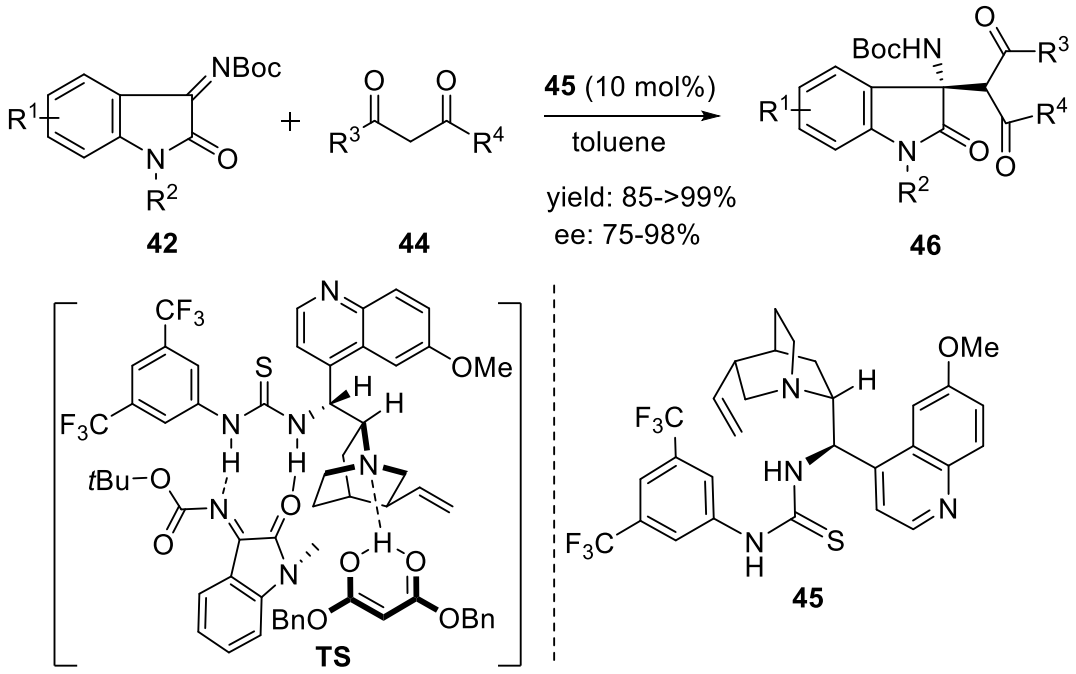
In 2012, Wang and co-workers first reported the synthesis of N-alkoxycarbonyl ketimines derived from isatins by using the aza-Wittig reaction (Scheme 12a).[21] Almost at the same time, Shibata *et al.* developed another approach to obtain this kind of compounds (Scheme 12b).[22] But the second method showed a limitation for substrates bearing H or EWG on the nitrogen.



Scheme 12. *Strategies for the synthesis of ketimines derived from isatins.*

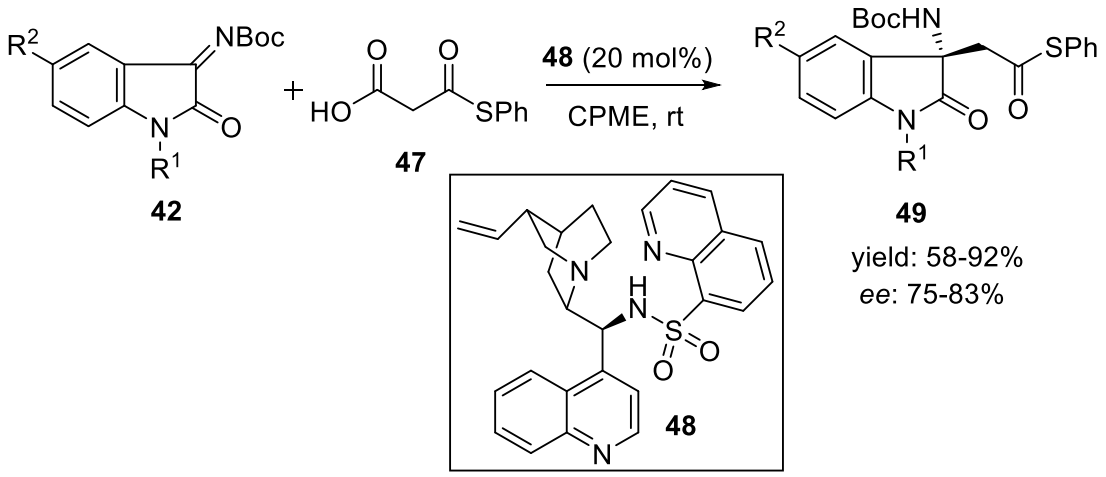
1.2.2 Organocatalytic reactions of isatin-derived ketimines.

In 2012, Wang and co-workers reported the synthesis of isatin-derived N-Boc ketimines and explored the synthetic utility of this sort of compounds. The enantioselective addition of 1,3-dicarbonyl compounds **44** to ketimines **42** was realized by using a bifunctional thiourea catalyst (**45**), yielding the chiral 3-aminoxindoles **46** in high yields and excellent enantioselectivities (Scheme 13).[21]



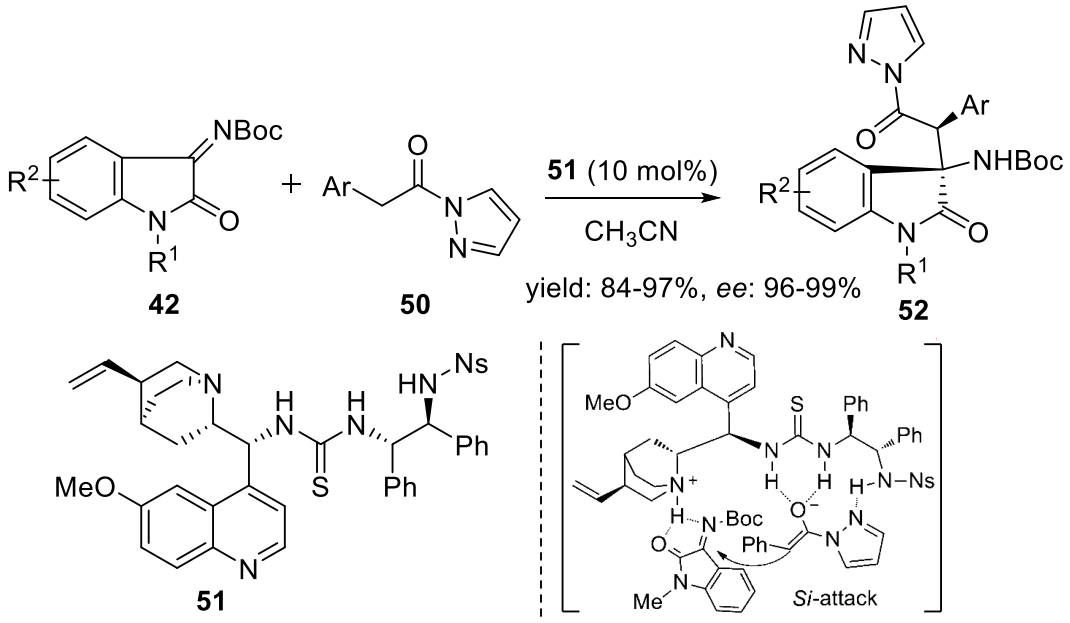
Scheme 13. *Quinidine derived thiourea catalyzed asymmetric addition of 1,3-dicarbonyl compounds to N-Boc ketimines.*

After that, the group of Shibata developed a highly enantioselective decarboxylative Mannich reaction between malonic acid half thioesters (MATHs) **47** and isatin imines **42**. A novel 8-sulfonylated quinolone organocatalyst **48** was used and the final products **49** were synthesized in 58-92% yield and 75-83% *ee* values (Scheme 14).[22]



Scheme 14. *Organocatalytic decarboxylation addition of MATHs to isatin imines.*

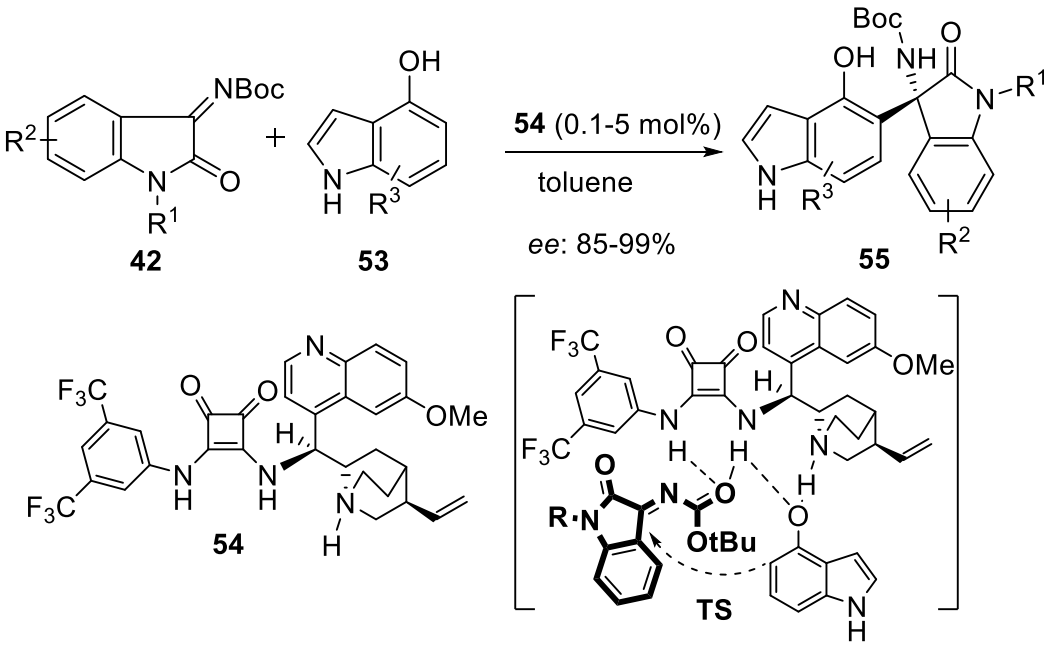
Recently, Wu *et al.* reported the organocatalytic enantioselective Mannich reaction of pyrazoleamides **50** with *N*-Boc ketimines derived from isatins. Employing molecular sieves as additive and 10 mol% of **51** as the catalyst, a series of isatin-derived β-amino amides **52** could be synthesized in 84-97% yield with excellent diastereo- and enantioselectivities. The author also prestented a plausible transition state to explain the stereocontrol of this reaction (Scheme 15).[23]



Scheme 15. *Organocatalytic Mannich reaction of pyrazoleamides to isatin imines.*

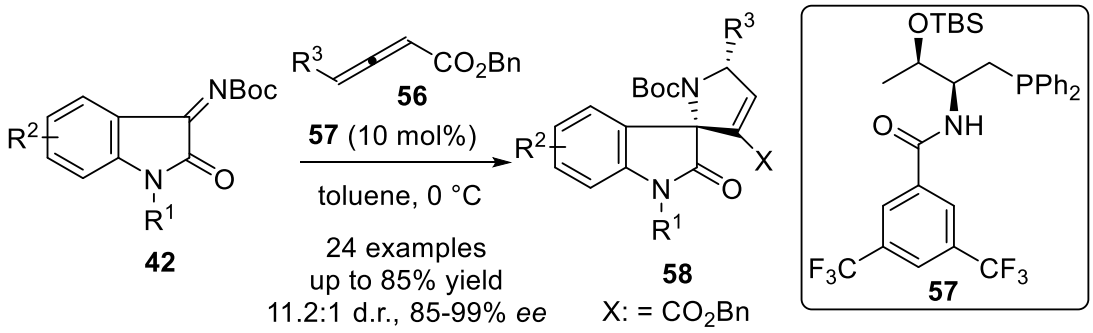
Simultaneously, the research group of Pedro disclosed a general method for the

asymmetric Friedel-Crafts reaction of isatin-derived ketimines **42** with hydroxyindoles **53** by using a squaramide type catalyst. In this report, the catalyst loading was 0.1-5 mol% and hydroxyindoles react in the benzene ring rather than in the azole part to afford the corresponding products **55** in good to excellent enantioselectivities (Scheme 16).[24]



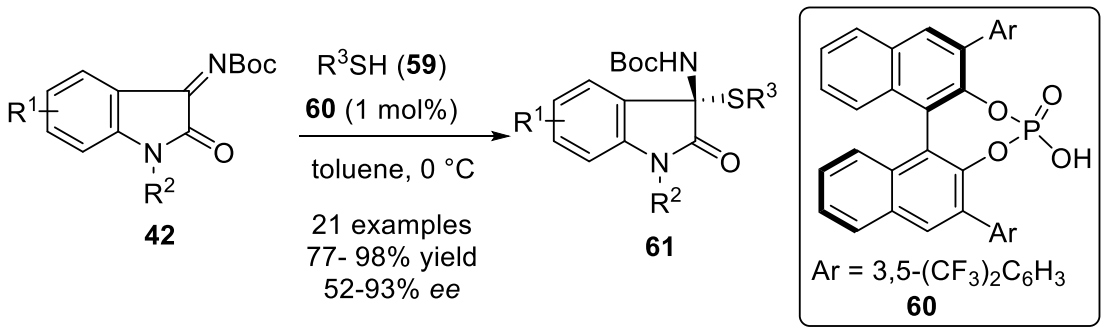
Scheme 16. *Asymmetric Friedel-Crafts reaction of hydroxyindoles with isatin imines.*

Recently, a highly enantioselective [3+2] annulation reaction between allenoates **56** and isatin-derived ketimines **42** was developed by Lu and co-workers. Using a chiral amino acid-derived phosphine catalyst this protocol could lead to the facile synthesis of 3,2'-pyrrolidinyl spirooxindoles **58** in excellent yields and with perfect enantioselectivities (>98% *ee* in all examples) (Scheme **17**).[25]



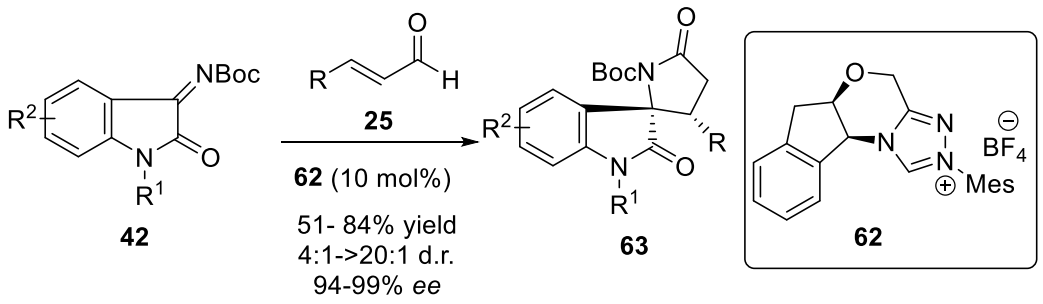
Scheme 17. *Asymmetric [3+2] cycloaddition reaction of allenoates with isatin-derived ketimines.*

In 2015, our group reported the organocatalytic asymmetric nucleophilic addition of thiols **59** to ketimines derived from isatin. In this reaction, only 1 mol% of a chiral phosphoric acid (**59**) was used, and a variety of chiral isatin-derived *N*,S-acetals **61** were synthesized in 77-98% yields and modest to high enantioselectivities (52-93% ee) (Scheme 18).[26]



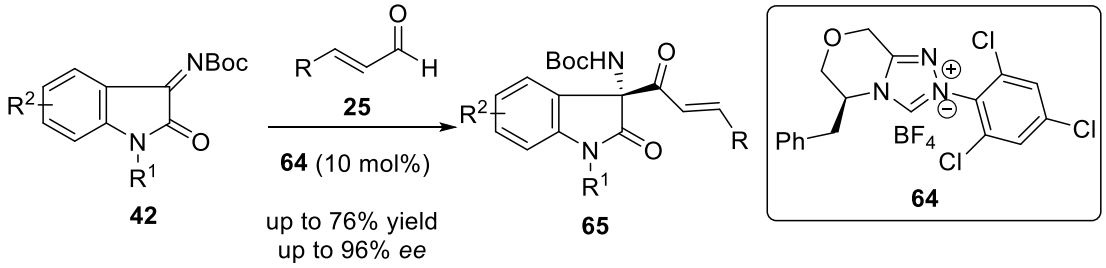
Scheme 18. *Phosphoric acids catalyzed addition of thiols to isatin-derived ketimines.*

Furthermore, *N*-heterocyclic carbene catalyzed reactions based on isatin-derived ketimines have been also studied by several research groups. In 2012, Chi and co-workers demonstrated an NHC-catalyzed annulation reaction between enals **25** and *N*-Boc ketimines for the synthesis of spirocyclic γ-lactams **63**. This method allows for a facile construction of spirocyclic oxindole-γ-lactams in 51-84% yields, excellent enantioselectivities (94-99% ee) and good to excellent diastereoselectivities (4:1- >20:1 d.r.) (Scheme 19).[27]



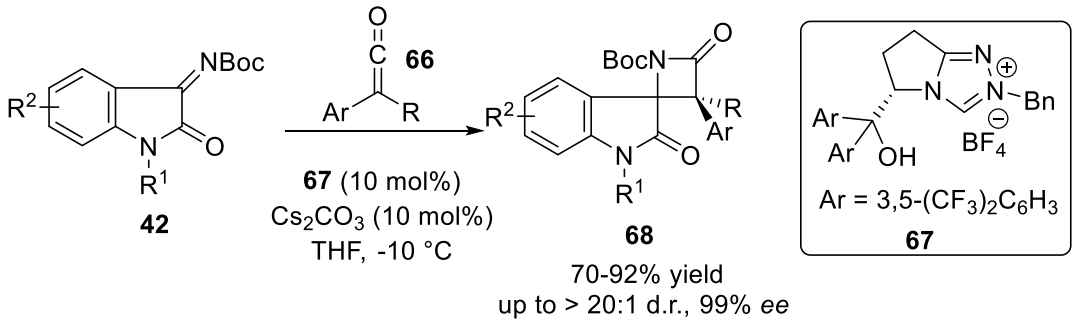
Scheme 19. *NHCs catalyzed asymmetric addition of enals to isatin imines.*

Later, the same group reported the NHC-promoted intermolecular cross-aza-benzoin reaction between enals and ketimines **42**. They found that the chemoselectivity (the acyl anion pathway versus the homoenolate or enolate pathway) can be controlled by choosing different catalysts. The aza-benzoin reaction, through the acyl anion pathway, was favored when the electron-deficient carbene catalyst **64** was used. The chiral aminooxindoles **65** were obtained in 10-76% yields and up to 96% *ee* (Scheme 20).[28]



Scheme 20. *NHCs catalyzed cross-aza-benzoin reaction of enals with isatin imines.*

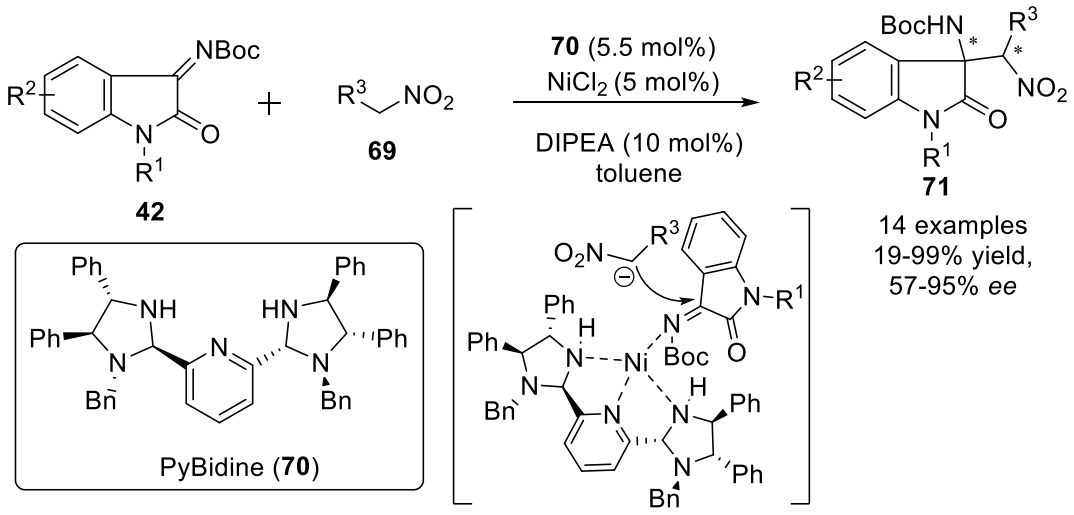
In 2015, Ye and co-workers reported a bifunctional NHC-catalyzed enantioselective Staudinger reaction of ketenes **66** with isatin-derived ketimines **42** for the synthesis of spirocyclic-*β*-lactams **68**. The free hydroxyl group in **67** was proved to be critical for this transformation, and the corresponding products featuring tetrasubstituted stereocentres could be afforded in 70-92% yields and with 87-99% *ee* (Scheme 21).[29]



Scheme 21. *NHCs catalyzed Staudinger ketene-imine cycloaddition.*

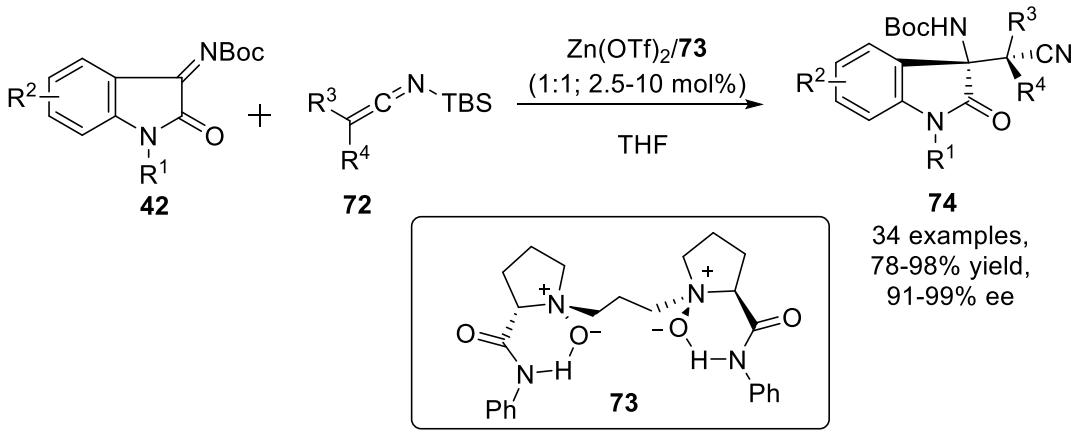
1.2.3 Metal-catalyzed reactions of isatin-derived ketimines.

In 2014, Arai *et al*. reported the asymmetric nitro-Mannich reaction of the isatin-derived ketimines **42** by using a PyBidine-$NiCl_2$ complex as the catalyst. A series of chiral 3-substituted 3-amino-2-oxindole derivatives **71** were synthesized in 19-99% yields and 57-95% *ee* (Scheme 22).[30]



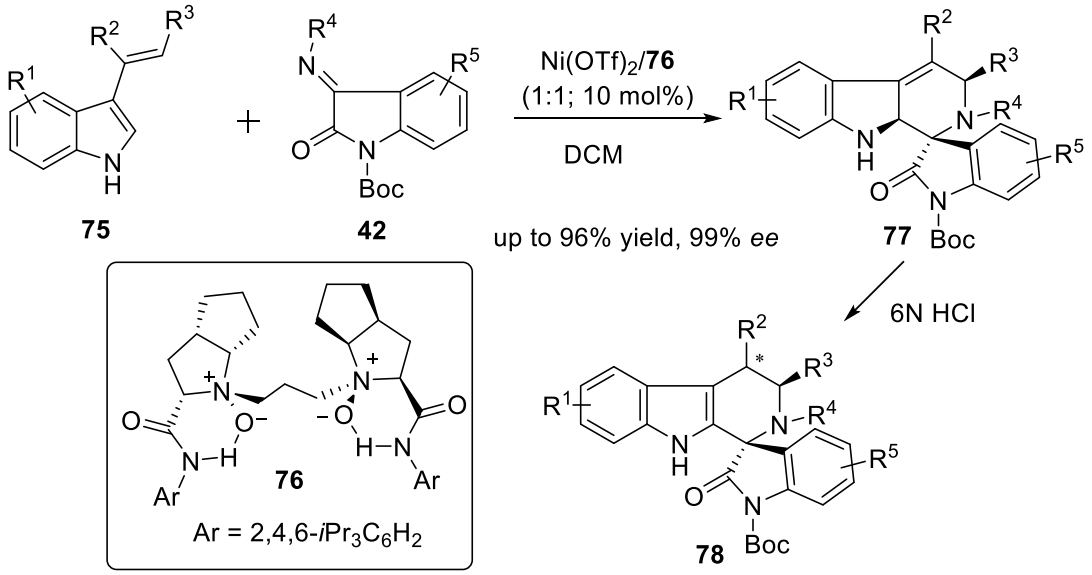
Scheme 22. *PyBidine-$NiCl_2$ catalyzed nitro-Mannich reaction of ketimines.*

In 2015, Feng and co-workers demonstrated a highly enantioselective Mannich reaction between silylketene imines **72** and isatin-derived ketimines **42** using a chiral N,N'-dioxide/Zn complex as the catalyst. The desired 3-amino oxindoles **74** bearing two vicinal tetrasubstituted stereocenters were formed in excellent yields and enantioselectivities (up to 98% yield, 99% *ee*) (Scheme 23).[31]



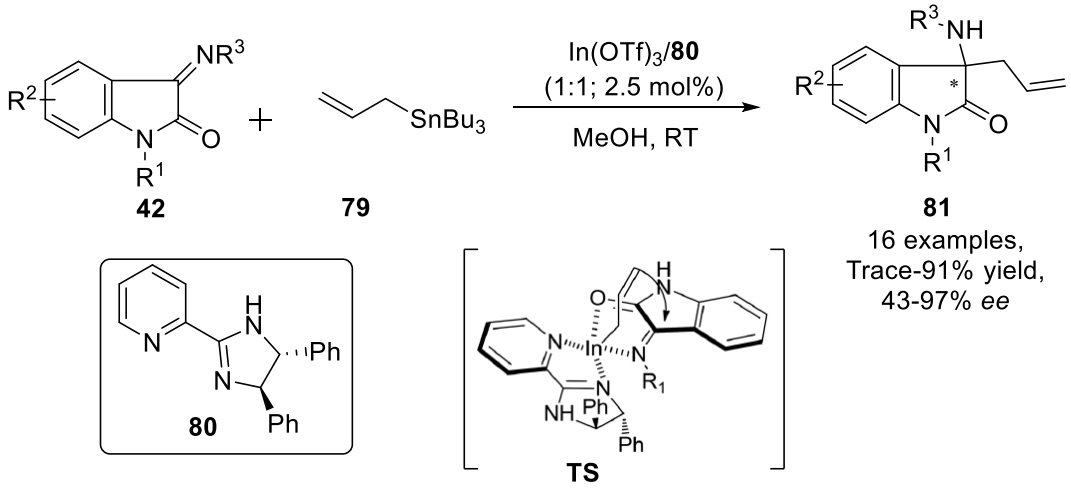
Scheme 23. *N,N-dioxide/Zn^{II} catalyzed Mannich reaction of silyl imines to isatin-derived ketimines.*

After this work, the asymmetric *aza-Diels-Alder* reaction between 3-vinylindoles **75** and isatin-derived ketimines **42** was reported by the same group. Several spiroindolone derivatives **77** could be obtained, and good yields and excellent enantioselectivities were also achieved by using a chiral *N,N*-dioxide $Ni(OTf)_2$ complex as the catalyst. In addition, the antimalarial compound NITD609 was synthesized in an overall yield of 40.6% in 3 steps (Scheme 24).[32]



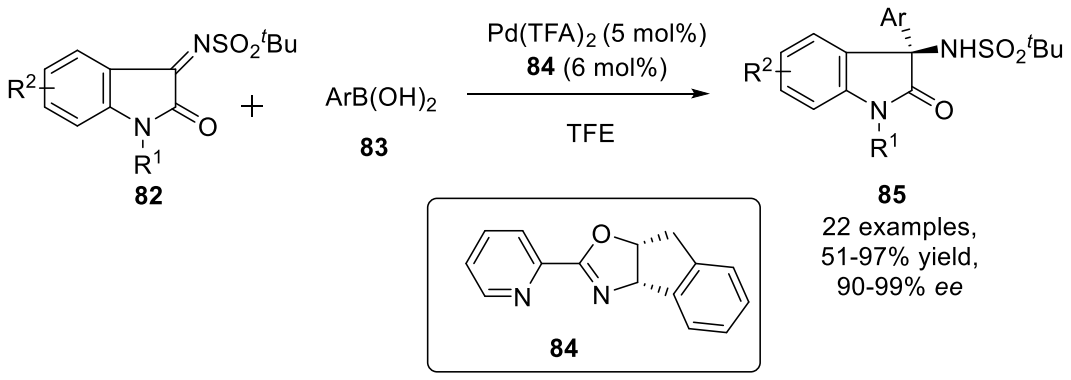
Scheme 24. *Regio- and enantioselective Aza-Diel-Alder reaction of 3-vinylindoles with isatin-derived ketimines.*

In 2016, Cai *et al*. disclosed the asymmetric allylation of ketimines derived from isatins. In the presence of only 2.5 mol% of $In(OTf)_3$ and an imidazolylpyridine ligand, a series of 3-allyl 3-aminooxindole derivatives (**81**) were smoothly prepared in high yields with moderate to very good enantiomeric excesses. According to the stereochemical outcome of the reaction, the author also proposed a transition state (Scheme 25).[33]



Scheme 25. *$In(OTf)_3$ catalyzed asymmetric allylation of isatin ketimines.*

Quite recently, Zhang *et al.* reported a Pd(II)/Pyrox-catalyzed asymmetric addition of arylboronic acids **83** to 3-ketimino oxindoles **82** to synthesize the chiral 3-amino-2-oxindoles **85** bearing a quaternary stereocenter in 51-97% yields and with 90-99% enantioselectivities. This reaction is the first case of a palladium-catalyzed addition of an arylboronic species to exocyclic ketimines (Scheme 26).[34]

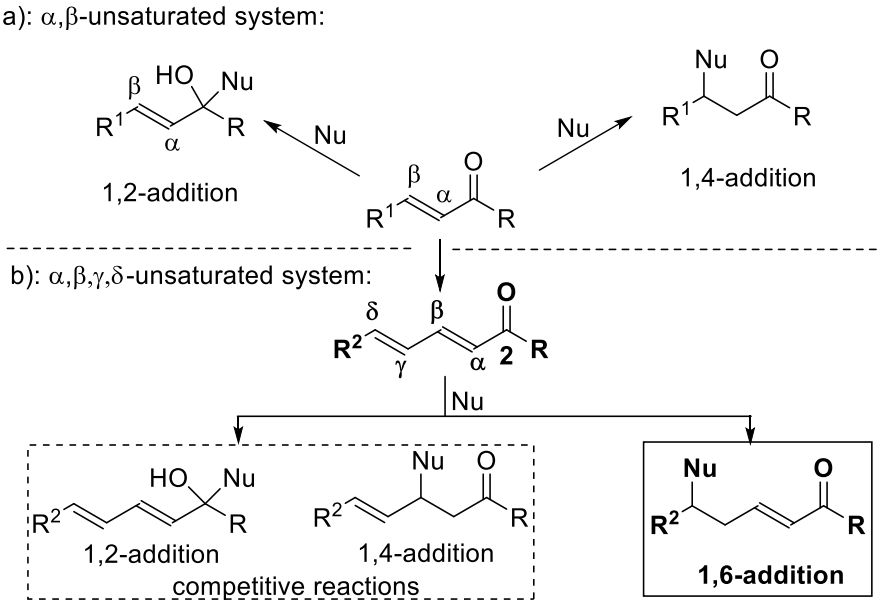


Scheme 26. *Pd(II)-catalyzed addition of arylboronic acids to isatin-derived ketimines.*

1.3 *para*-Quinone methide: a new 1,6-Michael acceptor

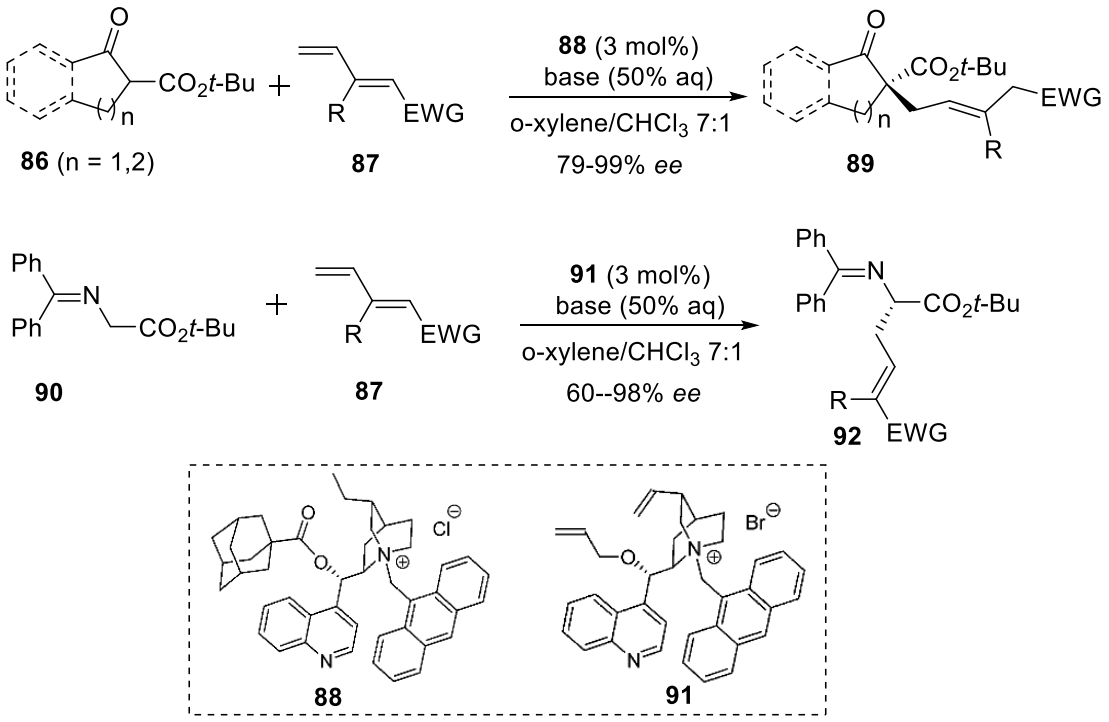
1.3.1 Background of organocatalytic 1,6-addition reactions

There is no doubt that the Michael addition reaction is one of the most atom-economic and powerful methods for the formation of C-C or C-X bonds in modern synthesis. The organocatalytic Michael reactions, using α,β-unsaturated systems as the Michael acceptors, have been studied in great detail[35] and several excellent reviews on this topic are available (Scheme 27a). In contrast, the α,β,γ,δ- doubly unsaturated system has been less investigated, especially in the organocatalysis community.[36] As shown in Scheme 27b, beside *δ* position there are two more reactivity sites (2- and *β*-positions) for the nucleophilic attack, resulting in competitive reactions like 1,2-additions and 1,4-additions. The presence of those potential competitive reactions poses the difficulty for chemists to explore 1,6-conjugated addition reactions. Moreover, some calculational and experimental studies have demonstrated that the 1,4-addition is generally favored over the 1,6-addition. So it is extremely challenging to develop 1,6-Michael acceptors, which is very critical for the organocatalytic 1,6-conjugated addition.



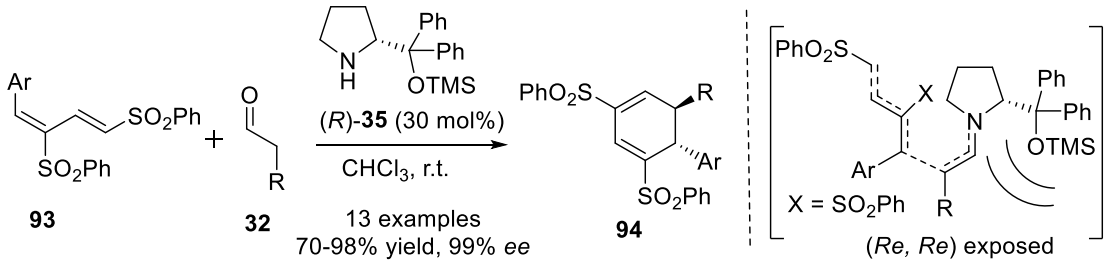
Scheme 27. *General reaction pathways for the 1,2-, 1,4- and 1,6- conjugated addition to unsaturated systems.*

In order to fill this gap, several research groups have reported some elegant examples based on organocatalytic strategies. In 2007, Jørgensen *et al.* reported the first asymmetric organocatalytic 1,6-addition reaction. Under phase-transfer conditions employing catalysts **88** or **91**, 1,6-Michael acceptors **87** were attacked by *β*-ketoesters **86** and benzophenones imines **90**, giving the corresponding products in 49-99% yields and with 60-99% *ee* (Scheme 28).[37]



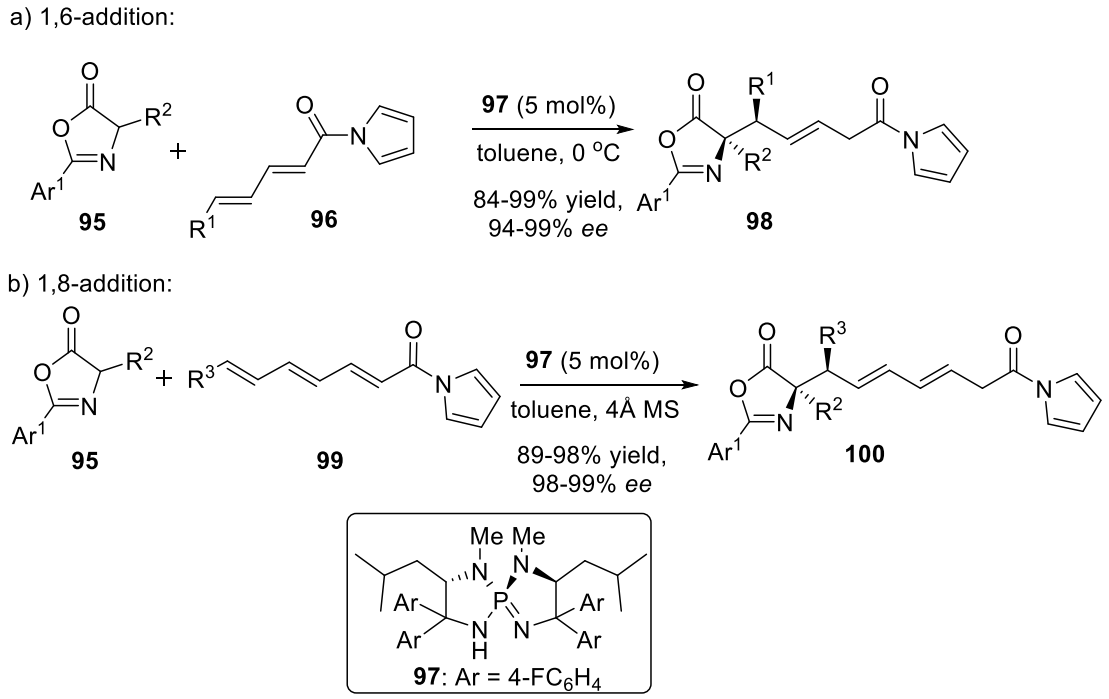
Scheme 28. *Asymmetric organocatalyzed 1,6-additions of ketoesters and glycine imines to activated dienes.*

In 2011, Alexakis and Stephens developed an asymmetric enamine 1,6-conjugated addition using 1,3-bis-(sulfonyl)-butadienes **93** as the 1,6-acceptors and the versatile dienes **94** were obtained in excellent yields and stereoselectivities. The key of this reaction is the introduction of the second electro-withdrawing group at the *γ*-carbon atom. The second sulfone renders the *δ*-positon more electrophilic and allows to achieve exclusively 1,6-addition. The huge steric repulsion away from the pyrrolidine ring is critical for the excellent stereoselectivities (Scheme 29).[38]



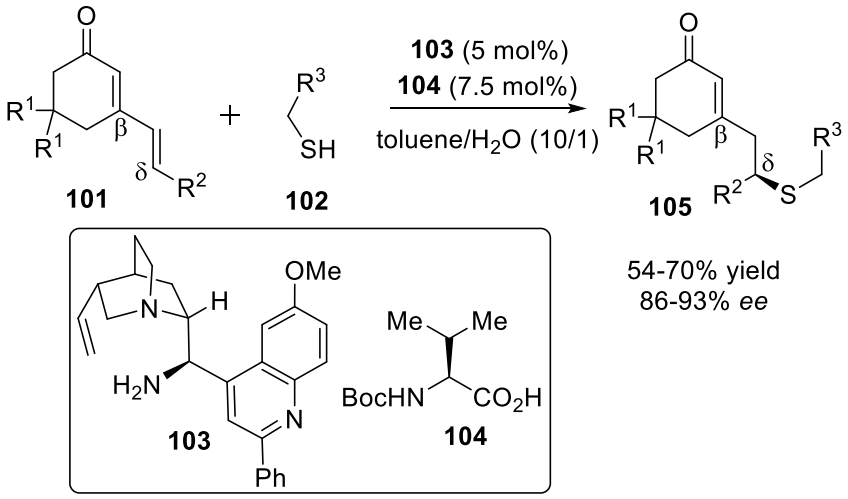
Scheme 29. *Organocatalyzed 1,6-additions of aldehyde to dienic sulfones.*

In 2012, Ooi and co-worker demonstrated a 1,6-addition of azlactones **95** to *δ*-substituted dienyl N-acylpyrroles **96** with excellent regio-, diastereo-, and enantioselectivities using chiral P-spiro triaminoiminophosphorane **97** as a catalyst (Scheme 30a). Furthermore, they also achieved the bis-vinylogous 1,8-addition between **95** and trienyl N-acylpyrroles **99** by slightly changing the reaction condition through the adding of 4A molecular sieves (Scheme 30b).[39]



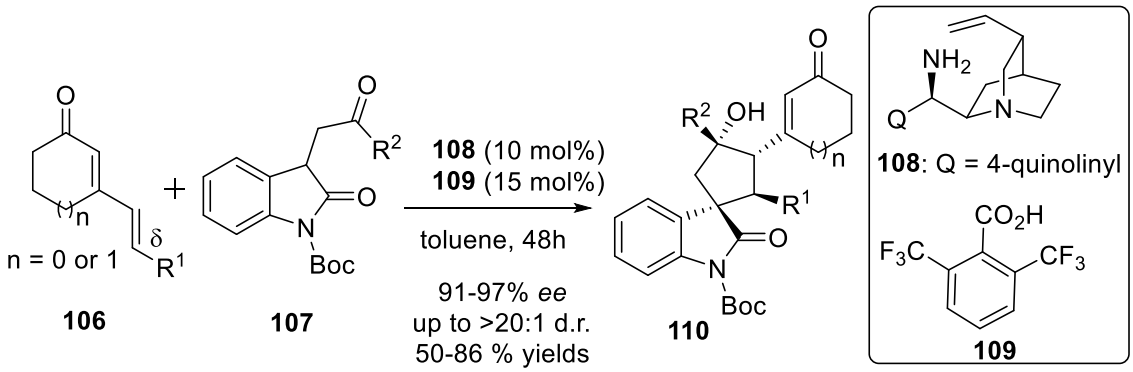
Scheme 30. *Organocatalyzed 1,6-additions or 1,8-addition of azlactones to dienyl or trienyl N-acylpyrroles.*

Besides compounds **87**, **93** and **96**, 2,4-dienones have also been used as the vinylogous Michael acceptors by the research groups of Melchiorre, Dixon and Ye. In 2012, Melchiorre *et al.* reported a case of organocatalytic enantioselective 1,6-addition reactions between alkyl thiols **102** and cyclic dienones **101** based on the vinylogous iminium strategy. The catalytic system, combining of a cinchona alkaloid derivative **103** and Boc-valine **104**, allows the reaction to occur with high stereocontrol (Scheme 31).[40]



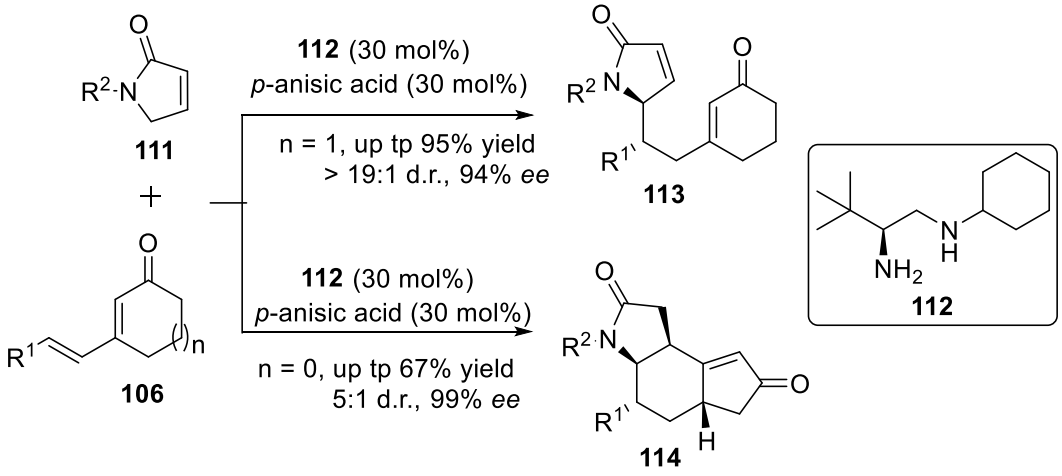
Scheme 31. *Enantioselective 1,6-addition reaction between thiols and dienones based on vinylogous iminium activation.*

Later, the same group successfully explored cyclic dienones **106** as bifunctional substrates in an organocatalyzed domino reaction employing the cinchona catalyst **108**. This cascade process was initiated by an organocatalytic 1,6-addition *via* vinylogous iminium ion activation, followed by an intramolecular aldol reaction, forming the products **110** in moderate to good yields (50-86%) and excellent stereoselectivities (up to > 20:1 d.r., 97% *ee*) (Scheme 32).[41]



Scheme 32. *Vinylogous organocascade catalysis: 1,6-addition/aldol sequence.*

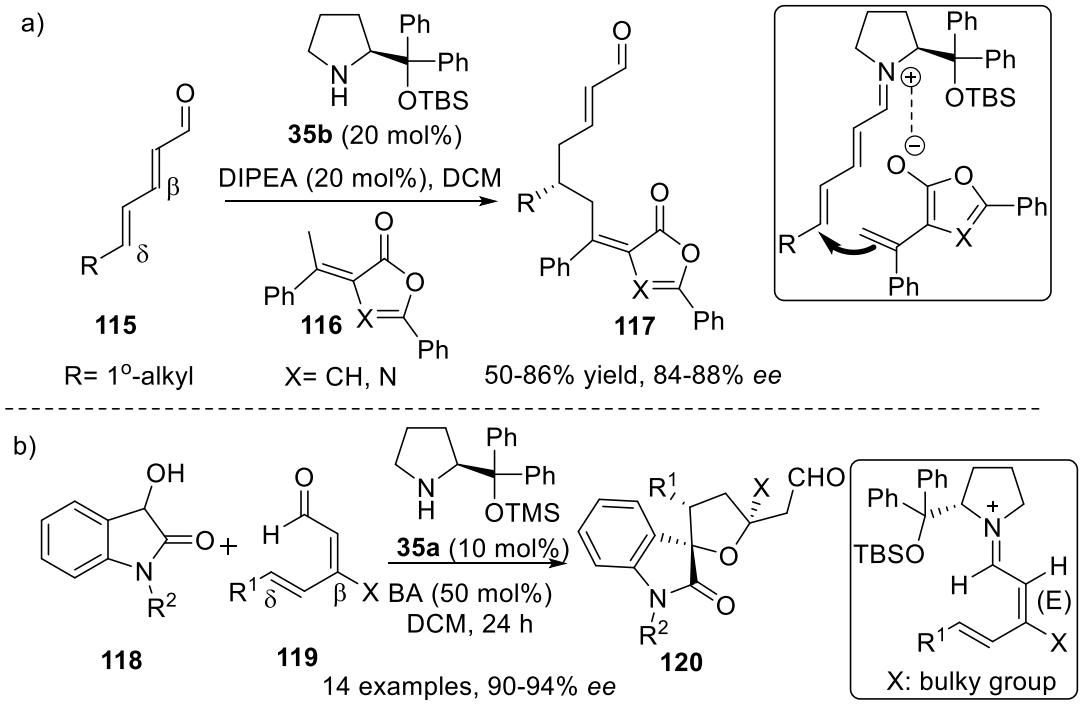
Very recently, Dixon and Ye reported an organocatalytic double vinylogous Michael addition of γ-butyrolactams **111** to β-substituted dienones **106** with very good site-, diastereo-, and enantioselectivities using a bifunctional diamine catalyst **112**. Interestingly, when five-membered dienones were used, the complex tricyclic γ-lactams could be obtain through a cascade reaction, which involves a vinylogous Michael addition/vinylogous Michael reaction followed by a isomerization reaction (Scheme 33).[42]



Scheme 33. *Organocatalyzed asymmetric double vinylogous Michael addition (DVMA).*

Recently, the groups of Jørgensen and Melchiorre have independently found that linear

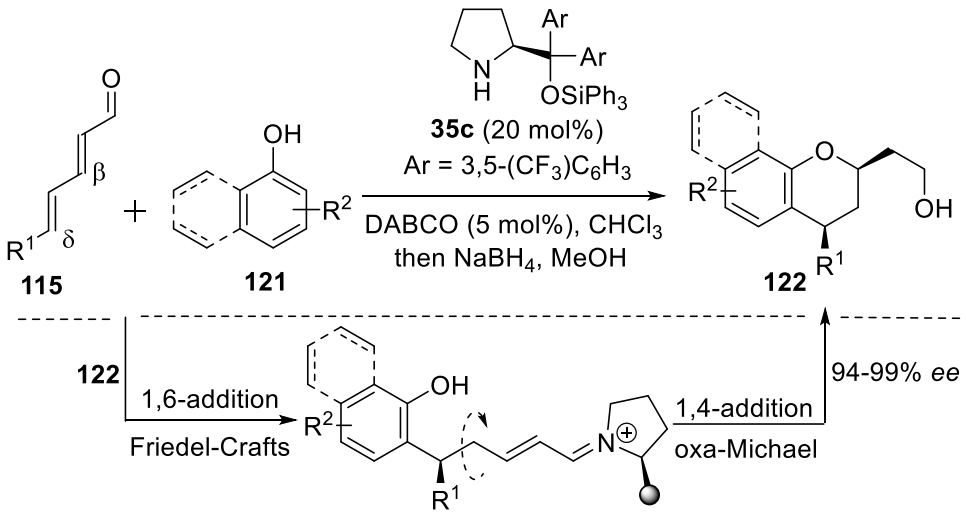
2,4-dienals could be employed in 1,6-addition reactions. In 2013, the first 1,6-addition to linear 2,4-dienals was reported by Jørgensen and co-workers. Through remote iminium-stereocontrol, in the presence of 20 mol% of the catalyst **35b** alkyl dienals **115** reacted with lactones **116** to yield the products **117**. The author also proposed a plausible transition state to explain the results (Scheme 34a).[43] Almost at the same time, Melchiorre *et al.* reported a regio- and stereoselective organocatalytic 1,6-addition of **118** to linear 2,4-dienals **119** with excellent δ-site and stereoselectivities, leading to very valuable tetrahydrofuran spirooxindoles **120**. Furthermore, they found that the huge group at the *β*-position of dienals was very critical to achieve good diastereo- and enantioselectivities (Scheme 34b).[44]



Scheme 34. *Organocatalyzed vinylogous Michael addition to linear 2,4-dienals.*

Quite recently, Jørgensen and co-workers have disclosed an elegant organocatalytic 1,6-Friedel-Crafts/1,4-oxa-Michael cascade reaction between hydroxyarenes **121** and 2,4-dienals **115**. This cascade reaction proceeds with excellent regio- and stereoselectivities, thus providing several chiral chroman derivatives **122** in 43–91%

yield and 94-99% *ee* (Scheme 35).[45]



Scheme 35. *Organocatalytic 1,6-Friedel-Crafts/1,4-oxa-Michael cascade reaction.*

1.3.2 Organocatalytic reactions of *para*-quinone methides.

para-Quinone methides (*p*-QMs) have been known by chemist for more than one century.[46] As depicted in figure 2, *para*-quinone methides consist of a carbonyl group and a cyclohexadiene with a methylene, and can be considered as vinylogous Michael acceptors. *p*-QMs can also been drawn as a mesomeric zwitterionic resonance structure, which indicates the high reactivity.[47] A wide range of biological and medicinal processes, such as enzyme inhibition and DNA alkylation, are based on the intrinsic electrophilic property of *p*-QMs. Meanwhile, the *para*-quinone methide unit is frequently encountered in several biological active natural products, thus *p*-QMs have been seen as key intermediates in biosynthesis.[48]

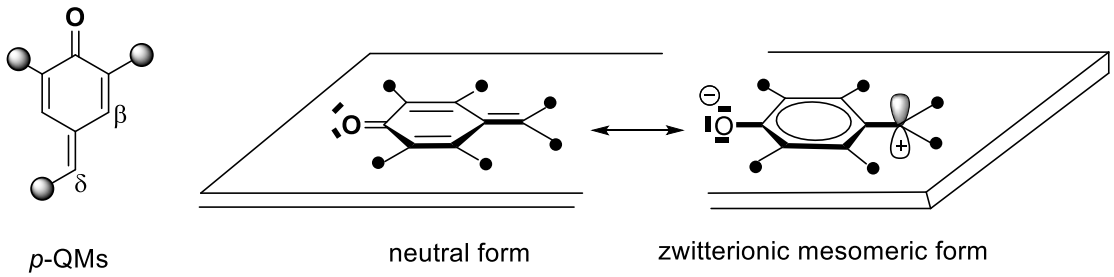
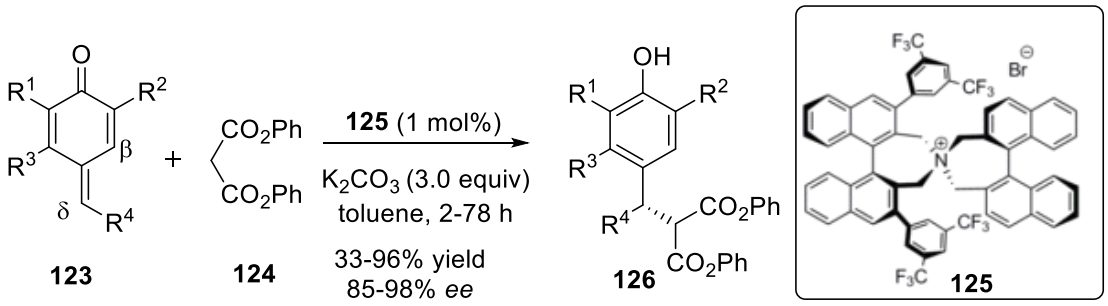


Figure 2. *The structure of pare-quinone methides.*

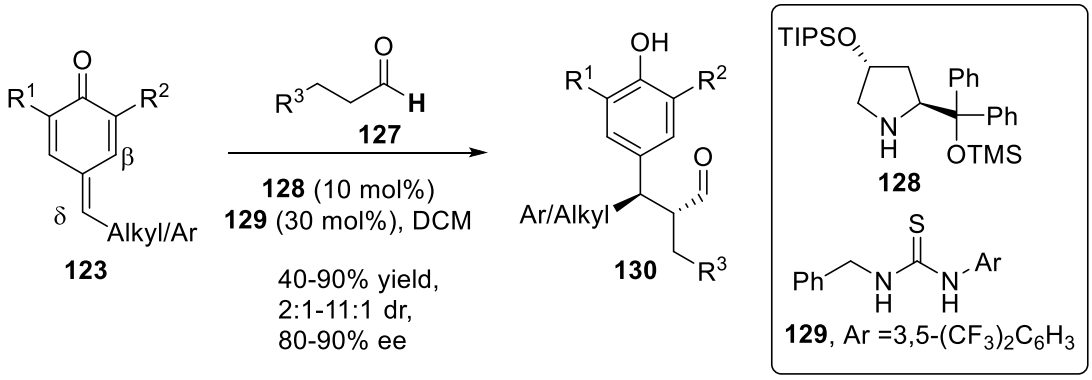
In contrast to the well-studied *ortho*-quinone methides,[49] *p*-QMs have been less used in asymmetric synthesis, especially in a catalytic fashion.[50] In the following section, several recent examples based on *p*-QMs will be discussed.

In 2013, Fan and co-workers first reported the use of *p*-QMs in a catalytic asymmetric reaction. In the presence of a phase-transfer catalyst, a novel 1,6-addition of malonates **124** to *p*-QMs **123** has been realized. This reaction provided a new entry to asymmetric synthesis of highly functionalized diarylalkanes **126** in high yields with excellent stereocontrol (Scheme 36).[51]



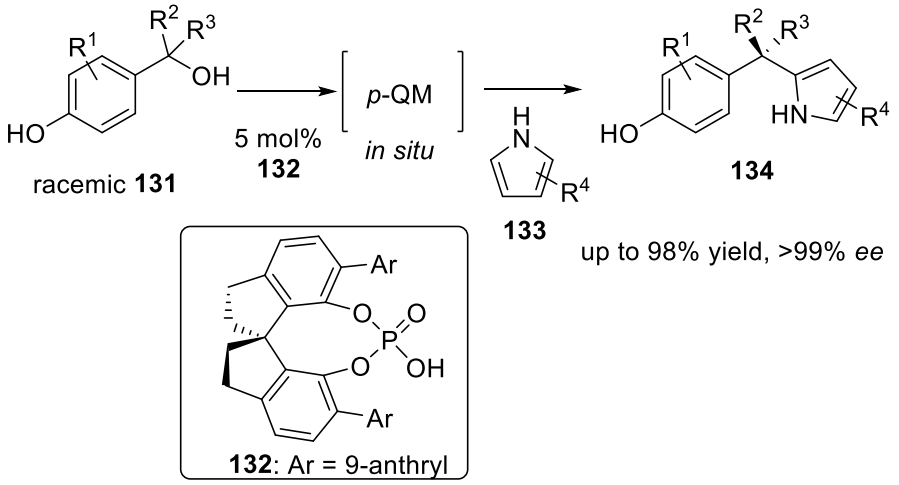
Scheme 36. *Asymmetric 1,6-addition of malonates to para-quinone methides.*

After this work, the Jørgensen group reported a novel strategy for the asymmetric α-alkylation of aldehydes through 1,6-addition of enamine-activated aldehydes to *p*-QMs. In this case, using a new secondary amine catalyst **128**, a wide range of compounds **130** could be obtained in 40-90% yields and 80-99% ee values (Scheme 37).[52]



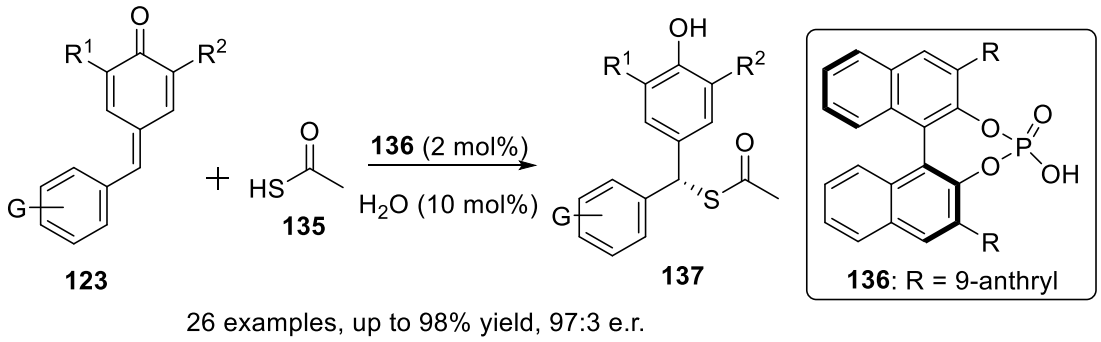
Scheme 37. *Asymmetric 1,6-addition of enamine-activated aldehydes to p-QMs.*

Very recently, Sun *et al*. reported chiral phosphoric acid catalyzed 1,6-conjugate addition of pyrroles (**133**) to *para*-quinone methides. This catalytic system allows in situ formation of *p*-QMs, thus expanding the scope of *p*-QMs and overcoming the limitation of previous reports. Meanwhile, this protocol enables efficient construction of all-carbon quaternary centers in a highly enantioselective fashion (Scheme 38).[53]



Scheme 38. *Asymmetric 1,6-addition of pyrroles to p-QMs.*

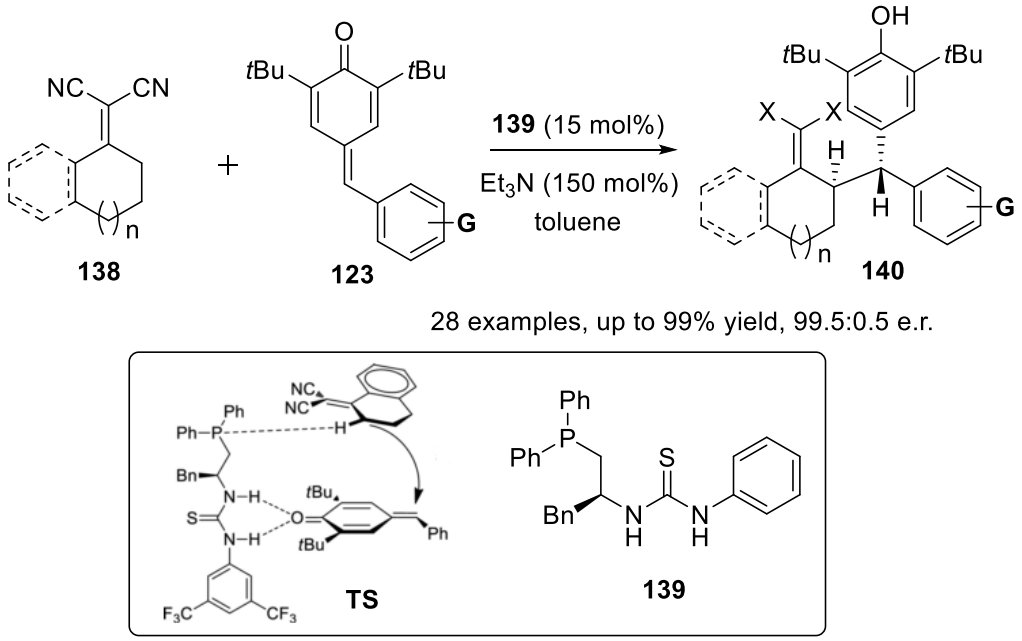
Almost simultaneously, Cheng and co-workers disclosed an enantioselective 1,6-conjugate addition between thioacetic acid **135** and *para*-quinone methides **123** by employing a chiral phosphoric acid catalysis. A variety of chiral diphenylmethane-type products **137** could be synthesized with high yields and good to excellent enantioselectivities. Interestingly, the author found that adding extra water is critical to achieve high stereoselectivity (Scheme 39).[54]



Scheme 39. *Asymmetric 1,6-addition of thioacetic acids to p-QMs.*

In 2016, Yao *et al*. presented a chiral thiourea catalyzed asymmetric 1,6-conjugated addition of dicyanoolefins (**138**) to *p*-QMs. In this report, the chiral diarylmethine skeletons were efficiently constructed in good yields and high diastereo- and enantioselectivities (>20:1 dr, up to 99.5:0.5 e.r.). Through mechanistic studies, they

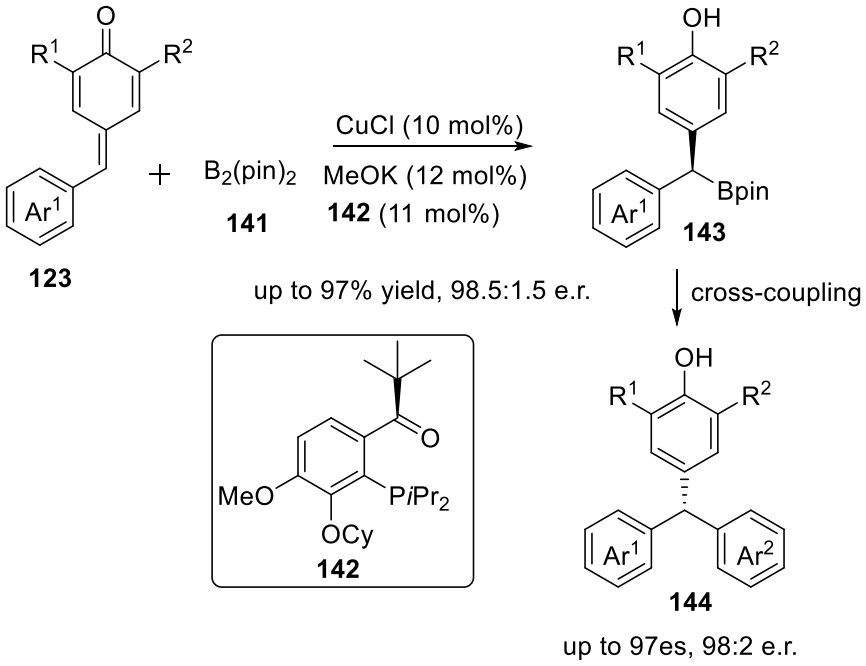
found that the high stereocontrol was realized through a hydrogen-bonding interaction between the catalyst and the substrate (Scheme 40).[55]



Scheme 40. *Asymmetric 1,6-addition of dicyanoolefins to p-QMs.*

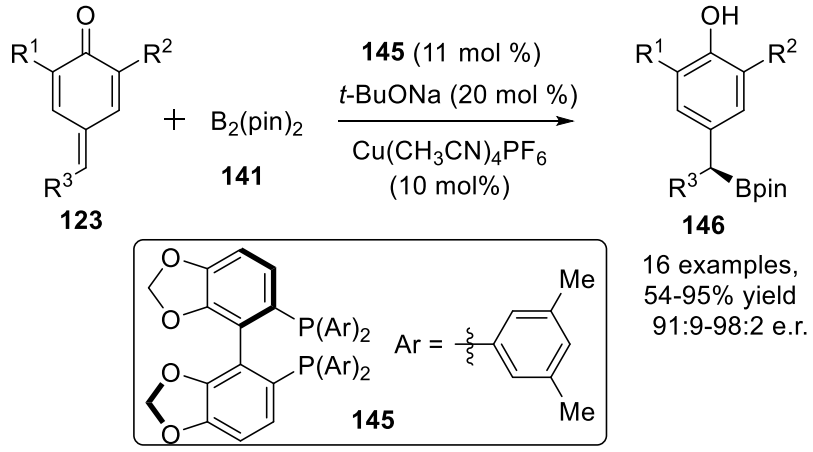
1.3.3 Metal-catalytic reactions of *para*-quinone methides.

In 2015, Liao *et al.* demonstrated that copper-catalyzed 1,6-addition of bis(pinacolato)diboron **141** to *para*-quinone methides **123** generated gem-diarylmethine boronates **143** in good yields (71-98%) and good to excellent stereoselectivities (up to 98.5:1.5 er). In addition, further transformation of the potassium trifluoroborates into enantioenriched triaryls was also realized through a cross-coupling reaction (Scheme 41).[56]



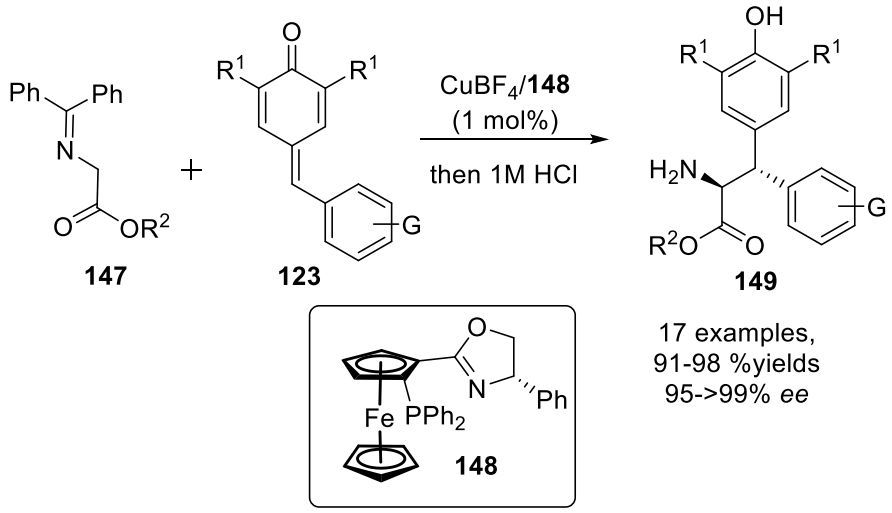
Scheme 41. *Copper-catalyzed enantioselective 1,6-boration of p-QMs.*

Another copper-catalyzed enantioselective borylation of *para*-quinone methides was reported by Tortosa and co-workers. They found that DM-Segphos-Cu complexes are ideal catalysts for this transformation, and can provide high enantioselectivities. Similar to Liao's report, several monoaryl, diaryl and triaryl derivatives have been synthesized through further manipulations of the newly formed C-B bound (Scheme 42).[57]



Scheme 42. *Copper-catalyzed borylative aromatization of p-QMs.*

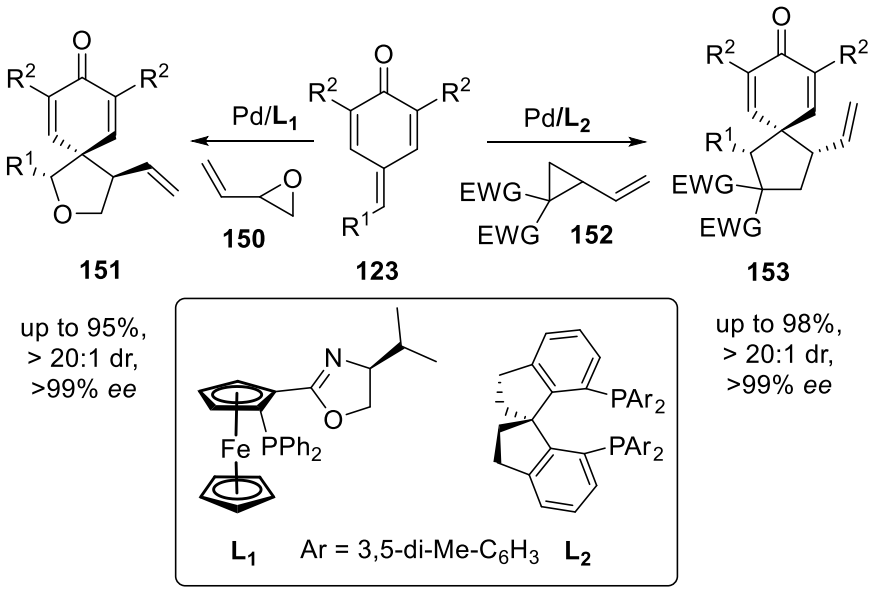
In 2016, Deng's group reported the enantioselective 1,6-addition of Schiff bases **147** to *para*-quinone methides. In the presence of 1 mol% $Cu(CH_3CN)_4$/Ph-Foxap complex, the adducts **149** were generated in very high yields and excellent diastereo- and enantioselectivities (> 99% *ee* in most examples). It is noteworthy that the products could be smoothly converted to several useful building blocks (Scheme 43).[58]



Scheme 43. *Copper-catalyzed asymmetric addition of Schiff bases to p-QMs.*

In 2016, the Pd-catalyzed [3+2] cycloaddition of *para*-quinone methides with cyclopropanes **152** and epoxides **150** was developed by Zhao and co-workers. They used commercially available catalysts, and this protocol delivered the spiro[4.5]decane

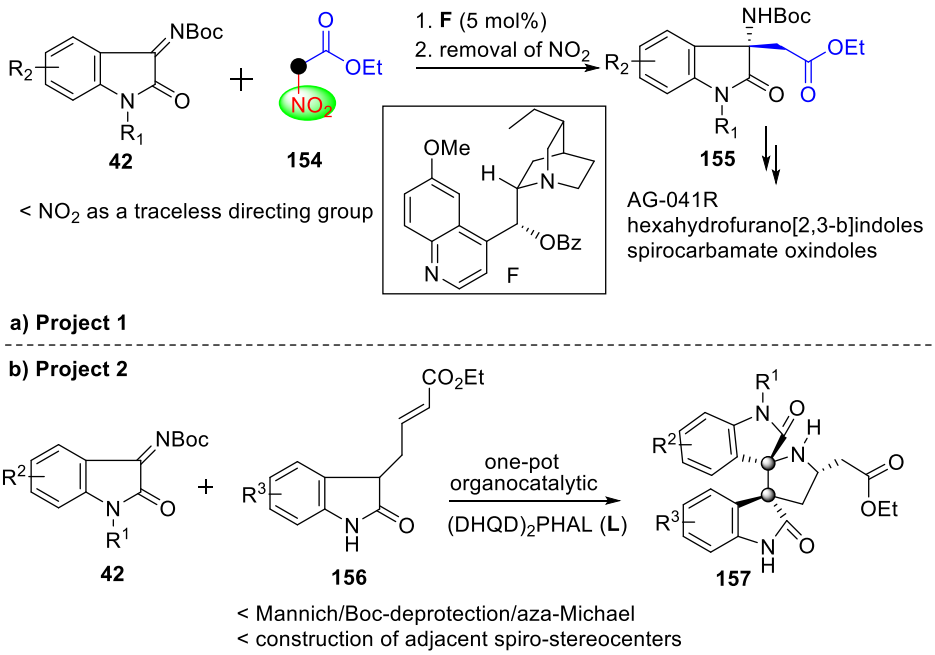
compounds with excellent efficiency and stereocontrol (Scheme 44).[59]



Scheme 44. *Pd-catalyzed asymmetric [3+2] cycloaddition of p-QMs.*

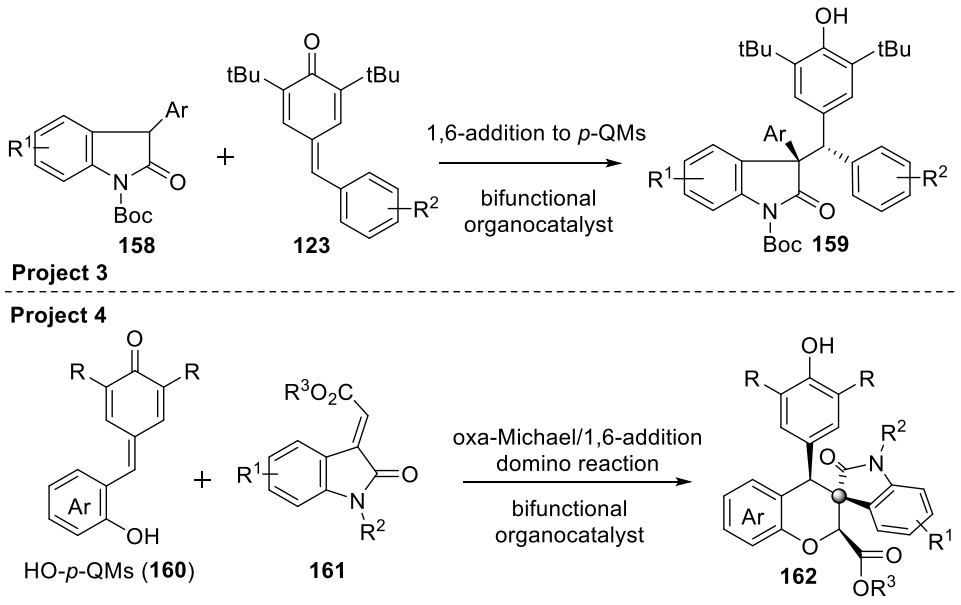
1.4 Overview of the doctoral work

My doctoral work mainly includes four research projects. The first two mainly focused on the development of reactions based on isatin-derived *N*-Boc ketimines. Given the excellent reactivity of these species, the ethyl nitro acetate and 3-substituted oxindoles were successfully used as new reaction components in project 1 and project 2, respectively. As shown in Scheme 45, project 1 consist in the development of an organocatalytic Mannich/denitration reaction to synthesize chiral 3-ethylacetate-substituted 3-amino-2-oxindoles. From this key building block, the formal synthesis of AG-041R was achieved. In project 2, *N*-Boc-protected isatin–derived ketimines were further employed in a one-pot reaction, which contains a Mannich reaction and a Boc-deprotection/aza-Michael sequence. This new method provided a short entry into chiral 3,3'-pyrrolidinyl-dispirooxindoles with potential medical values.



Scheme 45. *Asymmetric synthesis of 3-ethylacetate-substituted 3-amino-2-oxindoles and 3,3'-pyrrolidinyl-dispirooxindoles.*

The last two research projects focused on the development of 1,6-conjugate addition reactions based on *para*-quinone methides. As illustrated in Scheme 46, project 3 disclosed the asymmetric synthesis of 3-diarlymethine-substituted oxindoles via 1,6-conjugate addition to *p*-QMs. Project 4 reported the application of *ortho*-hydroxyphenyl-substituted *para*-quinone methides in a novel asymmetric organocatalytic domino oxa-Michael/1,6-addition reaction. Using a bifunctional catalyst, this protocol affords 4-aryl-substituted chromans containing spiro-connected oxindole part and three contiguous stereogenic centers in high yields and excellent stereoselectivities.



Scheme 46. *Asymmetric synthesis of 3-diarlymethine-substituted oxindoles and 4-aryl-substituted chromans.*

2. Results and Discussion

2.1 Asymmetric synthesis of 3-ethylacetate-substituted 3-amino-2-oxindoles and formal synthesis of AG-041R

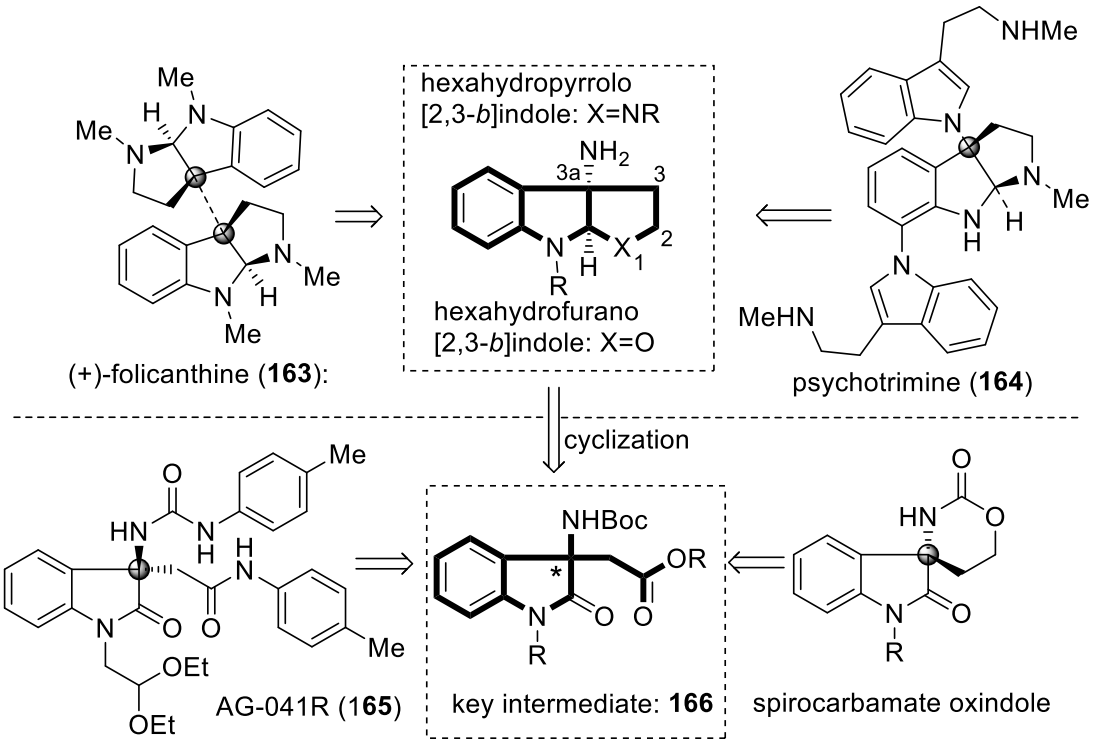
2.1.1 Background and motivation

The hexahydropyrrolo[2,3-*b*]indole unit is frequently found in natural products such as pyrroloindoline alkaloids.[60] Those alkaloids not only bear complex structures but also display a broad array of biological activities. For example, (+)-folicanthine (**163**), as the representative of the dimeric pyrrolidinoindoline, exhibits antifungal properties.[61] Psychotrimine (**164**) was first isolated from the leaves of psychotria rostrate, and shows antitumor activity and antibacterial effects.[62] Given that their promising medical values and the structural complexity, several methods have been developed for the synthesis of those alkaloids. One of them is using pyrroloindolines as precursors.[63] However, to the best of our knowledge, reports on catalytic syntheses of chiral pyrroloindolines with a C3a amine group are still less.

Furthermore, the 3-substituted-3-amino-2-oxindole skeleton, featuring a tetrasubstituted stereogenic center (C3), is a privileged structural core which can be found in several pharmaceutical reagents. For instance, the lead compound AG-041R (**165**) exhibiting anti-cancer and systemic chondrogenic properties, is a cholecystokinin-B/gastrin receptor antagonist.[64] After literature searching we found there are several methods for the synthesis of this clinical candidate, but most of them are based on a chiral auxiliary or metal-catalytic reactions.[65] So it is very necessary to develop a simpler and efficient approach to obtain this enantioenriched lead compound, especially using organocatalytic strategies.

Keeping those considerations in mind, we tried to find a protocol for the collective synthesis of two pyrroloindoline alkaloids and lead compound AG-041R. Our

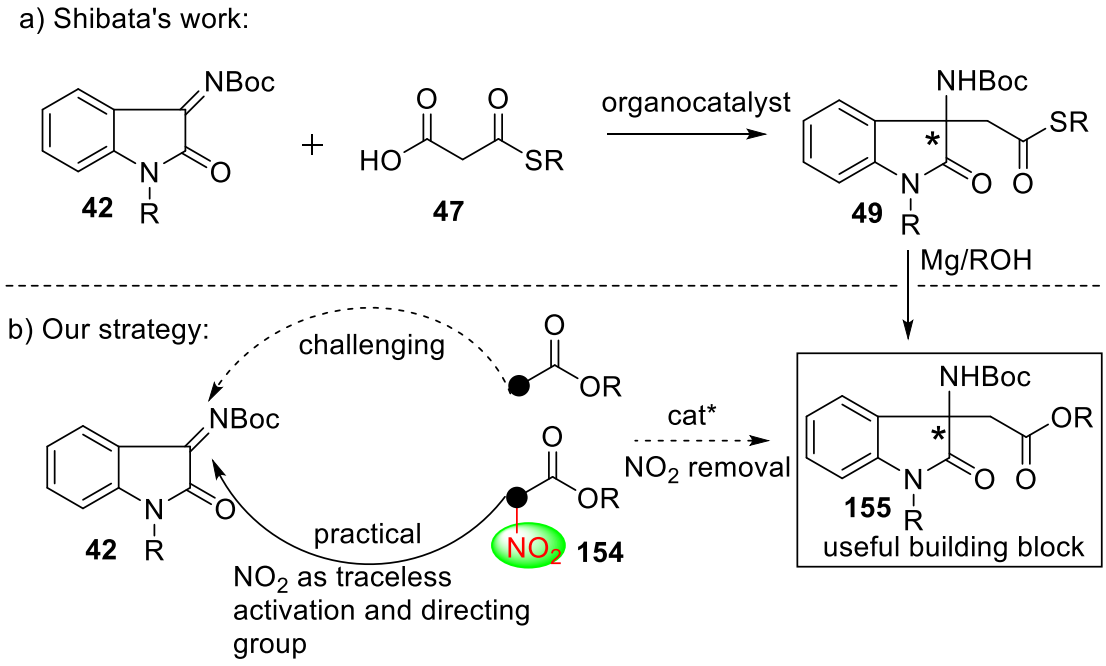
retrosynthetic analysis is shown in Scheme 47 and we envisioned that compound **166** might be used as the key intermediate in this project. The hexahydropyrrolo[2,3-*b*]indole, a chiron for the synthesis of psychotrimine and folicanthine, could be assembled through cyclization of the chiral building block **166**. Meanwhile, the spirocarbamate as well as AG-041R also could be obtained from the common build block **166** after several classic reactions.



Scheme 47. *Representative alkaloids and pharmaceuticals; retrosynthetic analysis.*

Quite recently, Shibata *et al*. disclosed an organocatalytic Mannich reaction between isatin imines **42** and malonic acid half thioesters **47**. The desired compounds could be formed with 58-90% yields and moderate enantioselectivities (73-83% *ee*). Moreover, they found that the products could be easily converted into the desired intermediate **155**.[22] We wanted to synthesize this compound using another strategy, which is depicted in Scheme 48b. We proposed that if the ester part was added to the isatin-derived N-Boc ketimines **42**, the intermediate **155** might be delivered in a concise way. Due to the very low activity of the α-position of the ester group, this assumption is

really hard to realize. So compound **154** was used as the nucleophile in our reaction. Because the nitro group is not only critical to enhance the activity of the α-position and also can be easily removed after the reaction, serving as a traceless activation group.[66]



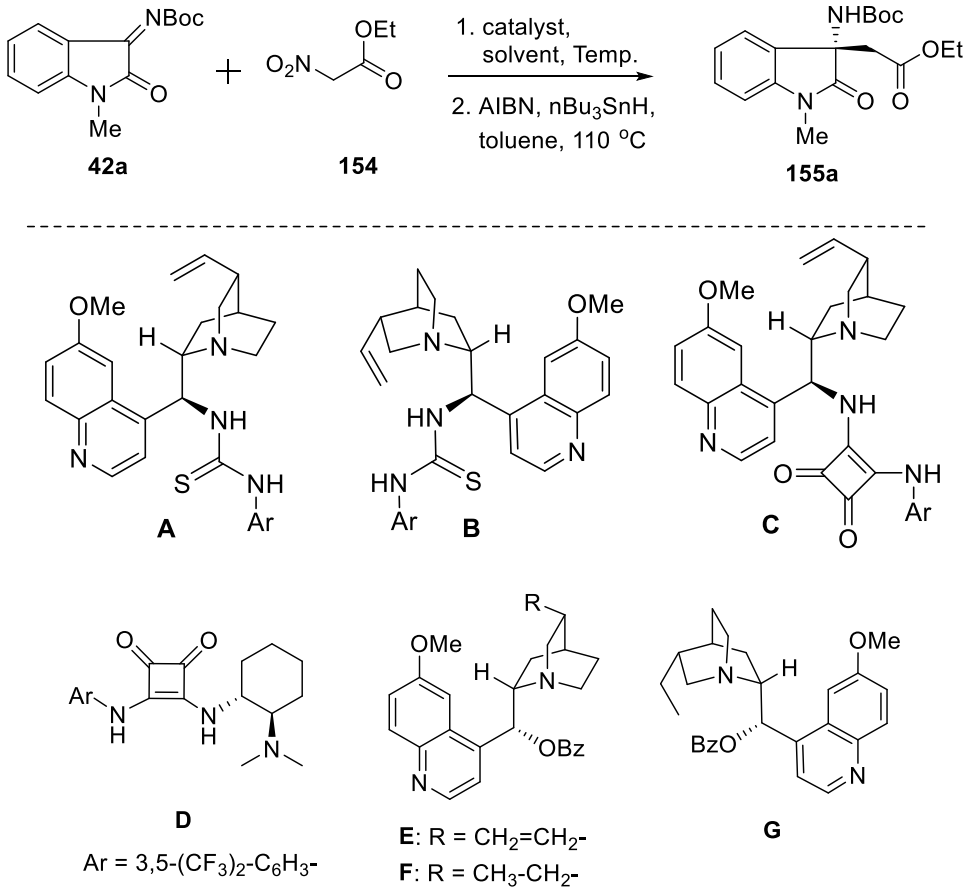
Scheme 48. *Organocatalytic asymmetric synthesis of the key building block.*

2.1.2 Optimization of the reaction conditions

To test the feasibility of our above described strategy, N-Boc ketimine **42a** and compound **154** were used as model substrates to conduct a systematic screening of the reaction conditions. Initially, the easily available ketimine **42a** and commercially available compound **154** were exposed to trimethylamine in DCM for 12 h, followed by a denitration reaction. To our delight, the expected reaction proceeded readily and the corresponding product **155a** was isolated in 77% yield (Table **1**, entry 1). Next, the bifunctional thiourea catalysts **A** and **B** were examined, and compound **155a** could be obtained in yields of 64% and 74%, respectively, albeit with moderate enantiomeric excesses (Table **1**, entries 2 and 3). Squaramide type catalysts **C** and **D** resulted in moderate results (Table **1**, entries 4 and 5). Gratifyingly, when catalyst **E,** derived from

quinine, was employed, the desired product **155a** was afforded in excellent yield (86%) and 92% *ee* (Table **1**, entry 6). Further screening revealed that the enantioselectivity slightly increased through lowering the reaction temperature (Table **1**, entries 6 and 7). Conducting the reaction at -20 °C, 94% *ee* was observed. Switching to the catalyst **F**, acting as a general base, led to 88% yield and 95% ee (Table **1**, entry 8). Further screening was focused on the solvent, including toluene and $CHCl_3$. Although the reaction worked readily, no improvement in enantioselectivity was observed (Table **1**, entries 9 and 10). Finally, when 5 mol% of catalyst was used, the desired product **155a** was synthesized in 88% yield and 96% ee (Table **1**, entry 11). It's noteworthy that the enantiomeric product was provided easily with the pseudo-enantiomeric catalyst **G** (Table **1**, entry 12)**.**

Table 1 *Optimization of the reaction conditions.*



entry[a]	cat.	solvent	mol [%]	T [°C]	yield [%][b]	ee [%][c]
1	Et_3N	DCM	15	0	77	n.d.

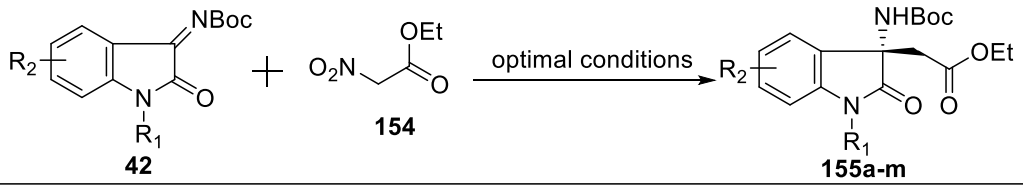
2	**A**	DCM	15	0	64	66
3	**B**	DCM	15	0	74	–83
4	**C**	DCM	15	0	82	48
5	**D**	DCM	15	0	67	49
6	**E**	DCM	15	0	86	92
7	**E**	DCM	15	–20	83	94
8	**F**	DCM	15	–20	88	95
9	**F**	$CHCl_3$	15	–20	84	95
10	**F**	toluene	15	–20	84	87
11	**F**	**DCM**	**5**	**–20**	**88**	**96**
12	**G**	DCM	5	–20	88	–91

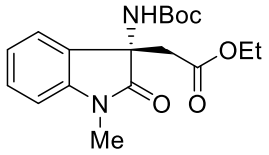
[a] All reactions were conducted with 0.15 mmol of **42a** (1 equiv), 0.18 mmol of **154** (1.2 equiv) in solvent (1.5 mL). After 12 h, the nitro group was removed with 0.03 mmol of AIBN (0.2 equiv), 0.3 mmol of nBu$_3$SnH (2.0 equiv) in toluene (1.5 mL) at 110 °C for 1 hour. [b] Yield of isolated **155a** (two steps). [c] Determined by chiral stationary phase HPLC analysis. n.d. = not determined.

2.1.3 Investigation of the substrate scope of the reaction

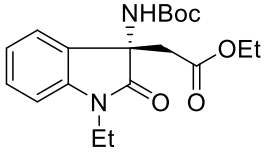
With the optimized reaction conditions in hand, we next investigated the substrate scope of the N-Boc ketimines **42**. As illustrated in Table **2**, a wide range of isatin-derived ketimines could be employed in this protocol to afford the corresponding adducts **155a-m** in 51-91% yields and with 92-99% ee. Our initial investigation focused on the substituent on the oxindole atom. We found that the common groups, like Me-, Et-, Bn-, PMB-, MOM- and Ph, were tolerated, and the corresponding products could be synthesized with satisfactory results (Table 2, **155a-f**). Then, the substituents of the benzene ring of ketimines **42** were evaluated. Substrates with electron-donating groups, such as 5-Me, 5-MeO, 5-CF_3O, gave the desired products **155g-i** in good yields (70%-88%) with 92-96% ee. Furthermore, N-Boc ketimines, which contain electron-withdrawing groups (5-Cl, 5-F, 7-F), could also be processed to deliver the corresponding products with very good stereoselectivities (Table 2, **155j-l**).

Table 2. *Scope of the asymmetric oxindole synthesis.*

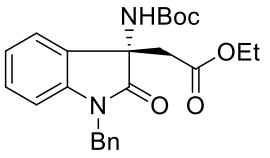




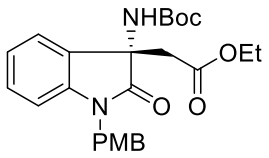
155a: 87%; 96% *ee*



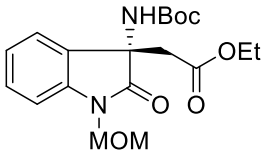
155b: 84%; 96% *ee*



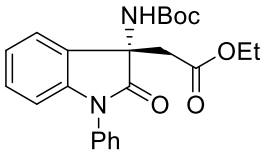
155c: 64%; 93% *ee*



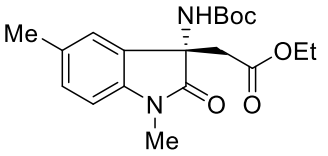
155d: 72%; 93% *ee*



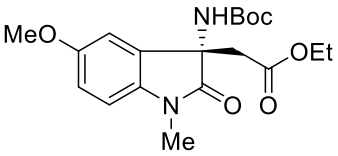
155e: 64%; 94% *ee*



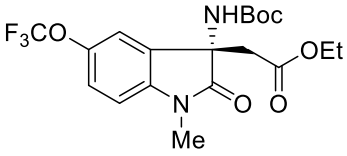
155f: 68%; 99% *ee*



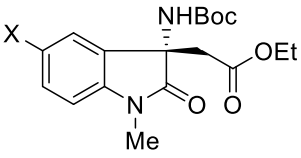
155g: 70%; 96% *ee*



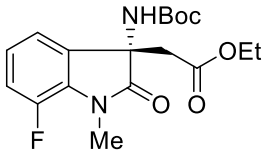
155h: 88%; 95% ee



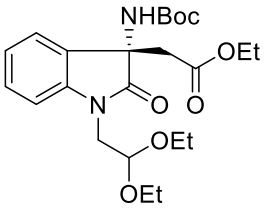
155i: 78%; 92% *ee*



155j: 82%; 92% *ee* (X=Cl)
155k: 91%; 92% *ee* (X=F)



155l: 51%; 92% *ee*

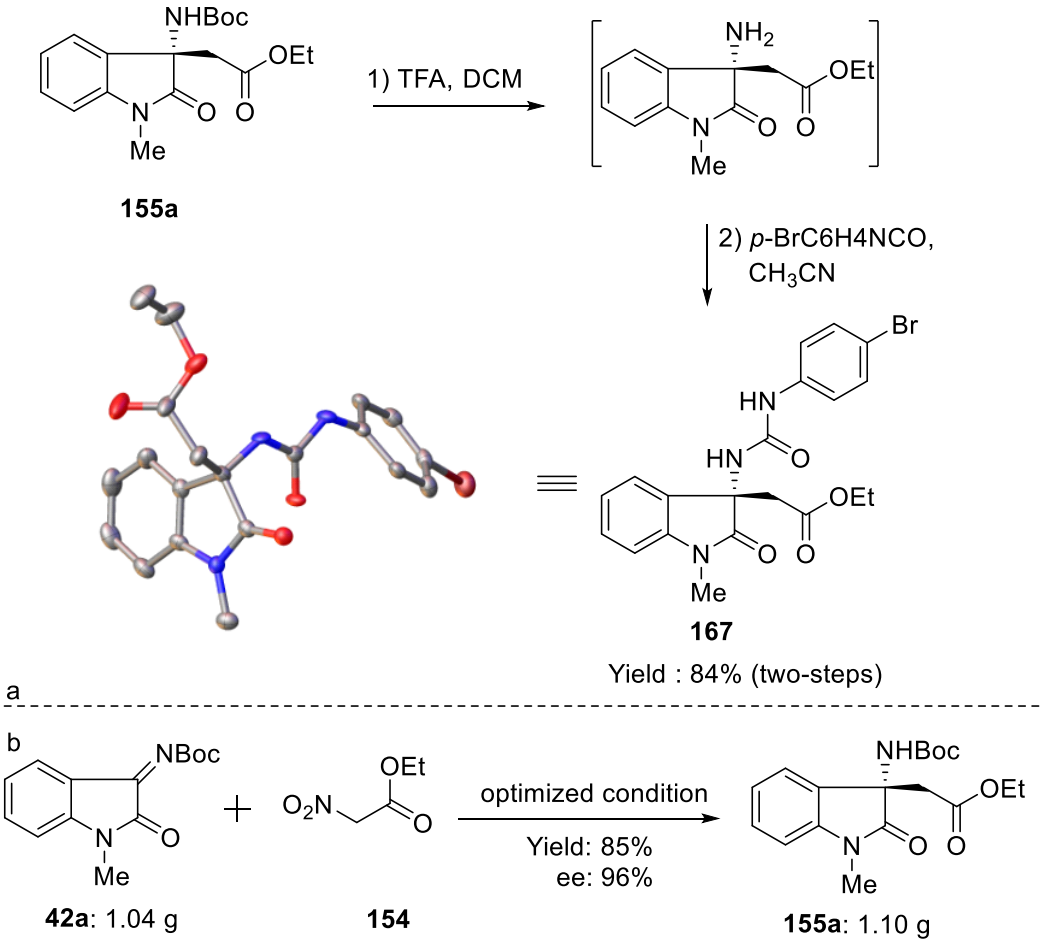


155m: 77%; 96% *ee*

All reactions were carried out with ketimines **42** (0.45 mmol), **154** (0.54 mmol) and catalyst **F** (0.02 mmol) in DCM (4.5 mL) at -20 °C. After 12 hours the nitro group was removed with AIBN (0.09 mmol), *n*Bu_3SnH (0.9 mmol) in toluene (4.5 mL) at 110 °C for 1 hour. Yield of products **155** after column chromatography. The *ee* values were determined by HPLC on a chiral stationary phase.

2.1.4 Determination of the absolute configuration and gram-scale reaction

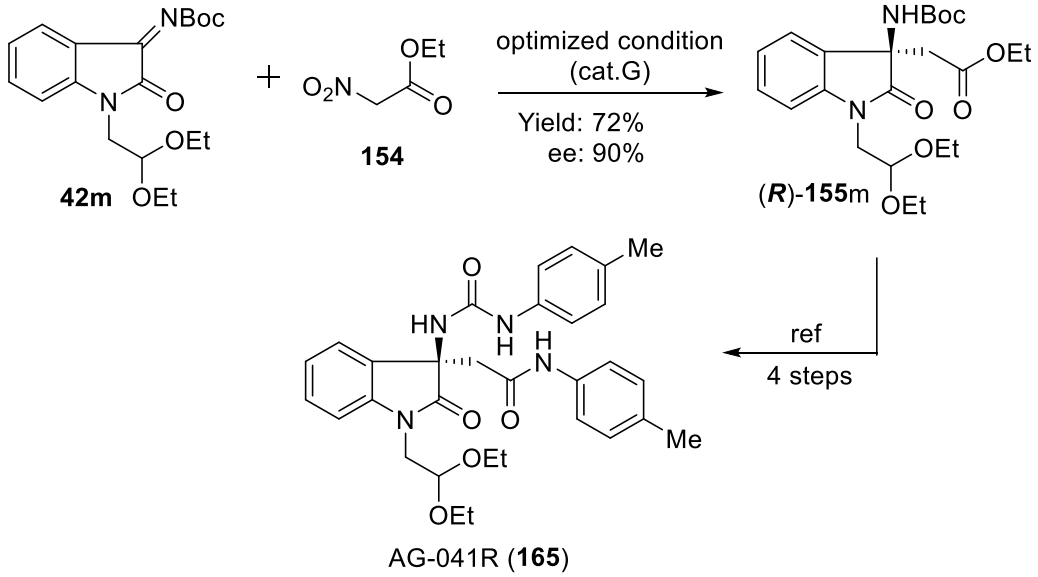
In order to know the absolute configuration of the 3-ethylacetate-substituted 3-amino-2-oxindoles, several transformations were conducted. As shown in Scheme 49a, after two steps we obtained the crystalline compound **167**, the absolute configuration of which was determined based on the X-ray crystallography.[67] Moreover, to examine the robustness of this protocol, we conducted the Mannich/denitration reaction on a gram-scale, and it was found the desired compound **155a** was obtained in 85% yield and with 96% ee value (Scheme 49b).



Scheme 49. *X-ray crystal structure of* ***167*** *and gram-scale reaction.*

2.1.5 Formal synthesis of AG-041R and derivatization of the product

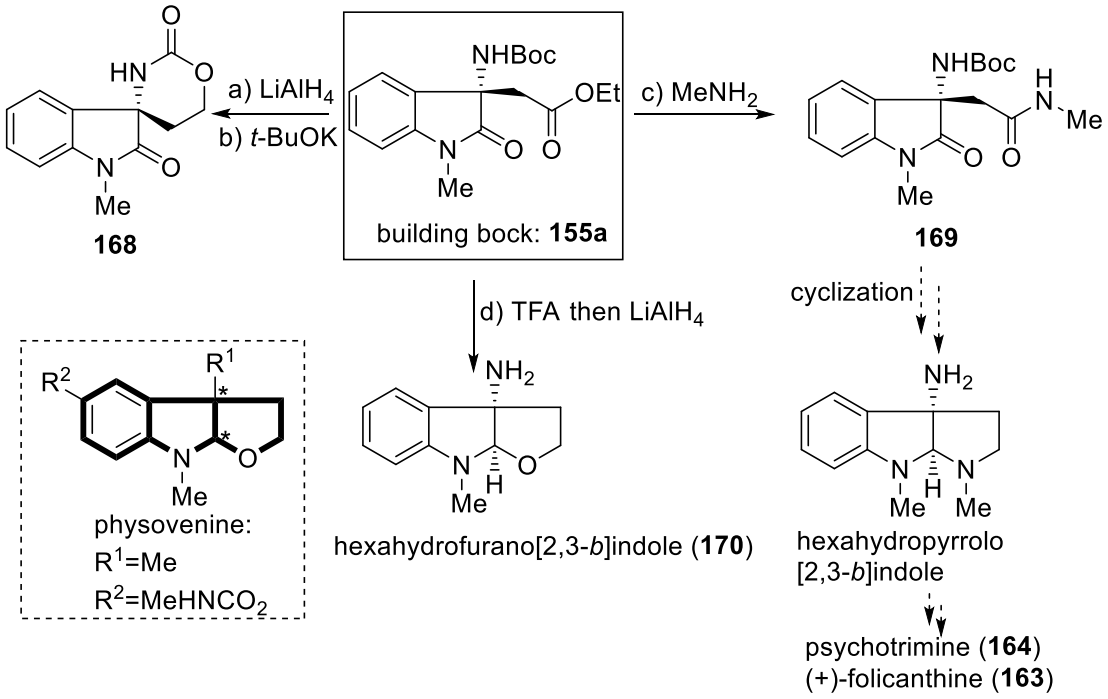
With this method in hand, we then turned our attention to its applications. According to our retrosynthetic plan, (*R*)-**155m** would be the key intermediate for the synthesis of the lead compound AG-041R. After extensive investigation, we found that when catalyst **G** was employed in this reaction, (*R*)- **155m** could be efficiently synthesized in a good result (72% yield, 90% ee), thus finishing the formal synthesis of AG-041R (Scheme 50).



Scheme 50. *Formal synthesis of AG-041R.*

With the highly enantiomerically enriched key intermediate **155a** in hand, we started to synthesize several useful derivatives. Reduction of the ethyl ester group with lithium aluminium hydride, followed by treatment of the alcohol product with *t*-BuOK afforded the spirocarbamate compound **168**. Treatment of **155a** with methylamine gave the amide **169**, which could be considered as a possible precursor for the synthesis of psychotrimine (**164**) and folicanthine (**163**). Moreover, after deprotection of the Boc group using trifluoroacetic acid, the free amine compound was exposed to $LiAlH_4$ and a cyclization reaction occurred to deliver compound **170**, which contains the

skeleton of physoveninel (Scheme 51).[68]



Scheme 51. *Synthesis of useful derivatives from the common building block.*

2.2 Organocatalytic asymmetric synthesis of 3,3'-pyrrolidinyl-dispirooxindoles via a one-pot reaction

2.2.1 Importance of the 3,3'-pyrrolidinyl-dispirooxindole core

The 3,3'-pyrrolidinyl-spirooxindole core (Figure 3, top left) is a very important structural skeleton, appearing not only in numerous pharmaceutical reagents but also in a plethora of bioactive oxindole alkaloids.[69] For example, compound MI-888 (**171**) is a potent MDM2 inhibitor.[70] Spirotryprostatin A (**172**), which was first isolated from Aspergillus fumigates, exhibits anticancer activity.[71] Their synthetic challenges, combined with potential pharmaceutical values, have drawn much attention among chemists, and up to date several synthetic methods to approach those spirooxindoles have been developed.[72] On the other hand, several 3,3'-pyrrolidinyl-dispirooxindoles (**173** and **174**) have also been studied to exhibit some interesting bioactivities, such as anticancer and anti-microbial properties.[73] From a structural perspective, the 3,3'-pyrrolidinyl-dispirooxindoles feature more complex structures. These compounds, bearing two vicinal spiro-stereocenters, consist of a pyrrolidinyl core (A) and two oxindole moieties (B and C). (Figure 3, bottom left).

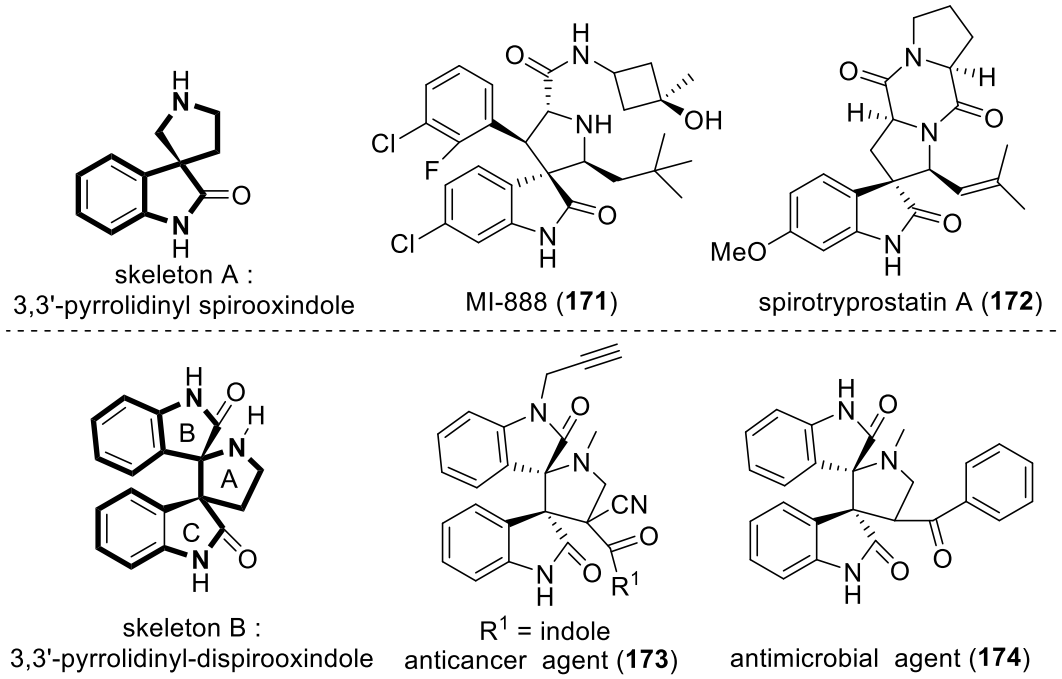
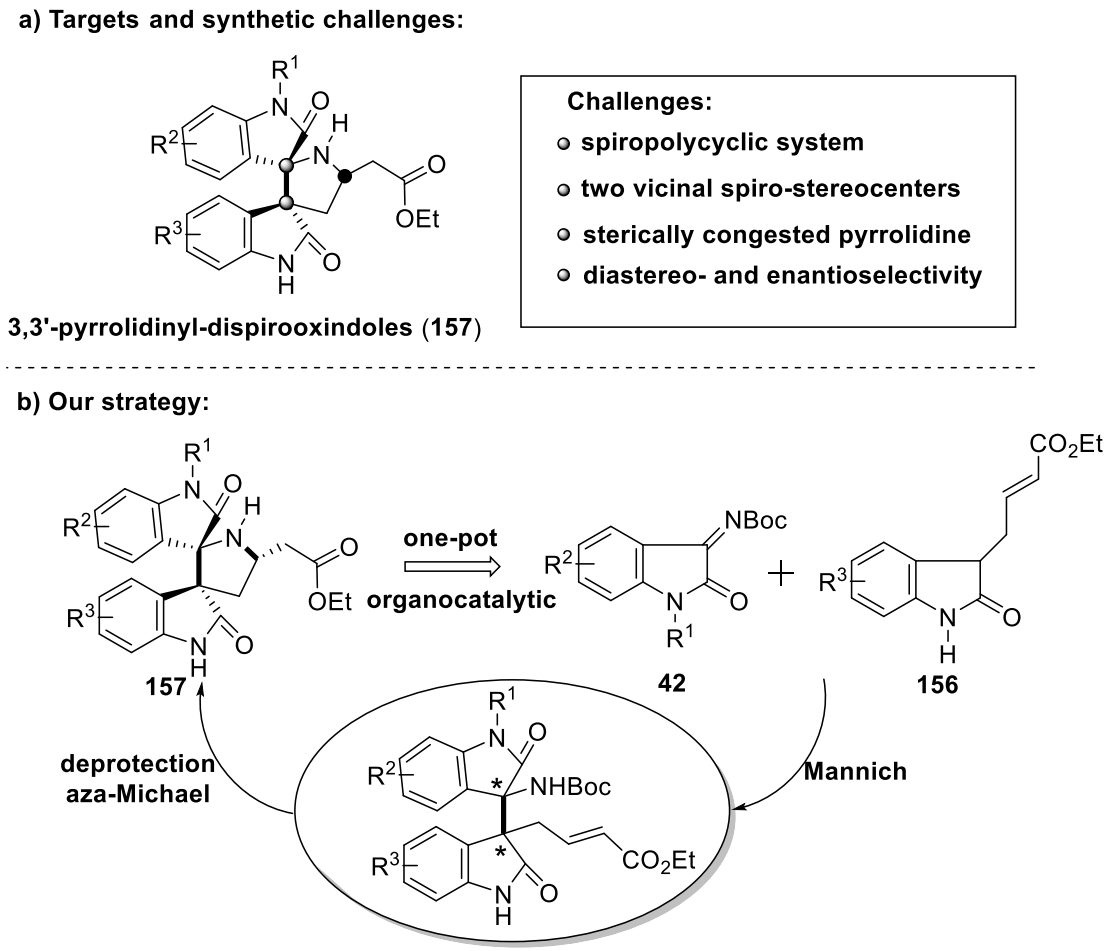


Figure 3. *3,3'-Pyrrolidinyl-(di)spirooxindole derivatives with biologically activities.*

2.2.2 Background and motivation

The construction of spiro-stereocenters, especially two of them are adjacent, has been considered as a formidable issue in organic synthesis.[74] To the best of our knowledge, almost all the reported methods for the synthesis of 3,3'-pyrrolidinyl-dispirooxindoles are either only racemic versions or based on the chiral pools.[75] Only one catalytic asymmetric case appeared recently. Quite recently, the Shi group reported an elegant method to synthesize the skeleton B through a chiral phosphoric acid catalyzed 1,3-dipolar cycloaddition of isatin-derived azomethine ylides with methyleneindolinones.[76] However, it's still necessary to develop a concise method to enantioselectively construct the 3,3'-pyrrolidinyl-dispirooxindole skeleton based on organocatalytic strategies.

Keeping these facts in mind, we chose compound **157** as our target in this project and sought to develop an approach to obtain them. We envisioned that the assembly of this skeleton might be achieved through the union of isatin-derived ketimines **42** and the bifunctional donor-Michael acceptor compound **156** via a one-pot reaction. As depicted in Scheme 52, this sequence contains a Mannich reaction, a Boc-deprotection and an aza-Michael sequence. Furthermore, by employing an ideal chiral organocatalyst this proposed reaction could be rendered enantioselective and provides enantioenriched 3,3'-pyrrolidinyl-dispirooxindoles **157**. However, in order to realize this transformation, several challenges had to be solved: a) the stereoselectivity issue including diastereo- and enantioselectivity, b) the steric effects from the highly congested pyrrolidine system.



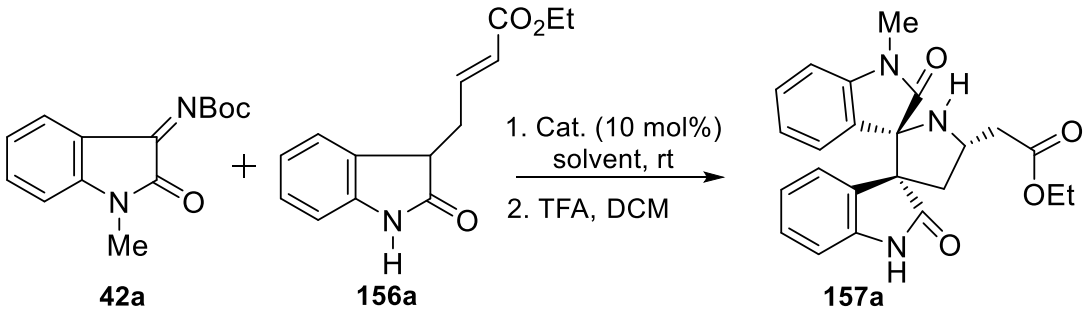
Scheme 52. *Our strategy for the 3,3'-pyrrolidinyl-dispirooxindole skeleton synthesis.*

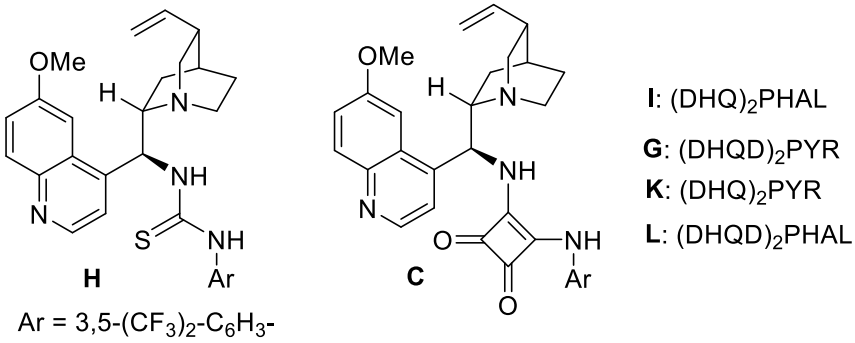
2.2.3 Optimization of the reaction conditions

To examine the feasibility of our proposed reaction, we selected the N-Boc ketimine **42a** and the 3-substituted oxindole **156a**[77] as the model substrates to optimize the reaction conditions. Initially, the bifunctional catalyst **H** was tested. We were pleased to find that the expected reaction proceeded smoothly, and the 3,3'-pyrrolidinyl-dispiroxoindole **157a** was obtained with excellent diastereoselectivity, albeit with a low yield (31%) and very low *ee* (Table 3, entry 1). In order to improve the efficiency and enantioselectivity of this reaction, the squaramide catalyst **C** was used, but only trace amount of the desired product could be detected (Table 3, entry 2). We noted several previous reports involving functionalization of 3-substituted oxindoles where Sharpless ligands were the optimal catalyst.[78] In our case, we reckoned that the attractive

aromatic interaction between Sharpless ligands and the substrates might be beneficial for this transformation. Indeed, the ligand $(DHQ)_2PHAL$ yielded the product with a significantly increased e.r. (Table 3, entry 3). Further catalyst screening revealed that catalyst **L** was the best choice in term of yield and stereoselectivity (Table 3, entry 6). Finally, the effect of different solvent was also investigated, and MTBE afforded the best result (Table 3, entry 7).

Table 3 *Optimization of the reaction conditions.*





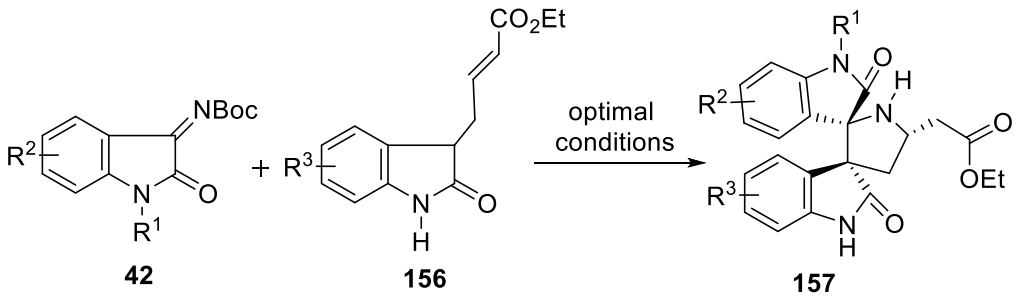
entry[a]	cat.	solvent	yield [%][b]	d.r.[c]	e.r.[d]
1	**H**	toluene	31	>20:1	58:42
2	**C**	toluene	trace	n.d.	n.d.
3	**I**	toluene	85	>20:1	5:95
4	**G**	toluene	69	>20:1	97:3
5	**K**	toluene	79	>20:1	4:96
6	**L**	toluene	87	>20:1	97:3
7	**L**	**MTBE**	**82**	**>20:1**	**99:1**
8	**L**	$CHCl_3$	63	>20:1	92:8

[a] All reactions were performed on 0.21 mmol of **42a** (1.05 equiv), 0.2 mmol of **156a** (1.0 equiv) and 10 mol % of the catalyst in a solvent (2.0 mL) at room temperature for 12 h. After evaporation of the solvent, DCM (1.5 mL) and TFA (0.4 mL) were added. [b] Yield of isolated **157a** after chromatography. [c] d.r. determined by ^{1}H NMR. [d] The e.r. were determined by chiral stationary phase HPLC analysis. n.d. = not determined.

2.2.4 Investigation of the substrate scope of the reaction

With the optimized conditions in hand (Table 3, entry 7), we then started to investigate the substrate scope of this reaction and the results are summarized in Table 4. Initially, the generality of the N-Boc ketimine component was evaluated. In general, a broad scope of ketimines could react with **156a** to furnish the corresponding 3,3'-pyrrolodinyl-dispirooxindoles **157a-m** in good yields (41-87%) with good to excellent stereoselectivities (up to 99:1 er). In detail, variation of R^1 group was first examined. It was found that the common substituents (Me-, Et-, Bn-, 4-Br-Bn-) were tolerated, and the desired enantioenriched products **157a-d** could be synthesized in 73-87% yields. Next, variation on the benzene ring of **42** was also tested. The substrates containing both electron-donating groups (5-OMe, 5-Me) or electron-withdrawing groups (5-F, 5-Cl, 5-Br, 5-NO_2, 7-F, 7-Cl) reacted readily with **156a** under the optimal condition, providing the corresponding 3,3'-pyrrolodinyl-dispirooxindole derivatives **157e-m** in good yields (41-79%). Furthermore, when the oxindole **156b** was employed, this newly developed reaction still smoothly occurred to yield the product **156b** in 77% yield with 86:14 er.

Table 4 *Evaluation of substrate scope* [a].



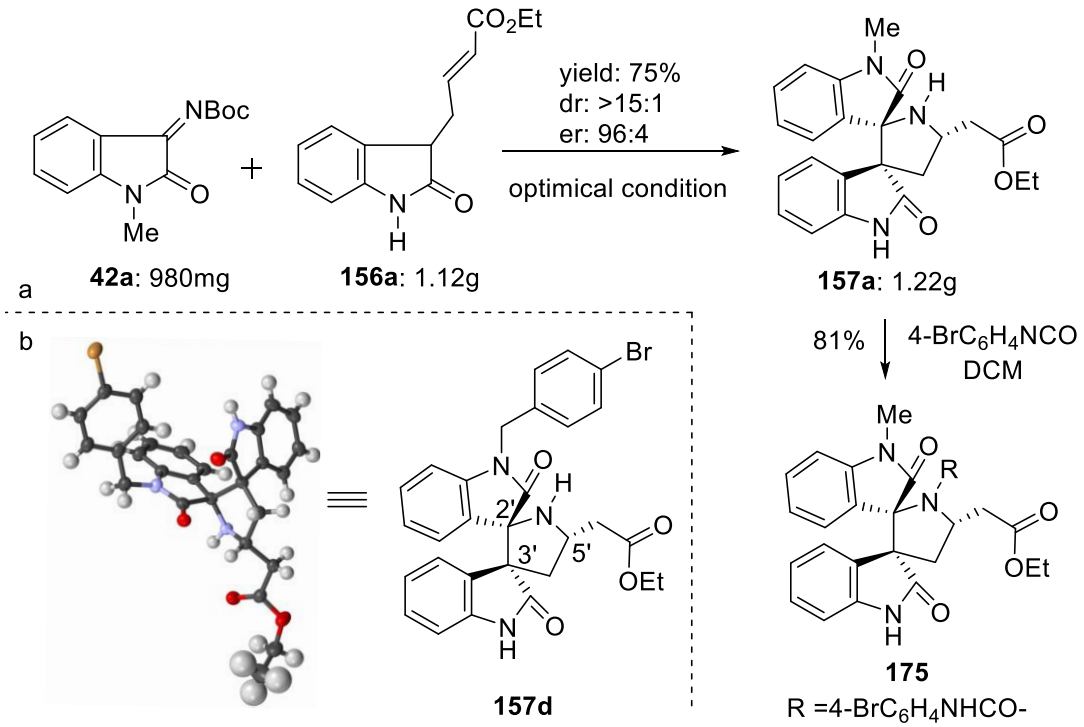
Product	R^1	R^2	R^3	Yield [%][b]	d.r.[c]	e.r.[d]
157a	Me	H	H	81	>20:1	99:1
157b	Et	H	H	73	>20:1	96:4
157c	Bn	H	H	87	>20:1	98:2
157d	4-Br-Bn	H	H	84	>20:1	98:2
157e	Me	5-Me	H	75	>20:1	97:3
157f	Me	5-OMe	H	79	11:1	99:1
157g	Me	5-OCF_3	H	63	8:1	98:2
157h	Me	5-F	H	67	>20:1	99:1
157i	Me	5-Cl	H	62	>20:1	99:1
157j	Me	5-Br	H	53	>20:1	98:2
157k	Me	5-NO_2	H	41	>20:1	95:5
157l	Me	7-F	H	71	10:1	95:5
157m	Me	7-Cl	H	68	>15:1	97:3
157n	Me	H	5-Cl	77	>20:1	86:14

[a] Unless otherwise noted, the reactions were performed on 0.42 mmol of **42** (1.05 equiv), 0.40 mmol of **156** (1.0 equiv) and 10 mol % of the catalyst **L** in MTBE (4.0 mL) at room temperature for 12 h. Upon evaporation of the solvent, DCM (4.0 mL) and TFA (0.8 mL) were added. [b] Yield of isolated **157** after chromatography. [c] The d.r. were determined by ^{1}H NMR. [d] The e.r. were determined by chiral stationary phase HPLC analysis.

2.2.5 Gram-scale reaction and determination of the absolute configuration

Given the potential biological activity of this kind of compounds, we planned to conduct this Mannich/Boc-deprotection/aza-Michael sequence on a gram scale using our optimized conditions. As expected, the gram scale reaction worked very well, and the corresponding product **157a** could be afforded in 75% yield and excellent stereoselectivity (>15:1 dr, 96:4 er). Moreover, dispirooxindole **157a** reacted with 4-bromophenyl isocyanate, yielding the urea compound **175** (Scheme 53a). As

demonstrated in Scheme 53b, the relative and absolute configuration was determined through studying the X-ray structure of compound **157d**, and the configuration of other 3,3'-pyrrolidinyl-dispirooxindoles could be assigned as (2'*S*, 3'*R*,5'*S*) by analogy.[79]



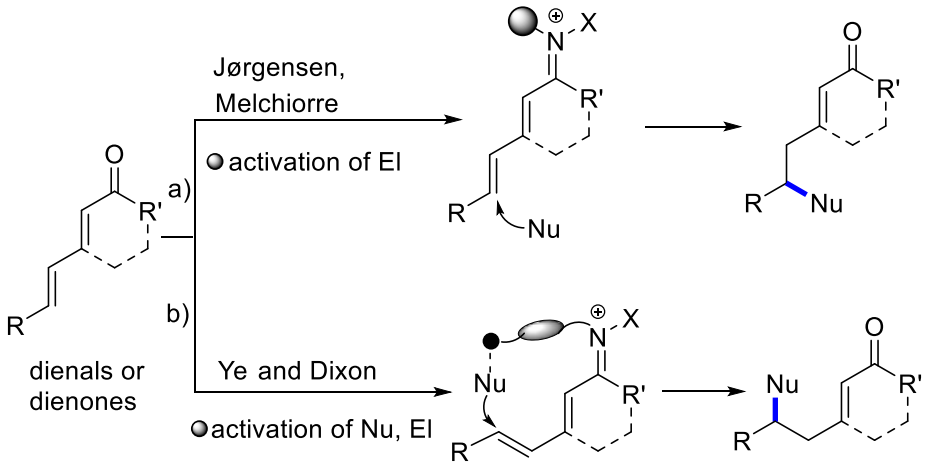
Scheme 53. *Gram-scale reaction and X-ray crystal structure.*

2.3 Asymmetric synthesis of 3-diarylmethine-substituted oxindoles via 1,6-addition to *para*-quinone methides

2.3.1 The challenge in activation of 1,6-Michael acceptors

There is no doubt that asymmetric organocatalytic 1,4-additions have been considered as one of the most powerful methods for the stereoselective construction of C-C or C-X bonds in modern organic synthesis.[35a-d, 35f] As discussed in the *Introduction 1.3.1*, asymmetric 1,6-additions have also drawn extensive attention in the organocatalytic community.[36] To the best of our knowledge, most of the reports on 1,6-addition are based on the activation of nucleophiles. There is a long distance between the catalyst binding site and the newly formed bond, so it's very challenging to activate 1,6-Michael acceptors through the use of an organocatalyst.

Recently, the research groups of Jørgensen[43] and Melchiorre[40] independently reported the activation of dienals or dienones through a vinylogous iminium strategy by using primary and secondary amine catalysis, respectively (Scheme 54a). Quite recently Ye and Dixon disclosed an elegant asymmetric 1,6-addition of γ-butyrolactams to cyclic dienones. In this report, they employed a bifunctional diamine catalyst to activate Michael donors as well as the vinylogous Michael acceptors (Scheme 1b).[42] Despite these achievements, it's still very desirable to pursue the new 1,6-Michael acceptors, which could be activated by suitable organocatalysts.

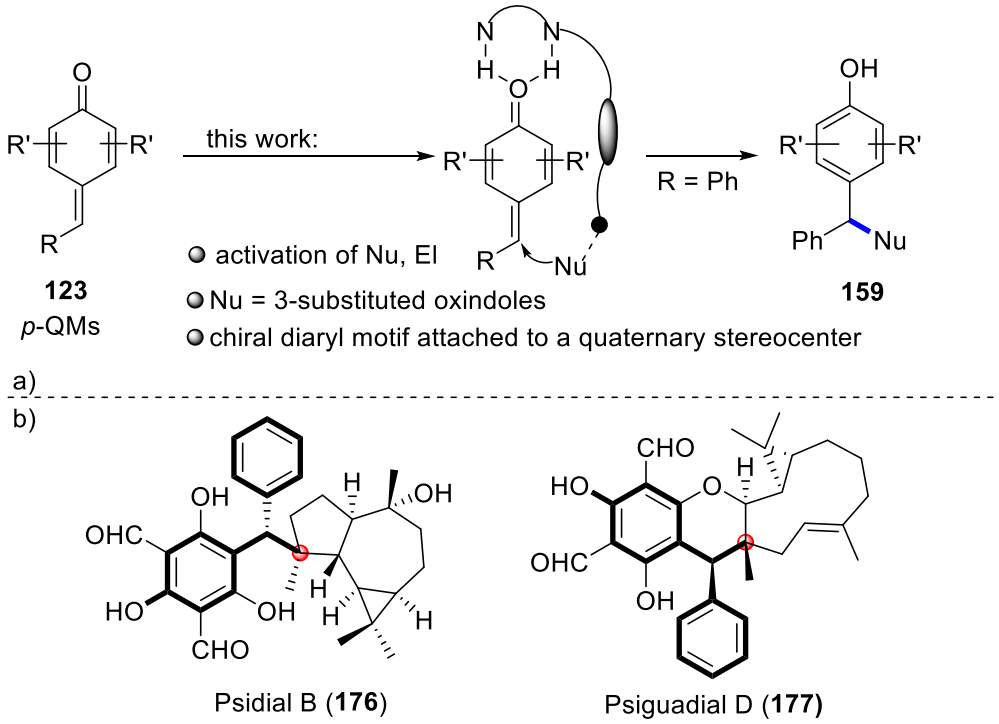


Scheme 54. *Catalytic asymmetric 1,6-addition to dienals or dienones.*

2.3.2 Our motivation

As mentioned in the *Introduction 1.3*, *para*-quinone methides are ideal 1,6-Michael acceptors and are increasingly being studied among chemists. When we started this project, there was no report involving the activation of this species. Inspired by Ye's work,[42] we thought that a 1,6-addition might occur by using a bifunctional organocatalyst. As demonstrated in Scheme 55a, the catalyst could not only activates the *para*-quinone methides via the hydrogen bonding interaction between the carbonyl parts of *p*-QMs and the N-H groups but also enhance the activity of the nucleophile. At that time, the asymmetric addition of prochiral species (enolized oxindoles or 3-substituted indoles) to *para*-quinone methides, has not been reported. In this context, 3-substituted oxindoles were chose as the nucleophile in this project.

This proposed 1,6-addition reaction could not only utilize the intrinsic electrophilic reactivity of the *para*-quinone methides but also make use of the nucleophilicity of the oxindole C3-position. In addition, this proposed reaction might be performed in an enantioselective fashion, thus providing a quick access to enantioenriched products **159** containing a diarylmethine group attached to an all-carbon quaternary stereocenter, which are frequently found in several natural products (Scheme 55b, **176** and **177**).[80]



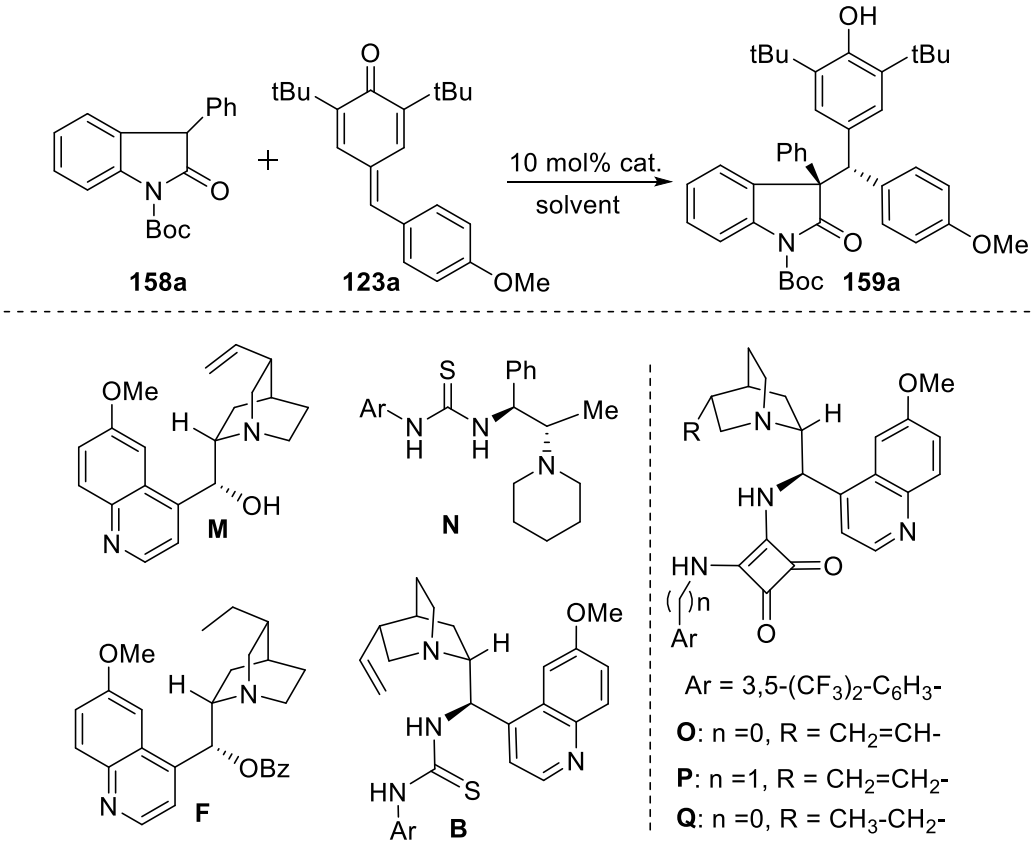
Scheme 55. *Our design and examples of diarylmethine attached to a quaternary stereocenter.*

2.3.3 Optimization of the conditions

To probe the feasibility of our proposed 1,6-addition reaction, we used 3-substituted oxindole **158a** and *para*-quinone methide **123a** as the model substrates to explore the reaction conditions (Table 5). An initial experiment was carried out in CH_2Cl_2 at room temperature in the presence of 10 mol% of **M**. We isolated the expected product **159a** in 43% yield with perfect diastereoselectivity, albeit with no enantiomeric excess (entry 1). Catalyst **F**, which was used as a general base, provided comparable results (entry 2). Better results were observed with the thiourea catalysts (**N** and **B**), but the efficiency of this reaction remained very low (entries 3 and 4). At this stage, we reckoned that bifunctional catalysts with stronger hydrogen bond donors could activate *p*-QM **123a** through hydrogen bonding, thus improving the yield and stereoselectivity of this transformation. Consistent with our hypothesis, employing the quinidine-derived catalyst **O**, the desired product was isolated in 77% yield with better diastereo- and

enantiocontrol (>20:1 d.r., 90:10 e.r.). Replacing catalyst **O** with catalyst **P** gave an inferior result (entry 6). Further catalyst screening revealed that squaramide **Q** was the best catalyst (entry 7). In order to further improve the stereoselectivity, we continued our investigation by screening the reaction solvent and temperature. We found that some non-polar solvents such as DCE, CCl_4 or toluene didn't give better results (entries 8-10). The optimal condition was obtained by performing the reaction at –40 ^oC, and the desired adduct **159a** could be isolated in 79% yield and 96:4 er.

Table 5 *Optimization of the reaction conditions.*



entry[a]	cat.	solvent	T [°C]	Yield [%][b]	d.r. [c]	e.r.[d]
1	**M**	DCM	25	43	>20:1	50:50
2	**F**	DCM	25	39	>15:1	52:48
3	**N**	DCM	25	40	>20:1	60:40
4	**B**	DCM	25	46	>20:1	70:30
5	**O**	DCM	25	77	>20:1	90:10

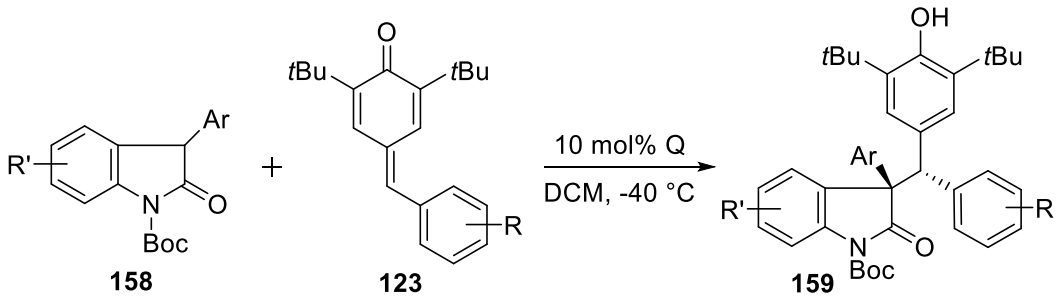
6	**P**	DCM	25	56	>20:1	74:26
7	**Q**	DCM	25	76	>20:1	92:8
8	**Q**	DCE	25	65	>20:1	89:11
9	**Q**	CCl_4	25	59	>20:1	89:11
10	**Q**	toluene	25	65	>20:1	90:10
11	**Q**	DCM	0	81	>20:1	92:8
12	**Q**	DCM	–20	73	>20:1	95:5
13	**Q**	**DCM**	**–40**	**79**	**>20:1**	**96:4**
14	**Q**	DCM	–78	75	>20:1	94:6

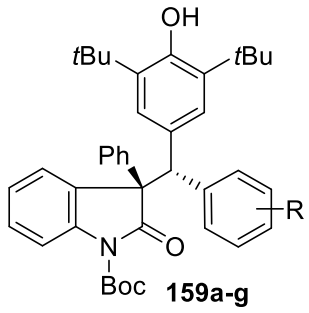
[a] All reactions were conducted with 0.2 mmol of **158a** (1 equiv), 0.3 mmol of **123a** (1.5 equiv) and 10 mol% of catalyst in a solvent (2.0 mL) at the indicated temperature for 1d. [b] Yield of isolated **159a**. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Determined by chiral stationary phase HPLC analysis.

2.3.4 Investigation of the substrate scope

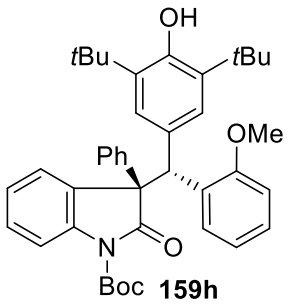
With the optimal reaction conditions in hand (Table 5, entry 13), the generality of this 1,6-addition reaction was explored. First, we investigated the scope of the *p*-QM component (Table 6, **159a-m**). It was found that a wide range of *p*-quinone methides could react with **158a**, yielding the desired adducts in high yields (68-96%) with good to excellent stereoselectivities. For instance, both electron-donating groups (R = 4-OMe, 4-Me) and electron-withdrawing groups (R = 4-Br, 4-NO_2, 2-Cl, 2-Br) could be well tolerated, delivering the corresponding products with high asymmetric induction (**159a-h**). Furthermore, we were pleased to find that the disubstituted *p*-QMs were suitable substrates and the desired products (**159i, j**) were obtained with good results under the optimized reaction conditions. Finally, substrates containing naphthyl, furyl or thienyl moieties, could also readily be transformed to the corresponding products with good stereoselectivities (**159k-m**).

Table 6 *Evaluation of substrate scope* [a].

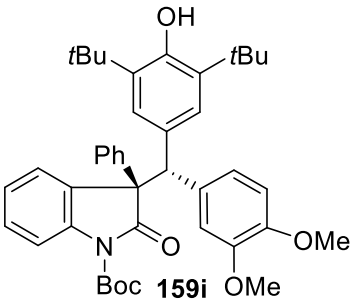




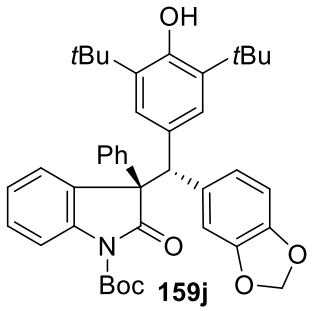
159a R = 4-OMe, 81% yield, >20:1 dr, 96:4 er
159b R = H, 88% yield, >20:1 dr, 96:4 er
159c R = 4-Me, 84% yield, 13:1 dr, 95:5 er
159d R = 4-Br, 84% yield, 10:1 dr, 95:5 er
159e R = 4-NO_2, 89% yield, >20:1 dr, 93:7 er
159f R = 2-Cl, 74% yield, >20:1 dr, 96:4 er
159g R = 2-Br, 68% yield, >20:1 dr, 93:7 er



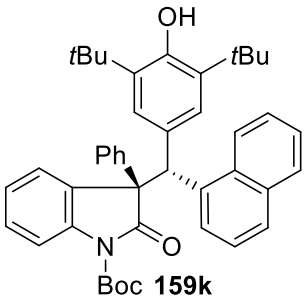
83% yield, >20:1 dr, 96:4 er



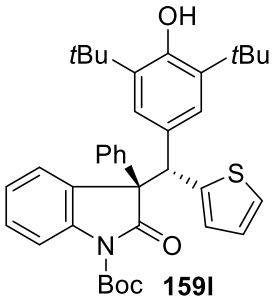
96% yield, >20:1 dr, 95:5 er



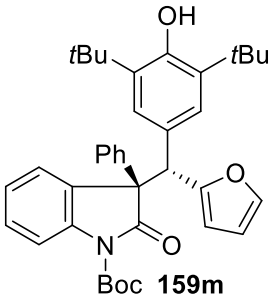
85% yield, >20:1 dr, 94:6 er



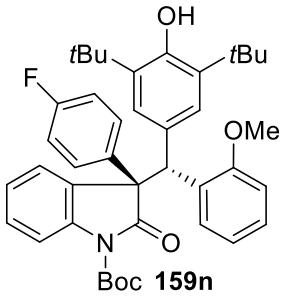
84% yield, >20:1 dr, 93:7 er



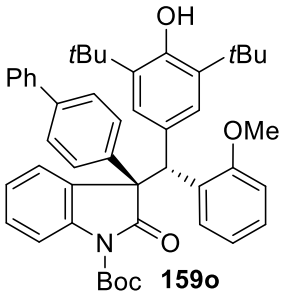
86% yield, 10:1 dr, 94:6 er



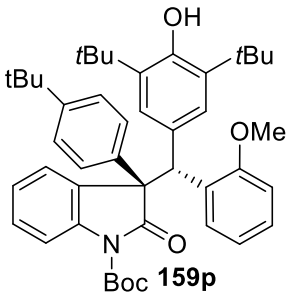
68% yield, 5:1 dr, 94:6 er



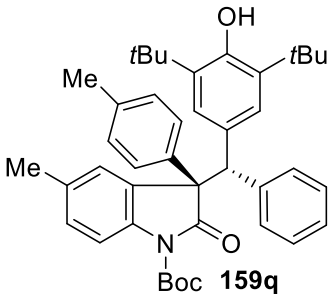
89% yield, >20:1 dr, 92:8 er



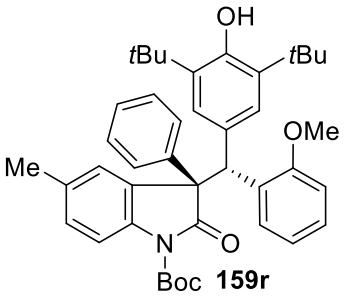
85% yield, >20:1 dr, 97:3 er



83% yield, >20:1 dr, 94:6 er



89% yield, 12:1 dr, 96:4 er



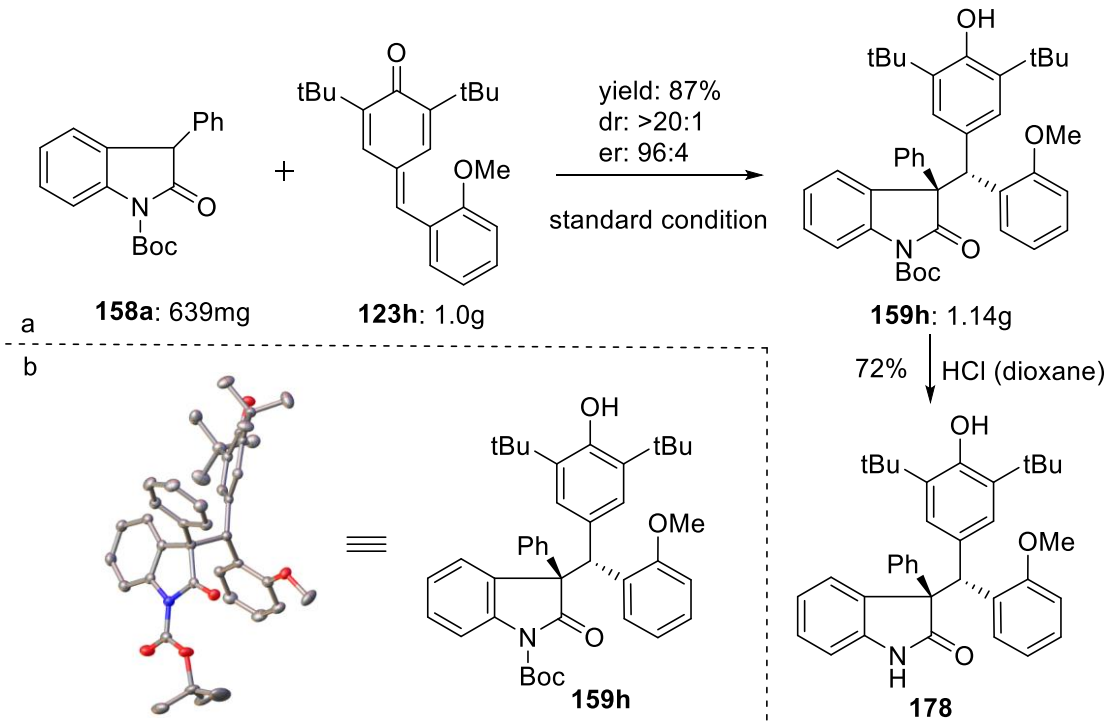
80% yield, >20:1 dr, 96:4 er

[a] All reactions were conducted with 0.4 mmol of **158** (1.0 equiv), 0.6 mmol of **123** (1.5 equiv) and 10 mol % of catalyst **Q** in DCM (4.0 mL) at -40 °C for 1d. Yields are those of isolated products **159** after column chromatography. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. The enantiomeric ratio was determined by chiral stationary phase HPLC analysis.

Next, we evaluated the tolerance of the functionality of the oxindole part (Table 6, **159n-r**). Generally speaking, several 3-aryl oxindoles, containing an electron-withdrawing group (4-F) or electron-donating groups (4-Ph, 4-Me, 4-*t*Bu) on the benzene ring or electron-donating groups (4-Me) on the aromatic ring of the oxindole moiety, could be used in this reaction, and the desired products (**159n-r)** were obtained in 80-89% yield with good to very good diastereo- and enantioselectivities.

2.3.5 Gram-scale reaction and determination of the absolute configuration

In order to test the general utility and robustness of this newly developed protocol, we conducted this 1,6-addition reaction on a gram-scale using our standard reaction conditions. As shown in Scheme 56a, the reaction worked readily, and 1.14g of compound **159h** was synthesized in 87% yield, >20:1 d.r. and 96:4 er. The deprotected compound **178** could be obtained smoothly without erosion of its optical purity. Additionally, the relative and absolute configuration of compound **159h** could be unambiguously determined by X-ray crystallography and the configurations of the other adducts were easily assigned by analogy (Scheme 56b).[81]



Scheme 56. *Gram-scale synthesis and X-ray structure of compound* ***159h****.*

2.4 Asymmetric synthesis of chromans bearing oxindole scaffolds via organocatalytic domino oxa-Michael/1,6-addition reaction

2.4.1 Importance of the chroman skeleton

The chroman scaffold is an important structural moiety not only in numerous bioactive natural products but also in a lot of pharmaceutical reagents.[82] Among them, chiral 4-phenyl substituted chroman derivatives, which bear several stereogenic centers, have gained much interest in the synthesis community because of their structural complexity as well as their potential medical value. As demonstrated in Figure 4, ormeloxifene (**179**) is a selective estrogen receptor modulator which is currently being marketed in India.[83] Compound NSC 381582 (**180**), a podophylotoxin analogue, displays antineoplastic activity;[84] (+)-hematoxylin (**181**) is a promising protein tyrosine kinase inhibitor and play important roles in histology.[85] Myristinin A (**182**), which is a flavonoid isolated from Myristica cinnamomea and Knema elegans, exhibits DNA polymerase β inhibitory and antifungal activities.[86] As a consequence, several methods for the enantioselective construction of this privileged scaffolds have been developed over the last several years. One of these is based on *ortho*-quinone methides intermediates.[49] This strategy has been proven very reliable and powerful by the research groups of Schneider,[87] Shi[88] and Rueping.[89] Although very high efficiency and stereoselectivity have been achieved in the aforementioned reports, the reaction partners were still limited to enamides, electron-rich olefins and oxonium ylides, which reacted with *ortho*-quinone methides to synthesize chiral phenyl substituted chromans. Therefore, it's still very desirable to develop another reliable methods besides *o*-QM intermediates.

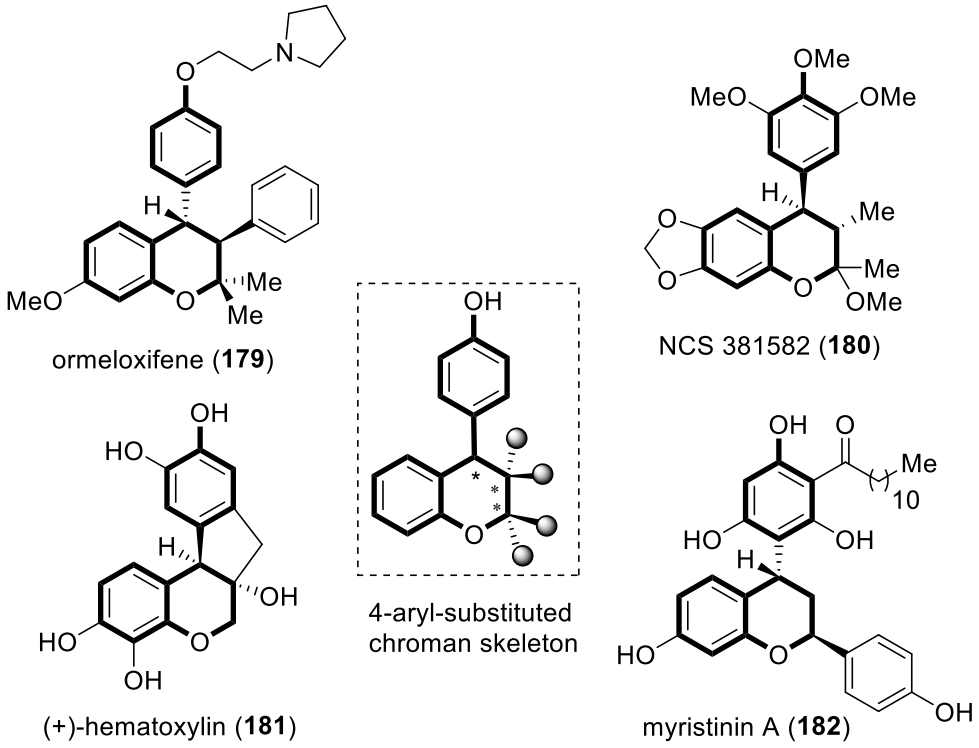


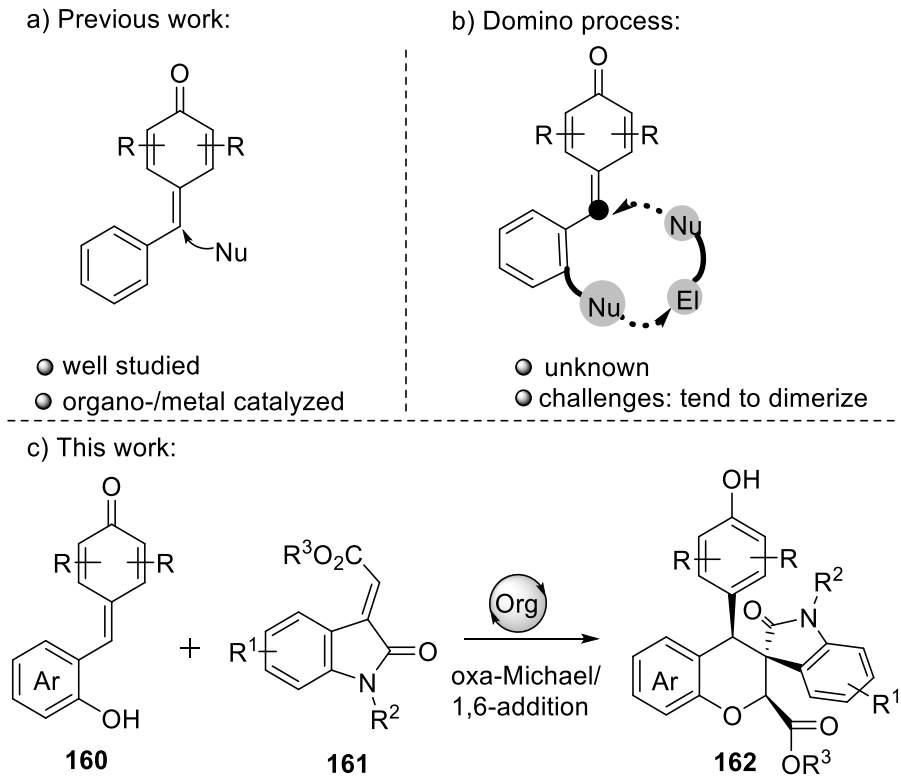
Figure 4. *Pharmaceuticals and natural products containing a chiral 4-phenyl chroman skeleton.*

2.4.2 Our motivation

para-Quinone methides have been increasingly studied in organic synthesis and the 1,6-addition to *p*-QMs has been considered as a powerful method to synthesize chiral diarylmethine compounds.[50] For instance, in 2013, Fan and co-worker first reported an organocatalytic 1,6-addition reactions between *para*-quinone methides and malonates.[51] Later, Jørgensen *et al.* realized the asymmetric α-alkylation of aldehydes via 1,6-additon of enamines to *p*-QMs by using a chiral secondary amine catalyst.[52] Quite recently, Sun's group demonstrated an elegant strategy where *para*-quinone methides could be formed in situ and then trapped with another species such as pyrroles[53] and naphthols.[90] Besides these, more representative cases have been presented in the *Introduction 1.3*.

It is noteworthy that domino reactions have been demonstrated as one of the most powerful tools in modern organic synthesis.[15] Surprisingly, there is no report involving applications of the *para*-quinone methides in asymmetric domino reactions. In this context, we started to carry out this project.

As described in Scheme 57, we thought of adding a suitable nucleophilic site in the *p*-QMs skeleton, which could therefore convert *para*-quinone methides into donor-Michael acceptor compounds. This substrate could be then used in a domino reaction. However, we realized later that this assumption is very challenging because of the potential dimerization of such species. After many experiments, we found that *ortho*-hydroxyphenyl substituted *para*-quinone methides **160** are ideal substrates.[91] Furthermore, to the best of our knowledge, there were no reports about using this interesting bifunctional synthon in synthesis. To fill this gap, we proposed a novel domino oxa-Michael/1,6-addition reaction (Scheme 57c).[92] In addition, the asymmetric version of this domino reaction might be realized by using a suitable chiral organocatalyst. Through such domino reaction, a series of chiral highly functionalized chromans (**162**) could be synthesized, and the expected products not only contain an oxindole scaffold but also bear three contiguous stereogenic centers.



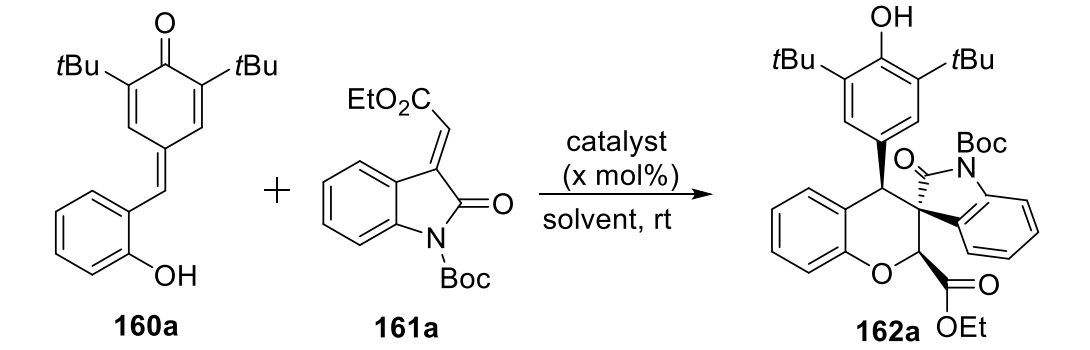
Scheme 57. *Reported methods based on p-QMs (a), our domino strategy (b) and asymmetric oxa-Michael/1,6-addition reactions to form 4-phenyl-substituted chromans bearing spiro-connected oxindole scaffolds (c).*

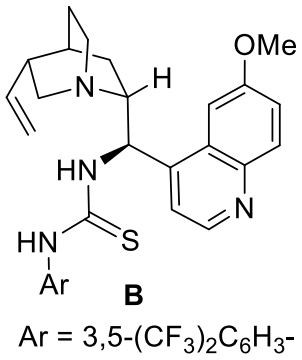
2.4.3 Optimization of the reaction conditions

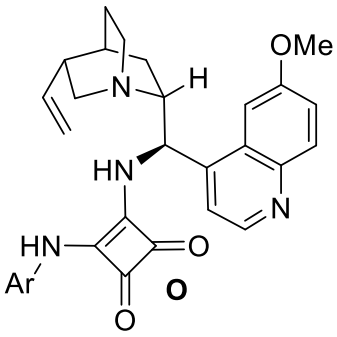
To probe the feasibility of this domino reaction, we chose the model reaction of **160a** and **161a**[77c, 93] to optimize this reaction. Initially, the bifunctional thiourea catalyst **B** was examined. It was found that the proposed domino reaction proceeded smoothly, and the expected product **162a** was obtained in 45% yield with very high enantioselectivity, albeit with very low diastereoselectivity (Table 7, entry 1). The squaramide catalyst **O** gave similar results (Table 7, entry 2). Next, several thiourea organocatalysts **N**-**V** were tested (Table 7, entries 3-8) and we found that catalyst **U** was the best catalyst for this domino reaction, yielding excellent efficiency and stereoselectivity (Table 7, entry 7). The catalyst loading was then lowered from 20 mol% to 5 mol%, and the efficiency slightly improved and the stereoselectivities were remained at very high levels (Table 7, entries 9 and 10). No better results could be

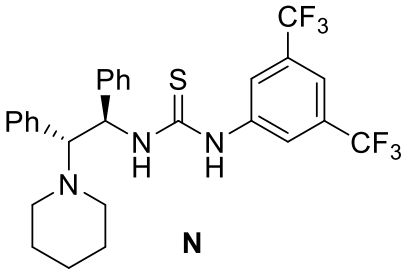
obtained when some other solvents (DCM, DCE, Et_2O, $PhCF_3$) were employed (Table 7, entries 11-14). Above all, the optimal reaction conditions was entry 10, which delivered compound **162a** in 89% yield with 99% *ee* and 17:1 dr.

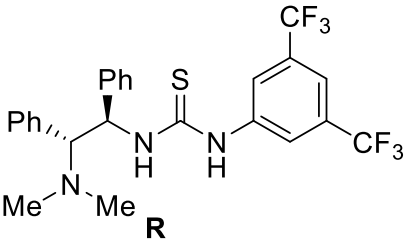
Table 7 *Optimization of the reaction conditions.*

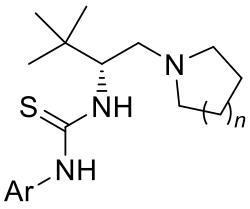


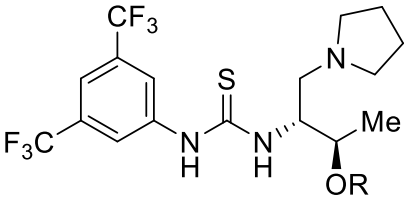












entry[a]	cat.	solvent	mol %	yield [%][b]	d.r. [c]	ee [%] [d]
1	**B**	toluene	20	45	1:1.3	94
2	**O**	toluene	20	42	1:1.5	94
3	**N**	toluene	20	63	3:1	–45
4	**R**	toluene	20	69	5:1	–97
5	**S**	toluene	20	81	10:1	96
6	**T**	toluene	20	80	8:1	83

7	**U**	toluene	20	82	16:1	98
8	**V**	toluene	20	trace	n.d.	n.d.
9	**U**	toluene	20	88	17:1	98
10	**U**	**toluene**	**5**	**89**	**17:1**	**99**
11	**U**	DCM	5	62	4:1	95
12	**U**	DCE	5	75	7:1	96
13	**U**	Et_2O	5	70	6:1	99
14	**U**	$PhCF_3$	5	81	12:1	98

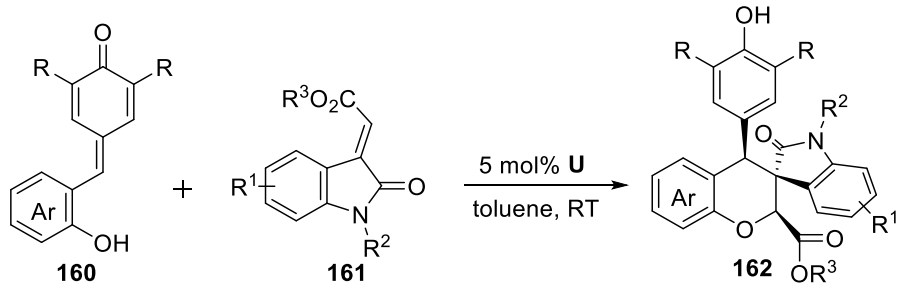
[a] All reactions were conducted with 0.2 mmol of **160a** (1 equiv), 0.24 mmol of **161a** (1.2 equiv) and 5-20 mol% of catalyst in a solvent (2.0 mL) at room temperature for 48 h. [b] Yield of isolated **162a**. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral stationary phase HPLC analysis. n.d. = not determined.

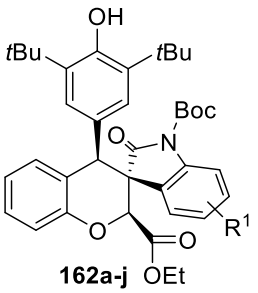
2.4.4 Substrates scope and discussion

With the optimal reaction conditions in hand (Table 7, entry 10), we then explored the substrate scope of this oxa-Michael/1,6-addition domino reaction. Initially, the scope of the reaction component **161** was examined (Table 8, top). In general, a wide range of 3-olefinic oxindoles could be used in this transformation, furnishing the desired products **162a-p** in good yields (58-98%) with excellent enantioselectivities (92 to > 99% *ee*). For example, substrates containing electron-neutral (R = H), electron-donating groups (R^1 = 5-Me, 5-OMe) or electron-withdrawing groups (R^1 = 5-F, 5-Cl, 5-Br, 5-I, 5-NO_2, 5-OCF_3, 6-Cl) at different positions of the benzene ring underwent this transformation readily to deliver the corresponding chromans in good to excellent yields with excellent enantioselectivities (**162a-k**). Moreover, various substituted groups (methyl ester, phenyl ester and Cbz) on the oxindole nitrogen atom could be well tolerated, giving excellent results (**162l-n**). In addition, it was found that the R^3 group had no effect on the efficiencies and stereoselectivities, and the corresponding products **162o** and **162q** could be synthesized in 90% yield, 97% ee and 75% yield, 98% ee, respectively

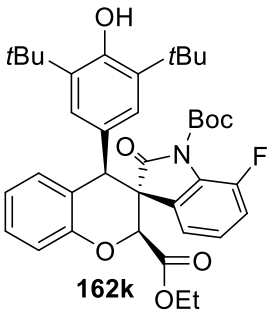
Next, we investigated the functionality and the substitution of the hydroxyphenyl-substituted *p*-QMs **160**. Both electron-withdrawing groups (Cl, Br) and electron-donating substituents (Me, OMe) in the *para-*, *meta-*, and *ortho*-positions of the phenyl ring of the substrates **160** could be well tolerated, and the desired products were obtained in good yields and excellent stereoselectivities (**162q-x**). The naphthyl-substituted hydroxyl-substituted *p*-QM also took part in this domino reaction and yielded product **162y**. It is worth mentioning that switching the R substituent of the *p*-QM from the tert-butyl group to an isopropyl group has not influenced the stereoselectivity of this reaction (**162z**).

Table 8 *Optimization of the reaction conditions*



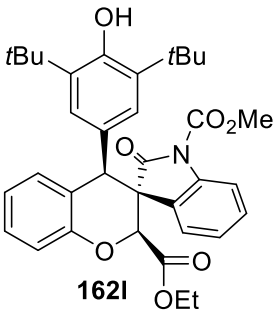


162a	R_1 = 5-H,	89%, 17:1 dr, 99% ee
162b	R_1 = 5-Me,	63%, 13:1 dr, 98% ee
162c	R_1 = 5-OMe,	58%, 10:1 dr, 96% ee
162d	R_1 = 5-F,	86%, >20:1 dr, 98% ee
162e	R_1 = 5-Cl,	92%, >20:1 dr, 98% ee
162f	R_1 = 5-Br,	94%, >20:1 dr, 98% ee
162g	R_1 = 5-I,	91%, >20:1 dr, 97% ee
162h	R_1 = 5-NO_2,	98%, >20:1 dr, 98% ee
162i	R_1 = 5-OCF_3,	92%, >20:1 dr, 96% ee
162j	R_1 = 6-Cl,	64%, >20:1 dr, 97% ee



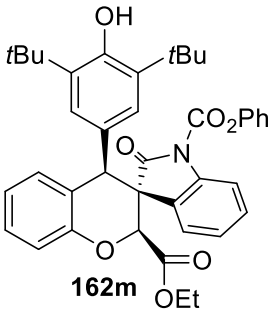
162k

77%, 15:1 dr, >99% *ee*



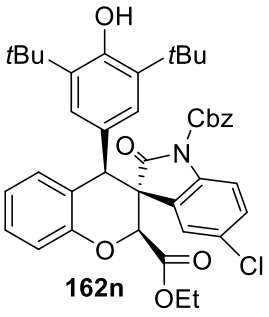
162l

65%, 10:1 dr, 92% *ee*



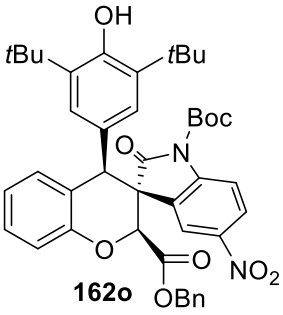
162m

70%, >20:1 dr, 96% *ee*



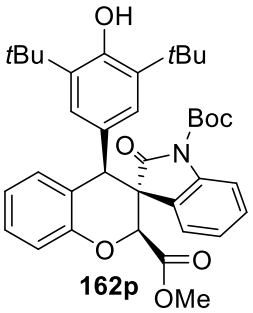
162n

62%, 14:1 dr, 93% *ee*



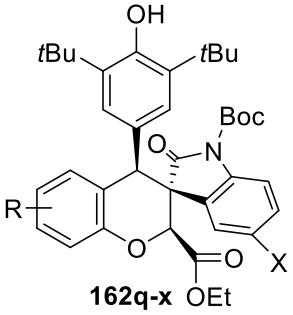
162o

90%, >20:1 dr, 97% *ee*



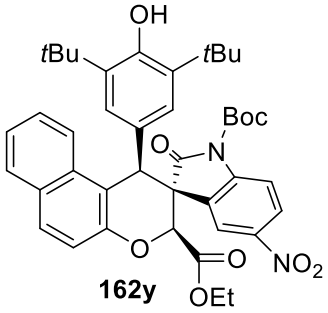
162p

75%, 15:1 dr, 98% *ee*



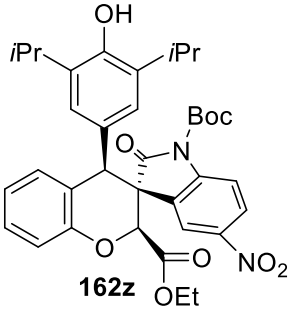
162q-x

162q	R = 4-Cl,	X= NO_2,	74%, >20:1 dr,	99% *ee*
162r	R = 4-Cl,	X= H,	72%, >20:1 dr,	>99% *ee*
162s	R = 4-Br,	X= NO_2,	88%, >20:1 dr,	95% *ee*
162t	R = 4-Me,	X= NO_2,	81%, >20:1 dr,	98% *ee*
162u	R = 4-OMe,	X= NO_2,	66%, >20:1 dr,	95% *ee*
162v	R = 5-OMe,	X= H,	6 2%, 13:1 dr,	>99% *ee*
162w	R = 5-OMe,	X= NO_2,	70%, >20:1 dr,	96% *ee*
162x	R = 6-OMe,	X= NO_2,	51%, >20:1 dr,	95% *ee*



162y

92%, >20:1 dr, 78% *ee*



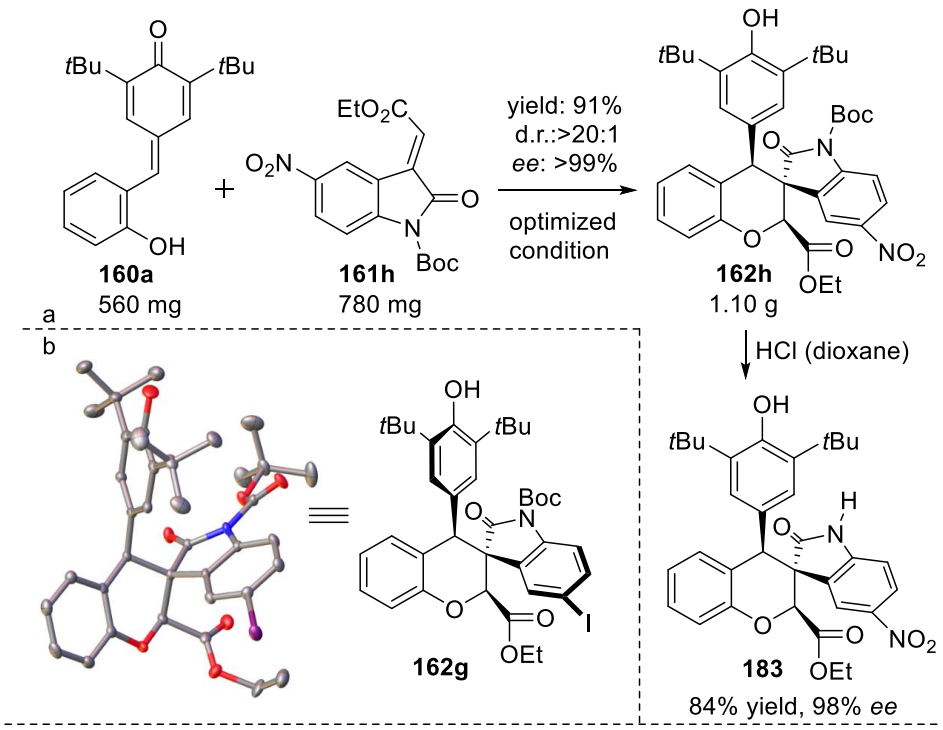
162z

43%, >20:1 dr, 93% *ee*

[a] All reactions were conducted with 0.4 mmol of **160** (1.0 equiv), 0.48 mmol of **161** (1.2 equiv) and 5 mol% of catalyst **U** in toluene (4.0 mL) at room temperature for 12-72 h. Yields of isolated products **162** after column chromatography. The diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. The ee values were determined by chiral stationary phase HPLC analysis.

2.4.5 Gram scale reaction and determination of the absolute configuration of the products

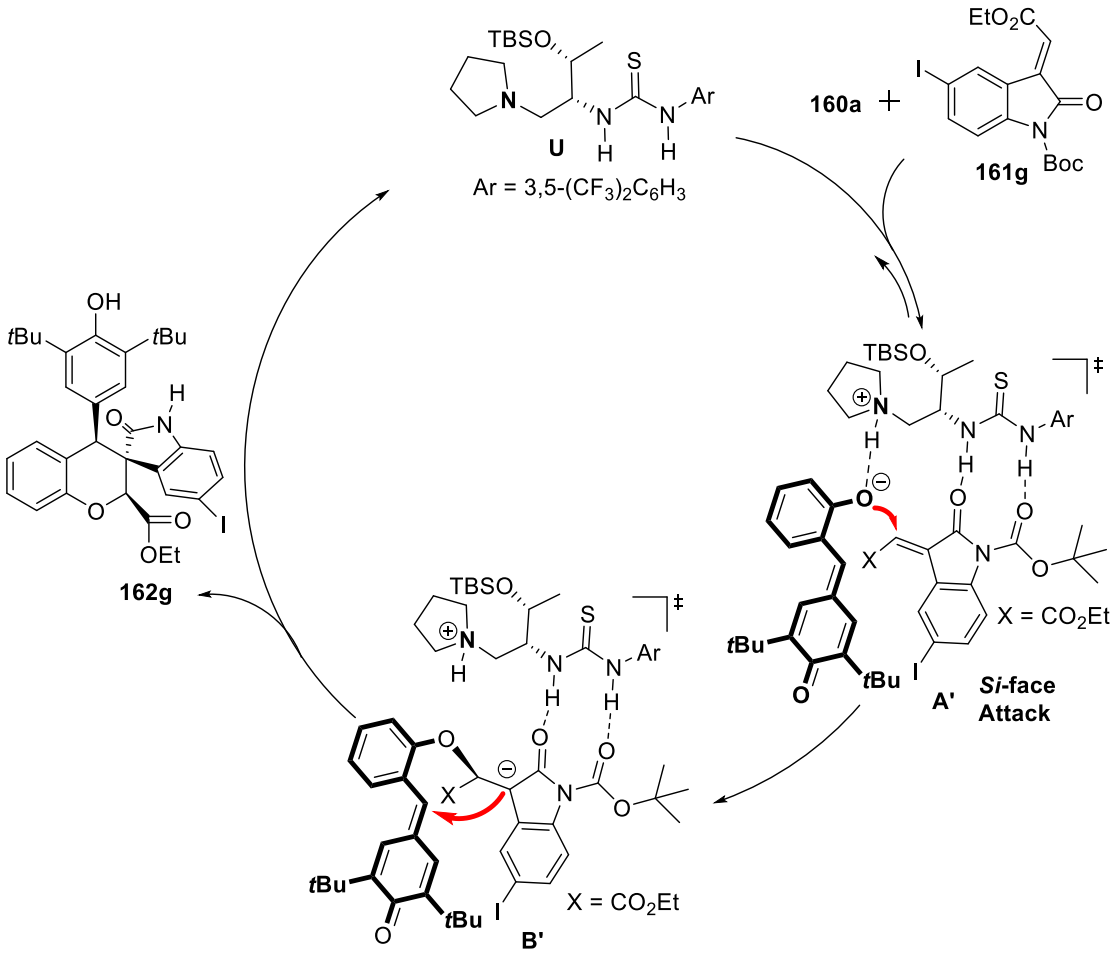
To evaluate the practical utility of this oxa-Michael/1,6-addition domino reaction, a gram-scale reaction using **160a** and **161h** was carried out under the standard conditions. As depicted in Scheme 58a, compound **162h** could be synthesized with similar results (91% yield, >20:1 d.r. and >99% ee). Furthermore, the removal of the N-Boc group was easily realized under mild conditions without any erosion of the stereoisomeric purity. The relative and absolute configuration of compound **162g** was determined by an X-ray crystallographic study, and the configurations of other products were assigned by analogy to **162g**.[94]



Scheme 58. *Gram-scale synthesis of* ***162h*** *and X-ray structure of* ***162g****.*

2.4.6 Mechanism of the domino reaction

A plausible catalytic cycle for this oxa-Michael/1,6-addition domino reaction between hydroxyl-substituted *p*-QMs and isatin-derived enoates is shown in Scheme 59. In the case of substrates **160a** and **161g** for example, the bifunctional catalyst **U** activates substrate **161g** through hydrogen-bonding interactions whereas its amino group serves as a base to activate the *p*-QMs **160a** through deprotonation, thus forming intermediate **A'**. Then, this intermediate undergoes an oxa-Michael addition to give the intermediate **B'**. Next, an intramolecular 1,6-addition would occur, and subsequent proton transfer delivers the final product **160g** with the release of catalyst **U**.

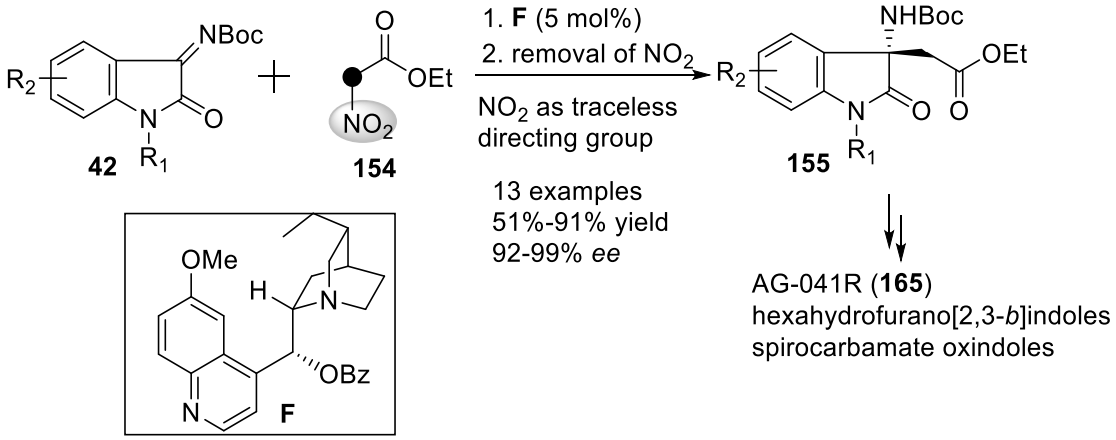


Scheme 59. *Plausible catalytic cycle.*

3. Research Summary

In this thesis four organocatalytic methodologies ranging from sequential reactions, one-pot reactions to domino reactions have been presented and the research results were published in peer-reviewed journals. The conclusion of these four projects will be briefly listed as follows:

3.1 Asymmetric synthesis of 3-ethylacetate-substituted 3-amino-2-oxindoles and formal synthesis of AG-041R

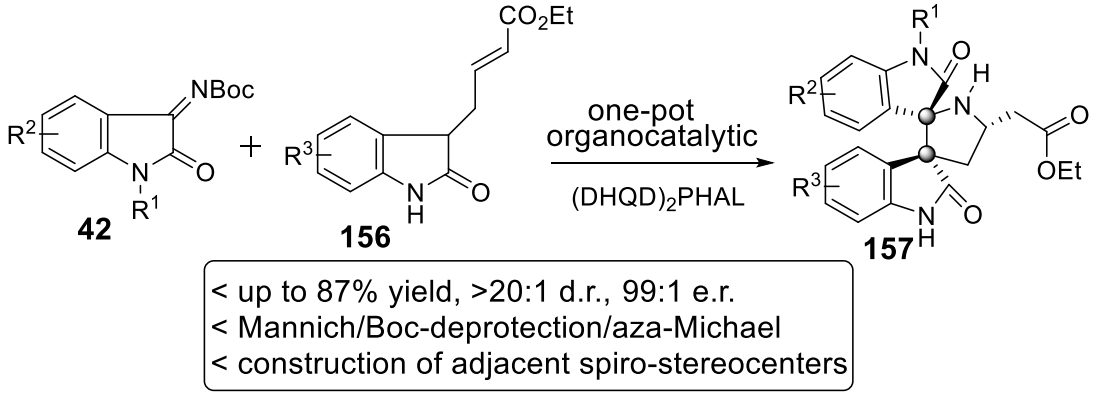


Scheme 60. *Asymmetric synthesis of 3-ethylacetate-substituted 3-amino-2-oxindoles via organocatalytic Mannich/denitration reaction.*

In the first project, the nucleophilic addition of ethyl nitroacetate to isatin-derived ketimines, followed by the removal of the nitro group to synthesize chiral 3-substituted 3-amino-2-oxindoles was realized. A cinchona derivative (**F**) was employed as the catalyst and the nitro group was used as a traceless activation group. This new protocol can easily be scaled up to gram amounts and its practical applicability was demonstrated with the formal synthesis of AG-041R (**165**).

3.2 Organocatalytic asymmetric synthesis of 3,3'-pyrrolidinyl-dispirooxindoles

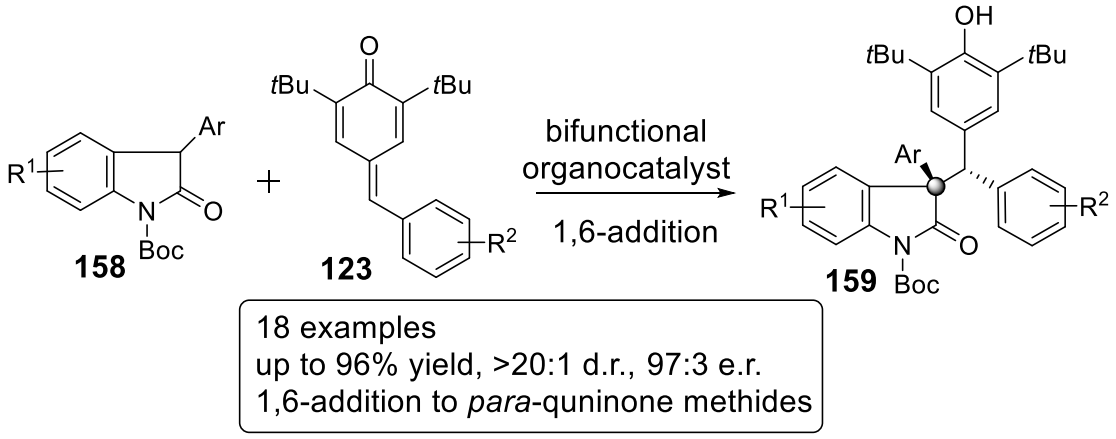
In this project, we developed a highly stereoselective one-pot synthesis of 3,3'-pyrrolidinyl-dispirooxindoles featuring three stereocenters including two adjacent spiro-centers. Our protocol is based on a Mannich/Boc-deprotection/aza-Michael sequence carried out in one pot and two consecutive steps. The first stereogenic Mannich reaction was catalyzed by the commercially available $(DHQD)_2PHAL$, followed by a Boc deprotection and an intramolecular aza-Michael sequence.



Scheme 61. *Asymmetric synthesis of 3,3'-pyrrolidinyl-dispirooxindoles.*

A series of 3,3'-pyrrolidinyl-dispirooxindoles **157** could be obtained in good yields and excellent stereoselectivities and are of interest as characteristic core structures of bioactive compounds including antimicrobial and anticancer agents. The practicability of this method was demonstrated in a gram-scale reaction.

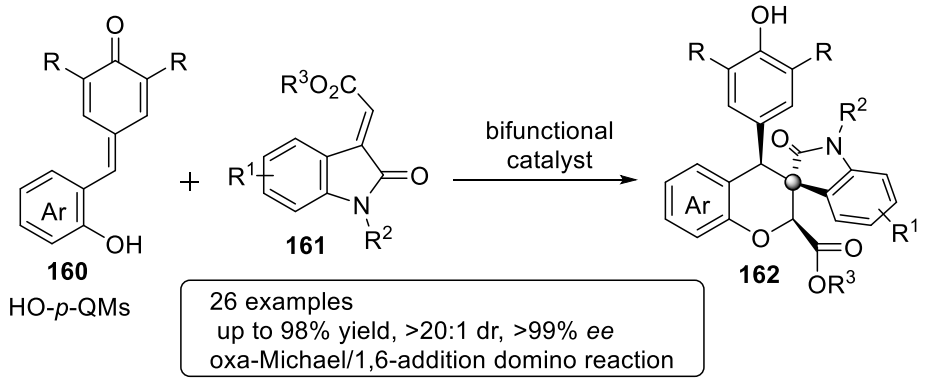
3.3 Organocatalytic asymmetric synthesis of 3-diarylmethine-substituted oxindoles



Scheme 62. *Organocatalytic 1,6-addition of 3-substituted oxindoles to p-QMs.*

In the third project, a highly stereoselective construction of an all-carbon quaternary stereocenter was achieved via a bifunctional squaramide catalyzed 1,6-addion of 3-substituted oxindoles to *para*-quinone methides. Using this newly developed protocol, a series of chiral oxindole derivatives **159**, bearing the diarylmethine motif attached to a quaternary stereogenic center, could be obtained in a scalable manner with high yields, excellent diastereoselectivities and good enantioselectivities. We reckoned that the *para*-quinone methides might be activated by a hydrogen bonding interaction between the carbonyl moiety and the N-H group.

3.4 Organocatalytic asymmetric synthesis of chromans bearing oxindole scaffolds

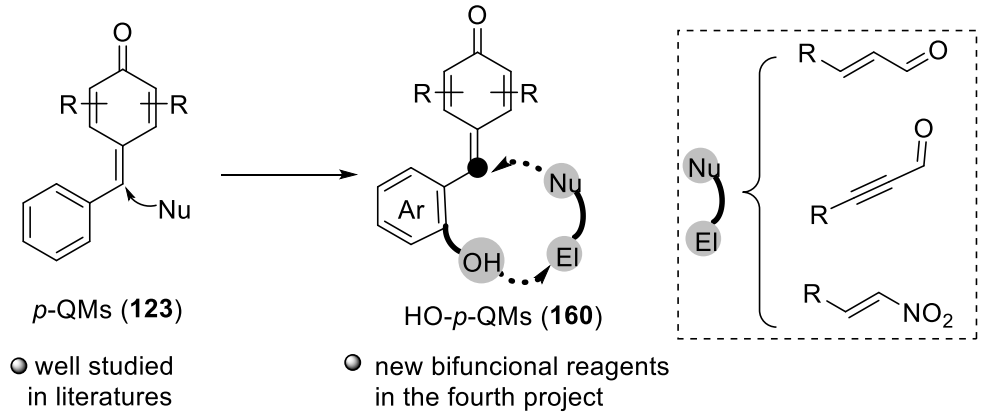


Scheme 63. *Asymmetric organocatalytic oxa-Michael/1,6-addition domino reactions.*

In the fourth and last project, we developed a new efficient domino strategy as a direct catalytic entry to chiral 4-phenyl chromans based on *ortho*-hydroxyphenyl-para-quinone methides (**160**) as bifunctional substrates. In the presence of 5 mol% of a thiourea organocatalyst, hydroxyl-substituted *p*-QMs and isatin-derived enoates (**161**) were combined in a domino oxa-Michael/1,6-addition reaction to form the desired compounds in high yields and excellent stereoselectivities (up to > 20:1 dr, >99% ee). In this process, three contiguous stereocenters, including one all carbon spiro center, could be constructed with high stereocontrol. These spiro oxindole-connected 4-phenyl-chroman compounds might bear potential bioactivities. In addition, this new protocol could be easily scaled up to gram amounts.

4. Perspectives and outlook

As discussed in *Introduction 1.3*, *para*-quinone methides **123** have been well studies during the last two or three years. But we found that applications of *para*-quinone methides in domino reactions are still rare. In project 4, the hydroxyl-substituted *p*-QMs (**160**) were successfully used in an oxa-Michael/1,6-addition domino reaction. It is realistic that hydroxyl-*p*-QMs can be further used in other domino reactions. One possible extension will be the choice of other type of bifunctional compounds as demonstrated in Scheme 64.



Scheme 64. *Further applications of HO-p-QMs in domino reactions.*

5. Experimental part

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 an IKA rotary evaporator.

Solvent

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.

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. 0.2 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.

Analytical Methods:

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); coupling constants; number of protons and assignment.

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).

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}.

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 AS (10 µm) (250 mm x 4.6 mm)

Chiralpak OD (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 OJ (10 µm) (250 mm x 4.6 mm)

Chiralpak IC (5 µm) (150 mm x 4.6 mm)

Melting points

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

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 $CHCl_3$ was used as solvent. The concentrations (c) are given in g·100 mL^{-1}.

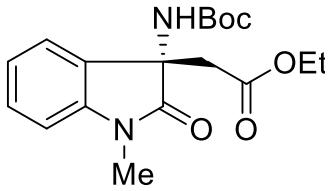
General Procedure (GP) and Analytical Data

GP 1 for the first project and analytical data of synthesized compounds

A glass tube equipped with a stirring bar was charged with the ketimine **42** (0.45 mmol, 1.0 equiv), catalyst **F** (9.7 mg, 5 mol %) and dry DCM (4.5 mL). The resulting solution of the reaction mixture was cooled to -20 °C and then the ethyl nitroacetate **154** (0.54 mmol, 1.2 equiv) was added via a syringe. The mixture was stirred at -20 °C for 12 h, transferred into a long glass tube and concentrated in *vacuo*. Then the resulting residue was dissolved in dry toluene (4.5 mL) to which AIBN (0.09 mmol, 0.2 equiv) and *n*Bu_3SnH (0.9 mmol, 2.0 equiv) were added. After the reaction mixture was stirred at 110 °C for 1 h, the solvent was evaporated to give the crude product, which was directly

purified by flash chromatography (pentane/EtOAc = 5/1 to 3/1) to provide the desired product **155**.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)acetate (155a)



According to **GP 1**, **155a** was obtained as a colorless solid (136.2 mg, 87% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 3:1)

Melting Point: 106-108 °C.

$[\alpha]_D^{25}$ = -45.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AS; *n*-heptane/EtOH = 90/10; flow rate 1.0 mL/min; T= 30 °C; retention time: 6.48 min (major), 8.19 min (minor), 96% *ee*.

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

δ = 7.29 – 7.23 (m, 2H, Ar-*H*), 7.00 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.81 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.28 (s, 1H, N*H*Boc), 4.17 – 4.05 (m, 2H, $CO_2CH_2CH_3$), 3.21 (s, 3H, CH_3), 2.87 (d, J = 15.0 Hz, 1H, C*H*HCO_2Et), 2.49 (d, J = 15.0 Hz, 1H, CH*H*CO_2Et), 1.22 (s, 9H, $CO_2C(CH_3)_3$), 1.17 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

δ = 175.4 (CO_2Et), 169.7 ($CONCH_3$), 153.8 ($CO_2C(CH_3)_3$), 143.2 (C_{Ar}), 129.5 (C_{Ar}), 129.2 (C_{Ar}), 123.0 (C_{Ar}), 122.7 (C_{Ar}), 108.3 (C_{Ar}), 80.2 ($CO_2C(CH_3)_3$), 61.3 (*C*NHBoc), 59.2 ($CO_2CH_2CH_3$), 40.8 (CH_2CO_2Et), 28.0 (3C, $CO_2C(CH_3)_3$), 26.6 (NCH_3), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3279, 2979, 2934, 1708, 1611, 1568, 1532, 1466, 1422, 1368, 1253, 1161, 1125, 1091, 1022, 938, 893, 827, 702, 666 cm^{-1}.

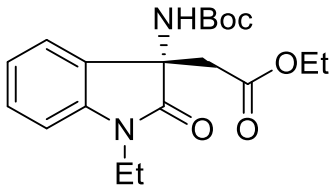
MS (EI, 70 eV): *m/z* (%) = 348 [M^+] (100), 292 (55), 161 (88).

HRMS (ESI): calcd for $C_{18}H_{24}O_5N_2Na$ [M + Na]$^+$: 371.1577, found 371.1583.

The gram scale reaction for the synthesis of **155a** was carried out in an analogous manner.

A 100 mL round flask with a stirring bar was charged with ketimine **42a** (4.0 mmol, 1.0 equiv), catalyst **F** (86.0 mg, 5 mol %) and dry DCM (45.0 mL). The resulting reaction mixture was cooled to -20 °C and then the ethyl nitroacetate **154** (48.0 mmol, 1.2 equiv) was added via a syringe. The mixture was stirred at -20 °C for 12 h and concentrated under vacuum. The resulting residue was dissolved in dry toluene (40.0 mL) to which AIBN (131.0 mg, 0.8 mmol, 0.2 equiv) and *n*Bu_3SnH (2.3 g, 8.0 mmol, 2.0 equiv) were added. The reaction mixture was stirred at 110 °C for 1 h. The solvent was evaporated to give a crude product, which was directly purified by flash chromatography (pentane/EtOAc = 5/1 to 3/1) to provide the product **155a** (1.10 g, 85% yield, 96% *ee*). The analytical data of the gram scale reaction of **155a** are consistent with those of the 0.45 mmol scale experiment.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1-ethyl-2-oxoindolin-3-yl)acetate (155b)



According to **GP 1**, **155b** was obtained as a colorless solid (136.8 mg, 84% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 3:1)

Melting Point: 127-128 °C.

$[\alpha]_D^{25}$ = -56.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 90/10; flow rate 0.7 mL/min; T= 30 °C; retention time: 21.59 min (major), 10.33 min (minor), 96% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$):

δ = 7.33 – 7.13 (m, 2H, Ar-*H*), 6.95 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.17 (s, 1H, N*H*Boc), 4.16 – 3.98 (m, 2H, $CO_2CH_2CH_3$), 3.84 (dd, *J* = 12.7, 5.7 Hz, 1H, NC*H*HCH_3), 3.72 – 3.53 (m, 1H, NCH*H*CH_3), 2.84 (d, *J* = 15.0 Hz, 1H, C*H*HCO_2Et), 2.45 (d, *J* = 15.0 Hz, 1H, CH*H*CO_2Et), 1.27 – 1.11 (m, 15H, $CO_2C(CH_3)_3$,

$CO_2CH_2CH_3$, NCH_2CH_3) ppm.

^{13}C NMR (75MHz, $CDCl_3$):

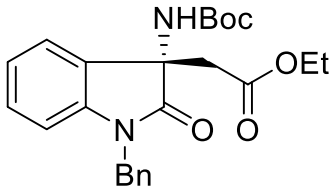
δ = 175.0 (*C*O_2Et), 169.7 (*C*ONCH_2CH_3), 153.8 (*C*$O_2C(CH_3)_3$), 142.3 (C_{Ar}), 129.7 (C_{Ar}), 129.1 (C_{Ar}), 123.3 (C_{Ar}), 122.4 (C_{Ar}), 108.4 (C_{Ar}), 80.2 ($CO_2C(CH_3)_3$), 61.2 (*C*NHBoc), 59.0 ($CO_2CH_2CH_3$), 40.9 (CH_2CO_2Et), 35.0 (NCH_2CH_3), 28.1 (3C, $CO_2C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$), 12.5 (NCH_2CH_3) ppm.

IR (ATR): 3323, 2969, 1709, 1612, 1469, 1367, 1162, 1030, 868, 751 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 362 [M^+] (100), 306 (48), 175 (74).

HRMS (ESI): calcd for $C_{19}H_{26}O_5N_2Na$ [M + Na]$^+$: 385.1734, found 385.1737.

(*S*)-Ethyl 2-(1-benzyl-3-((tert-butoxycarbonyl)amino)-2-oxoindolin-3-yl)acetate (155c)



According to **GP 1**, **155c** was obtained as colorless oil (122.1 mg, 64% yield).

TLC: R_f = 0.50 (n-petane: EtOAC = 4:1)

$[\alpha]_D^{25}$ = -15.9 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 °C; retention time: 6.20 min (major), 5.36 min (minor), 93% *ee*.

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

δ = 7.37 – 7.22 (m, 6H, Ar-*H*), 7.16 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.98 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.69 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.37 (s, 1H, N*H*Boc), 5.08 (d, *J* = 15.6 Hz, 1H, C*H*HPh), 4.81 (s, 1H, CH*H*Ph), 4.15 (q, *J* = 7.6 Hz, 2H, $CO_2CH_2CH_3$), 2.93 (d, *J* = 15.0 Hz, 1H, C*H*HCO_2Et), 2.55 (d, *J* = 15.0 Hz, 1H, CH*H*CO_2Et), 1.28 (s, 9H, $CO_2C(CH_3)_3$), 1.20 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

δ = 175.5 (*C*O_2Et), 169.7 (*C*ONCH_2Ph), 153.7 (*C*$O_2C(CH_3)_3$), 142.2 (C_{Ar}), 135.5 (C_{Ar}),

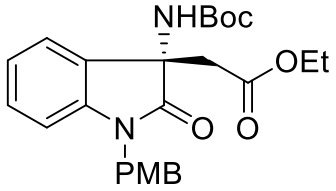
123.0 (C_{Ar}), 129.1 (C_{Ar}), 128.7 (C_{Ar}), 127.5 (C_{Ar}), 127.4 (C_{Ar}), 123.0 (C_{Ar}), 122.7 (C_{Ar}), 109.2 (C_{Ar}), 80.3 ($CO_2C(CH_3)_3$), 61.3 (CNHBoc), 59.3 ($CO_2CH_2CH_3$), 44.2 (CH_2Ph), 41.0 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3342, 2974, 2326, 2100, 1895, 1714, 1613, 1480, 1367, 1257, 1169, 1017, 923, 858, 745 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 424 [M^+] (100), 368 (23), 237 (84), 91 (88).

HRMS (ESI): calcd for $C_{24}H_{28}O_5N_2Na$ [M + Na]$^+$: 447.1890, found 447.1899.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1-(4-methoxybenzyl)-2-oxoindolin-3-yl)acetate (155d)



According to **GP1**, **155d** was obtained as colorless oil (147.1 mg, 72% yield).

TLC: R_f = 0.60 (n-petane:EtOAC = 4:1)

$[\alpha]_D^{25}$ = -25.0 (c = 0.6, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 ºC; retention time: 8.01 min (major), 6.07 min (minor), 93% *ee*.

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

δ = 7.30 - 7.24 (m, 3H, Ar-*H*), 7.16 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 6.97 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.71 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.35 (s, 1H, N*H*Boc), 4.99 (d, *J* = 12.0 Hz, 1H, NC*H*HAr), 4.76 (s, 1H, NCH*H*Ar), 4.14 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.75 (s, 3H, OCH_3), 2.91 (d, *J* = 15.0 Hz, 1H, C*H*HCO_2Et), 2.52 (d, *J* = 15.0 Hz, 1H, CH*H*CO_2Et), 1.28 - 1.18 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

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

δ = 175.3 (CO_2Et), 169.8 (CONCH$_2$Ph), 159.2 ($CO_2C(CH_3)_3$), 153.8 (C_{Ar}), 142.2 (C_{Ar}), 129.6 (C_{Ar}), 129.0 (C_{Ar}), 128.7 (C_{Ar}), 127.8 (C_{Ar}), 123.0 (C_{Ar}), 122.6 (C_{Ar}), 114.1 (C_{Ar}),

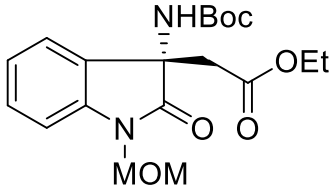
109.4 (C_{Ar}), 80.3 ($CO_2C(CH_3)_3$), 61.4 (*C*NHBoc), 59.4 ($CO_2CH_2CH_3$), 55.2 (OCH_3), 43.6 (NCH_2Ar), 40.9 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3877, 3352, 2927, 2307, 2041, 1898, 1714, 1611, 1491, 1364, 1247, 1164, 1021, 934, 827, 751 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 454 [M^+] (23), 398 (26), 337 (71), 121 (100).

HRMS (ESI): calcd for $C_{25}H_{30}O_6N_2Na$ [M + Na]$^+$: 477.1996, found 477.1997.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1-(methoxymethyl)-2-oxoindolin-3-yl)acetate (155e)



According to **GP1**, **155e** was obtained as colorless oil (108.9 mg, 64% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 3:1)

$[\alpha]_D^{25}$ = -22.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 °C; retention time: 20.35 min (major), 6.60 min (minor), 94% *ee*.

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

δ = 7.31 – 7.24 (m, 2H, Ar-*H*), 7.04 (t, *J* = 7.7 Hz, 2H, Ar-*H*), 6.34 (s, 1H, N*H*Boc), 5.20 – 5.09 (m, 2H, NCH_2OCH_3), 4.19 – 4.09 (m, 2H, $CO_2CH_2CH_3$), 3.39 (s, 3H, CH_2OCH_3), 2.86 (d, *J* = 14.9 Hz, 1H, C*H*HCO$_2$Et), 2.55 (d, *J* = 14.9 Hz, 1H, CH*H*CO$_2$Et), 1.26 – 1.17 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

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

δ = 176.0 (CO_2Et), 169.6 (*C*ONCH$_2$Ph), 153.7 ($CO_2C(CH_3)_3$), 141.5 (C_{Ar}), 129.3 (C_{Ar}), 129.1 (C_{Ar}), 123.2 (C_{Ar}), 123.0 (C_{Ar}), 109.7 (C_{Ar}), 80.4 ($CO_2C(CH_3)_3$), 71.8 (NCH_2OCH_3), 61.4 (*C*NHBoc), 59.5 ($CO_2CH_2CH_3$), 56.5 (NCH_2OCH_3), 41.1 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 14.0 ($CO_2CH_2CH_3$) ppm.

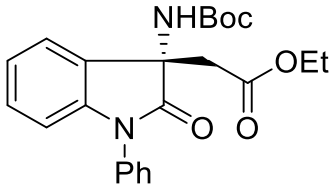
IR (ATR): 3345, 2932, 2294, 2041, 1720, 1613, 1478, 1358, 1242, 1163, 1085, 1023,

913, 754 cm^{-1}.

MS (ESI): *m/z* = 401.2 $[M+Na]^+$

HRMS (ESI): calcd for $C_{19}H_{26}O_6N_2Na$ $[M + Na]^+$: 401.1683, found 401.1685.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-2-oxo-1-phenylindolin-3-yl)acetate (155f)



According to **GP1**, **155f** was obtained as colorless oil (125.5 mg, 68% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 3:1)

$[\alpha]_D^{25}$ = -27.5 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK OJ; *n*-heptane/EtOH = 90/10; flow rate 1.0 mL/min; T= 30 °C; retention time: 5.47 min (major), 7.15 min (minor), 99% *ee*.

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

δ = 7.54 – 7.48 (m, 4H, Ar-*H*), 7.40 (t, *J* = 7.1 Hz, 1H, Ar-*H*), 7.36 (d, *J* = 7.4 Hz, 1H, Ar-*H*), 7.22 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.06 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 6.8 Hz, 1H, Ar-*H*), 6.30 (s, 1H, N*H*Boc), 4.23 – 4.10 (m, 2H, $CO_2CH_2CH_3$), 3.03 (d, *J* = 14.7 Hz, 1H, C*H*HCO$_2$Et), 2.72 (d, *J* = 15.0 Hz, 1H, CH*H*CO$_2$Et), 1.30 (s, 9H, $CO_2C(CH_3)_3$), 1.21 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

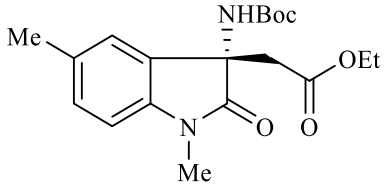
δ = 175.0 (*C*O$_2$Et), 169.7 (*C*ONPh), 153.9 ($CO_2C(CH_3)_3$), 143.4 (C_{Ar}), 134.5 (C_{Ar}), 129.6 (C_{Ar}), 129.2 (C_{Ar}), 129.1 (C_{Ar}), 128.0 (C_{Ar}), 126.6 (C_{Ar}), 123.4 (C_{Ar}), 123.1 (C_{Ar}), 109.6 (C_{Ar}), 80.5 ($CO_2C(CH_3)_3$), 61.3 (*C*NHBoc), 59.2 ($CO_2CH_2CH_3$), 41.2 (CH_2CO_2Et), 28.2 (3C, $CO_2C(CH_3)_3$), 14.2 ($CO_2CH_2CH_3$ ppm.

IR (ATR): 3458, 3279, 2970, 2288, 2164, 2111, 2020, 1958, 1736, 1610, 1503, 1462, 1369, 1294, 1214, 1087, 1012, 892, 815, 750, 698 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 410 $[M^+]$ (99), 354 (100), 223 (62).

HRMS (ESI): calcd for $C_{23}H_{26}O_5N_2Na$ [M + Na]$^+$: 433.1734, found 433.1733.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1,5-dimethyl-2-oxoindolin-3-yl)-acetate (155g)



According to **GP1**, **155g** was obtained as a colorless solid (114.1 mg, 70% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 3:1)

Melting Point: 113-114 ^{o}C.

$[\alpha]_D^{25}$ = -7.6 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 90/10; flow rate 0.7 mL/min; T= 30 ^{o}C; retention time: 23.29 min (major), 12.33 min (minor), 96% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$):

δ = 7.03 (d, *J* = 6.7 Hz, 2H, Ar-*H*), 6.66 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.22 (s, 1H, N*H*Boc), 4.17 – 4.00 (m, 2H, $CO_2CH_2CH_3$), 3.15 (s, 3H, NCH_3), 2.82 (d, *J* = 15.0 Hz, 1H, C*H*HCO_2Et), 2.44 (d, *J* = 14.9 Hz, 1H, CH*H*CO_2Et), 2.24 (s, 3H, ArCH_3), 1.27 – 1.03 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$):

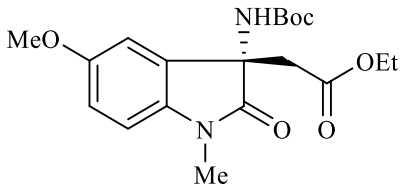
δ = 175.3 (CO_2Et), 169.7 ($CONCH_3$), 153.7 ($CO_2C(CH_3)_3$), 140.8 (C_{Ar}), 132.2 (C_{Ar}), 129.4 (C_{Ar}), 123.8 (C_{Ar}), 108.0 (C_{Ar}), 80.2 ($CO_2C(CH_3)_3$), 61.2 (*C*NHBoc), 59.2 ($CO_2CH_2CH_3$), 40.9 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 26.6 (NCH_3), 21.1 ($ArCH_3$), 14.1 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3335, 2963, 2162, 1722, 1618, 1494, 1364, 1256, 1023, 799, 686 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 362 [M$^+$] (100), 306 (50), 175 (78).

HRMS (ESI): calcd for $C_{19}H_{26}O_5N_2Na$ [M + Na]$^+$: 385.1734, found 385.1735.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-5-methoxy-1-methyl-2-oxoindolin-3-yl)acetate (155h)



According to **GP1**, **155h** was obtained as colorless oil (149.7 mg, 88% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 4:1)

$[\alpha]_D^{25}$ = -69.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 °C; retention time: 16.22 min (major), 8.27 min (minor), 95% *ee*.

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

δ = 6.89 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.80 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar-*H*), 6.72 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.26 (s, 1H, N*H*Boc), 4.18 – 4.08 (m, 2H, $CO_2CH_2CH_3$), 3.74 (s, 3H, OCH_3), 3.20 (s, 3H, NCH_3), 2.87 (d, *J* = 15.1 Hz, 1H, C*H*HCO_2Et), 2.49 (d, *J* = 15.1 Hz, 1H, CH*H*CO_2Et), 1.38 – 1.11 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

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

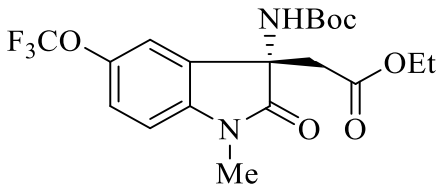
δ = 175.1 (CO_2Et), 169.7 (*C*ONCH_3), 156.1 (C_{Ar}), 153.7 ($CO_2C(CH_3)_3$), 136.6 (C_{Ar}), 130.8 (C_{Ar}), 113.4 (C_{Ar}), 110.5 (C_{Ar}), 108.6 (C_{Ar}), 80.3 ($CO_2C(CH_3)_3$), 61.3 (*C*NHBoc), 59.5 ($CO_2CH_2CH_3$), 55.8 (OCH_3), 40.8 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 26.6 (NCH_3), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3327, 2972, 1714, 1615, 1487, 1366, 1250, 1158, 1027, 865, 802 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 378 [M^+] (100), 322 (79), 191 (63).

HRMS (ESI): calcd for $C_{19}H_{26}O_6N_2Na$ [M + Na]$^+$: 401.1683, found 401.1683.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1-methyl-2-oxo-5-(trifluoromethoxy) indolin-3-yl)acetate (155i)



According to **GP1**, **155i** was obtained as colorless oil (151.6 mg, 78% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 3:1)

$[\alpha]_D^{25}$ = -46.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 °C; retention time: 8.06 min (major), 6.14 min (minor), 92% *ee*.

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

δ = 7.16 (d, *J* = 7.1 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.29 (s, 1H, N*H*Boc), 4.12 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.23 (s, 3H, NCH_3), 2.90 (d, *J* = 15.0 Hz, 1H, $CHHCO_2Et$), 2.49 (d, *J* = 15.0 Hz, 1H, $CHHCO_2Et$), 1.25 - 1.16 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

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

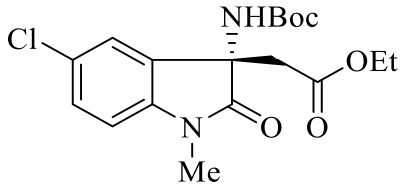
δ = 175.2 (CO_2Et), 169.5 ($CONCH_3$), 153.7 ($CO_2C(CH_3)_3$), 144.7 (C_{Ar}), 141.9 (C_{Ar}), 130.9 (OCF_3), 122.4 (C_{Ar}), 119.2 (C_{Ar}), 117.2 (C_{Ar}), 108.7 (C_{Ar}), 80.7 ($CO_2C(CH_3)_3$), 61.5 (*C*NHBoc), 59.2 ($CO_2CH_2CH_3$), 40.5 (CH_2CO_2Et), 28.0 (3C, $CO_2C(CH_3)_3$), 26.7 (NCH_3), 13.8 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3870, 3096, 2964, 2472, 2309, 2014, 1899, 1711, 1618, 1489, 1365, 1250, 1159, 1050, 946, 905, 830, 674 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 432 [M^+] (100), 376 (58), 245 (35).

HRMS (ESI): calcd for $C_{19}H_{23}O_6N_2F_3Na$ [M + Na]$^+$: 455.1400, found 455.1405.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-5-chloro-1-methyl-2-oxoindolin-3-yl) acetate (155j)



According to **GP1**, **155j** was obtained as colorless oil (141.0 mg, 82% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 3:1)

$[\alpha]_D^{25}$ = -41.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 °C; retention time: 10.21 min (major), 7.04 min (minor), 92% *ee*.

^{1}H NMR (300 MHz, $CDCl_3$):

δ = 7.28 – 7.17 (m, 2H, Ar-*H*), 6.72 (dd, *J* = 8.9, 1.2 Hz, 1H, Ar-*H*), 6.21 (s, 1H, N*H*Boc), 4.22 – 4.00 (m, 2H, $CO_2CH_2CH_3$), 3.18 (s, 3H, NCH_3), 2.84 (d, *J* = 15.0 Hz, 1H, C*H*HCO_2Et), 2.45 (d, *J* = 15.0 Hz, 1H, CH*H*CO_2Et), 1.23 – 1.15 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$):

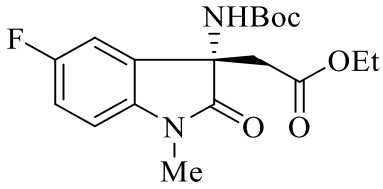
δ = 175.0 (CO_2Et), 169.5 (CONCH$_3$), 153.7 ($CO_2C(CH_3)_3$), 141.8 (C_{Ar}), 131.1 (C_{Ar}), 129.1 (C_{Ar}), 128.1 (C_{Ar}), 123.6 (C_{Ar}), 109.3 (C_{Ar}), 80.6 ($CO_2C(CH_3)_3$), 61.5 (CNHBoc), 59.1 ($CO_2CH_2CH_3$), 40.6 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 26.7 (NCH_3), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3348, 2933, 2222, 1982, 1713, 1610, 1476, 1362, 1266, 1163, 1102, 1022, 863, 814, 743, 663 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 382 [M^+] (93), 326 (57), 195 (100).

HRMS (ESI): calcd for $C_{18}H_{23}O_5N_2ClNa$ [M + Na]$^+$: 405.1188, found 405.1193.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-5-fluoro-1-methyl-2-oxoindolin-3-yl) acetate (155k)



According to **GP1**, **155k** was obtained as a colorless solid (149.9 mg, 91% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 3:1)

Melting Point: 102-104 °C.

$[\alpha]_D^{25}$ = -28.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 70/30; flow rate 0.7 mL/min; T= 30 °C; retention time: 11.45 min (major), 7.06 min (minor), 92% *ee*.

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

δ = 7.05 (dd, *J* = 7.7, 2.4 Hz, 1H, Ar-*H*), 6.99 (td, *J* = 8.9, 2.5 Hz, 1H, Ar-*H*), 6.75 (dd, *J* = 8.5, 4.0 Hz, 1H, Ar-*H*), 6.27 (s, 1H, N*H*Boc), 4.20 – 4.03 (m, 2H, $CO_2CH_2CH_3$), 3.22 (s, 3H, NCH_3), 2.90 (d, *J* = 15.2 Hz, 1H, C*H*HCO_2Et), 2.50 (d, *J* = 15.3 Hz, 1H, CH*H*CO_2Et), 1.27– 1.19 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

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

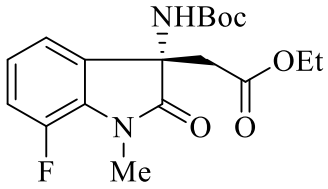
δ = 175.2 (CO_2Et), 169.6 (*C*ONCH_3), 159.2 (d, *J* = 225 Hz, C_{Ar}), 153.7 ($CO_2C(CH_3)_3$), 139.1 (C_{Ar}), 131.0 (C_{Ar}), 115.4 (d, *J* = 22.5 Hz, C_{Ar}), 111.4 (d, *J* = 25.5 Hz, C_{Ar}), 108.8 (C_{Ar}), 80.5 ($CO_2C(CH_3)_3$), 61.3 (*C*NHBoc), 59.3 ($CO_2CH_2CH_3$), 40.6 (CH_2CO_2Et), 28.1 (3C, $CO_2C(CH_3)_3$), 26.8 (NCH_3), 13.9 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3337, 2965, 1713, 1621, 1487, 1366, 1261, 1160, 1119, 1018, 924, 866, 806, 689 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 366 [M^+] (100), 310 (46), 179 (85).

HRMS (ESI): calcd for $C_{18}H_{23}O_5N_2FNa$ [M + Na]$^+$: 389.1483, found 389.1480.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-7-fluoro-1-methyl-2-oxoindolin-3-yl) acetate (155l)



According to **GP1**, **155l** was obtained as a colorless solid (84.0 mg, 51% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 3:1)

Melting Point: 99-101 °C.

$[\alpha]_D^{25}$ = -36.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 90/10; flow rate 1.0 mL/min; T= 30 °C; retention time: 10.90 min (major), 8.48 min (minor), 92% *ee*.

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

δ = 7.07 – 6.83 (m, 3H, Ar-*H*), 6.29 (s, 1H, N*H*Boc), 4.21 – 4.06 (m, 2H, $CO_2CH_2CH_3$), 3.44 (d, *J* = 2.7 Hz, 3H, NCH_3), 2.86 (d, *J* = 15.2 Hz, 1H, C*H*HCO_2Et), 2.50 (d, *J* = 15.2 Hz, 1H, CH*H*CO_2Et), 1.36 – 1.12 (m, 12H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$) ppm.

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

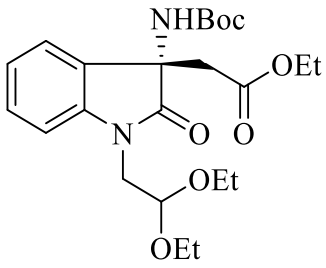
δ = 175.1 (CO_2Et), 169.5 (*C*ONCH_3), 153.7 ($CO_2C(CH_3)_3$), 147.7 (d, *J* = 245 Hz, C_{Ar}), 129.7 (C_{Ar}), 123.2 (d, *J* = 6 Hz, C_{Ar}), 118.7 (d, *J* = 3 Hz, C_{Ar}), 117.3 (C_{Ar}), 117.2 (C_{Ar}), 80.5 ($CO_2C(CH_3)_3$), 61.4 (*C*NHBoc), 59.1 ($CO_2CH_2CH_3$), 40.8 (CH_2CO_2Et), 29.1 (3C, $CO_2C(CH_3)_3$), 28.0 (NCH_3), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3264, 2923, 2856, 2650, 2407, 2295, 2166, 2084, 2018, 1939, 1700, 1631, 1524, 1479, 1369, 1247, 1162, 1116, 1017, 936, 888, 781, 734, 673 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 366 [M^+] (100), 310 (82), 179 (87).

HRMS (ESI): calcd for $C_{18}H_{23}O_5N_2FNa$ [M + Na]$^+$: 389.1483, found 389.1485.

(*S*)-Ethyl 2-(3-((tert-butoxycarbonyl)amino)-1-(2,2-diethoxyethyl)-2-oxoindolin-3-yl)acetate (155m)



According to **GP1**, **155m** was obtained as colorless oil (155.9 mg, 77% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 4:1)

$[\alpha]_D^{25}$ = -77.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AS; *n*-heptane/EtOH = 90/10; flow rate 1.0 mL/min; T= 30 °C; retention time: 4.25 min (major), 6.54 min (minor), 96% *ee*.

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

δ = 7.26 – 7.22 (m, 2H, Ar-*H*), 7.03 (d, *J* = 7.7 Hz, 1H, Ar-*H*), 6.98 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.30 (s, 1H, N*H*Boc), 4.73 (t, *J* = 5.4 Hz, 1H, $CH_2CH(OEt)_2$), 4.14 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.99 (d, *J* = 20.5 Hz, 1H, C*H*HCH(OEt)$_2$), 3.76 – 3.68 (m, 3H, CH*H*CH(OEt)$_2$, CH(OCH_2CH$_3$)$_2$), 3.59 – 3.48 (m, 2H, CH(OCH_2CH$_3$)$_2$), 2.86 (d, *J* = 15.0 Hz, 1H, C*H*HCO$_2$Et), 2.48 (d, *J* = 15.0 Hz, 1H, CH*H*CO$_2$Et), 1.38 – 1.07 (m, 18H, $CO_2C(CH_3)_3$, $CO_2CH_2CH_3$, CH(OCH$_2$CH_3)$_2$) ppm.

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

δ = 175.7 (*C*O$_2$Et), 169.9 (*C*ONCH$_3$), 153.8 ($CO_2C(CH_3)_3$), 142.9 (C_{Ar}), 129.4 (C_{Ar}), 128.8 (C_{Ar}), 122.7 (C_{Ar}), 122.4 (C_{Ar}), 109.9 (NCH$_2$*C*H(OEt)$_2$), 100.5 (C_{Ar}), 80.1 ($CO_2C(CH_3)_3$), 63.5 (2C, NCH$_2$CH(O*C*H$_2$CH$_3$)$_2$), 61.3 (*C*NHBoc), 59.0 ($CO_2CH_2CH_3$), 43.7 (NCH$_2$CH(OEt)$_2$), 40.9 (*C*H$_2$CO$_2$Et), 28.0 (3C, $CO_2C(CH_3)_3$), 15.3 (2C, NCH$_2$CH(OCH$_2$*C*H$_3$)$_2$), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3341, 2975, 2932, 2321, 2106, 1720, 1612, 1483, 1367, 1251, 1162, 1058, 1023, 940, 889, 752, 704, 665 cm^{-1}.

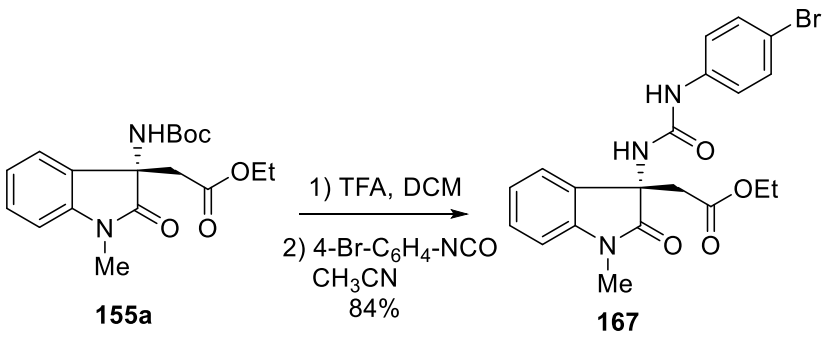
MS (ESI): *m/z* = 473.2 $[M+Na]^+$.

HRMS (ESI): calcd for $C_{23}H_{34}O_7N_2Na$ $[M + Na]^+$: 473.2258, found 473.2263.

Using catalyst **G**, (***R***)-**155m** was obtained as colorless oil (145.9 mg, 72% yield).

HPLC: CHIRALPAK AS; *n*-heptane/EtOH = 90/10; flow rate 1.0 mL/min; T= 30 °C; retention time: 6.50 min (major), 4.24 min (minor), 90% *ee*.

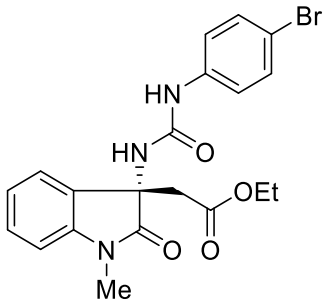
[α]$_D^{25}$ = +61.0 (c = 1.0, $CHCl_3$).



1) To a vial containing a solution of **155a** (104.4 mg, 0.30 mmol) in DCM (4.0 mL) was added TFA (136.6 mg, 1.20 mmol) slowly at room temperature. The mixture was stirred at room temperature for 10 h, and then saturated $NaHCO_3$ solution (1.0 mL) was added to quench the reaction. The resulting solution was extracted with EtOAc (3×5.0 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. After evaporation, the residue was directly used for the next step.

2) To a vial containing a solution of the residue obtained above in dry acetonitrile (4.0 mL) was added 4-bromophenyl isocyanate (89.2 mg, 0.46 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h. Then the solvent was removed on a rotary evaporator and the residue was purified by flash chromatography to afford the desired product **167** as a colorless solid (112.6 mg, 84% yield).

(*S*)-Ethyl 2-(3-(3-(4-bromophenyl)ureido)-1-methyl-2-oxoindolin-3-yl)acetate (167)



TLC: R_f = 0.30 (n-petane:EtOAC = 2:1)

Melting Point: 202-204 °C.

$[\alpha]_D^{25}$ = -35.4 (c = 1.0, $CHCl_3$).

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

δ = 7.72 (s, 1H,N*H*CONH), 7.30 (td, *J* = 7.7, 1.2 Hz, 1H, Ar-*H*), 7.23 (dd, *J* = 7.6, 0.9 Hz, 1H, Ar-*H*), 7.12 – 7.07 (m, 2H, Ar-*H*), 7.04 (td, *J* = 7.6, 0.9 Hz, 1H, Ar-*H*), 7.00 (s, 1H,NHCON*H*), 6.97 – 6.93 (m, 2H, Ar-*H*), 6.89 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 4.16 – 4.02 (m, 2H, $CO_2CH_2CH_3$), 3.31 (s, 3H, NCH_3), 2.99 (d, *J* = 14.8 Hz, 1H, C*H*HCO_2Et), 2.58 (d, *J* = 14.8 Hz, 1H, CH*H*CO_2Et), 1.15 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

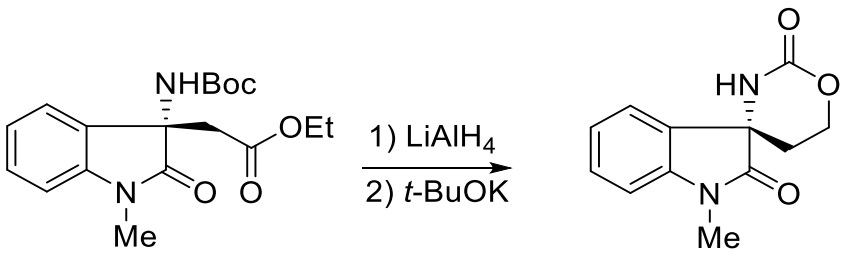
^{13}C NMR (100 MHz, $CDCl_3$):

δ = 177.1 (CO_2Et), 169.9 (*C*ONCH$_3$), 153.5 (NH*C*ONH), 142.9 (C_{Ar}), 137.7 (C_{Ar}), 131.3 (2C, C_{Ar}), 129.6 (C_{Ar}), 129.3 (C_{Ar}), 123.0 (C_{Ar}), 122.8 (C_{Ar}), 120.8 (2C, C_{Ar}), 114.9 (C_{Ar}), 108.9 (C_{Ar}), 61.4 (*C*NHCONH), 59.6 ($CO_2CH_2CH_3$), 40.9 (CH_2CO_2Et), 26.8 (NCH_3), 14.0 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3849, 3648, 3322, 3080, 2926, 2291, 1893, 1729, 1608, 1551, 1484, 1373, 1306, 1188, 1130, 1018, 939, 888, 822, 753, 675 cm^{-1}.

MS (ESI): *m/z* = 468.1 $[M+Na]^+$.

HRMS (ESI): calcd for $C_{20}H_{20}O_4N_3BrNa$ $[M + Na]^+$: 468.0529, found 468.0537.



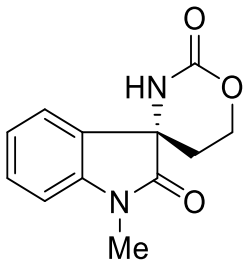
155a **168**

1) To a vial containing a solution of **155a** (103.5 mg, 0.3 mmol) in dry THF (4.0 mL) was added $LiAlH_4$ (57.0 mg, 1.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h and then quenched with saturated NaCl solution (1.0 mL). The resulting solution was extracted with EtOAc (3×5.0 mL). The organic phases were combined, washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was used directly for the next step.

2) The above residue was dissolved in dry THF (3.0 mL) and transferred into a 10 mL flask and *t*-BuOK (50.4 mg, 0.45 mmol) was added at 0 °C. The mixture was heated to

reflux at 70 °C for 48 h. After cooling to room temperature, saturated NH_4Cl solution (1.0 mL) was added to quench the reaction. The mixture was extracted with EtOAc (3×5.0 mL) and the organic layers were combined, washed with saturated NaCl and dried over anhydrous Na_2SO_4. The solvent was evaporated in *vacuo* to give the crude product, which was purified by flash chromatography (pentane/EtOAc = 1/1) to afford the product **168** as a colorless solid (13.2 mg, 19% yield).

(*S*)-1-Methylspiro[indoline-3,4'-[1,3]oxazinane]-2,2'-dione (168)



TLC: R_f = 0.50 (n-petane:EtOAC = 1:1)

Melting Point: 239-240 °C.

$[\alpha]_D^{25}$ = -140.0 (c = 0.6, $CHCl_3$).

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

δ = 7.40 – 7.31 (m, 2H, Ar-*H*), 7.12 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-*H*), 6.85 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.62 (s, 1H, N*H*CO), 5.01 – 4.95 (m, 1H, CO_2CHHCH_2), 4.34 – 4.31 (m, 1H, CO_2CHHCH_2), 3.19 (s, 3H, NCH_3), 2.25 – 2.17 (m, 1H, CO_2CH_2CHH), 2.06 – 2.00 (m, 1H, CO_2CH_2CHH) ppm.

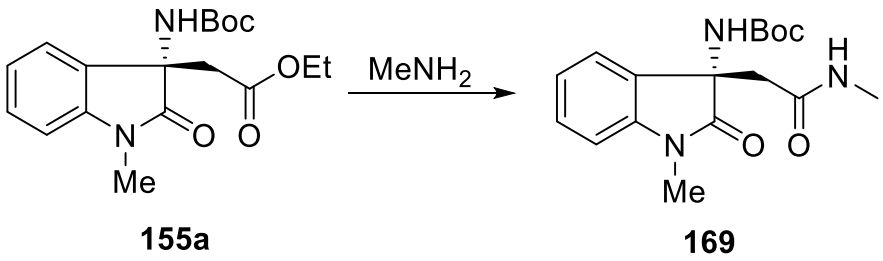
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 175.9 ($NHCO_2$), 153.1 ($CONCH_3$), 142.7 (C_{Ar}), 130.5 (C_{Ar}), 128.8 (C_{Ar}), 123.6 (C_{Ar}), 123.5 (C_{Ar}), 108.9 (C_{Ar}), 62.6 (*C*NH), 59.1 ($CO_2CH_2CH_2$), 30.6 ($CO_2CH_2CH_2$), 26.5 (NCH_3) ppm.

IR (ATR): 3856, 3621, 3297, 3044, 2975, 2652, 2303, 2174, 1980, 1792,1681, 1609, 1528,1362, 1253, 1163, 1050, 1017, 993, 878, 790, 744 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 232 [M^+] (100), 188 (31), 159 (78).

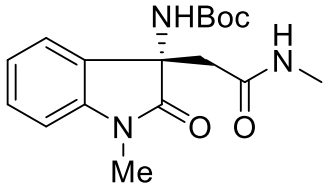
HRMS (ESI): calcd for $C_{12}H_{12}O_3N_2Na$ $[M + Na]^+$: 255.0740, found 255.0746.



155a **169**

To a sealed tube containing **155a** (104.4 mg, 0.30 mmol) was added $MeNH_2$ (10.0 mL, 30% in ethanol) at room temperature and then the mixture was heated to 60 °C. After full conversion (about 36 h), the reaction mixture was concentrated to give the residue, which was purified by column chromatography (pentane/EtOAc =1/1) to provide compound **169** as a colorless solid (83.0 mg, 83% yield).

(*S*)-Tert-Butyl (1-methyl-3-(2-(methylamino)-2-oxoethyl)-2-oxoindolin-3-yl)carbamate (169)



TLC: R_f = 0.30 (n-petane:EtOAC = 1:1)

Melting Point: 103-105 °C.

$[\alpha]_D^{25}$ = -56.0 (c = 1.0, $CHCl_3$).

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

δ = 7.35 (t, *J* = 7.7 Hz, 1H, Ar-*H*), 7.28 (d, *J* = 7.4 Hz, 1H, Ar-*H*), 7.23 – 7.21 (m, 1H, CON*H*CH_3), 7.09 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 6.87 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.03 (s, 1H, N*H*Boc), 3.22 (s, 3H, NCH_3), 2.84 (d, *J* = 4.8 Hz, 3H, CONHCH_3), 2.79 (d, *J* = 14.4 Hz, 1H, C*H*HCO_2Et), 2.18 (d, *J* = 14.4 Hz, 1H, CH*H*CO_2Et), 1.29 (s, 9H, $CO_2C(CH_3)_3$) ppm.

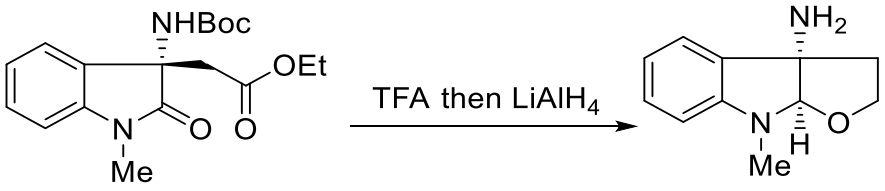
^{13}C NMR (150 MHz, $CDCl_3$):

δ = 176.1 (*C*ONHCH$_3$), 169.3 (*C*ONCH$_3$), 153.9 (*C*O$_2$C(CH$_3$)$_3$), 142.8 (*C*$_{Ar}$), 130.0 (*C*$_{Ar}$), 129.3 (*C*$_{Ar}$), 123.0 (*C*$_{Ar}$), 108.4 (*C*$_{Ar}$), 80.1 (CO$_2$*C*(CH$_3$)$_3$), 59.7 (*C*NHBoc), 42.0 (*C*H$_2$CONHCH$_3$), 28.1 (3C, CO$_2$C(*C*H$_3$)$_3$), 26.6 (NCH$_3$), 26.4 (CONH*C*H$_3$) ppm.

IR (ATR): 3841, 3605, 3323, 3104, 2934, 2703, 2486, 2296, 1991, 1713, 1652, 1561, 1475, 1362, 1251, 1160, 1074, 1022, 864, 752 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 333 [M^+] (100), 277 (22), 161 (71).

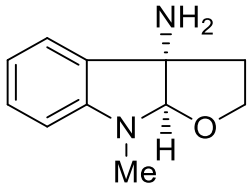
HRMS (ESI): calcd for $C_{17}H_{23}O_4N_3Na$ [M + Na]$^+$: 356.1581, found 356.1583.



155a **170**

To a vial containing a solution of **155a** (104.4 mg, 0.30 mmol) in DCM (2.0 mL) was added TFA (136.6 mg, 1.20 mmol) at room temperature and the resulting mixture was stirred overnight. Then saturated $NaHCO_3$ solution (2.0 mL) was added to quench the reaction and the mixture was extracted with EtOAc (3×5.0 mL). The organic phases were combined, washed with brine and dried over Na_2SO_4. The solvent was evaporated to give the residue which was used for the next step without purification. To a vial containing a solution of the above residue in dry THF (3.0 mL) was slowly added $LiAlH_4$ (68.4 mg, 1.8 mmol). The mixture was stirred for 5 h at room temperature. After that H_2O (2.0 mL) was added carefully to quench the reaction and the suspension was filtered over celite. The filtrate was concentrated under reduced pressure. The crude product was directly purified by silica gel flash column chromatography (pentane/acetone = 1/1) to afford the product **170** as a colorless oil (40.4 mg, 71% yield).

(3a*S*,8a*R*)-8-Methyl-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indol-3a-amine (170)



TLC: R_f = 0.30 (n-petane:acetone = 1:1)

$[\alpha]_D^{25}$ = +55.5 (c = 1.0, $CHCl_3$).

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

δ = 7.21 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 7.14 (td, *J* = 7.8, 1.2 Hz, 1H, Ar-*H*), 6.70 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 6.38 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.06 (s, 1H, NC*H*O), 4.03 – 3.98 (m, 1H, OC*H*HCH$_2$), 3.56 – 3.51 (m, 1H, OCH*H*CH$_2$), 2.89 (s, 3H, NC*H*$_3$), 2.28 – 2.13 (m, 2H, OCH$_2$C*H*$_2$), 2.04 (s, 2H, N*H*$_2$) ppm.

^{13}C NMR (100 MHz, CDCl$_3$):

δ = 150.5 (*C*$_{Ar}$), 132.4 (*C*$_{Ar}$), 129.3 (*C*$_{Ar}$), 123.1 (*C*$_{Ar}$), 117.7 (*C*$_{Ar}$), 106.5 (*C*$_{Ar}$), 105.4 (N*C*HO), 69.4 (*C*NH$_2$), 67.3 (O*C*H$_2$CH$_2$), 42.4 (OCH$_2$*C*H$_2$), 31.1 (N*C*H$_3$) ppm.

IR (ATR): 3861, 3370, 2925, 2846, 2329, 2103, 1950, 1648, 1553, 1497, 1406, 1308, 1261, 1221, 1115, 1016, 749 cm^{-1}.

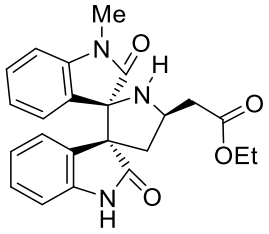
MS (EI, 70 eV): *m/z* (%) = 190 [M$^+$] (100), 161 (88), 133 (38).

HRMS (ESI): calcd for C$_{11}$H$_{15}$ON$_2$ [M + H]$^+$: 191.1179, found 191.1182.

GP 2 for the second project and analytical data of synthesized compounds:

A 10 mL flask equipped with a stirring bar was charged with 3-substituted oxindole **156** (0.40 mmol, 1.0 equiv), the ketimine **42** (0.42 mmol, 1.05 equiv), catalyst **L** (0.04 mmol, 10 mol %) and MTBE (4.0 mL). The resulting solution was stirred at room temperature for 12 h. Then the solvent was evaporated to give the residue, which was dissolved in DCM (4.0 mL) and TFA (0.8 mL) was added at 0 °C. The mixture was stirred at room temperature for 12 h, and then saturated NaHCO$_3$ solution was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3×10.0 mL). The organic layers were combined, washed with brine and dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated in *vacuo* to give the crude product, which was purified by flash chromatography (pentane/EtOAc = 2/1 to 1/2) to provide the desired product **157**.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157a)



According to **GP2**, 15**7a** was obtained as a colorless solid (131.2 mg, 81% yield).

TLC: R_f = 0.30 (n-petane:EtOAC = 1:1)

Melting Point: 114-116 °C.

$[\alpha]_D^{25}$ = –89.2 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 13.34 min (major), 11.30 min (minor), er: 99:1.

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

δ = 8.05 (s, 1H, N*H*CO), 7.46 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.18 – 7.13 (m, 2H, Ar-*H*), 6.99 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.75 – 6.67 (m, 3H, Ar-*H*), 6.60 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.00 – 4.96 (m, 1H, NHC*H*CH_2), 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H}_2CH_3$), 3.22 (dd, *J* = 13.2, 9.6 Hz, 1H, C*H*HCO_2Et), 3.02 (s, 3H, NCH_3), 2.88 (dd, *J* = 15.6, 9.6 Hz, 1H, CC*H*HCH), 2.77 (dd, *J* = 15.6, 5.4 Hz, 1H, CCH*H*CH), 2.03 (dd, *J* = 13.2, 4.8 Hz, 1H, CH*H*CO_2Et), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H}_3$) ppm.

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

δ = 176.9 (*C*ONH), 176.8 (*C*ONCH_3), 171.8 (*C*O_2Et), 144.1 (C_{Ar}), 140.4 (C_{Ar}), 131.3 (C_{Ar}), 129.4 (C_{Ar}), 128.5 (C_{Ar}), 126.3 (C_{Ar}), 126.1 (C_{Ar}), 125.4 (C_{Ar}), 121.8 (C_{Ar}), 121.6 (C_{Ar}), 109.6 (C_{Ar}), 107.6 (C_{Ar}), 73.8 (*C*NHCH), 60.6 ($CO_2\mathit{C}H_2CH_3$), 60.1 (*C*CH_2CH), 51.5 (NH*C*HCH_2), 41.7 (*C*H_2CO_2Et), 39.4 (N*C*H_3), 26.0 (C*C*H_2CH), 14.3 ($CO_2CH_2\mathit{C}H_3$) ppm.

IR (ATR): 3276, 2942, 1948, 1716, 1609, 1469, 1343, 1255, 1184, 1110, 1012, 867, 748 cm^{-1}.

MS (ESI): *m/z* = 406.2 $[M+H]^+$, 428.2 $[M+Na]^+$.

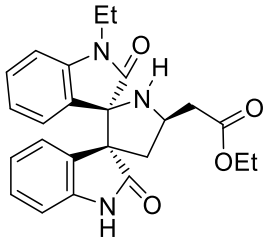
HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{24}N_3O_4^+$: 406.1761; found 406.1770.

The gram scale reaction for the synthesis of **157a** was carried out in a similar manner.

A 100 mL flask equipped with a stirring bar was charged with **156a** (980 mg, 4.0 mmol,

1.0 equiv), the ketimine **42a** (1.12 g, 4.2 mmol, 1.05 equiv), catalyst **L** (311 mg, 0.4 mmol, 10 mol %) and MTBE (40 mL). The resulting solution was stirred at room temperature for 24 h. The solvent was evaporated to give the residue, which was dissolved in DCM (40 mL) and TFA (8 mL) was added at 0 °C. The mixture was stirred at room temperature for 20 h, and then saturated $NaHCO_3$ solution was carefully added to quench the reaction. The resulting solution was extracted with EtOAc (3×50.0 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated in *vacuo* to give the crude product, which was purified by flash chromatography (pentane/EtOAc = 2/1 to 1/1) to provide the desired product **157a** as a colorless solid (1.22 g, 75% yield, er: 96:4). The analytical data of the gram scale reaction of **157a** are consistent with those of the 0.40 mmol scale experiment.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1-ethyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157b)



According to **GP2**, **157b** was obtained as a colorless solid (122.3 mg, 73% yield).

TLC: R_f = 0.30 (n-petane:EtOAC = 1:1)

Melting Point: 106-107 °C.

$[\alpha]_D^{25}$ = –86.1 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 7.27 min (major), 6.31 min (minor), er: 96:4.

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

δ = 7.99 (s, 1H, N*H*CO), 7.31 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.15 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 6.94 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.78 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.75 – 6.68 (m, 2H, Ar-*H*), 6.61 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.01 – 4.97 (m, 1H, NHC*H*CH_2), 4.16 (q, *J* = 7.2

Hz, 2H, $CO_2CH_2CH_3$), 3.81 – 3.72 (m, 1H, $NCHHCH_3$), 3.44 – 3.38 (m, 1H, $NCHHCH_3$), 3.17 (dd, *J* = 13.2, 9.6 Hz, 1H, $CHHCO_2Et$), 3.01 (s, 1H, CNHCH), 2.89 (dd, *J* = 16.2, 9.0 Hz, 1H, CCHHCH), 2.78 (dd, *J* = 16.2, 5.4 Hz, 1H, CCHHCH), 2.07 (dd, *J* = 13.2, 5.4 Hz, 1H, $CHHCO_2Et$), 1.27 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.03 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3) ppm.

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

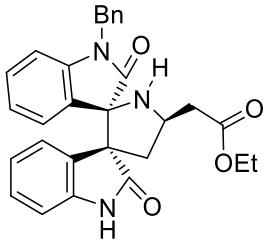
δ = 177.0 (*C*ONH), 176.2 (*C*ONEt), 171.8 (CO_2Et), 143.1 (C_{Ar}), 140.5 (C_{Ar}), 130.8 (C_{Ar}), 129.3 (C_{Ar}), 128.4 (C_{Ar}), 126.9 (C_{Ar}), 125.9 (C_{Ar}), 125.5 (C_{Ar}), 121.7 (C_{Ar}), 121.5 (C_{Ar}), 109.4 (C_{Ar}), 107.7 (C_{Ar}), 73.8 (*C*NHCH), 60.6 ($CO_2CH_2CH_3$), 60.5 (CCH_2CH), 51.8 ($NHCHCH_2$), 41.8 (CH_2CO_2Et), 39.3 (NCH_2CH_3), 34.4 (CCH_2CH), 14.3 ($CO_2CH_2CH_3$), 12.2 (NCH_2CH_3) ppm.

IR (ATR): 3309, 2976, 2299, 2049, 1715, 1609, 1468, 1363, 1293, 1187, 1024, 854, 747, 679 cm^{-1}.

MS (ESI): *m/z* = 420.2 $[M+H]^+$, 442.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}N_3O_4^+$: 420.1918; found 420.1909.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1-benzyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157c)



According to the general procedure, 15**7c** was obtained as a colorless solid (167.4 mg, 87% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 1:1)

Melting Point: 120-121 °C.

$[\alpha]_D^{25}$ = –55.7 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 23.34 min (major), 11.96 min (minor), er: 98:2.

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

δ = 8.36 (s, 1H, N*H*CO), 7.19 – 7.11 (m, 2H, Ar-*H*), 7.06 – 6.96 (m, 4H, Ar-*H*), 6.96 – 6.85 (m, 4H, Ar-*H*), 6.79 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-*H*), 6.67 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.38 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.15 (d, *J* = 16.0 Hz, 1H, NC*H*HPh), 5.03 – 4.96 (m, 1H, NHC*H*CH_2), 4.32 (d, *J* = 16.0 Hz, 1H, NCH*H*Ph), 4.16 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.13 (dd, *J* = 13.2, 8.8 Hz, 1H, C*H*HCO_2Et), 2.91 (dd, *J* = 16.0, 9.2 Hz, 1H, CC*H*HCH), 2.78 (dd, *J* = 16.0, 5.6 Hz, 1H, CCH*H*CH), 2.17 (dd, *J* = 13.2, 6.4 Hz, 1H, CH*H*CO_2Et), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

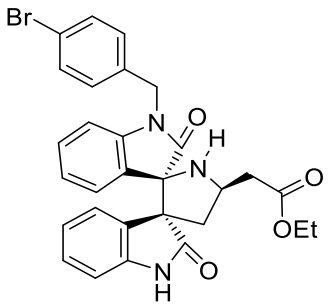
δ = 177.4 (*C*ONH), 176.4 (*C*ONBn), 171.8 (*C*O_2Et), 143.2 (C_{Ar}), 140.7 (C_{Ar}), 135.3 (C_{Ar}), 129.9 (C_{Ar}), 129.4 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.4 (C_{Ar}), 127.5 (C_{Ar}), 127.2 (C_{Ar}), 126.6 (2C, C_{Ar}), 125.7 (C_{Ar}), 125.5 (C_{Ar}), 121.9 (C_{Ar}), 121.8 (C_{Ar}), 109.8 (C_{Ar}), 109.0 (C_{Ar}), 73.9 (*C*NHCH), 60.7 ($CO_2CH_2CH_3$), 60.6 (*C*CH_2CH), 52.1 (NH*C*HCH_2), 43.7 (N*C*H_2Ph), 41.9 (*C*H_2CO_2Et), 39.8 (C*C*H_2CH), 14.2 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3297, 2973, 2289, 2163, 1898, 1719, 1475, 1355, 1219, 1247, 1021, 826, 746 cm^{-1}.

MS (ESI): *m/z* = 482.2 $[M+H]^+$, 985.4 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{28}N_3O_4^+$: 482.2074; found 482.2067.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1-(4-bromobenzyl)-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indo-lin]-5'-yl)acetate (157d)



According to **GP2**, 15**7d** was obtained as a colorless solid (187.8 mg, 84% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 1:12)

Melting Point: 140-142 ^{o}C.

$[\alpha]_D^{25}$ = –34.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 14.72 min (major), 11.36 min (minor), er: 98:2.

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

δ = 7.64 (s, 1H, N*H*CO), 7.29 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.19 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.08 – 7.02 (m, 2H, Ar-*H*), 7.00 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.87 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.83 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.74 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.36 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.08 (d, *J* = 16.2 Hz, 1H, NC*H*HAr), 5.03 – 4.98 (m, 1H, NHC*H*CH_2), 4.28 (d, *J* = 16.2 Hz, 1H, NCH*H*Ar), 4.17 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.08 (dd, *J* = 13.2, 9.0 Hz, 1H, C*H*HCO_2Et), 2.92 (dd, *J* = 16.2, 9.0 Hz, 1H, CC*H*HCH), 2.80 (dd, *J* = 16.2, 5.4 Hz, 1H, CCH*H*CH), 2.23 (dd, *J* = 13.2, 6.6 Hz, 1H, CH*H*CO_2Et), 1.28 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

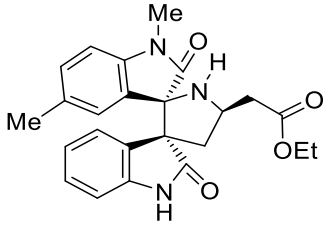
δ = 176.8 (*C*ONH), 176.0 (*C*ONAr), 171.7 (*C*O_2Et), 142.8 (C_{Ar}), 140.7 (C_{Ar}), 134.4 (C_{Ar}), 131.7 (2C, C_{Ar}), 129.4 (C_{Ar}), 129.3 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 125.7 (C_{Ar}), 125.5 (C_{Ar}), 122.2 (C_{Ar}), 121.9 (C_{Ar}), 121.2 (C_{Ar}), 109.5 (C_{Ar}), 108.9 (C_{Ar}), 74.0 (*C*NHCH), 60.9 ($CO_2CH_2CH_3$), 60.6 (*C*CH_2CH), 52.4 (NH*C*HCH_2), 43.3 (N*C*H_2Ar), 41.9 (*C*H_2CO_2Et), 39.8 (C*C*H_2CH), 14.3 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3327, 2997, 2168, 2040, 1733, 1613, 1456, 1366, 1213, 1017, 903, 745 cm^{-1}.

MS (ESI): *m/z* = 562.1 $[M+H]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{27}N_3O_4Br^+$: 560.1180; found 560.1166.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1,5-dimethyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157e)



According to **GP2**, **157e** was obtained as a colorless solid (125.7 mg, 75% yield).

TLC: R_f = 0.30 (n-petane:EtOAC = 1:1)

Melting Point: 131-133 °C.

$[\alpha]_D^{25}$ = –75.1 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 11.18 min (major), 9.93 min (minor), er: 97:3.

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

δ = 7.69 (s, 1H, N*H*CO), 7.46 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.16 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-*H*), 6.99 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.92 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.68 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.48 – 6.45 (m, 2H, Ar-*H*), 5.02 – 4.94 (m, 1H, NHC*H*CH_2), 4.14 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H}_2CH_3$), 3.22 (dd, *J* = 13.2, 9.6 Hz, 1H, C*H*HCO_2Et), 3.02 (s, 3H, $NC\mathit{H}_3$), 2.94 (bs, 1H, N*H*), 2.87 (dd, *J* = 16.0, 9.2 Hz, 1H, CC*H*HCH), 2.76 (dd, *J* = 16.0, 5.2 Hz, 1H, CCH*H*CH), 2.08 – 1.98 (m, 4H, CH*H*CO_2Et, Ar$C\mathit{H}_3$), 1.25 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H}_3$) ppm.

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

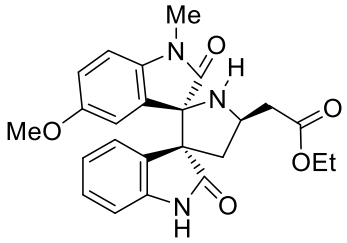
δ = 176.8 (*C*ONH), 176.7 (*C*ONCH_3), 171.8 (*C*O_2Et), 141.7 (C_{Ar}), 140.4 (C_{Ar}), 131.4 (C_{Ar}), 131.0 (C_{Ar}), 129.5 (C_{Ar}), 128.4 (C_{Ar}), 126.4 (C_{Ar}), 126.2 (C_{Ar}), 126.1 (C_{Ar}), 121.7 (C_{Ar}), 109.5 (C_{Ar}), 107.2 (C_{Ar}), 74.0 (*C*NHCH), 60.5 ($CO_2\mathit{C}H_2CH_3$), 60.0 (*C*CH_2CH), 51.5 (NH*C*HCH_2), 41.7 (*C*H_2CO_2Et), 39.2 (C*C*H_2CH), 26.0 (N*C*H_3), 20.8 (Ar*C*H_3), 14.2 ($CO_2CH_2\mathit{C}H_3$) ppm.

IR (ATR): 3258, 2925, 2320, 2163, 1989, 1719, 1612, 1468, 1345, 1293, 1245, 1178, 1030, 880, 818, 750, 686 cm^{-1}.

MS (ESI): *m/z* = 420.2 $[M+H]^+$, 442.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}N_3O_4^+$: 420.1918; found 420.1912.

Ethyl 2-((3*R*,3'*R*,5'*R*)-5-methoxy-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indo-lin]-5'-yl)acetate (157f)



According to **GP2**, **157f** was obtained as a colorless solid (137.5 mg, 79% yield).

TLC: R_f = 0.60 (n-petane:EtOAC = 1:2)

Melting Point: 152-153 °C.

$[\alpha]_D^{25}$ = –84.2 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 8/2; flow rate 0.7 mL/min; T= 30 °C; retention time: 21.23 min (major), 18.94 min (minor), er: 99:1.

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

δ = 7.66 – 7.52 (m, 2H, Ar-*H*, N*H*CO), 7.18 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.04 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.70 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 6.66 (dd, *J* = 8.4, 2.8 Hz, 1H, Ar-*H*), 6.49 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.23 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 5.03 – 4.96 (m, 1H, NHC*H*CH_2), 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H}_2CH_3$), 3.42 (s, 3H, $OC\mathit{H}_3$), 3.28 (dd, *J* = 13.2, 10.0 Hz, 1H, C*H*HCO_2Et), 3.03 (s, 3H, $NC\mathit{H}_3$), 2.87 (dd, *J* = 16.0, 9.2 Hz, 1H, CC*H*HCH), 2.76 (dd, *J* = 16.0, 5.2 Hz, 1H, CCH*H*CH), 1.99 (dd, *J* = 13.2, 4.8 Hz, 1H, CH*H*CO_2Et), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H}_3$) ppm.

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

δ = 176.7 (*C*ONH), 176.5 (*C*ONCH_3), 171.8 (*C*O_2Et), 155.0 (C_{Ar}), 140.3 (C_{Ar}), 137.6 (C_{Ar}), 131.8 (C_{Ar}), 128.5 (C_{Ar}), 126.7 (C_{Ar}), 126.3 (C_{Ar}), 121.7 (C_{Ar}), 115.1 (C_{Ar}), 111.9 (C_{Ar}), 109.6 (C_{Ar}), 107.9 (C_{Ar}), 74.0 (*C*NHCH), 60.6 ($CO_2\mathit{C}H_2CH_3$), 59.8 (*C*CH_2CH), 55.7 (O*C*H_3), 51.3 (NH*C*HCH_2), 41.6 (*C*H_2CO_2Et), 39.1 (C*C*H_2CH), 26.0 (N*C*H_3), 14.3 ($CO_2CH_2\mathit{C}H_3$) ppm.

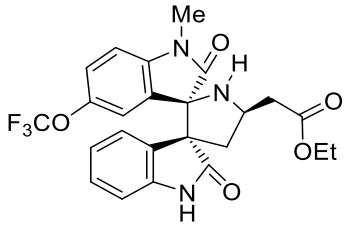
IR (ATR): 3278, 2954, 2231, 1715, 1464, 1361, 1208, 1091, 859, 750 cm^{-1}.

MS (ESI): *m/z* = 436.2 $[M+H]^+$, 458.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{24}H_{25}N_3O_5Na^+$: 458.1686; found 458.1672.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1-methyl-2,2''-dioxo-5-(trifluoromethoxy)dispiro[indoline-

3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157g)



According to **GP2**, **157g** was obtained as a colorless solid (123.2 mg, 63% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 1:2)

Melting Point: 107-109 °C.

$[\alpha]_D^{25}$ = –105.1 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 8/2; flow rate 0.7 mL/min; T= 30 °C; retention time: 20.61 min (major), 15.26 min (minor), er: 98:2.

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

δ = 7.73 (s, 1H, N*H*CO), 7.61 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.19 (td, *J* = 7.6, 0.8 Hz, 1H, Ar-*H*), 7.06 (td, *J* = 7.6, 1.2 Hz, 1H, Ar-*H*), 6.98 (dd, *J* = 7.6, 1.6 Hz, 1H, Ar-*H*), 6.70 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.56 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 6.48 (d, *J* = 1.2 Hz, 1H, Ar-*H*), 5.01 – 4.94 (m, 1H, NHC*H*CH_2), 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.29 (dd, *J* = 13.2, 9.6 Hz, 1H, C*H*HCO_2Et), 3.05 (s, 3H, NCH_3), 2.91 (s, 1H, N*H*), 2.86 (dd, *J* = 16.0, 9.2 Hz, 1H, CC*H*HCH), 2.75 (dd, *J* = 16.0, 5.2 Hz, 1H, CCH*H*CH), 1.96 (dd, *J* = 13.2, 4.8 Hz, 1H, CH*H*CO_2Et), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

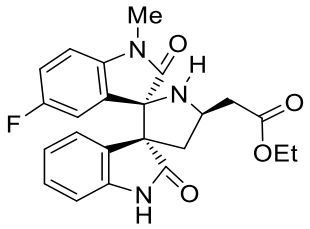
δ = 177.1 (*C*ONH), 176.4 (*C*ONCH_3), 171.8 (*C*O_2Et), 143.7 (C_{Ar}), 142.8 (C_{Ar}), 140.0 (C_{Ar}), 131.4 (C_{Ar}), 128.9 (O*C*F_3), 127.0 (C_{Ar}), 126.1 (C_{Ar}), 122.6 (C_{Ar}), 122.2 (C_{Ar}), 119.7 (C_{Ar}), 109.7 (C_{Ar}), 107.7 (C_{Ar}), 73.6 (*C*NHCH), 60.6 ($CO_2CH_2CH_3$), 59.7 (*C*CH_2CH), 51.2 (NH*C*HCH_2), 41.4 (*C*H_2CO_2Et), 39.0 (C*C*H_2CH), 26.1 (NCH_3), 14.2 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3305, 2945, 2175, 1720, 1619, 1471, 1351, 1226, 818, 749, 677 cm^{-1}.

MS (ESI): *m/z* = 490.2 $[M+H]^+$, 979.3 $[2M+H]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{23}N_3O_5F_3^+$: 490.1584; found 490.1572.

Ethyl 2-((3*R*,3'*R*,5'*R*)-5-fluoro-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157h)



According to **GP2**, **157h** was obtained as a colorless solid (113.4 mg, 67% yield).

TLC: R_f = 0.50 (n-petane:EtOAC = 1:1)

Melting Point: 120-122 °C.

$[\alpha]_D^{25}$ = –107.1 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 8/2; flow rate 1.0 mL/min; T= 30 °C; retention time: 15.00 min (major), 13.41 min (minor), er: 99:1.

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

δ = 7.78 (s, 1H, N*H*CO), 7.55 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.21 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.05 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.84 (td, *J* = 8.4, 2.4 Hz, 1H, Ar-*H*), 6.74 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.52 (dd, *J* = 8.4, 4.2 Hz, 1H, Ar-*H*), 6.40 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 5.01 – 4.96 (m, 1H, NHC*H*CH_2), 4.16 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H}_2CH_3$), 3.27 (dd, *J* = 13.2, 10.2 Hz, 1H, C*H*HCO_2Et), 3.06 (s, 3H, NCH_3), 2.87 (dd, *J* = 16.2, 9.6 Hz, 1H, CC*H*HCH), 2.76 (dd, *J* = 16.2, 5.4 Hz, 1H, CCH*H*CH), 1.99 (dd, *J* = 13.2, 4.8 Hz, 1H, CH*H*CO_2Et), 1.27 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H}_3$) ppm.

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

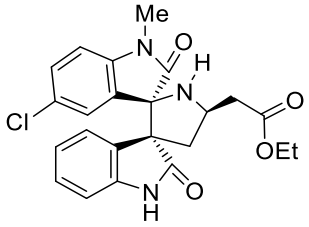
δ = 176.8 (*C*ONH), 176.5 (*C*ONCH_3), 171.8 (*C*O_2Et), 158.9 (d, *J* = 238.4 Hz, C_{Ar}), 140.2 (C_{Ar}), 140.1 (C_{Ar}), 131.2 (C_{Ar}), 128.8 (C_{Ar}), 127.6 (d, *J* = 8.0 Hz, C_{Ar}), 126.1 (C_{Ar}), 122.1 (C_{Ar}), 115.6 (d, *J* = 23.4 Hz, C_{Ar}), 113.8 (d, *J* = 25.7 Hz, C_{Ar}), 109.7 (C_{Ar}), 107.9 (d, *J* = 7.8 Hz, C_{Ar}), 73.8 (*C*NHCH), 60.6 ($CO_2\mathit{C}H_2CH_3$), 59.8 (*C*CH_2CH), 51.4 (NH*C*HCH_2), 41.5 (*C*H_2CO_2Et), 39.2 (C*C*H_2CH), 26.2 (N*C*H_3), 14.3 ($CO_2CH_2\mathit{C}H_3$) ppm.

IR (ATR): 3303, 2938, 2287, 1715, 1616, 1469, 1336, 1270, 1183, 1109, 1025, 872, 807, 751, 682 cm^{-1}.

MS (ESI): *m/z* = 424.2 $[M+H]^+$, 446.1 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}N_3O_4F^+$: 424.1667; found 424.1661.

Ethyl 2-((3*R*,3'*R*,5'*R*)-5-chloro-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indol-in]-5'-yl)acetate (157i)



According to **GP2**, **157i** was obtained as a colorless solid (108.9 mg, 62% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 1:1)

Melting Point: 123-125 °C.

$[\alpha]_D^{25}$ = –77.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 23.45 min (major), 19.13 min (minor), er: 99:1.

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

δ = 7.94 (s, 1H, N*H*CO), 7.50 (s, 1H, Ar-*H*), 7.22 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.12 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.06 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.76 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.63 (s, 1H, Ar-*H*), 6.53 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 5.00 – 4.95 (m, 1H, NHC*H*CH_2), 4.16 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.29 – 3.19 (m, 1H, C*H*HCO_2Et), 3.05 (s, 3H, NCH_3), 2.89 (dd, *J* = 16.2, 9.6 Hz, 1H, CC*H*HCH), 2.77 (dd, *J* = 16.2, 4.8 Hz, 1H, CCH*H*CH), 2.04 – 1.99 (m, 1H, CH*H*CO_2Et), 1.27 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

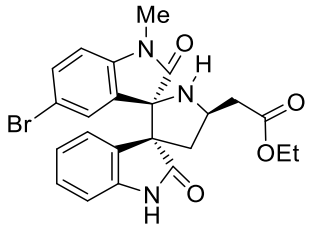
δ = 176.6 (*C*ONH), 176.5 (*C*ONCH_3), 171.7 (*C*O_2Et), 142.6 (C_{Ar}), 140.2 (C_{Ar}), 130.9 (C_{Ar}), 130.8 (C_{Ar}), 129.3 (C_{Ar}), 128.9 (C_{Ar}), 127.5 (C_{Ar}), 127.1 (C_{Ar}), 126.0 (C_{Ar}), 122.2 (C_{Ar}), 109.9 (C_{Ar}), 108.5 (C_{Ar}), 73.7 (*C*NHCH), 60.7 ($CO_2CH_2CH_3$), 60.0 (*C*CH_2CH), 51.5 (NH*C*HCH_2), 41.3 (*C*H_2CO_2Et), 39.0 (C*C*H_2CH), 26.2 (N*C*H_3), 14.2 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3278, 2954, 2231, 1715, 1464, 1361, 1208, 1091, 859, 750 cm^{-1}.

MS (ESI): *m/z* = 440.1 $[M+H]^+$, 462.1 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}N_3O_4Cl^+$: 440.1372; found 440.1361.

Ethyl 2-((3*R*,3'*R*,5'*R*)-5-bromo-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157j)



According to **GP2**, **157j** was obtained as a colorless solid (102.4 mg, 53% yield).

TLC: R_f = 0.40 (n-petane:EtOAC = 1:1)

Melting Point: 115-116 °C.

$[\alpha]_D^{25}$ = –57.5 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 12.63 min (major), 9.97 min (minor), er: 98:2.

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

δ = 7.58 (s, 1H, N*H*CO), 7.56 (s, 1H, Ar-*H*), 7.25 – 7.18 (m, 2H, Ar-*H*), 7.10 – 7.05 (m, 1H, Ar-*H*), 6.72 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.68 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 6.47 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 5.00 – 4.93 (m, 1H, NHC*H*CH_2), 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2C\mathit{H}_2CH_3$), 3.26 (dd, *J* = 13.2, 9.6 Hz, 1H, C*H*HCO_2Et), 3.04 (s, 3H, NCH_3), 2.90 (s, 1H, N*H*), 2.88 (dd, *J* = 16.0, 9.2 Hz, 1H, CC*H*HCH), 2.75 (dd, *J* = 16.0, 5.2 Hz, 1H, CCH*H*CH), 1.98 (dd, *J* = 13.2, 4.8 Hz, 1H, CH*H*CO_2Et), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2C\mathit{H}_3$) ppm.

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

δ = 176.6 (*C*ONH), 176.2 (*C*ONCH_3), 171.8 (*C*O_2Et), 143.2 (C_{Ar}), 140.1 (C_{Ar}), 132.1 (C_{Ar}), 131.3 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 127.7 (C_{Ar}), 126.2 (C_{Ar}), 122.1 (C_{Ar}), 114.2 (C_{Ar}), 109.7 (C_{Ar}), 108.8 (C_{Ar}), 73.7 (*C*NHCH), 60.6 ($CO_2\mathit{C}H_2CH_3$), 59.8 (*C*CH_2CH),

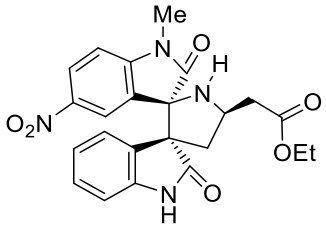
51.3 (NH*C*HCH$_2$), 41.4 (*C*H$_2$CO$_2$Et), 38.9 (C*C*H$_2$CH), 26.1 (N*C*H$_3$), 14.2 (CO$_2$CH$_2$*C*H$_3$) ppm.

IR (ATR): 3290, 2940, 2639, 2318, 1960, 1706, 1609, 1465, 1342, 1230, 1103, 1035, 824, 765, 676 cm^{-1}.

MS (ESI): *m/z* = 484.1 [M+H]$^+$, 969.2 [2M+H]$^+$.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{23}H_{23}N_3O_4Br^+$: 484.0867; found 484.0863.

Ethyl 2-((3*R*,3'*R*,5'*R*)-1-methyl-5-nitro-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157k)



According to **GP2**, **157k** was obtained as a brown solid (73.8 mg, 41% yield).

TLC: R$_f$ = 0.60 (n-petane:EtOAC = 1:2)

Melting Point: 144-145 ^{o}C.

[α]$_D^{25}$ = –48.8 (c = 1.0, CHCl$_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 ^{o}C; retention time: 15.24 min (major), 12.50 min (minor), er: 95:5.

^{1}H NMR (400 MHz, CDCl$_3$):

δ = 8.08 (dd, *J* = 8.8, 2.4 Hz, 1H, N*H*CO), 7.77 – 7.75 (m, 1H, Ar-*H*), 7.44 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.31 (s, 1H, Ar-*H*), 7.23 – 7.16 (m, 2H, Ar-*H*), 6.71 – 6.66 (m, 2H, Ar-*H*), 5.01 – 4.94 (m, 1H, NHC*H*CH$_2$), 4.17 (q, *J* = 7.2 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.32 (dd, *J* = 13.2, 10.0 Hz, 1H, C*H*HCO$_2$Et), 3.16 (s, 3H, NC*H*$_3$), 2.96 (s, 1H, N*H*), 2.89 (dd, *J* = 16.4, 9.6 Hz, 1H, CC*H*HCH), 2.78 (dd, *J* = 16.4, 4.8 Hz, 1H, CCH*H*CH), 1.99 (dd, *J* = 13.2, 4.4 Hz, 1H, CH*H*CO$_2$Et), 1.28 (t, *J* = 7.2 Hz, 3H, CO$_2$CH$_2$C*H*$_3$) ppm.

^{13}C NMR (100 MHz, CDCl$_3$):

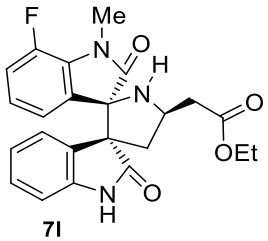
δ = 177.5 (*C*ONH), 176.1 (*C*ONCH$_3$), 171.9 (*C*O$_2$Et), 149.8 (*C*$_{Ar}$), 142.5 (*C*$_{Ar}$), 139.8 (*C*$_{Ar}$), 131.2 (*C*$_{Ar}$), 129.2 (*C*$_{Ar}$), 126.5 (*C*$_{Ar}$), 126.3 (*C*$_{Ar}$), 126.1 (*C*$_{Ar}$), 122.6 (*C*$_{Ar}$), 121.5 (*C*$_{Ar}$), 109.9 (*C*$_{Ar}$), 107.0 (*C*$_{Ar}$), 72.9 (*C*NHCH), 60.7 (CO$_2$*C*H$_2$CH$_3$), 59.7 (*C*CH$_2$CH), 51.1 (NH*C*HCH$_2$), 41.1 (*C*H$_2$CO$_2$Et), 38.8 (C*C*H$_2$CH), 26.4 (N*C*H$_3$), 14.2 (CO$_2$CH$_2$*C*H$_3$) ppm.

IR (ATR): 3313, 2927, 2668, 2307, 1718, 1608, 1471, 1329, 1291, 1186, 1027, 827, 750, 681 cm^{-1}.

MS (ESI): *m/z* = 473.1 [M+Na]$^+$.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{23}H_{22}N_4O_6Na^+$: 473.1432; found 473.1416.

Ethyl 2-((3*R*,3'*R*,5'*R*)-7-fluoro-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157l)



7l

According to **GP2**, **157l** was obtained as a colorless solid (120.1 mg, 71% yield).

TLC: R$_f$ = 0.40 (n-petane:EtOAC = 1:1)

Melting Point: 107-109 °C.

[α]$_D^{25}$ = –90.0 (c = 1.0, CHCl$_3$).

HPLC: (s,s)-Whelk Ol; *n*-heptane/EtOH = 8/2; flow rate 1.0 mL/min; T= 30 °C; retention time: 9.38 min (major), 12.12 min (minor), er: 95:5.

^{1}H NMR (600 MHz, CDCl$_3$):

δ = 8.12 (s, 1H, N*H*CO), 7.43 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.18 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.99 (t, *J* = 7.68 Hz, 1H, Ar-*H*), 6.87 (dd, *J* = 11.4, 8.4 Hz, 1H, Ar-*H*), 6.75 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.63 – 6.60 (m, 1H, Ar-*H*), 6.53 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.00 – 4.95 (m, 1H, NHC*H*CH$_2$), 4.16 (q, *J* = 7.2 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.25 (d, *J* = 2.4 Hz, 3H, NC*H*$_3$), 3.24 – 3.18 (m, 1H, C*H*HCO$_2$Et), 2.99 (s, 1H, N*H*), 2.87 (dd, *J* = 16.2, 9.6 Hz,

1H, CC*H*HCH), 2.76 (dd, *J* = 16.2, 4.8 Hz, 1H, CCH*H*CH), 2.02 (dd, *J* = 13.2, 5.4 Hz, 1H, CH*H*CO_2Et), 1.27 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

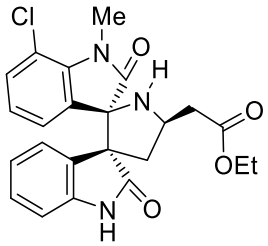
δ = 176.8 (*C*ONH), 176.6 (*C*ONCH_3), 171.8 (*C*O_2Et), 147.2 (d, *J* = 242.1 Hz, C_{Ar}), 140.4 (C_{Ar}), 130.9 (C_{Ar}), 130.7 (d, *J* = 8.1 Hz), 129.1 (d, *J* = 2.9 Hz, C_{Ar}), 128.6 (C_{Ar}), 126.0 (C_{Ar}), 122.0 (d, *J* = 6.2 Hz, C_{Ar}), 121.9 (C_{Ar}), 121.3 (d, *J* = 3.0 Hz, C_{Ar}), 117.4 (d, *J* = 19.1 Hz), 109.7 (C_{Ar}), 73.8 (*C*NHCH), 60.6 ($CO_2CH_2CH_3$), 60.2 (*C*CH_2CH), 51.5 (NH*C*HCH$_2$), 41.6 (*C*H_2CO_2Et), 39.3 (C*C*H_2CH), 28.5 (d, *J* = 6.2 Hz, N*C*H_3), 14.3 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3321, 2971, 2189, 1730, 1614, 1466, 1366, 1209, 1027, 908, 749 cm^{-1}.

MS (ESI): *m/z* = 424.2 $[M+H]^+$, 446.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}N_3O_4FNa^+$: 446.1487; found 446.1476.

Ethyl 2-((3*R*,3'*R*,5'*R*)-7-chloro-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157m)



According to **GP2**, **157m** was obtained as a colorless solid (119.4 mg, 68% yield).

TLC: R_f = 0.30 (n-petane:EtOAC = 1:1)

Melting Point: 105-106 °C.

$[\alpha]_D^{25}$ = –111.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 23.45 min (major), 19.13 min (minor), er: 97:3.

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

δ = 8.19 (s, 1H, N*H*CO), 7.44 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.16 (td, *J* = 8.0, 1.2 Hz, 1H, Ar-*H*), 7.06 – 6.96 (m, 2H, Ar-*H*), 6.78 – 6.73 (m, 1H, Ar-*H*), 6.63 – 6.61 (m, 1H, Ar-*H*), 6.59 – 6.52 (m, 1H, Ar-*H*), 5.00 – 4.92 (m, 1H, NHC*H*CH_2), 4.14 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.38 (s, 3H, NCH_3), 3.20 (dd, *J* = 13.2, 9.6 Hz, 1H, C*H*HCO_2Et), 2.92 (s, 1H, N*H*), 2.85 (dd, *J* = 16.0, 9.6 Hz, 1H, CC*H*HCH), 2.74 (dd, *J* = 16.0, 5.2 Hz, 1H, CCH*H*CH), 1.97 (dd, *J* = 13.2, 5.2 Hz, 1H, CH*H*CO_2Et), 1.25 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

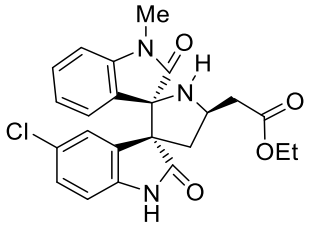
δ = 177.4 (*C*ONH), 176.7 (*C*ONCH_3), 171.8 (*C*O_2Et), 140.4 (C_{Ar}), 139.9 (C_{Ar}), 131.7 (C_{Ar}), 131.0 (C_{Ar}), 129.0 (C_{Ar}), 128.7 (C_{Ar}), 126.1 (C_{Ar}), 124.0 (C_{Ar}), 122.2 (C_{Ar}), 121.8 (C_{Ar}), 114.8 (C_{Ar}), 109.8 (C_{Ar}), 73.2 (*C*NHCH), 60.6 ($CO_2CH_2CH_3$), 60.2 (*C*CH_2CH), 51.4 (NH*C*HCH_2), 41.5 (*C*H_2CO_2Et), 39.2 (C*C*H_2CH), 29.4 (NCH_3), 14.2 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3289, 2926, 2660, 2330, 2089, 1729, 1461, 1366, 1215, 1032, 743 cm^{-1}.

MS (ESI): *m/z* = 440.1 $[M+H]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}N_3O_4Cl^+$: 440.1372; found 440.1360.

Ethyl 2-((3*R*,3'*R*,5'*R*)-5''-chloro-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (157n)



According to **GP2**, **157n** was obtained as a colorless solid (135.2 mg, 77% yield).

TLC: R_f = 0.30 (n-petane:EtOAC = 1:1)

Melting Point: 112-113 °C.

$[\alpha]_D^{25}$ = –101.9 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IB; *n*-heptane/EtOH = 7/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 9.71 min (major), 11.46 min (minor), er: 86:14.

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

δ = 7.91 (s, 1H, N*H*CO), 7.38 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.20 – 7.11 (m, 2H, Ar-*H*), 6.80 – 6.73 (m, 2H, Ar-*H*), 6.65 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.61 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 5.00 – 4.93 (m, 1H, NHC*H*CH_2), 4.15 (q, *J* = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 3.18 (dd, *J* = 13.2, 9.6 Hz, 1H, C*H*HCO_2Et), 3.02 (s, 3H, NC*H*$_3$), 2.99 (s, 1H, N*H*), 2.84 (dd, *J* = 16.0, 8.8 Hz, 1H, CC*H*HCH), 2.75 (dd, *J* = 16.0, 5.6 Hz, 1H, CCH*H*CH), 2.07 – 1.96 (m, 1H, CH*H*CO_2Et), 1.26 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

δ = 176.5 (*C*ONH), 176.4 (*C*ONCH_3), 171.7 (*C*O_2Et), 144.0 (C_{Ar}), 138.9 (C_{Ar}), 132.8 (C_{Ar}), 129.7 (C_{Ar}), 128.4 (C_{Ar}), 127.2 (C_{Ar}), 126.3 (C_{Ar}), 126.0 (C_{Ar}), 125.3 (C_{Ar}), 121.9 (C_{Ar}), 110.5 (C_{Ar}), 107.8 (C_{Ar}), 73.7 (*C*NHCH), 60.6 ($CO_2CH_2CH_3$), 60.3 (*C*CH_2CH), 51.5 (NH*C*HCH_2), 41.6 (*C*H_2CO_2Et), 39.4 (C*C*H_2CH), 26.0 (N*C*H_3), 14.2 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3161, 2941, 2657, 2159, 1973, 1719, 1613, 1464, 1368, 1203, 1101, 1025, 839, 739 cm^{-1}.

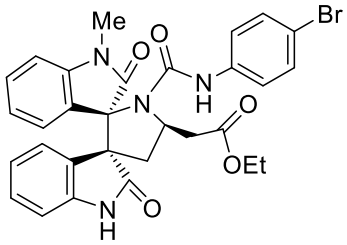
MS (ESI): *m/z* = 440.1 $[M+H]^+$, 462.1 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{22}N_3O_4ClNa^+$: 462.1191; found 462.1180.

The rocedure for the synthesis of **175**:

To a vial containing a solution of **156a** (156.4 mg, 0.40 mmol, 1.0 equiv) in dry DCM (4.0 mL) was added 4-bromophenyl isocyanate (119.0 mg, 0.60 mmol, 1.5 equiv) at 0^{o}C. The mixture was stirred at room temperature for 12 h. Then the solvent was removed on a rotary evaporator and the residue was purified by flash chromatography (pentane/EtOAc = 1/1 to 1/2) to afford the desired product **175** as a colorless solid (195.1 mg, 81% yield).

Ethyl 2-((3*R*,3'*R*,5'*R*)-1'-((4-bromophenyl)carbamoyl)-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indolin]-5'-yl)acetate (175)



TLC: R_f = 0.60 (n-petane:EtOAC = 1:2)

Melting Point: 175-177 °C.

$[\alpha]_D^{25}$ = +21.7 (c = 1.0, $CHCl_3$).

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

δ = 8.68 (d, *J* = 13.8 Hz, 1H, NCON*H*), 7.58 (s, 1H, N*H*CO), 7.39 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.32 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.24 – 7.19 (m, 4H, Ar-*H*), 7.13 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.98 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.65 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.53 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.19 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 5.49 – 5.42 (m, 1H, NHC*H*CH_2), 4.20 – 4.11 (m, 2H, $CO_2CH_2CH_3$), 3.41 (dd, *J* = 16.2, 4.8 Hz, 1H, C*H*HCO_2Et), 2.96 – 2.91 (m, 4H, NCH_3, CC*H*HCH), 2.83 (dd, *J* = 13.2, 7.2 Hz, 1H, CCH*H*CH), 2.59 (dd, *J* = 13.2, 8.4 Hz, 1H, CH*H*CO_2Et), 1.22 (td, *J* = 7.2, 1.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

δ = 176.9 (*C*ONH), 172.3 (*C*ONCH_3), 171.8 (*C*O_2Et), 171.7 (N*C*ONH), 152.0 (C_{Ar}), 143.5 (C_{Ar}), 142.0 (C_{Ar}), 137.9 (C_{Ar}), 131.5 (2C, C_{Ar}), 130.0 (C_{Ar}), 129.2 (C_{Ar}), 128.5 (C_{Ar}), 124.4 (C_{Ar}), 123.8 (C_{Ar}), 122.2 (C_{Ar}), 121.2 (C_{Ar}), 120.9 (2C, C_{Ar}), 115.2 (C_{Ar}), 110.1 (C_{Ar}), 108.7 (C_{Ar}), 73.5 (*C*NHCH), 61.6 ($CO_2CH_2CH_3$), 58.6 (*C*CH_2CH), 53.6 (NH*C*HCH_2), 41.3 (*C*H_2CO_2Et), 40.6 (C*C*H_2CH), 26.6 (N*C*H_3), 14.1 ($CO_2CH_2CH_3$) ppm.

IR (ATR): 3272, 2927, 2651, 2077, 1990, 1723, 1603, 1483, 1353, 1235, 1162, 1013, 936, 823, 752, 683 cm^{-1}.

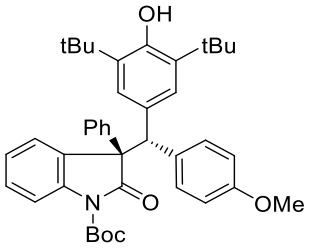
MS (ESI): *m/z* = 603.1 $[M+H]^+$, 1229.2 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{28}N_4O_5Br^+$: 603.1238; found 603.1223.

GP 3 for the third project and analytical data of synthesized compounds

A glass tube equipped with a stirring bar was charged with 3-substituted oxindole **158** (0.40 mmol, 1.0 equiv), *para*-quinone methides **123** (0.6 mmol, 1.5 equiv), catalyst **Q** (0.04 mmol, 10 mol %) and DCM (4.0 mL). The resulting solution of the reaction mixture was cooled to -40 °C and the mixture was stirred at -40 °C for 24 h. Aftre that, the solvent was evaporated to give the crude product, which was directly purified by flash chromatography (pentane/Et_2O = 30/1 to 10/1) to provide the desired product **159**.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(4-methoxyphenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159a)



According to **GP3**, **159a** was obtained as a colorless solid (205.1 mg, 81% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 10:1)

Melting Point: 175-177 °C.

$[\alpha]_D^{25}$ = -45.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 97/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 3.22 min (major), 2.65 min (minor), er: 96:4.

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

δ = 7.86 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.61 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.36 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.33 – 7.25 (m, 3H, Ar-*H*), 7.14 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.80 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.78 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.71 (s, 2H, Ar-*H*), 6.61 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 5.26 (s, 1H, ArO*H*), 5.00 (s, 1H, ArC*H*Ar), 3.72 (s, 3H, OCH_3), 1.46 (s, 9H, $NCO_2C(CH_3)_3$), 1.26 (s, 18H, 2 × $ArC(CH_3)_3$).

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

δ = 175.3 (N*C*O), 158.1 (C_{Ar}), 152.5 (C_{Ar}), 149.0 (NCO_2), 140.6 (C_{Ar}), 138.9 (C_{Ar}), 135.0 (2C, C_{Ar}), 131.5 (C_{Ar}), 131.1 (2C, C_{Ar}), 129.8 (2C, C_{Ar}), 128.5 (2C, C_{Ar}), 128.3

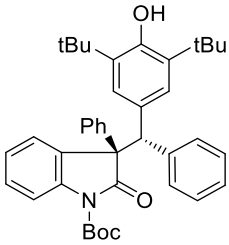
(C_{Ar}), 128.2 (2C, C_{Ar}), 127.8 (C_{Ar}), 127.4 (C_{Ar}), 126.5 (2C, C_{Ar}), 123.3 (C_{Ar}), 115.3 (C_{Ar}), 112.7 (2C, C_{Ar}), 83.6 ($NCO_2C(CH_3)_3$), 61.4 (Ph*C*CO), 58.9 (O*C*H$_3$), 55.1 (Ar*C*HAr), 34.1 (2C, 2 × Ar*C*(CH$_3$)$_3$), 30.2 (6C, 2 × ArC(*C*H$_3$)$_3$), 28.0 (3C, $NCO_2C(CH_3)_3$).

IR (ATR): 3623, 2956, 2324, 2163, 2061, 1989, 1958, 1766, 1727, 1604, 1510, 1462, 1346, 1289, 1247, 1149, 1092, 1033, 838, 761, 720, 697 cm^{-1}.

MS (ESI): *m/z* = 1289.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{82}H_{94}N_2O_{10}Na^+$: 1289.6801; found 1289.6807.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159b)



According to **GP3**, **159b** was obtained as a colorless solid (212.3 mg, 88% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 15:1)

Melting Point: 165-168 °C.

$[\alpha]_D^{25}$ = -22.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 3.80 min (major), 3.43 min (minor), er: 96:4.

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

δ = 7.81 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.62 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.39 (t, *J* = 8.4 Hz, 1H, Ar-*H*), 7.32 – 7.29 (m, 2H, Ar-*H*), 7.28 – 7.24 (m, 1H, Ar-*H*), 7.13 – 7.10 (m, 4H, Ar-*H*), 6.92 – 6.90 (m, 2H, Ar-*H*), 6.64 – 6.62 (m, 3H, Ar-*H*), 5.24 (s, 1H, ArO*H*), 5.03 (s, 1H, ArC*H*Ar), 1.45 (s, 9H, $NCO_2C(CH_3)_3$), 1.18 (s, 18H, 2 × ArC(C*H*$_3$)$_3$) ppm.

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

δ = 175.5 (N*C*O), 152.5 (C_{Ar}), 148.9 (NCO_2), 140.6 (C_{Ar}), 139.6 (C_{Ar}), 138.7 (C_{Ar}),

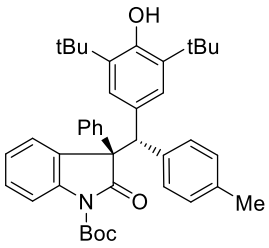
134.4 (2C, C_{Ar}), 129.8 (2C, C_{Ar}), 128.7 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.4 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.1 (C_{Ar}), 127.9 (2C, C_{Ar}), 127.8 (C_{Ar}), 127.4 (C_{Ar}), 127.0 (2C, C_{Ar}), 126.7 (C_{Ar}), 123.0 (C_{Ar}), 115.0 (C_{Ar}), 83.8 ($NCO_2C(CH_3)_3$), 61.3 (Ph*C*CO), 60.5 (Ar*C*HAr), 34.2 (2C, 2 × Ar$C(CH_3)_3$), 30.1 (6C, 2 × ArC(CH_3)$_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3618, 2957, 2321, 2166, 2113, 1987, 1953, 1767, 1727, 1604, 1445, 1348, 1291, 1247, 1148, 1091, 1004, 842, 756, 705 cm^{-1}.

MS (ESI): *m/z* = 1229.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{80}H_{90}N_2O_8Na^+$: 1229.6589; found 1229.6589.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(p-tolyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159c)



According to **GP3**, **159c** was obtained as a colorless solid (207.4 mg, 84% yield, dr: 13:1).

TLC: R_f = 0.30 (n-petane:Et_2O = 15:1)

Melting Point: 176-179 °C.

$[\alpha]_D^{25}$ = -27.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 95/5; flow rate 0.5 mL/min; T= 30 °C; retention time: 8.00 min (major), 10.78 min (minor), er: 95:5.

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

δ = 7.80 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.61 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.38 (td, *J* = 8.0, 1.2 Hz, 1H, Ar-*H*), 7.32 – 7.22 (m, 3H, Ar-*H*), 7.09 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.91 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.76 (d, *J* = 8.1 Hz, 2H, Ar-*H*), 6.63 (s, 2H, Ar-*H*), 6.58 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.19 (s, 1H, ArO*H*), 5.01 (s, 1H, ArC*H*Ar), 2.21 (s, 3H, CH_3), 1.44 (s, 9H, $NCO_2C(CH_3)_3$), 1.18 (s, 18H, 2 × ArC(CH_3)$_3$) ppm.

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

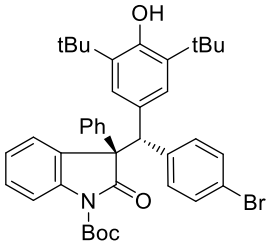
δ = 175.5 (N*C*O), 152.5 (*C*$_{Ar}$), 148.9 (N*C*O$_2$), 140.7 (*C*$_{Ar}$), 138.7 (*C*$_{Ar}$), 136.3 (*C*$_{Ar}$), 136.1 (*C*$_{Ar}$), 134.3 (2C, *C*$_{Ar}$), 129.6 (2C, *C*$_{Ar}$), 128.7 (*C*$_{Ar}$), 128.6 (2C, *C*$_{Ar}$), 128.5 (2C, *C*$_{Ar}$), 128.4 (*C*$_{Ar}$), 128.2 (2C, *C*$_{Ar}$), 128.0 (*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 127.4 (*C*$_{Ar}$), 126.9 (2C, *C*$_{Ar}$), 122.9 (*C*$_{Ar}$), 114.9 (*C*$_{Ar}$), 83.6 (NCO$_2$*C*(CH$_3$)$_3$), 61.4 (Ph*C*CO), 60.2 (Ar*C*HAr), 34.2 (2C, 2 × Ar*C*(CH$_3$)$_3$), 30.1 (6C, 2 × ArC(*C*H$_3$)$_3$), 27.9 (3C, NCO$_2$C(*C*H$_3$)$_3$), 20.9 (*C*H$_3$) ppm.

IR (ATR): 3628, 2956, 2322, 2161, 1999, 1955, 1763, 1731, 1606, 1438, 1346, 1298, 1247, 1150, 1096, 1049, 843, 763, 727, 697 cm^{-1}.

MS (ESI): *m/z* = 640.3 [M+Na]$^+$, 1257.7 [2M+Na]$^+$.

HRMS (ESI): *m/z* [2M+Na]$^+$ calcd for $C_{82}H_{94}N_2O_8Na^+$: 1257.6902; found 1257.6899.

(*R*)-Tert-butyl 3-((*S*)-(4-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159d)



According to **GP3**, **159d** was obtained as a colorless solid (228.9 mg, 84% yield, dr: 10:1).

TLC: R$_f$ = 0.40 (n-petane:Et$_2$O = 15:1)

Melting Point: 180-182 °C.

[α]$_D^{25}$ = -31.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 8.13 min (major), 16.71 min (minor), er: 95:5.

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

δ = 7.79 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.41 – 7.37 (m, 1H, Ar-*H*), 7.33 – 7.29 (m, 2H, Ar-*H*), 7.27 – 7.25 (m, 3H, Ar-*H*), 7.12 (t, *J* = 7.8 Hz, 1H,

Ar-*H*), 6.82 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.67 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.58 (s, 2H, Ar-*H*), 5.19 (s, 1H, ArO*H*), 5.05 (s, 1H, ArC*H*Ar), 1.48 (s, 9H, $NCO_2C(CH_3)_3$), 1.18 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

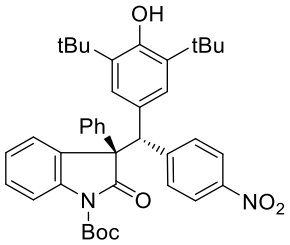
δ = 175.4 (N*C*O), 152.7 (C_{Ar}), 148.7 (NCO_2), 140.5 (C_{Ar}), 138.7 (C_{Ar}), 138.4 (C_{Ar}), 137.2 (C_{Ar}), 134.5 (2C, C_{Ar}), 131.6 (2C, C_{Ar}), 131.0 (2C, C_{Ar}), 128.9 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 127.7 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 126.8 (2C, C_{Ar}), 123.1 (C_{Ar}), 120.8 (C_{Ar}), 115.0 (C_{Ar}), 84.1 ($NCO_2C(CH_3)_3$), 61.2 (Ph*C*CO), 59.8 (Ar*C*HAr), 34.2 (2C, 2 × $ArC(CH_3)_3$), 30.0 (6C, 2 × $ArC(CH_3)_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3630, 2960, 2324, 2162, 2111, 1978, 1954, 1764, 1725, 1605, 1479, 1348, 1299, 1246, 1148, 1096, 1005, 836, 764, 696 cm^{-1}.

MS (ESI): *m/z* = 1387.5 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{80}H_{88}N_2O_8Br_2Na^+$: 1385.4800; found 1385.4811.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(4-nitrophenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159e)



According to **GP3**, **159e** was obtained as a colorless solid (230.8 mg, 89% yield, dr: > 20:1).

TLC: R_f = 0.30 (n-petane:Et_2O = 10:1)

Melting Point: 175-177 °C.

$[\alpha]_D^{25}$ = -40.6 (c = 1.0, $CHCl_3$).

HPLC: (s, s) - Whelk ol; *n*-heptane/iPrOH = 9/1; flow rate 0.7 mL/min; T= 30 °C; retention time: 14.65 min (major), 11.44 min (minor), er: 93:7.

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

δ = 8.00 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.76 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.52 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.39 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.32 – 7.26 (m, 3H, Ar-*H*), 7.23 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.16 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.52 (s, 2H, Ar-*H*), 5.32 (s, 1H, ArO*H*), 5.09 (s, 1H, ArC*H*Ar), 1.48 (s, 9H, $NCO_2C(CH_3)_3$), 1.19 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

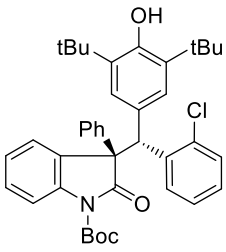
δ = 175.4 (N*C*O), 152.9 (C_{Ar}), 148.5 (NCO_2), 148.0 (C_{Ar}), 146.5 (C_{Ar}), 140.0 (C_{Ar}), 138.3 (C_{Ar}), 134.8 (2C, C_{Ar}), 130.8 (2C, C_{Ar}), 129.0 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.1 (2C, C_{Ar}), 127.7 (C_{Ar}), 127.2 (C_{Ar}), 126.9 (2C, C_{Ar}), 126.8 (2C, C_{Ar}), 123.5 (C_{Ar}), 123.1 (2C, C_{Ar}), 115.1 (C_{Ar}), 84.4 ($NCO_2C(CH_3)_3$), 61.1 (Ph*C*CO), 60.0 (Ar*C*HAr), 34.2 (2C, 2 × $ArC(CH_3)_3$), 30.0 (6C, 2 × $ArC(CH_3)_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3629, 2958, 2322, 2159, 2087, 1979, 1958, 1788, 1733, 1601, 1521, 1468, 1438, 1345, 1299, 1245, 1149, 1099, 1005, 855, 754, 699 cm^{-1}.

MS (ESI): *m/z* = 1319.6 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{80}H_{88}N_4O_{12}Na^+$: 1319.6291; found 1319.6299.

(*R*)-Tert-butyl 3-((*S*)-(2-chlorophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl-)-2-oxo-3-phenylindoline-1-carboxylate (159f)



According to **GP3**, **159f** was obtained as a wax (188.6 mg, 74% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 15:1)

$[\alpha]_D^{25}$ = -47.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 98/2; flow rate 0.5 mL/min; T= 30 °C; retention time: 8.28 min (major), 14.04 min (minor), er: 96:4.

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

δ = 7.76 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.51 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.37 – 7.32 (m, 2H, Ar-*H*), 7.29 – 7.27 (m, 2H, Ar-*H*), 7.22 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.18 (d, *J* = 6.6 Hz, 1H, Ar-*H*), 7.13 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.06 (td, *J* = 7.8, 1.8 Hz, 1H, Ar-*H*), 7.00 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 6.72 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.53 (s, 2H, Ar-*H*), 5.86 (s, 1H, ArO*H*), 5.03 (s, 1H, ArC*H*Ar), 1.50 (s, 9H, $NCO_2C(CH_3)_3$), 1.19 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

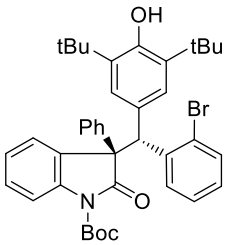
δ = 175.5 (N*C*O), 152.7 (C_{Ar}), 148.8 (NCO_2), 140.0 (C_{Ar}), 139.3 (C_{Ar}), 138.1 (C_{Ar}), 135.1 (C_{Ar}), 134.4 (2C, C_{Ar}), 130.0 (C_{Ar}), 129.8 (C_{Ar}), 129.5 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 127.6 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (C_{Ar}), 127.0 (2C, C_{Ar}), 126.6 (C_{Ar}), 126.1 (C_{Ar}), 123.4 (C_{Ar}), 114.8 (C_{Ar}), 84.0 ($NCO_2C(CH_3)_3$), 61.6 (Ph*C*CO), 55.5 (Ar*C*HAr), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 30.0 (6C, 2 × ArC(CH_3)$_3$), 28.0 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3632, 2959, 2323, 2163, 2110, 1956, 1787, 1732, 1610, 1468, 1344, 1289, 1245, 1148, 1096, 1002, 841, 752, 699 cm^{-1}.

MS (ESI): *m/z* = 1299.6 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{80}H_{88}N_2O_8Cl_2Na^+$: 1297.5810; found 1297.5815.

(*R*)-Tert-butyl 3-((*S*)-(2-bromophenyl)(3,5-di-tert-butyl-4-hydroxyphenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159g)



According to **GP3**, **159g** was obtained as a colorless solid (185.3 mg, 68% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 15:1)

Melting Point: 175-177 °C.

$[\alpha]_D^{25}$ = -32.2 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 95/5; flow rate 0.5 mL/min; T= 30 °C; retention time: 7.46 min (major), 11.38 min (minor), er: 93:7.

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

δ = 7.75 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.55 – 7.49 (m, 3H, Ar-*H*), 7.37 – 7.33 (m, 1H, Ar-*H*), 7.30 – 7.25 (m, 2H, Ar-*H*), 7.23 – 7.20 (m, 2H, Ar-*H*), 7.13 (td, *J* = 7.2, 1.2 Hz, 1H, Ar-*H*), 7.06 – 7.02 (m, 1H, Ar-*H*), 6.97 (td, *J* = 7.8, 1.2 Hz, 1H, Ar-*H*), 6.74 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.53 (s, 2H, Ar-*H*), 5.84 (s, 1H, ArO*H*), 5.02 (s, 1H, ArC*H*Ar), 1.50 (s, 9H, $NCO_2C(CH_3)_3$), 1.19 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

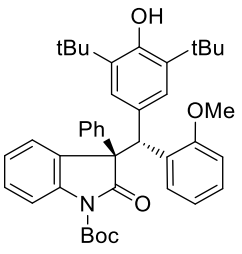
δ = 175.5 (N*C*O), 152.7 (C_{Ar}), 148.7 (NCO_2), 140.0 (C_{Ar}), 139.6 (C_{Ar}), 139.3 (C_{Ar}), 134.4 (2C, C_{Ar}), 133.2 (C_{Ar}), 130.1 (C_{Ar}), 129.6 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.4 (2C, C_{Ar}), 128.2 (C_{Ar}), 127.9 (C_{Ar}), 127.3 (C_{Ar}), 127.1 (2C, C_{Ar}), 127.0 (C_{Ar}), 126.7 (C_{Ar}), 126.6 (C_{Ar}), 126.4 (C_{Ar}), 123.5 (C_{Ar}), 114.8 (C_{Ar}), 84.0 ($NCO_2C(CH_3)_3$), 61.8 (Ph*C*CO), 58.6 (Ar*C*HAr), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3631, 2958, 2074, 1925, 1733, 1611, 1467, 1345, 1291, 1246, 1150, 1098, 1022, 909, 840, 736 cm^{-1}.

MS (ESI): *m/z* = 705.2 $[M+Na]^+$, 1387.5 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{40}H_{44}NO_4Na^+$: 704.2346; found 704.2354.

(*R*)-Tert-butyl 3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159h)



According to **GP3**, **159h** was obtained as a colorless solid (210.3 mg, 83% yield, dr: > 20:1).

TLC: R_f = 0.60 (n-petane:Et_2O = 15:1)

Melting Point: 148-151 °C.

$[\alpha]_D^{25}$ = -51.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 4.21 min (major), 6.28 min (minor), er: 96:4.

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

δ = 7.79 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.57 (d, *J* = 7.8 Hz, 2H, Ar-*H*), 7.35 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.28 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.23 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.11 – 7.06 (m, 2H, Ar-*H*), 6.81 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.71 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.65 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 6.62 (s, 2H, Ar-*H*), 6.49 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 5.96 (s, 1H, ArO*H*), 5.00 (s, 1H, ArC*H*Ar), 3.82 (s, 3H, OCH_3), 1.47 (s, 9H, $NCO_2C(CH_3)_3$), 1.18 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

δ = 175.6 (N*C*O), 157.3 (C_{Ar}), 152.5 (C_{Ar}), 149.0 (N*C*O_2), 140.4 (C_{Ar}), 139.5 (C_{Ar}), 134.2 (2C, C_{Ar}), 129.0 (C_{Ar}), 128.7 (2C, C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (2C, C_{Ar}), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 127.2 (C_{Ar}), 127.0 (2C, C_{Ar}), 126.3 (C_{Ar}), 122.9 (C_{Ar}), 119.7 (C_{Ar}), 114.8 (C_{Ar}), 111.2 (C_{Ar}), 83.6 ($NCO_2C(CH_3)_3$), 61.5 (Ph*C*CO), 56.1 (Ar*C*HAr), 50.3 (O*C*H_3), 34.2 (2C, 2 × $ArC(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3628, 2960, 2362, 2125, 2066, 1992, 1957, 1765, 1730, 1600, 1463, 1344, 1294, 1247, 1151, 1112, 1028, 846, 753, 718 cm^{-1}.

MS (ESI): *m/z* = 656.3 $[M+Na]^+$, 1289.7 $[2M+Na]^+$.

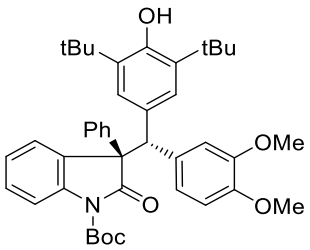
HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{41}H_{47}NO_5Na^+$: 656.3347; found 656.3348.

The gram scale reaction for the synthesis of **159h** was carried out in a similar manner.

A glass tube equipped with a stirring bar was charged with 3-substituted oxindole **158a** (639.0 mg, 2.07 mmol, 1.0 equiv), *para*-quinone methide **123h** (1.0 g, 3.10 mmol, 1.5 equiv), catalyst **Q** (131.0 mg, 0.21 mmol, 10 mol %) and DCM (20.0 mL). The resulting solution of the reaction mixture was cooled to -40 °C and the mixture was stirred at -40

°C for 24 h. After the reaction finished, the solvent was evaporated to give the crude product, which was directly purified by flash chromatography (pentane/Et_2O = 30/1 to 15/1) to provide the desired product **159h** as a colorless solid (1.14 g, 87% yield, dr: > 20:1, er: 96:4). The analytical data of the gram scale reaction of **159h** were consistent with those of the 0.40 mmol scale experiment.

(*R*)-Tert-butyl 3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(3,4-dimethoxyphenyl)-methyl)-2-oxo-3-phenylindoline-1-carboxylate (159i)



According to **GP3**, **159i** was obtained as a colorless solid (254.7 mg, 96% yield, dr: > 20:1).

TLC: R_f = 0.30 (n-petane:Et_2O = 10:1)

Melting Point: 145-148 °C.

$[\alpha]_D^{25}$ = -34.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 8.56min (major), 11.29 min (minor), er: 95:5.

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

δ = 7.82 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.62 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.38 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.31 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.28 – 7.25 (m, 1H, Ar-*H*), 7.12 (t, *J* = 6.6 Hz, 1H, Ar-*H*), 6.69 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.66 – 6.64 (m, 3H, Ar-*H*), 6.61 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.34 (s, 1H, Ar-*H*), 5.18 (s, 1H, ArO*H*), 5.03 (s, 1H, ArC*H*Ar), 3.80 (s, 3H, OCH_3), 3.52 (s, 3H, OCH_3), 1.46 (s, 9H, $NCO_2C(CH_3)_3$), 1.19 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

δ = 175.5 (N*C*O), 152.6 (C_{Ar}), 148.8 (NCO_2), 148.0 (C_{Ar}), 147.6 (C_{Ar}), 146.9 (C_{Ar}), 141.3 (C_{Ar}), 140.8 (C_{Ar}), 138.6 (C_{Ar}), 134.3 (2C, C_{Ar}), 132.0 (C_{Ar}), 128.6 (C_{Ar}), 128.5

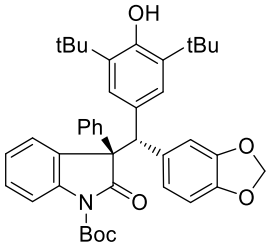
(2C, C_{Ar}), 128.3 (2C, C_{Ar}), 128.1 (C_{Ar}), 127.4 (C_{Ar}), 126.8 (2C, C_{Ar}), 122.9 (C_{Ar}), 122.8 (C_{Ar}), 115.0 (C_{Ar}), 111.9 (C_{Ar}), 110.7 (C_{Ar}), 83.9 ($NCO_2C(CH_3)_3$), 61.4 (Ph*C*CO), 59.9 (Ar*C*HAr), 55.6 (OCH_3), 55.2 (OCH_3), 34.2 (2C, 2 × Ar$C(CH_3)_3$), 30.1 (6C, 2 × ArC(CH_3)$_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3627, 2958, 2325, 2161, 2109, 1979, 1956, 1766, 1727, 1603, 1512, 1463, 1347, 1288, 1248, 1148, 1094, 1028, 838, 763, 726, 667 cm^{-1}.

MS (ESI): *m/z* = 1349.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{84}H_{98}N_2O_{12}Na^+$: 1349.7012; found 1349.7017.

(*R*)-Tert-butyl 3-((*R*)-benzo[d][1,3]dioxol-5-yl(3,5-di-tert-butyl-4-hydroxyphenyl) methyl)-2-oxo-3-phenylindoline-1-carboxylate (159j)



According to **GP3**, **159j** was obtained as a colorless solid (220.1 mg, 85% yield, dr: > 20:1).

TLC: R_f = 0.40 (n-petane:Et_2O = 10:1)

Melting Point: 176-178 °C.

$[\alpha]_D^{25}$ = -30.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 8.31 min (major), 9.31 min (minor), er: 94:6.

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

δ = 7.80 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.38 (td, *J* = 8.4, 1.2 Hz, 1H, Ar-*H*), 7.31 – 7.29 (m, 2H, Ar-*H*), 7.27 – 7.23 (m, 1H, Ar-*H*), 7.11 (td, *J* = 7.2, 1.2 Hz, 1H, Ar-*H*), 6.65 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.61 (s, 2H, Ar-*H*), 6.57 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.43 – 6.39 (m, 2H, Ar-*H*), 5.86 (d, *J* = 1.2 Hz, 1H, OC*H*HO), 5.83 (d,

J = 1.2 Hz, 1H, OCH*H*O), 5.16 (s, 1H, ArO*H*), 5.03 (s, 1H, ArC*H*Ar), 1.50 (s, 9H, $NCO_2C(CH_3)_3$), 1.19 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

δ = 175.5 (N*C*O), 152.5 (C_{Ar}), 148.9 (NCO_2), 147.2 (C_{Ar}), 146.1 (C_{Ar}), 140.5 (C_{Ar}), 138.7 (C_{Ar}), 134.4 (2C, C_{Ar}), 133.5 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 128.1 (C_{Ar}), 127.8 (C_{Ar}), 127.4 (C_{Ar}), 126.8 (2C, C_{Ar}), 123.0 (C_{Ar}), 122.9 (C_{Ar}), 115.0 (C_{Ar}), 110.4 (C_{Ar}), 107.7 (C_{Ar}), 100.7 (OCH_2O), 83.9 ($NCO_2C(CH_3)_3$), 61.3 (Ph*C*CO), 60.0 (Ar*C*HAr), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

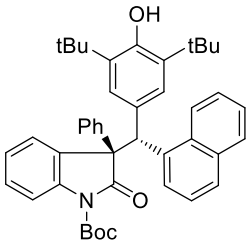
IR (ATR): 3787, 3376, 2967, 2932, 2321, 2067, 1728, 1605, 1484, 1347, 1290, 1150, 1095, 1037, 930, 882, 762, 723 cm^{-1}.

MS (ESI): *m/z* = 1317.6 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{82}H_{90}N_2O_{12}Na^+$: 1317.6386; found 1317.6394.

(*R*)-Tert-butyl 3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(naphthalen-1-yl)meth

yl)-2-oxo-3-phenylindoline-1-carboxylate (159k)



According to **GP3**, **159k** was obtained as a wax (219.4 mg, 84% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 15:1)

$[\alpha]_D^{25}$ = -36.6 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/EtOH = 97/3; flow rate 0.7 mL/min; T= 30 ºC; retention time: 5.90 min (major), 6.29 min (minor), er: 93:7.

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

δ = 8.19 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.86 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.78 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.65 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.56 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.48 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.43 – 7.39 (m, 2H, Ar-*H*), 7.31 – 7.28 (m, 2H, Ar-*H*), 7.27 – 7.25

(m, 1H, Ar-*H*), 7.20 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.16 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 6.73 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.60 (s, 2H, Ar-*H*), 6.11 (s, 1H, ArO*H*), 5.01 (s, 1H, ArC*H*Ar), 1.46 (s, 9H, $NCO_2C(CH_3)_3$), 1.17 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

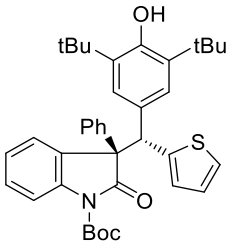
δ = 175.7 (N*C*O), 152.8 (C_{Ar}), 148.9 (NCO_2), 140.2 (C_{Ar}), 139.7 (C_{Ar}), 136.4 (C_{Ar}), 134.4 (2C, C_{Ar}), 134.2 (C_{Ar}), 132.3 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.3 (2C, C_{Ar}), 127.9 (C_{Ar}), 127.5 (C_{Ar}), 127.3 (C_{Ar}), 127.2 (C_{Ar}), 126.7 (2C, C_{Ar}), 126.1 (C_{Ar}), 125.8 (C_{Ar}), 125.1 (C_{Ar}), 124.7 (C_{Ar}), 123.6 (C_{Ar}), 123.3 (C_{Ar}), 115.1 (C_{Ar}), 83.9 ($NCO_2C(CH_3)_3$), 61.4 (Ph*C*CO), 54.9 (Ar*C*HAr), 34.1 (2C, 2 × Ar*C*$(CH_3)_3$), 30.0 (6C, 2 × $ArC(CH_3)_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3742, 2958, 2351, 2261, 2064, 1968, 1921, 1785, 1731, 1608, 1464, 1344, 1287, 1247, 1148, 1097, 1001, 886, 757, 695 cm^{-1}.

MS (ESI): *m/z* = 1329.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{88}H_{94}N_2O_8Na^+$: 1329.6902; found 1329.6907.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(thiophen-2-yl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159l)



According to **GP3**, **159l** was obtained as a colorless solid (209.6 mg, 86% yield, dr: 10:1).

TLC: R_f = 0.30 (n-petane:Et_2O = 10:1)

Melting Point: 155-158 °C.

$[\alpha]_D^{25}$ = -35.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 6.01 min (major), 9.01 min (minor), er: 94:6.

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

δ = 7.84 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.62 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.42 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.30 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.27 – 7.25 (m, 1H, Ar-*H*), 7.15 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.05 (d, *J* = 5.4 Hz, 1H, Ar-*H*), 6.81 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.73 – 6.71 (m, 3H, Ar-*H*), 6.57 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 5.54 (s, 1H, ArO*H*), 5.04 (s, 1H, ArC*H*Ar), 1.50 (s, 9H, $NCO_2C(CH_3)_3$), 1.21 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

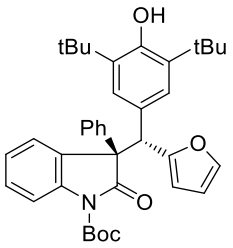
δ = 175.2 (N*C*O), 152.8 (C_{Ar}), 148.9 (NCO_2), 141.2 (C_{Ar}), 141.1 (C_{Ar}), 137.7 (C_{Ar}), 134.3 (2C, C_{Ar}), 129.0 (C_{Ar}), 128.9 (2C, C_{Ar}), 128.6 (2C, C_{Ar}), 128.2 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 127.1 (2C, C_{Ar}), 126.8 (C_{Ar}), 126.8 (C_{Ar}), 126.2 (C_{Ar}), 124.3 (C_{Ar}), 122.8 (C_{Ar}), 115.1 (C_{Ar}), 83.9 ($NCO_2C(CH_3)_3$), 61.4 (Ph*C*CO), 55.4 (Ar*C*HAr), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 30.1 (6C, 2 × ArC(*C*$H_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3627, 2961, 2323, 2163, 2055, 1765, 1731, 1604, 1467, 1345, 1290, 1247, 1148, 1100, 999, 840, 755, 696 cm^{-1}.

MS (ESI): *m/z* = 1241.6 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{76}H_{86}N_2O_8Na^+$: 1241.5718; found 1241.5713.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(furan-2-yl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (159m)



According to **GP3**, **159m** was obtained as a colorless solid (162.1 mg, 68% yield, dr: 5:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 10:1)

Melting Point: 162-165 °C.

$[\alpha]_D^{25}$ = -22.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 6.15 min (major), 8.25 min (minor), er: 94:6.

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

δ = 7.85 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.58 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.40 – 7.36 (m, 1H, Ar-*H*), 7.30 (t, *J* = 7.2 Hz, 2H, Ar-*H*), 7.26 (t, *J* = 7.2 Hz, 1H, Ar-*H*), 7.19 (d, *J* = 1.2 Hz, 1H, Ar-*H*), 7.11 (td, *J* = 7.2, 1.2 Hz, 1H, Ar-*H*), 6.68 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.59 (s, 2H, Ar-*H*), 6.15 (dd, *J* = 3.6, 1.8 Hz, 1H, Ar-*H*), 5.64 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 5.33 (s, 1H, ArO*H*), 5.05 (s, 1H, ArC*H*Ar), 1.55 (s, 9H, $NCO_2C(CH_3)_3$), 1.21 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

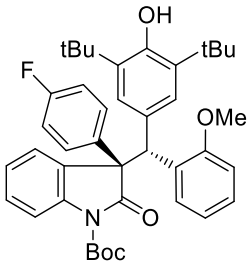
δ = 175.4 (N*C*O), 152.9 (C_{Ar}), 149.0 (NCO_2), 140.9 (C_{Ar}), 140.5 (C_{Ar}), 137.6 (C_{Ar}), 134.4 (2C, C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.2 (2C, C_{Ar}), 128.0 (C_{Ar}), 127.6 (C_{Ar}), 127.4 (C_{Ar}), 127.0 (2C, C_{Ar}), 126.1 (C_{Ar}), 122.8 (C_{Ar}), 114.9 (C_{Ar}), 110.2 (C_{Ar}), 107.8 (C_{Ar}), 84.0 ($NCO_2C(CH_3)_3$), 60.0 (Ph*C*CO), 53.6 (Ar*C*HAr), 34.2 (2C, 2 × $ArC(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3623, 2959, 2321, 2158, 2110, 1759, 1729, 1604, 1579, 1464, 1346, 1289, 1250, 1147, 1097, 1021, 840, 731, 698 cm^{-1}.

MS (ESI): *m/z* = 616.3 $[M+Na]^+$, 1209.6 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{43}NO_5Na^+$: 616.3033; found 616.3037.

(*R*)-Tert-butyl 3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-3-(4-fluorophenyl)-2-oxoindoline-1-carboxylate (159n)



According to **GP3**, **159n** was obtained as a colorless solid (231.9 mg, 89% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 15:1)

Melting Point: 177-180 °C.

$[\alpha]_D^{25}$ = -52.6(c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.5 mL/min; T= 30 °C; retention time: 8.31 min (major), 12.56 min (minor), er: 92:8.

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

δ = 7.80 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.58 – 7.53 (m, 2H, Ar-*H*), 7.37 (td, *J* = 8.4, 1.2 Hz, 1H, Ar-*H*), 7.13 – 7.06 (m, 2H, Ar-*H*), 6.97 (t, *J* = 8.4 Hz, 2H, Ar-*H*), 6.81 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.69 – 6.64 (m, 2H, Ar-*H*), 6.62 (s, 2H, Ar-*H*), 6.49 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 5.89 (s, 1H, ArO*H*), 5.02 (s, 1H, ArC*H*Ar), 3.82 (s, 3H, OCH_3), 1.47 (s, 9H, $NCO_2C(CH_3)_3$), 1.21 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

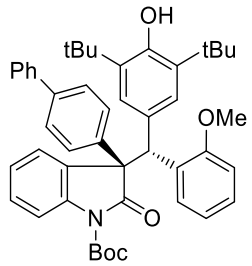
δ = 175.6 (N*C*O), 162.6 (C_{Ar}), 161.2 (d, *J* = 247.3 Hz, C_{Ar}), 157.3 (C_{Ar}), 152.6 (C_{Ar}), 148.9 (NCO_2), 140.4 (C_{Ar}), 135.3 (C_{Ar}), 134.3 (2C, C_{Ar}), 130.3 (C_{Ar}), 130.2 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 128.4 (C_{Ar}), 127.9 (C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 127.0 (2C, C_{Ar}), 123.1 (C_{Ar}), 119.7 (C_{Ar}), 115.0 (C_{Ar}), 114.9 (C_{Ar}), 114.8 (C_{Ar}), 114.7 (C_{Ar}), 111.1 (C_{Ar}), 83.8 ($NCO_2C(CH_3)_3$), 60.9 (Ph*C*CO), 56.0 (Ar*C*HAr), 50.5 (OCH_3), 34.2 (2C, 2 × $ArC(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3634, 2956, 2320, 2061, 1766, 1722, 1602, 1461, 1349, 1296, 1247, 1150, 1092, 1026, 952, 837, 755, 682 cm^{-1}.

MS (ESI): *m/z* = 674.3 $[M+Na]^+$, 1325.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{41}H_{46}NO_5FNa^+$: 674.3252; found 674.3256.

(*R*)-Tert-butyl 3-(biphenyl-4-yl)-3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-2-oxoindoline-1-carboxylate (159o)



According to **GP3**, **159o** was obtained as a colorless solid (241.2 mg, 85% yield, dr: > 20:1).

TLC: R_f = 0.60 (n-petane:Et_2O = 15:1)

Melting Point: 190-193 °C.

$[\alpha]_D^{25}$ = -37.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 6.86 min (major), 10.08 min (minor), er: 97:3.

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

δ = 7.81 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.65 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.54 – 7.47 (m, 4H, Ar-*H*), 7.44 – 7.39 (m, 2H, Ar-*H*), 7.37 – 7.30 (m, 2H, Ar-*H*), 7.12 – 7.05 (m, 2H, Ar-*H*), 6.82 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.67 – 6.60 (m, 4H, Ar-*H*), 6.45 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.99 (s, 1H, ArO*H*), 5.00 (s, 1H, ArC*H*Ar), 3.83 (s, 3H, OCH_3), 1.46 (s, 9H, $NCO_2C(CH_3)_3$), 1.17 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

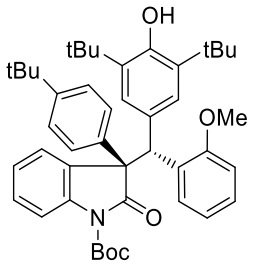
δ = 175.6 (N*C*O), 157.4 (C_{Ar}), 152.6 (C_{Ar}), 149.0 (NCO_2), 140.9 (C_{Ar}), 140.5 (C_{Ar}), 140.3 (C_{Ar}), 138.6 (C_{Ar}), 134.3 (2C, C_{Ar}), 129.0 (2C, C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (2C, C_{Ar}), 128.6 (C_{Ar}), 128.1 (C_{Ar}), 127.9 (C_{Ar}), 127.6 (C_{Ar}), 127.3 (C_{Ar}), 127.2 (C_{Ar}), 127.1 (2C, C_{Ar}), 127.0 (2C, C_{Ar}), 126.9 (2C, C_{Ar}), 123.0 (C_{Ar}), 119.7 (C_{Ar}), 114.9 (C_{Ar}), 111.2 (C_{Ar}), 83.7 ($NCO_2C(CH_3)_3$), 61.3 (Ph*C*CO), 56.1 (Ar*C*HAr), 50.4 (OCH_3), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$).

IR (ATR): 3631, 2955, 2321, 2050, 1764, 1721, 1601, 1483, 1348, 1296, 1247, 1150, 1092, 1028, 951, 838, 756, 691 cm^{-1}.

MS (ESI): *m/z* = 732.4 $[M+Na]^+$, 1442.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{47}H_{51}NO_5Na^+$: 732.3659; found 732.3663.

(*R*)-Tert-butyl 3-(4-tert-butylphenyl)-3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-2-oxoindoline-1-carboxylate (159p)



According to **GP3**, **159p** was obtained as a colorless solid (228.9 mg, 83% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 15:1)

Melting Point: 175-177 °C.

$[\alpha]_D^{25}$ = -36.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 5.32 min (major), 6.8 min (minor), er: 94:6.

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

δ = 7.81 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.53 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.40 – 7.29 (m, 3H, Ar-*H*), 7.11 – 7.02 (m, 2H, Ar-*H*), 6.82 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.64 – 6.60 (m, 3H, Ar-*H*), 6.50 – 6.46 (m, 1H, Ar-*H*), 6.31 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 5.99 (s, 1H, ArO*H*), 5.00 (s, 1H, ArC*H*Ar), 3.83 (s, 3H, OCH_3), 1.44 (s, 9H, $NCO_2C(CH_3)_3$), 1.29 (s, 9H, $ArC(CH_3)_3$), 1.17 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

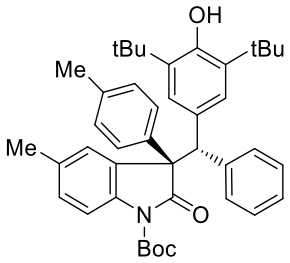
δ = 175.6 (N*C*O), 157.4 (C_{Ar}), 152.5 (C_{Ar}), 150.0 (C_{Ar}), 149.0 (N*C*O_2), 140.6 (C_{Ar}), 136.2 (C_{Ar}), 134.1 (2C, C_{Ar}), 128.7 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (C_{Ar}), 128.3 (2C, C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 127.5 (C_{Ar}), 127.1 (2C, C_{Ar}), 125.1 (2C, C_{Ar}), 122.7 (C_{Ar}), 119.6 (C_{Ar}), 114.8 (C_{Ar}), 111.3 (C_{Ar}), 83.5 ($NCO_2C(CH_3)_3$), 61.0 (Ph*C*CO), 56.1 (Ar*C*HAr), 50.0 (O*C*H_3), 34.4 (Ar*C*$(CH_3)_3$), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 31.3 (3C, $ArC(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 27.9 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3618, 2956, 2322, 2062, 1766, 1716, 1602, 1462, 1347, 1298, 1246, 1149, 1093, 1028, 929, 889, 838, 755, 679 cm^{-1}.

MS (ESI): *m/z* = 712.4 $[M+Na]^+$, 1401.8 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{45}H_{55}NO_5Na^+$: 712.3972; found 712.3974.

(*R*)-Tert-butyl 3-((*S*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(phenyl)methyl)-5-methyl-2-oxo-3-p-tolylindoline-1-carboxylate (159q)



According to **GP3**, **159q** was obtained as a wax (224.8 mg, 89% yield, dr: 12:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 10:1)

$[\alpha]_D^{25}$ = -37.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 4.37 min (major), 8.21 min (minor), er: 96:4.

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

δ = 7.69 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.49 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.19 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.13 – 7.09 (m, 5H, Ar-*H*), 6.93 – 6.91 (m, 2H, Ar-*H*), 6.63 (s, 2H, Ar-*H*), 6.53 (s, 1H, Ar-*H*), 5.17 (s, 1H, ArO*H*), 5.02 (s, 1H, ArC*H*Ar), 2.34 (s, 3H, ArCH_3), 2.31 (s, 3H, ArCH_3), 1.45 (s, 9H, $OCO_2C(CH_3)_3$), 1.20 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

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

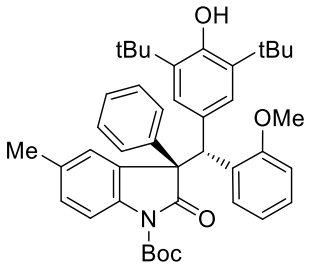
δ = 175.8 (N*C*O), 152.4 (C_{Ar}), 149.0 (NCO_2), 139.7 (C_{Ar}), 139.6 (C_{Ar}), 138.2 (C_{Ar}), 137.0 (C_{Ar}), 135.8 (C_{Ar}), 134.3 (2C, C_{Ar}), 132.4 (C_{Ar}), 129.8 (2C, C_{Ar}), 129.0 (C_{Ar}), 128.9 (2C, C_{Ar}), 128.6 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.2 (C_{Ar}), 127.9 (2C, C_{Ar}), 127.0 (2C, C_{Ar}), 126.6 (C_{Ar}), 114.8 (C_{Ar}), 83.5 ($NCO_2C(CH_3)_3$), 60.8 (Ph*C*CO), 60.4 (Ar*C*HAr), 34.2 (2C, 2 × Ar*C*$(CH_3)_3$), 30.0 (6C, 2 × ArC(CH_3)$_3$), 27.9 (3C, $NCO_2C(CH_3)_3$), 21.4 (ArCH_3), 20.8 (ArCH_3) ppm.

IR (ATR): 3632, 3375, 2958, 2110, 1772, 1730, 1611, 1486, 1366, 1300, 1247, 1152, 1115, 1023, 911, 819, 733, 699 cm^{-1}.

MS (ESI): *m/z* = 654.4 $[M+Na]^+$, 1285.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[2M+Na]^+$ calcd for $C_{84}H_{98}N_2O_8Na^+$: 1285.7215; found 1285.7218.

(*R*)-Tert-butyl 3-((*R*)-(3,5-di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-5-methyl-2-oxo-3-phenylindoline-1-carboxylate (159r)



According to **GP3**, **159r** was obtained as a colorless solid (207.2 mg, 80% yield, dr: > 20:1).

TLC: R_f = 0.50 (n-petane:Et_2O = 10:1)

Melting Point: 165-168 °C.

$[\alpha]_D^{25}$ = -38.6 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 5.96 min (major), 8.88 min (minor), er: 96:4.

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

δ = 7.65 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.61 – 7.56 (m, 2H, Ar-*H*), 7.30 – 7.25 (m, 2H, Ar-*H*), 7.24 – 7.19 (m, 1H, Ar-*H*), 7.17 – 7.12 (m, 1H, Ar-*H*), 7.10 – 7.05 (m, 1H, Ar-*H*), 6.82 – 6.78 (m, 1H, Ar-*H*), 6.71 (dd, *J* = 7.6, 1.2 Hz, 1H, Ar-*H*), 6.64 (dd, *J* = 8.4, 1.2 Hz, 1H, Ar-*H*), 6.62 (s, 2H, Ar-*H*), 6.39 (d, *J* = 1.2 Hz, 1H, Ar-*H*), 5.93 (s, 1H, ArO*H*), 4.98 (s, 1H, ArC*H*Ar), 3.80 (s, 3H, OCH_3), 2.30 (s, 3H, ArCH_3), 1.44 (s, 9H, $NCO_2C(CH_3)_3$), 1.18 (s, 18H, 2 × $ArC(CH_3)_3$) ppm.

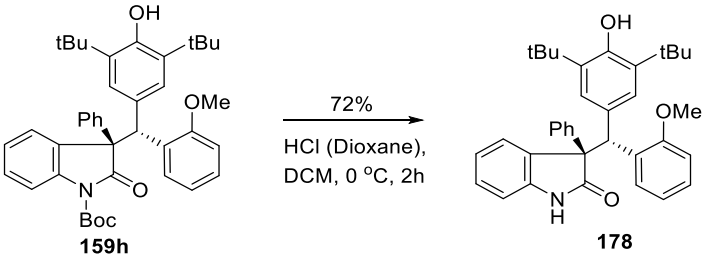
^{13}C NMR (100 MHz, $CDCl_3$):

δ = 175.8 (N*C*O), 157.3 (C_{Ar}), 152.4 (C_{Ar}), 149.0 (NCO_2), 139.6 (C_{Ar}), 138.0 (C_{Ar}), 134.2 (2C, C_{Ar}), 132.4 (C_{Ar}), 129.1 (C_{Ar}), 128.9 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (2C, C_{Ar}), 128.3 (C_{Ar}), 128.1 (2C, C_{Ar}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 127. (C_{Ar})1, 127.0 (2C, C_{Ar}), 119.7 (C_{Ar}), 114.6 (C_{Ar}), 111.2 (C_{Ar}), 83.4 ($NCO_2C(CH_3)_3$), 61.5 (Ph*C*CO), 56.1 (Ar*C*HAr), 50.0 (OCH_3), 34.1 (2C, 2 × $ArC(CH_3)_3$), 30.1 (6C, 2 × $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$), 21.4 ($ArCH_3$) ppm.

IR (ATR): 3628, 2962, 2119, 1765, 1728, 1596, 1487, 1435, 1341, 1299, 1246, 1156, 1052, 1027, 895, 852, 814, 724 cm^{-1}.

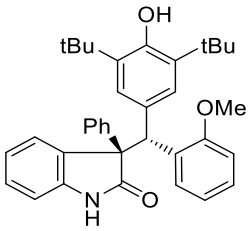
MS (ESI): *m/z* = 670.4 $[M+Na]^+$, 1317.7 $[2M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{42}H_{49}NO_5Na^+$: 670.3503; found 670.3507.



To a vial containing a solution of **159h** (63.3 mg, 0.10 mmol, 1.0 equiv) in DCM (1.0 mL) was added 4N HCl in Dioxane (0.5 mL, 2.0 mmol, 20.0 equiv) slowly at 0 °C. The mixture was stirred at the same temperature for 2 h, and then saturated $NaHCO_3$ solution (1.0 mL) was added to quench the reaction. The resulting solution was extracted with EtOAc (3×5.0 mL). The organic layers were combined, washed with brine and dried over anhydrous Na_2SO_4. Then the solvent was removed on a rotary evaporator and the residue was purified by flash chromatography (pentane/Et_2O = 10/1 to 4/1) to afford the desired product **178** as a colorless solid (38.4 mg, 72% yield).

(*R*)-3-((*R*)-(3,5-Di-tert-butyl-4-hydroxyphenyl)(2-methoxyphenyl)methyl)-3-phenylindolin-2-one (178)



TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 197-200 °C.

$[\alpha]_D^{25}$ = -35.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 7/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 5.72 min (major), 8.55 min (minor), er: 96:4.

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

δ = 7.64 – 7.60 (m, 2H, Ar-*H*), 7.49 (s, 1H, Ar-*H*), 7.31 – 7.22 (m, 4H, Ar-*H*), 7.12 – 7.01 (m, 1H, Ar-*H*), 6.97 (td, *J* = 7.8, 1.2 Hz, 1H, Ar-*H*), 6.83 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 6.70 – 6.60 (m, 4H, Ar-*H*), 6.48 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 5.90 (s, 1H, ArO*H*), 5.01 (s, 1H, ArC*H*Ar), 3.83 (s, 3H, OCH_3), 1.20 (s, 18H, 2 × ArC(CH_3)$_3$) ppm.

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

δ = 179.2 (N*C*O), 157.3 (C_{Ar}), 152.4 (C_{Ar}), 141.4 (C_{Ar}), 139.6 (C_{Ar}), 134.0 (2C, C_{Ar}), 130.4 (C_{Ar}), 129.4 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.4 (2C, C_{Ar}), 128.3 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (2C, C_{Ar}), 128.0 (C_{Ar}), 127.5 (C_{Ar}), 127.1 (2C, C_{Ar}), 121.0 (C_{Ar}), 119.7 (C_{Ar}), 111.2 (C_{Ar}), 109.5 (C_{Ar}), 61.4 (Ph*C*CO), 56.1 (Ar*C*HAr), 49.6 (O*C*H$_3$), 34.2 (2C, 2 × Ar*C*(CH$_3$)$_3$), 30.1 (6C, 2 × ArC(*C*H$_3$)$_3$) ppm.

IR (ATR): 3780, 3629, 3189, 2953, 2646, 2313, 2032, 1702, 1613, 1464, 1365, 1230, 1156, 1030, 935, 883, 798, 743, 696 cm^{-1}.

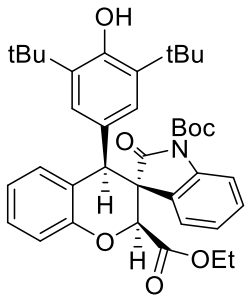
MS (ESI): *m/z* = 556.3 [M+Na]$^+$, 1089.6 [2M+Na]$^+$.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{36}H_{39}NO_3Na^+$: 556.2822; found 556.2824

GP 4 for the fourth project and analytical data of synthesized compounds

A 10 mL glass tube equipped with a stirring bar was charged with *p*-QMs **160** (0.40 mmol, 1.0 equiv.), 3-olefinic oxindoles **161** (0.48 mmol, 1.2 equiv.), catalyst **U** (0.02 mmol, 5 mol %) and toluene (4.0 mL). The resulting solution was stirred at room temperature for the indicated time. The solvent was evaporated under reduced pressure and the crude product was directly purified by flash column chromatography to provide the desired product **162**.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162a)



According to **GP4**, **162a** was obtained as a colorless solid (0.223 g, 89% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 96-98 °C.

$[\alpha]_D^{25}$ = +5.9 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 9/1; flow rate 0.7 mL/min; T= 30 °C; retention time: 6.73 min (major), 7.41 min (minor), ee: 99%.

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

δ = 7.51 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.28 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.23 – 7.22 (m, 1H, Ar-*H*), 7.14 (t, *J* = 7.8 Hz, 1H, Ar-*H*), 7.08 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.05 (s, 1H, Ar-*H*), 6.99 – 6.95 (m, 2H, Ar-*H*), 6.92 – 6.90 (m, 1H, Ar-*H*), 5.97 (s, 1H, Ar-*H*), 5.23 (s, 1H, O*H*), 4.98 (s, 1H, ArOC*H*CO_2Et), 4.86 (s, 1H, ArC*H*Ar), 4.04 – 3.96 (m, 1H, CO_2C*H*HCH_3), 3.94 – 3.89 (m, 1H, CO_2CH*H*CH_3), 1.57 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 0.98 (s, 9H, $ArC(CH_3)_3$), 0.94 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

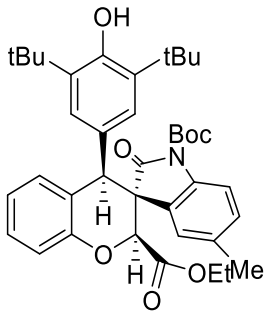
δ = 174.6 (N*C*O), 166.8 (*C*O_2Et), 153.1 (C_{Ar}), 152.9 (C_{Ar}), 148.6 (N*C*O_2), 140.1 (C_{Ar}), 134.9 (C_{Ar}), 134.8 (C_{Ar}), 129.7 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 125.7 (C_{Ar}), 125.4 (C_{Ar}), 125.3 (C_{Ar}), 125.2 (C_{Ar}), 124.2, (C_{Ar}) 123.0 (C_{Ar}), 121.6 (C_{Ar}), 116.9 (C_{Ar}), 114.2 (C_{Ar}), 84.0 ($NCO_2C(CH_3)_3$), 77.5 (ArO*C*HCO_2Et), 61.7 (C_{spiro}), 53.1 ($CO_2CH_2CH_3$), 51.1 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3622, 2956, 2317, 2107, 2061, 1743, 1597, 1455, 1357, 1219, 849, 754 cm^{-1}.

MS (ESI): *m/z* = 650.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{45}NO_7Na^+$: 650.3088; found 650.3083.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-methyl-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162b)



According to **GP4**, **162b** was obtained as a colorless solid (0.162 g, 63% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 163-164 °C.

$[\alpha]_D^{25}$ = +48.9 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk Ol; *n*-heptane/iPrOH = 8/2; flow rate 0.7 mL/min; T= 30 °C; retention time: 5.86 min (major), 6.73 min (minor), ee: 98%.

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

δ = 7.38 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.29 – 7.27 (m, 1H, Ar-*H*), 7.24 – 7.22 (m, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 6.98 – 6.96 (m, 1H, Ar-*H*), 6.93 – 6.90 (m, 2H, Ar-*H*), 6.88 (s, 1H, Ar-*H*), 6.01 (s, 1H, Ar-*H*), 5.20 (s, 1H, O*H*), 4.97 (s, 1H, ArOC*H*CO_2Et), 4.86 (s, 1H, ArC*H*Ar), 4.04 – 3.98 (m, 1H, CO_2C*H*HCH_3), 3.94 – 3.89 (m, 1H, CO_2CH*H*CH_3), 2.19 (s, 3H, ArC*H*$_3$), 1.57 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, ArC(CH_3)$_3$), 0.98 (s, 9H, ArC(CH_3)$_3$), 0.96 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

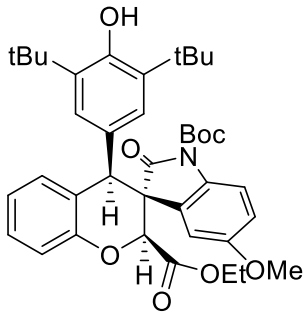
δ = 174.8 (N*C*O), 166.8 (*C*O_2Et), 153.01 (C_{Ar}), 152.9 (C_{Ar}), 148.7 (N*C*O_2), 137.7 (C_{Ar}), 134.8 (C_{Ar}), 134.7 (C_{Ar}), 133.5 (C_{Ar}), 129.7 (C_{Ar}), 129.3 (C_{Ar}), 128.3 (C_{Ar}), 127.8 (C_{Ar}), 126.0 (C_{Ar}), 125.9 (C_{Ar}), 125.4 (C_{Ar}), 125.3 (C_{Ar}), 123.1 (C_{Ar}), 121.7 (C_{Ar}), 117.0 (C_{Ar}), 114.0 (C_{Ar}), 83.8 ($NCO_2C(CH_3)_3$), 77.4 (ArO*C*HCO_2Et), 61.7 (C_{spiro}), 53.2 ($CO_2CH_2CH_3$), 51.0 (Ar*C*HAr), 34.1 (Ar*C*(CH_3)$_3$), 33.8 (Ar*C*(CH_3)$_3$), 30.3 (3C, ArC(*C*H_3)$_3$), 29.8 (3C, ArC(*C*H_3)$_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 21.1 (Ar*C*H_3), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3617, 2952, 2327, 2093 1767, 1747, 1595, 1458, 1157, 756 cm^{-1}.

MS (ESI): *m/z* = 664.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{47}NO_7Na^+$: 664.3245; found 664.3248.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-methoxy-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162c)



According to **GP4**, **162c** was obtained as a colorless solid (0.152 g, 58% yield).

TLC: R_f = 0.40 (n-petane:Et_2O = 4:1)

Melting Point: 151-152 °C.

$[\alpha]_D^{25}$ = +54.3 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 5.17 min (major), 6.76 min (minor), ee: 96%.

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

δ = 7.45 – 7.41 (m, 1H, Ar-*H*), 7.28 – 7.25 (m, 1H, Ar-*H*), 7.22 – 7.21 (m, 1H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 6.97 – 6.95 (m, 1H, Ar-*H*), 6.92 – 6.89 (m, 1H, Ar-*H*), 6.66 – 6.63 (m, 2H, Ar-*H*), 6.05 (s, 1H, Ar-*H*), 5.21 (s, 1H, O*H*), 4.98 (s, 1H, ArOC*H*CO_2Et), 4.85 (s, 1H, ArC*H*Ar), 4.05 – 4.00 (m, 1H, CO_2C*H*HCH_3), 3.96 – 3.91 (m, 1H, CO_2CH*H*CH_3), 3.62 (s, 3H, ArOCH_3), 1.57 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 1.00 (s, 9H, $ArC(CH_3)_3$), 0.97 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

δ = 174.7 (N*C*O), 166.7 (*C*O_2Et), 156.3 (C_{Ar}), 153.1 (C_{Ar}), 152.9 (C_{Ar}), 148.7 (N*C*O_2), 134.9 (C_{Ar}), 134.8 (C_{Ar}), 133.6 (C_{Ar}), 129.8 (C_{Ar}), 128.5 (C_{Ar}), 127.9 (C_{Ar}), 126.6 (C_{Ar}), 125.8 (C_{Ar}), 125.3 (C_{Ar}), 122.9 (C_{Ar}), 121.7 (C_{Ar}), 116.9 (C_{Ar}), 114.9 (C_{Ar}), 112.8 (C_{Ar}),

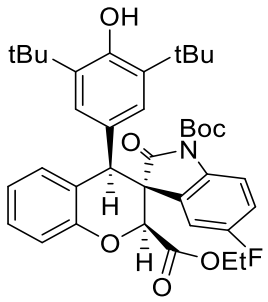
112.2 (C_{Ar}), 83.8 ($NCO_2C(CH_3)_3$), 77.4 ($ArOCHCO_2Et$), 61.7 (C_{spiro}), 55.3 ($ArOCH_3$), 53.3 ($CO_2CH_2CH_3$), 51.0 (ArCHAr), 34.1 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3625, 2951, 2322, 2091, 1743, 1599, 1458, 1156, 844, 758 cm^{-1}.

MS (ESI): *m/z* = 680.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{47}NO_8Na^+$: 680.3194; found 680.3192.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-fluoro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162d)



According to **GP4**, **162d** was obtained as a colorless solid (0.223 g, 86% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 129-131 °C.

$[\alpha]_D^{25}$ = +5.3 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk Ol; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 5.27 min (major), 6.31 min (minor), ee: 98%.

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

δ = 7.53 – 7.49 (m, 1H, Ar-*H*), 7.30 – 7.28 (m, 1H, Ar-*H*), 7.23 – 7.21 (m, 1H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 6.98 – 6.96 (m, 1H, Ar-*H*), 6.95 – 6.92 (m, 1H, Ar-*H*), 6.86 – 6.82 (m, 2H, Ar-*H*), 6.04 (s, 1H, Ar-*H*), 5.19 (s, 1H, O*H*), 5.01 (s, 1H, $ArOCHCO_2Et$), 4.89 (s, 1H, ArC*H*Ar), 4.07 – 4.02 (m, 1H, CO_2CHHCH_3), 3.98 – 3.93 (m, 1H, CO_2CHHCH_3), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 1.02 (s, 9H, $ArC(CH_3)_3$), 0.99 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

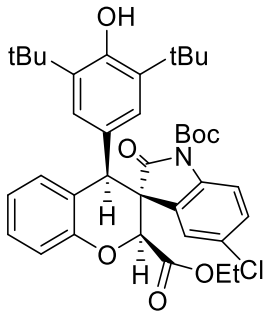
δ = 174.3 (N*C*O), 166.6 (*C*O_2Et), 159.5 (d, *J* = 243.3 Hz, C_{Ar}), 153.0 (C_{Ar}), 152.9 (C_{Ar}), 148.6 (N*C*O_2), 136.2 (C_{Ar}), 135.0 (C_{Ar}), 134.9 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (C_{Ar}), 127.1 (d, *J* = 8.3 Hz, C_{Ar}), 125.7 (C_{Ar}), 125.1 (C_{Ar}), 122.6 (C_{Ar}), 122.0 (C_{Ar}), 117.1 (C_{Ar}), 115.3 (d, *J* = 7.9 Hz, C_{Ar}), 115.0 (d, *J* = 22.8 Hz, C_{Ar}), 113.1 (d, *J* = 24.8 Hz, C_{Ar}), 84.2 (NCO_2*C*(CH_3)$_3$), 77.3 (ArO*C*HCO_2Et), 61.8 (C_{spiro}), 53.4 (CO_2*C*H_2CH_3), 51.1 (Ar*C*HAr), 34.1 (Ar*C*(CH_3)$_3$), 33.9 (Ar*C*(CH_3)$_3$), 30.3 (3C, ArC(*C*H_3)$_3$), 29.9 (3C, ArC(*C*H_3)$_3$), 28.1 (3C, NCO_2C(*C*H_3)$_3$), 13.5 (CO_2C$_2$*C*H_3) ppm.

IR (ATR): 3624, 2950, 2329, 2096, 1744, 1600, 1458, 1158, 845, 760 cm^{-1}.

MS (ESI): *m/z* = 668.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7FNa^+$: 668.2994; found 668.2994.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 5'-chloro-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162e)



According to **GP4**, **162e** was obtained as a colorless solid (0.242 g, 92% yield).

TLC: R_f = 0.40 (n-petane:Et_2O = 4:1)

Melting Point: 103-105 °C.

$[\alpha]_D^{25}$ = +70.1 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk Ol; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 4.95 min (major), 6.00 min (minor), ee: 97%.

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

δ = 7.48 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.31 – 7.28 (m, 1H, Ar-*H*), 7.24 – 7.22 (m, 1H, Ar-*H*), 7.10 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-*H*), 7.05 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H*), 7.00 – 6.98 (m, 1H, Ar-*H*), 6.96 – 6.93 (m, 1H, Ar-*H*), 6.06 (s, 1H, Ar-*H*), 5.17 (s, 1H, O*H*), 5.00 (s, 1H, ArOC*H*CO_2Et), 4.89 (s, 1H, ArC*H*Ar), 4.08 – 4.02 (m, 1H,

CO_2CHHCH_3), 3.99 – 3.93 (m, 1H, CO_2CHHCH_3), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.39 (s, 9H, $ArC(CH_3)_3$), 1.04 (s, 9H, $ArC(CH_3)_3$), 1.00 (t, J = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

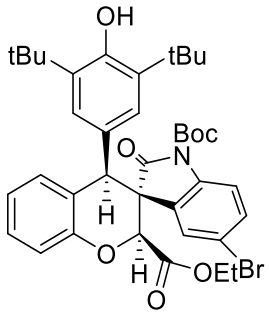
δ = 174.2 (NCO), 166.5 (CO_2Et), 153.0 (C_{Ar}), 152.9 (C_{Ar}), 148.5 (NCO_2), 138.7 (C_{Ar}), 135.0 (C_{Ar}), 134.9 (C_{Ar}), 129.8 (C_{Ar}), 129.5 (C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 127.5 (C_{Ar}), 127.4 (C_{Ar}), 125.8 (C_{Ar}), 125.5 (C_{Ar}), 125.3 (C_{Ar}), 122.6 (C_{Ar}), 122.0 (C_{Ar}), 117.2 (C_{Ar}), 115.4 (C_{Ar}), 88.4 ($NCO_2C(CH_3)_3$), 77.3 ($ArOCHCO_2Et$), 61.9 (C_{spiro}), 53.4 ($CO_2CH_2CH_3$), 51.0 (ArCHAr), 34.1 ($ArC(CH_3)_3$), 33.8 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3623, 2956, 2310, 2089, 1745, 1590, 1458, 1153, 757 cm^{-1}.

MS (ESI): *m/z* = 684.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7ClNa^+$: 684.2699; found 684.2697.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 5'-bromo-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162f)



According to **GP4**, **162f** was obtained as a colorless solid (0.265 g, 94% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 132-134 °C.

$[\alpha]_D^{25}$ = +100.7 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk Ol; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 5.02 min (major), 6.11 min (minor), ee: 98%.

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

δ = 7.42 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.31 – 7.28 (m, 1H, Ar-*H*), 7.27 – 7.22 (m, 2H, Ar-*H*), 7.19 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H*), 7.00 – 6.98 (m, 1H, Ar-*H*), 6.96 – 6.93 (m, 1H, Ar-*H*), 6.06 (s, 1H, Ar-*H*), 5.16 (s, 1H, O*H*), 5.00 (s, 1H, ArOC*H*CO_2Et), 4.89 (s, 1H, ArC*H*Ar), 4.08 – 4.03 (m, 1H, CO_2C*H*HCH_3), 3.99 – 3.95 (m, 1H, CO_2CH*H*CH_3), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.39 (s, 9H, $ArC(CH_3)_3$), 1.05 (s, 9H, $ArC(CH_3)_3$), 1.00 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

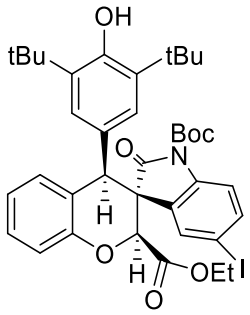
δ = 174.1 (N*C*O), 166.5 (*C*O_2Et), 153.0 (C_{Ar}), 152.9 (C_{Ar}), 148.5 (N*C*O_2), 139.2 (C_{Ar}), 135.1 (C_{Ar}), 135.0 (C_{Ar}), 131.6 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (C_{Ar}), 128.2 (C_{Ar}), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 125.8 (C_{Ar}), 125.3 (C_{Ar}), 122.6 (C_{Ar}), 122.1 (C_{Ar}), 117.2 (C_{Ar}), 117.1 (C_{Ar}), 115.8 (C_{Ar}), 84.5 ($NCO_2C(CH_3)_3$), 77.3 (ArO*C*HCO_2Et), 61.9 (C_{spiro}), 53.4 ($CO_2CH_2CH_3$), 51.1 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.8 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 30.0 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3830, 3625, 2957, 2654, 2311, 2090, 1969, 1746, 1586, 1456, 1219, 835, 752 cm^{-1}.

MS (ESI): *m/z* = 730.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7BrNa^+$: 728.2193; found 728.2189.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-iodo-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162g)



According to **GP4**, **162g** was obtained as a colorless solid (0.274 g, 91% yield).

TLC: R_f = 0.60 (n-petane:Et_2O = 4:1)

Melting Point: 172-173 °C.

$[\alpha]_D^{25}$ = +133.2 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; n-heptane/iPrOH = 9/1; flow rate 0.7 mL/min; T= 30 °C; retention time: 7.68 min (major), 9.48 min (minor), ee: 97%.

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

δ = 7.45 (dd, *J* = 9.0, 1.8 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.32 – 7.28 (m, 2H, Ar-*H*), 7.26 – 7.23 (m, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H*), 6.99 – 6.97 (m, 1H, Ar-*H*), 6.96 – 6.93 (m, 1H, Ar-*H*), 6.06 (s, 1H, Ar-*H*), 5.15 (s, 1H, O*H*), 5.00 (s, 1H, ArOC*H*CO_2Et), 4.88 (s, 1H, ArC*H*Ar), 4.07 – 4.02 (m, 1H, CO_2C*H*HCH_3), 4.00 – 3.95 (m, 1H, CO_2CH*H*CH_3), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.39 (s, 9H, $ArC(CH_3)_3$), 1.06 (s, 9H, $ArC(CH_3)_3$), 1.00 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

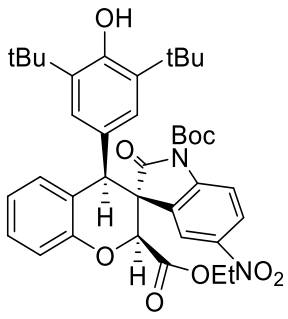
δ = 174.0 (N*C*O), 166.5 (*C*O_2Et), 153.0 (C_{Ar}), 152.9 (C_{Ar}), 148.5 (N*C*O_2), 140.0 (C_{Ar}), 137.6 (C_{Ar}), 135.1 (C_{Ar}), 135.0 (C_{Ar}), 133.8 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (C_{Ar}), 128.1 (C_{Ar}), 127.5 (C_{Ar}), 125.8 (C_{Ar}), 125.3 (C_{Ar}), 122.6 (C_{Ar}), 122.0 (C_{Ar}), 117.2 (C_{Ar}), 116.2 (C_{Ar}), 87.9 (C_{Ar}), 84.5 ($NCO_2C(CH_3)_3$), 77.3 (ArO*C*HCO_2Et), 61.9 (C_{spiro}), 53.3 ($CO_2CH_2CH_3$), 51.1 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 30.1 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3629, 2959, 2323, 2074, 1997, 1736, 1587, 1467, 1329, 1297, 1225, 1154, 1099, 1007, 884, 823, 755 cm^{-1}.

MS (ESI): *m/z* = 776.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7INa^+$: 776.2055; found 776.2058.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162h)



According to **GP4**, **162h** was obtained as a light yellow solid (0.263 g, 98% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 177-178 °C.

$[\alpha]_D^{25}$ = +84.8 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 7/3; flow rate 0.5 mL/min; T= 30 °C; retention time: 9.17 min (major), 10.79 min (minor), ee: 98%.

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

δ = 8.05 (dd, *J* = 9.2, 2.4 Hz, 1H, Ar-*H*), 7.90 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.69 (d, *J* = 9.2 Hz, 1H, Ar-*H*), 7.35 – 7.29 (m, 1H, Ar-*H*), 7.28 – 7.24 (m, 1H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 6.99 – 6.94 (m, 2H, Ar-*H*), 5.97 (s, 1H, Ar-*H*), 5.18 (s, 1H, O*H*), 4.99 (s, 1H, ArOC*H*CO_2Et), 4.94 (s, 1H, ArC*H*Ar), 4.09 – 3.93 (m, 2H, CO_2C*H*$_2CH_3$), 1.59 (s, 9H, $NCO_2C(CH_3)_3$), 1.37 (s, 9H, $ArC(CH_3)_3$), 1.03 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$), 0.92 (s, 9H, $ArC(CH_3)_3$) ppm.

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

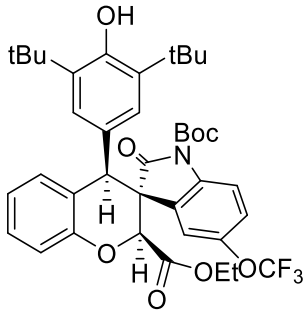
δ = 174.1 (N*C*O), 166.4 (*C*O_2Et), 153.1 (C_{Ar}), 153.0 (C_{Ar}), 148.2 (N*C*O_2), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 135.3 (C_{Ar}), 135.1 (C_{Ar}), 129.8 (C_{Ar}), 129.0 (C_{Ar}), 127.3 (C_{Ar}), 127.2 (C_{Ar}), 125.7 (C_{Ar}), 125.1 (C_{Ar}), 124.9 (C_{Ar}), 122.4 (C_{Ar}), 122.2 (C_{Ar}), 120.8 (C_{Ar}), 117.4 (C_{Ar}), 114.2 (C_{Ar}), 85.4 ($NCO_2C(CH_3)_3$), 77.5 (ArO*C*HCO_2Et), 62.1 (C_{spiro}), 53.3 ($CO_2CH_2CH_3$), 51.2 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.7 ($ArC(CH_3)_3$), 30.2 (3C, $ArC(CH_3)_3$), 29.8 (3C, $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3629, 2959, 2288, 2240, 2083, 1998, 1931, 1766, 1607, 1527, 1472, 1443, 1341, 1302, 1219, 1150, 1111, 1021, 841, 756, 659 cm^{-1}.

MS (ESI): *m/z* = 711.3 $[M+K]^+$.

HRMS (ESI): *m/z* $[M+K]^+$ calcd for $C_{38}H_{44}N_2O_9K^+$: 711.2678; found 711.2669.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxo-5'-(trifluoro-methoxy)spiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162i)



According to **GP4**, **162i** was obtained as a colorless solid (0.260 g, 92% yield).

TLC: R_f = 0.40 (n-petane:Et_2O = 4:1)

Melting Point: 138-140 °C.

$[\alpha]_D^{25}$ = +27.0 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 9/1; flow rate 0.7 mL/min; T= 30 °C; retention time: 4.40 min (major), 5.01 min (minor), ee: 96%.

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

δ = 7.58 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.32 – 7.29 (m, 1H, Ar-*H*), 7.24 – 7.22 (m, 1H, Ar-*H*), 7.06 – 7.01 (m, 2H, Ar-*H*), 6.96 – 6.90 (m, 3H, Ar-*H*), 5.99 (s, 1H, Ar-*H*), 5.23 (s, 1H, O*H*), 5.04 (s, 1H, ArOC*H*CO_2Et), 4.88 (s, 1H, ArC*H*Ar), 4.05 – 3.93 (m, 2H, CO_2CH_2CH), 1.57 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 1.00 (s, 9H, $ArC(CH_3)_3$), 0.97 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

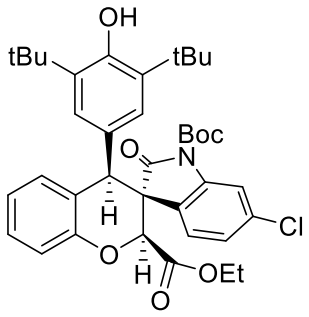
δ = 174.1 (N*C*O), 166.6 (*C*O_2Et), 153.1 (C_{Ar}), 153.0 (C_{Ar}), 148.4 (N*C*O_2), 145.5 (C_{Ar}), 138.7 (C_{Ar}), 135.2 (C_{Ar}), 135.1 (C_{Ar}), 129.6 (C_{Ar}), 128.7 (C_{Ar}), 128.0 (C_{Ar}), 127.3 (C_{Ar}), 125.3 (C_{Ar}), 124.8 (C_{Ar}), 122.5 (C_{Ar}), 122.0 (C_{Ar}), 120.7 (C_{Ar}), 120.3 (q, *J* = 255.0 Hz, C_{Ar}), 118.4 (C_{Ar}), 117.0 (C_{Ar}), 115.1 (C_{Ar}), 84.5 ($NCO_2C(CH_3)_3$), 77.6 (ArO*C*HCO_2Et), 61.8 (C_{spiro}), 53.3 ($CO_2CH_2CH_3$), 51.2 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.8 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.8 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3586, 2964, 2319, 2082, 1987, 1907, 1760, 1588, 1477, 1346, 1297, 1237, 1153, 1092, 1015, 943, 825, 752, 672 cm^{-1}.

MS (ESI): *m/z* = 734.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{44}NO_8F_3Na^+$: 734.2911; found 734.2912.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 6'-chloro-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro [chroman-3,3'-indoline]-1',2-dicarboxylate (162j)



According to **GP4**, **162j** was obtained as a colorless solid (0.170 g, 64% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 185-187 ^oC.

$[\alpha]_D^{25}$ = +45.9 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 ^oC; retention time: 4.93 min (major), 5.80 min (minor), ee: 97%.

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

δ = 7.59 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.30 – 7.27 (m, 1H, Ar-*H*), 7.22 – 7.20 (m, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 7.301 – 6.99 (m, 1H, Ar-*H*), 6.98 – 6.95 (m, 2H, Ar-*H*), 6.93 – 6.91 (m, 1H, Ar-*H*), 5.95 (s, 1H, Ar-*H*), 5.21 (s, 1H, O*H*), 5.03 (s, 1H, ArOC*H*CO_2Et), 4.85 (s, 1H, ArC*H*Ar), 4.06 – 4.01 (m, 1H, CO_2C*H*HCH), 3.99 – 3.93 (m, 1H, CO_2CH*H*CH), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 1.03 (s, 9H, $ArC(CH_3)_3$), 1.01 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

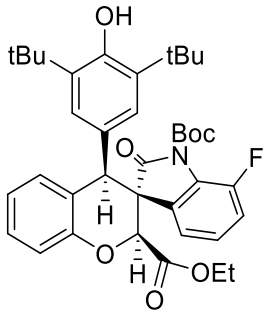
δ = 174.2 (N*C*O), 166.6 (*C*O_2Et), 153.1 (C_{Ar}), 153.0 (C_{Ar}), 148.4 (N*C*O_2), 141.1 (C_{Ar}), 135.1 (C_{Ar}), 135.0 (C_{Ar}), 134.7 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (C_{Ar}), 127.9 (C_{Ar}), 126.1 (C_{Ar}), 125.5 (C_{Ar}), 125.2 (C_{Ar}), 124.1 (C_{Ar}), 123.9 (C_{Ar}), 122.7 (C_{Ar}), 121.9 (C_{Ar}), 116.9 (C_{Ar}), 114.9 (C_{Ar}), 84.6 ($NCO_2C(CH_3)_3$), 77.3 (ArO*C*HCO_2Et), 61.9 (C_{spiro}), 53.0 ($CO_2CH_2CH_3$), 51.2 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.8 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3894, 3621, 2954, 2321, 2089, 1747, 1601, 1454, 1148, 842, 757 cm^{-1}.

MS (ESI): *m/z* = 684.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7ClNa^+$: 684.2699; found 684.2691.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-7'-fluoro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162k)



According to **GP4**, **162k** was obtained as a colorless solid (0.198 g, 77% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 5:1)

Melting Point: 128-130 °C.

$[\alpha]_D^{25}$ = +26.4 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 97/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 4.59 min (major), 12.85 min (minor), ee: > 99%.

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

δ = 7.30 – 7.26 (m, 1H, Ar-*H*), 7.22 – 7.20 (m, 1H, Ar-*H*), 7.08 (s, 1H, Ar-*H*), 6.98 – 6.89 (m, 5H, Ar-*H*), 5.95 (s, 1H, Ar-*H*), 5.22 (s, 1H, O*H*), 5.04 (s, 1H, ArOC*H*CO_2Et), 4.87 (s, 1H, ArC*H*Ar), 4.08 – 3.96 (m, 2H, CO_2CH_2CH), 1.53 (s, 9H, $NCO_2C(CH_3)_3$), 1.42 (s, 9H, $ArC(CH_3)_3$), 1.01 (s, 9H, $ArC(CH_3)_3$), 1.00 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

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

δ = 174.0 (N*C*O), 166.6 (*C*O_2Et), 153.2 (C_{Ar}), 153.0 (C_{Ar}), 148.3 (d, *J* = 249.5 Hz, C_{Ar}), 146.9 (N*C*O_2), 135.0 (d, *J* = 5.6 Hz, C_{Ar}), 129.7 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.5 (C_{Ar}), 128.2 (C_{Ar}), 127.1 (d, *J* = 9.5 Hz, C_{Ar}), 125.3 (C_{Ar}), 125.0 (d, *J* = 6.8 Hz, C_{Ar}), 124.8 (C_{Ar}), 122.7 (C_{Ar}), 121.8 (C_{Ar}), 121.3 (d, *J* = 3.3 Hz, C_{Ar}), 117.0 (d, *J* = 20.5 Hz, C_{Ar}), 116.9 (C_{Ar}), 84.5 ($NCO_2C(CH_3)_3$), 77.3 (ArOC*H*CO_2Et), 62.0 (C_{spiro}), 53.7

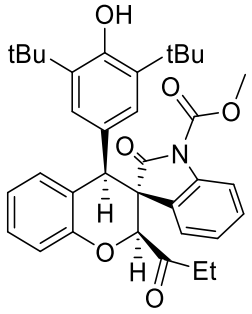
($CO_2CH_2CH_3$), 51.0 (Ar*C*HAr), 34.1 (Ar*C*(CH_3)$_3$), 34.0 (Ar*C*(CH_3)$_3$), 30.3 (3C, ArC(*C*H_3)$_3$), 29.9 (3C, ArC(*C*H_3)$_3$), 27.7 (3C, NCO_2C(*C*H_3)$_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3629, 2960, 2259, 2078, 1989, 1749, 1593, 1480, 1362, 1196, 1144, 1024, 909, 846, 732 cm^{-1}.

MS (ESI): *m/z* = 668.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7FNa^+$: 668.2994; found 668.2991.

(2*S*,3*R*,4*R*)-Methyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxo-2-propionylspiro [chroman-3,3'-indoline]-1'-carboxylate (162l)



According to **GP4**, **162l** was obtained as a colorless solid (0.178 g, 65% yield).

TLC: R_f = 0.30 (n-petane:Et_2O = 4:1)

Melting Point: 116-117 °C.

$[\alpha]_D^{25}$ = +16.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/iPrOH = 8/2; flow rate 1.0 mL/min; T= 30 °C; retention time: 3.97 min (major), 8.84 min (minor), ee: 92%.

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

δ = 7.58 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.30 – 7.27 (m, 1H, Ar-*H*), 7.24 – 7.21 (m, 1H, Ar-*H*), 7.18 – 7.15 (m, 1H, Ar-*H*), 7.11 – 7.08 (m, 1H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 7.03 – 6.97 (m, 2H, Ar-*H*), 6.93 – 6.90 (m, 1H, Ar-*H*), 5.95 (s, 1H, Ar-*H*), 5.27 (s, 1H, O*H*), 4.99 (s, 1H, ArOC*H*CO_2Et), 4.86 (s, 1H, ArC*H*Ar), 4.06 – 4.01 (m, 1H, CO_2C*H*HCH), 3.96 – 3.93 (m, 1H, CO_2CH*H*CH), 3.92 (s, 3H, CO_2C*H*$_3$), 1.38 (s, 9H, ArC(C*H*$_3$)$_3$), 0.97 (s, 9H, ArC(C*H*$_3$)$_3$), 0.91 (t, *J* = 7.2 Hz, 3H, CO_2C_2C*H*$_3$) ppm.

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

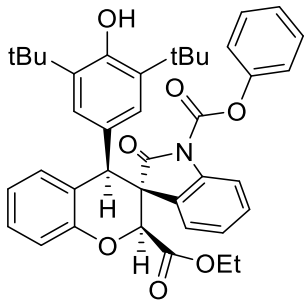
δ = 174.6 (N*C*O), 166.9 (*C*O_2Et), 153.1 (C_{Ar}), 153.0 (C_{Ar}), 150.8 (N*C*O_2), 139.8 (C_{Ar}), 135.0 (C_{Ar}), 134.8 (C_{Ar}), 129.7 (C_{Ar}), 128.8 (C_{Ar}), 128.5 (C_{Ar}), 127.9 (C_{Ar}), 125.5 (C_{Ar}), 125.4 (C_{Ar}), 125.2 (C_{Ar}), 125.1 (C_{Ar}), 124.5 (C_{Ar}), 122.7 (C_{Ar}), 121.7 (C_{Ar}), 116.9 (C_{Ar}), 114.4 (C_{Ar}), 77.5 (ArO*C*HCO$_2$Et), 61.8 (C_{spiro}), 53.6 (CO$_2$*C*H$_2$CH$_3$), 53.2 (CO$_2$*C*H$_3$), 51.4 (Ar*C*HAr), 34.1 (Ar*C*(CH$_3$)$_3$), 33.9 (Ar*C*(CH$_3$)$_3$), 30.2 (3C, ArC(*C*H$_3$)$_3$), 30.0 (3C, ArC(*C*H$_3$)$_3$), 13.5 (CO$_2$C$_2$*C*H$_3$) ppm.

IR (ATR): 3590, 2956, 2296, 2086, 1744, 1604, 1447, 1315, 1222, 1148, 1106, 888, 755, 675 cm^{-1}.

MS (ESI): *m/z* = 608.3 [M+Na]$^+$.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{35}H_{39}NO_7Na^+$: 608.2619; found 608.2615.

(2*S*,3*R*,4*R*)-2-Ethyl 1'-phenyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro [chroman-3,3'-indoline]-1',2-dicarboxylate (162m)



According to **GP4**, **162m** was obtained as a colorless solid (0.181 g, 70% yield).

TLC: R_f = 0.40 (n-petane:Et$_2$O = 4:1)

Melting Point: 168-170 ºC.

[α]$_D^{25}$ = +49.0 (c = 1.0, CHCl$_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 7/3; flow rate 0.5 mL/min; T= 30 ºC; retention time: 10.02 min (major), 13.27 min (minor), ee: 96%.

^{1}H NMR (600 MHz, CDCl$_3$):

δ = 7.63 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.43 – 7.40 (m, 2H, Ar-*H*), 7.33 – 7.25 (m, 3H, Ar-*H*), 7.23 – 7.19 (m, 3H, Ar-*H*), 7.14 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.12 (s, 1H, Ar-*H*), 7.07 – 7.05 (m, 1H, Ar-*H*), 7.00 – 6.98 (m, 1H, Ar-*H*), 6.95 – 6.93 (m, 1H, Ar-*H*), 5.99 (s,

1H, Ar-*H*), 5.33 (s, 1H, O*H*), 5.04 (s, 1H, ArOC*H*CO_2Et), 4.93 (s, 1H, ArC*H*Ar), 4.10 – 4.05 (m, 1H, CO_2C*H*HCH), 4.01 – 3.96 (m, 1H, CO_2CH*H*CH), 1.39 (s, 9H, ArC(CH_3)$_3$), 1.00 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$), 0.98 (s, 9H, ArC(CH_3)$_3$) ppm.

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

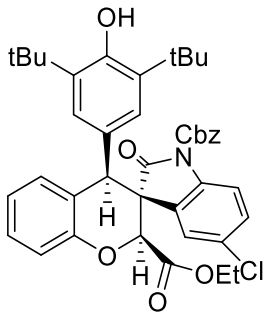
δ = 174.5 (N*C*O), 166.9 (*C*O_2Et), 153.2 (C_{Ar}), 153.1 (C_{Ar}), 150.1 (C_{Ar}), 148.5 (N*C*O_2), 139.6 (C_{Ar}), 135.1 (C_{Ar}), 135.0 (C_{Ar}), 129.7 (C_{Ar}), 129.5 (2C, C_{Ar}), 129.0 (C_{Ar}), 128.6 (C_{Ar}), 128.0 (C_{Ar}), 126.3 (C_{Ar}), 125.6 (C_{Ar}), 125.4 (C_{Ar}), 125.3 (C_{Ar}), 125.2 (C_{Ar}), 124.9 (C_{Ar}), 122.8 (C_{Ar}), 121.8 (C_{Ar}), 121.3 (2C, C_{Ar}), 116.9 (C_{Ar}), 114.6 (C_{Ar}), 77.6 (ArO*C*HCO$_2$Et), 61.9 (C_{spiro}), 53.3 (CO_2*C*H_2CH$_3$), 51.5 (Ar*C*HAr), 34.1 (Ar*C*(CH$_3$)$_3$), 33.9 (Ar*C*(CH$_3$)$_3$), 30.4 (3C, ArC(*C*H$_3$)$_3$), 29.9 (3C, ArC(*C*H$_3$)$_3$), 13.6 (CO_2C_2*C*H$_3$) ppm.

IR (ATR): 3943, 3791, 3611, 2952, 2673, 2327, 2094, 1749, 1591, 1461, 1305, 1209, 891, 755 cm^{-1}.

MS (ESI): *m/z* = 648.3 [M+H]$^+$.

HRMS (ESI): *m/z* [M+H]$^+$ calcd for $C_{40}H_{42}NO_7^+$: 648.2956; found 648.2950.

(2*S*,3*R*,4*R*)-1'-Benzyl 2-ethyl 5'-chloro-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162n)



According to **GP4**, **162n** was obtained as a colorless solid (0.181 g, 70% yield)..

TLC: R_f = 0.50 (n-petane:Et_2O = 3:1)

Melting Point: 134-136 °C.

[α]$_D^{25}$ = +63.2 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK AD; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 12.35 min (major), 5.81 min (minor), ee: 93%.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.51 – 7.49 (m, 2H, Ar-*H*), 7.41 – 7.38 (m, 2H, Ar-*H*), 7.36 – 7.34 (m, 1H, Ar-*H*), 7.33 – 7.29 (m, 1H, Ar-*H*), 7.25 – 7.23 (m, 1H, Ar-*H*), 7.12 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-*H*), 7.07 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.03 – 7.00 (m, 2H, Ar-*H*), 6.97 – 6.94 (m, 1H, Ar-*H*), 6.04 (s, 1H, Ar-*H*), 5.40 – 5.29 (m, 2H, NCO_2CH_2), 5.22 (s, 1H, O*H*), 5.00 (s, 1H, $ArOCHCO_2Et$), 4.90 (s, 1H, $ArCHAr$), 4.06 – 4.01 (m, 1H, CO_2CHHCH), 3.99 – 3.93 (m, 1H, CO_2CHHCH), 1.27 (s, 9H, $ArC(CH_3)_3$), 1.03 (s, 9H, $ArC(CH_3)_3$), 0.92 (t, *J* = 7.2 Hz, 3H, $CO_2C_2CH_3$) ppm.

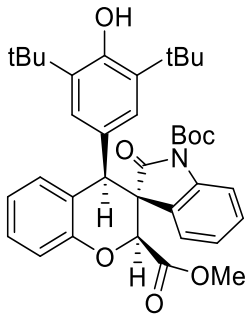
^{13}C NMR (150 MHz, $CDCl_3$): δ = 174.2 (N*C*O), 166.6 (*C*O_2Et), 153.1 (C_{Ar}), 153.0 (C_{Ar}), 150.0 (N*C*O_2), 138.3 (C_{Ar}), 135.1 (2C, C_{Ar}), 134.6 (C_{Ar}), 130.0 (C_{Ar}), 129.8 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (2C, C_{Ar}), 128.6 (C_{Ar}), 128.5 (C_{Ar}), 128.1 (2C, C_{Ar}), 127.6 (C_{Ar}), 127.5 (C_{Ar}), 125.5 (2C, C_{Ar}), 125.2 (C_{Ar}), 122.4 (C_{Ar}), 122.1 (C_{Ar}), 117.2 (C_{Ar}), 115.6 (C_{Ar}), 77.4 ($ArOCHCO_2Et$), 68.6 (NCO_2CH_2), 62.0 (C_{spiro}), 53.4 ($CO_2CH_2CH_3$), 51.4 ($ArCHAr$), 34.0 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.1 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 13.5 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3618, 2954, 2304, 2099, 1741, 1591, 1458, 1214, 1095, 745 cm^{-1}.

MS (ESI): *m/z* = 718.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{41}H_{42}NO_7ClNa^+$: 718.2542; found 718.2540.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-methyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162o)



According to **GP4**, **162o** was obtained as a colorless solid (0.184 g, 75% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 154-155 °C.

$[\alpha]_D^{25}$ = +13.2 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 9/1; flow rate 0.7 mL/min; T= 30 °C; retention time: 8.07 min (major), 9.77 min (minor), ee: 98%.

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

δ = 7.52 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.30 – 7.26 (m, 1H, Ar-*H*), 7.21 – 7.19 (m, 1H, Ar-*H*), 7.16 – 7.13 (m, 1H, Ar-*H*), 7.07 – 7.04 (m, 2H, Ar-*H*), 6.99 – 6.96 (m, 2H, Ar-*H*), 6.92 – 6.90 (m, 1H, Ar-*H*), 5.97 (s, 1H, Ar-*H*), 5.26 (s, 1H, O*H*), 4.99 (s, 1H, ArOC*H*CO_2Me), 4.87 (s, 1H, ArC*H*Ar), 3.52 (s, 3H, CO_2CH_3), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 0.98 (s, 9H, $ArC(CH_3)_3$) ppm.

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

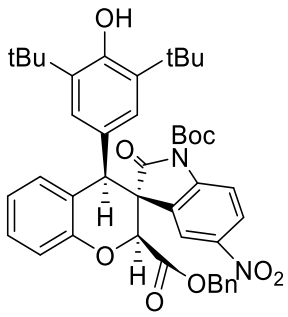
δ = 174.6 (N*C*O), 167.4 (*C*O_2Me), 153.2 (C_{Ar}), 153.0 (C_{Ar}), 148.6 (N*C*O_2), 140.2 (C_{Ar}), 134.9 (C_{Ar}), 134.8 (C_{Ar}), 129.8 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 128.0 (C_{Ar}), 125.7 (C_{Ar}), 125.3 (C_{Ar}), 125.2 (C_{Ar}), 125.1 (C_{Ar}), 124.1 (C_{Ar}), 123.1 (C_{Ar}), 121.8 (C_{Ar}), 116.8 (C_{Ar}), 114.4 (C_{Ar}), 83.9 ($NCO_2C(CH_3)_3$), 78.1 (ArO*C*HCO_2Me), 53.1 (CO_2CH_3), 52.5 (C_{spiro}), 51.0 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 385, 3631, 2956, 2645, 2322, 2080, 1979, 1734, 1593, 1444, 1361, 1294, 1226, 1151, 1088, 1002, 933, 844, 675 cm^{-1}.

MS (ESI): *m/z* = 652.3 $[M+K]^+$.

HRMS (ESI): *m/z* $[M+K]^+$ calcd for $C_{37}H_{43}NO_7K^+$: 652.2671; found 652.2661.

(2*S*,3*R*,4*R*)-2-Benzyl 1'-Tert-butyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162p)



According to **GP4**, **162p** was obtained as a colorless solid (0.264 g, 90% yield).

TLC: R_f = 0.60 (n-petane:Et_2O = 4:1)

Melting Point: 165-166 °C.

$[\alpha]_D^{25}$ = +76.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 97/3; flow rate 0.7 mL/min; T= 30 °C; retention time: 5.90min (major), 7.70 min (minor), ee: 97%.

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

δ = 7.95 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.85 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.50 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.35 – 7.32 (m, 1H, Ar-*H*), 7.28 – 7.24 (m, 2H, Ar-*H*), 7.22 – 7.19 (m, 2H, Ar-*H*), 7.07 – 7.05 (m, 2H, Ar-*H*), 7.00 (s, 1H, Ar-*H*), 6.99 – 6.95 (m, 2H, Ar-*H*), 5.93 (s, 1H, Ar-*H*), 5.26 (s, 1H, O*H*), 5.08 (d, *J* = 12.0 Hz, 1H, CO_2CHHPh), 5.00 (s, 1H, ArOC*H*CO_2Bn), 4.97 (d, *J* = 12.0 Hz, 1H, CO_2CH*H*Ph), 4.93 (s, 1H, ArC*H*Ar), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.37 (s, 9H, $ArC(CH_3)_3$), 0.91 (s, 9H, $ArC(CH_3)_3$) ppm.

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

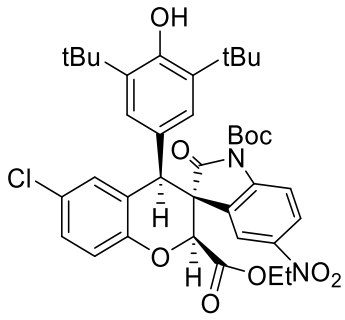
δ = 174.0 (N*C*O), 166.6 (*C*O_2Bn), 153.1 (C_{Ar}), 152.9 (C_{Ar}), 148.0 (N*C*O_2), 145.3 (C_{Ar}), 144.0 (C_{Ar}), 135.3 (C_{Ar}), 135.1 (C_{Ar}), 134.3 (C_{Ar}), 129.8 (C_{Ar}), 129.1 (C_{Ar}), 128.6 (2C, C_{Ar}), 128.5 (C_{Ar}), 128.4 (2C, C_{Ar}), 127.4 (C_{Ar}), 126.9 (C_{Ar}), 125.5 (C_{Ar}), 125.1 (C_{Ar}), 124.8 (C_{Ar}), 122.4 (C_{Ar}), 122.2 (C_{Ar}), 120.6 (C_{Ar}), 117.4 (C_{Ar}), 114.3 (C_{Ar}), 85.3 ($NCO_2C(CH_3)_3$), 77.5 (ArO*C*HCO_2Bn), 67.5 (C_{spiro}), 53.3 (CO_2CH_2Ph), 51.3 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.7 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.8 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$) ppm.

IR (ATR): 3633, 3456, 2960, 2646, 2294, 2116, 2012, 1933, 1735, 1604, 1522, 1453, 1347, 1301, 1238, 1146, 1111, 1017, 945, 904, 840, 750, 699 cm^{-1}.

MS (ESI): *m/z* = 757.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{43}H_{46}N_2O_9Na^+$: 757.3096; found 757.3095.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 6-chloro-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162q)



According to **GP4**, **162q** was obtained as a light yellow solid (0.208 g, 74% yield).

TLC: R_f = 0.40 (n-petane:Et_2O = 4:1)

Melting Point: 169-171 °C.

$[\alpha]_D^{25}$ = +156.6 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 8.02 min (major), 11.18 min (minor), ee: 99%.

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

δ = 8.07 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar-*H*), 7.87 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.70 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.31 – 7.27 (m, 1H, Ar-*H*), 7.22 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 7.01 – 6.95 (m, 2H, Ar-*H*), 5.95 (s, 1H, Ar-*H*), 5.15 (s, 1H, O*H*), 5.03 (s, 1H, ArOC*H*CO_2Et), 4.89 (s, 1H, ArC*H*Ar), 4.09 – 3.93 (m, 2H, $CO_2CH_2CH_3$), 1.59 (s, 9H, $NCO_2C(CH_3)_3$), 1.37 (s, 9H, $ArC(CH_3)_3$), 1.03 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.94 (s, 9H, $ArC(CH_3)_3$) ppm.

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

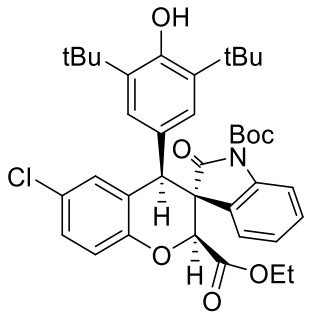
δ = 173.8 (N*C*O), 166.0 (*C*O_2Et), 153.3 (C_{Ar}), 151.6 (C_{Ar}), 148.1 (N*C*O_2), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 135.6 (C_{Ar}), 135.5 (C_{Ar}), 129.3 (C_{Ar}), 129.2 (C_{Ar}), 127.5 (C_{Ar}), 127.4 (C_{Ar}), 126.9 (C_{Ar}), 125.0 (C_{Ar}), 124.9 (C_{Ar}), 124.8 (C_{Ar}), 124.0 (C_{Ar}), 120.6 (C_{Ar}), 118.9 (C_{Ar}), 114.4 (C_{Ar}), 85.6 ($NCO_2C(CH_3)_3$), 77.6 (ArO*C*HCO_2Et), 62.2 (C_{spiro}), 52.9 ($CO_2CH_2CH_3$), 51.0 (Ar*C*HAr), 34.2 ($ArC(CH_3)_3$), 33.8 ($ArC(CH_3)_3$), 30.2 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.0 (3C, $NCO_2C(CH_3)_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3626, 2958, 2307, 2065, 2001, 1925, 1742, 1608, 1528, 1472, 1344, 1235, 1147, 1021, 937, 838, 755 cm^{-1}.

MS (ESI): *m/z* = 729.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{43}N_2O_9ClNa^+$: 729.2549; found 729.2546.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 6-chloro-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162r)



According to **GP4**, **162r** was obtained as a colorless solid (0.190 g, 72% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 3:1)

Melting Point: 95-96 °C.

$[\alpha]_D^{25}$ = +45.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 4.64 min (major), 5.22 min (minor), ee: > 99%.

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

δ = 7.52 (d, *J* = 7.8 Hz, 1H, Ar-*H*), 7.25 – 7.22 (m, 1H, Ar-*H*), 7.18 – 7.14 (m, 2H, Ar-*H*), 7.05 – 6.98 (m, 3H, Ar-*H*), 6.95 (s, 1H, Ar-*H*), 5.94 (s, 1H, Ar-*H*), 5.21 (s, 1H, O*H*), 5.03 (s, 1H, ArOC*H*CO_2Et), 4.80 (s, 1H, ArC*H*Ar), 4.02 – 3.95 (m, 1H, CO_2C*H*CHCH_3), 3.93 – 3.88 (m, 1H, CO_2CHC*H*CH_3), 1.57 (s, 9H, $NCO_2C(CH_3)_3$), 1.40 (s, 9H, $ArC(CH_3)_3$), 0.99 (s, 9H, $ArC(CH_3)_3$), 0.94 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

δ = 174.3 (N*C*O), 166.5 (*C*O_2Et), 153.2 (C_{Ar}), 151.7 (C_{Ar}), 148.5 (N*C*O_2), 140.2 (C_{Ar}), 135.1 (C_{Ar}), 135.0 (C_{Ar}), 129.2 (C_{Ar}), 128.9 (C_{Ar}), 128.5 (C_{Ar}), 128.1 (C_{Ar}), 126.7 (C_{Ar}), 125.1 (C_{Ar}), 125.0 (C_{Ar}), 124.9 (C_{Ar}), 124.8 (C_{Ar}), 124.7 (C_{Ar}), 124.2 (C_{Ar}), 118.3 (C_{Ar}), 114.4 (C_{Ar}), 84.1 ($NCO_2C(CH_3)_3$), 77.7 (ArO*C*HCO_2Et), 61.8 (C_{spiro}), 52.8 ($CO_2CH_2CH_3$), 50.9 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.9 ($ArC(CH_3)_3$), 30.3 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.4 ($CO_2C_2CH_3$) ppm.

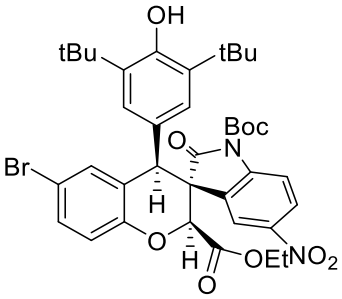
IR (ATR): 3624, 2954, 2610, 2308, 2074, 1744, 1611, 1462, 1229, 1148, 823, 750

cm^{-1}.

MS (ESI): *m/z* = 684.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{38}H_{44}NO_7ClNa^+$: 684.2699; found 684.2697.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 6-bromo-4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162s)



According to **GP4**, **162s** was obtained as a dark yellow solid (0.264 g, 88% yield).

TLC: R_f = 0.40 (n-petane:Et_2O = 4:1)

Melting Point: 162-163 ºC.

$[\alpha]_D^{25}$ = +118.4 (c = 1.0, $CHCl_3$).

HPLC: (*S***,** *S*) – Whelk Ol; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 ºC; retention time: 8.41 min (major), 11.79 min (minor), ee: 95%.

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

δ = 8.08 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.87 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.71 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.45 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.18 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.14 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.00 (s, 1H, Ar-*H*), 5.97 (s, 1H, Ar-*H*), 5.17 (s, 1H, O*H*), 5.05 (s, 1H, ArOC*H*CO_2Et), 4.91 (s, 1H, ArC*H*Ar), 4.09 – 3.96 (m, 2H, $CO_2CH_2CH_3$), 1.61 (s, 9H, $NCO_2C(CH_3)_3$), 1.39 (s, 9H, $ArC(CH_3)_3$), 1.04 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.96 (s, 9H, $ArC(CH_3)_3$) ppm.

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

δ = 173.8 (N*C*O), 166.0 (*C*O_2Et), 153.4 (C_{Ar}), 152.2 (C_{Ar}), 148.1 (N*C*O_2), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 135.6 (C_{Ar}), 135.4 (C_{Ar}), 132.3 (C_{Ar}), 132.1 (C_{Ar}), 127.4 (C_{Ar}), 126.8 (C_{Ar}), 125.1 (C_{Ar}), 125.0 (C_{Ar}), 124.8 (C_{Ar}), 124.5 (C_{Ar}), 120.6 (C_{Ar}), 119.3 (C_{Ar}), 114.8 (C_{Ar}),

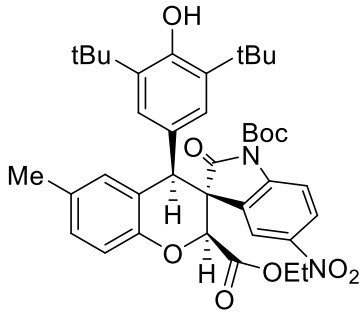
114.4 (C_{Ar}), 85.6 ($NCO_2C(CH_3)_3$), 77.6 (ArO*C*HCO$_2$Et), 62.3 (C_{spiro}), 52.9 ($CO_2CH_2CH_3$), 50.9 (Ar*C*HAr), 34.2 (Ar*C*(CH$_3$)$_3$), 33.8 (Ar*C*(CH$_3$)$_3$), 30.2 (3C, ArC(*C*H$_3$)$_3$), 29.9 (3C, ArC(*C*H$_3$)$_3$), 28.1 (3C, NCO$_2$C(*C*H$_3$)$_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3625, 3096, 2959, 2646, 2320, 2106, 1974, 1751, 1610, 1528, 1472, 1341, 1299, 1250, 1146, 1014, 908, 838, 734 cm^{-1}.

MS (ESI): *m/z* = 775.2 [M+Na]$^+$.

HRMS (ESI): *m/z* [M+Na]$^+$ calcd for $C_{38}H_{43}N_2O_9BrNa^+$: 773.2044; found 773.2043.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-6-methyl-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162t)



According to **GP4**, **162t** was obtained as a light yellow solid (0.223 g, 81% yield).

TLC: R_f = 0.50 (n-petane:Et$_2$O = 4:1)

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

[α]$_D^{25}$ = +136.2 (c = 1.0, CHCl$_3$).

HPLC: (*S***,** *S***)** – Whelk Ol; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 ^{o}C; retention time: 7.97 min (major), 10.15 min (minor), ee: 98%.

^{1}H NMR (600 MHz, CDCl$_3$):

δ = 8.06 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.92 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.70 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.17 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.13 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H*), 6.80 (s, 1H, Ar-*H*), 6.01 (s, 1H, Ar-*H*), 5.16 (s, 1H, O*H*), 5.01 (s, 1H, ArOC*H*CO$_2$Et), 4.93 (s, 1H, ArC*H*Ar), 4.08 – 3.96 (m, 2H, CO$_2$C*H*$_2$CH$_3$), 2.21 (s, 3H, ArC*H*$_3$), 1.61 (s, 9H, NCO$_2$C(C*H*$_3$)$_3$), 1.39 (s, 9H, ArC(C*H*$_3$)$_3$), 1.05 (t, *J* = 7.2 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 0.94 (s, 9H, ArC(C*H*$_3$)$_3$) ppm.

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

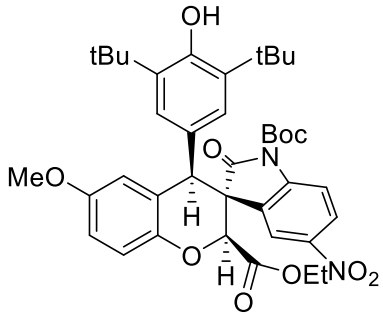
δ = 174.2 (N*C*O), 166.5 (*C*O_2Et), 153.1 (C_{Ar}), 150.9 (C_{Ar}), 148.3 (N*C*O_2), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 135.3 (C_{Ar}), 135.1 (C_{Ar}), 131.8 (C_{Ar}), 129.8 (2C, C_{Ar}), 127.3 (C_{Ar}), 127.2 (C_{Ar}), 125.8 (C_{Ar}), 125.3 (C_{Ar}), 124.8 (C_{Ar}), 121.7 (C_{Ar}), 121.0 (C_{Ar}), 117.2 (C_{Ar}), 114.2 (C_{Ar}), 85.4 (N$CO_2C(CH_3)_3$), 77.5 (ArO*C*HCO_2Et), 62.1 (C_{spiro}), 53.5 ($CO_2CH_2CH_3$), 51.2 (Ar*C*HAr), 34.2 (Ar*C*$(CH_3)_3$), 33.8 (Ar*C*$(CH_3)_3$), 30.3 (3C, ArC(*C*$H_3)_3$), 29.9 (3C, ArC(*C*$H_3)_3$), 28.1 (3C, NCO_2C(*C*$H_3)_3$), 20.6 (Ar*C*H_3), 13.7 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3621, 2952, 2637, 2324, 2095, 1755, 1616, 1471, 1239, 1146, 837, 759 cm^{-1}.

MS (ESI): *m/z* = 709.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{46}N_2O_9Na^+$: 709.3096 found 709.3093.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-6-methoxy-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162u)



According to **GP4**, **162u** was obtained as a light yellow solid (0.185 g, 66% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 176-178 °C.

$[\alpha]_D^{25}$ = +115.2 (c = 1.0, $CHCl_3$).

HPLC: (*S***,** *S***)** – Whelk Ol; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 11.67 min (major), 15.11 min (minor), ee: 95%.

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

δ = 8.06 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.93 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.70 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.22 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 6.91 (dd, *J* = 9.0,

2.4 Hz, 1H, Ar-*H*), 6.47 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.01 (s, 1H, Ar-*H*), 5.14 (s, 1H, O*H*), 5.01 (s, 1H, ArOC*H*CO_2Et), 4.93 (s, 1H, ArC*H*Ar), 4.10 – 4.02 (m, 1H, CO_2C*H*CHCH_3), 4.01 – 3.96 (m, 1H, CO_2CHC*H*CH_3), 3.64 (s, 3H, ArOCH_3), 1.61 (s, 9H, NCO_2C(CH_3)$_3$), 1.38 (s, 9H, ArC(CH_3)$_3$), 1.05 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.95 (s, 9H, ArC(CH_3)$_3$) ppm.

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

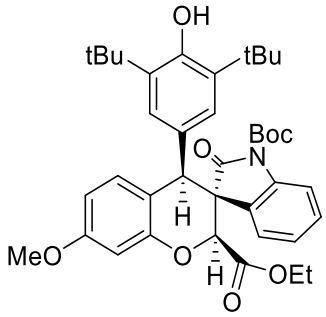
δ = 174.2 (N*C*O), 166.5 (*C*O_2Et), 154.7 (C_{Ar}), 153.1 (C_{Ar}), 148.2 (N*C*O_2), 147.0 (C_{Ar}), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 135.3 (C_{Ar}), 135.2 (C_{Ar}), 127.3 (C_{Ar}), 127.2 (C_{Ar}), 125.5 (C_{Ar}), 125.2 (C_{Ar}), 124.9 (C_{Ar}), 122.9 (C_{Ar}), 121.0 (C_{Ar}), 118.3 (C_{Ar}), 115.5 (C_{Ar}), 114.2 (C_{Ar}), 113.9 (C_{Ar}), 85.4 (NCO_2*C*(CH_3)$_3$), 77.6 (ArO*C*HCO_2Et), 62.1 (C_{spiro}), 55.8 (ArO*C*H_3), 53.4 (CO_2*C*H_2CH_3), 51.5 (Ar*C*HAr), 34.1 (Ar*C*(CH_3)$_3$), 33.8 (Ar*C*(CH_3)$_3$), 30.2 (3C, ArC(*C*H_3)$_3$), 29.9 (3C, ArC(*C*H_3)$_3$), 28.1 (3C, NCO_2C(*C*H_3)$_3$), 13.6 (CO_2C_2*C*H_3) ppm.

IR (ATR): 3460, 2972, 2427, 2197, 2049, 1951, 1740, 1366, 1215, 1097, 891, 768 cm^{-1}.

MS (ESI): *m/z* = 725.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{46}N_2O_{10}Na^+$: 725.3045; found 725.3043.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-7-methoxy-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162v)



According to **GP4**, **162v** was obtained as a colorless solid (0.163 g, 62% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 86-87 °C.

$[\alpha]_D^{25}$ = +32.7 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 7/3; flow rate 0.5 mL/min; T= 30 °C; retention time: 8.34 min (major), 9.95 min (minor), ee: > 99%.

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

δ = 7.50 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.16 – 7.13 (m, 1H, Ar-*H*), 7.08 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 7.00 – 6.98 (m, 1H, Ar-*H*), 6.84 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 6.79 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.50 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-*H*), 5.97 (s, 1H, Ar-*H*), 5.23 (s, 1H, O*H*), 4.97 (s, 1H, ArOC*H*CO_2Et), 4.79 (s, 1H, ArC*H*Ar), 4.02 – 3.97 (m, 1H, CO_2C*H*CHCH$_3$), 3.94 – 3.88 (m, 1H, CO_2CHC*H*CH$_3$), 3.85 (s, 3H, ArOC*H*$_3$), 1.57 (s, 9H, NCO_2C(C*H*$_3$)$_3$), 1.40 (s, 9H, ArC(C*H*$_3$)$_3$), 0.98 (s, 9H, ArC(C*H*$_3$)$_3$), 0.94 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

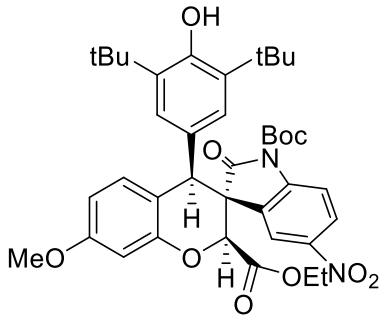
δ = 174.6 (N*C*O), 166.8 (*C*O_2Et), 159.7 (*C*$_{Ar}$), 153.9 (*C*$_{Ar}$), 152.9 (*C*$_{Ar}$), 148.7 (N*C*O_2), 140.1 (*C*$_{Ar}$), 134.9 (*C*$_{Ar}$), 134.7 (*C*$_{Ar}$), 130.4 (*C*$_{Ar}$), 128.7 (*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 125.8 (*C*$_{Ar}$), 125.4 (*C*$_{Ar}$), 125.2 (*C*$_{Ar}$), 125.1 (*C*$_{Ar}$), 124.1 (*C*$_{Ar}$), 114.8 (*C*$_{Ar}$), 114.2 (*C*$_{Ar}$), 109.1 (*C*$_{Ar}$), 101.1 (*C*$_{Ar}$), 84.0 (NCO_2*C*(CH$_3$)$_3$), 77.7 (ArO*C*HCO$_2$Et), 61.7 (*C*$_{spiro}$), 55.4 (ArO*C*H$_3$), 53.2 (CO_2*C*H$_2$CH$_3$), 50.7 (Ar*C*HAr), 34.1 (Ar*C*(CH$_3$)$_3$), 33.9 (Ar*C*(CH$_3$)$_3$), 30.3 (3C, ArC(*C*H$_3$)$_3$), 29.9 (3C, ArC(*C*H$_3$)$_3$), 28.1 (3C, NCO_2C(*C*H$_3$)$_3$), 13.4 (CO_2C_2*C*H$_3$) ppm.

IR (ATR): 3620, 2954, 2284, 2084, 1976, 1743, 1608, 1458, 1149, 834, 753 cm^{-1}.

MS (ESI): *m/z* = 696.3 [M+K]$^+$.

HRMS (ESI): *m/z* [M+K]$^+$ calcd for $C_{39}H_{47}NO_8K^+$: 696.2933; found 696.2929.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-7-methoxy-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162w)



According to **GP4**, **162w** was obtained as a light yellow solid (0.197 g, 70% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 3:1)

Melting Point: 107-109 °C.

$[\alpha]_D^{25}$ = +53.5 (c = 1.0, $CHCl_3$).

HPLC: (*S*, *S*) – Whelk O1; *n*-heptane/iPrOH = 9/1; flow rate 1.0 mL/min; T= 30 °C; retention time: 10.96 min (major), 15.95 min (minor), ee: 96%.

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

δ = 8.07 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.92 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.69 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 6.87 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 6.82 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 6.56 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 6.00 (s, 1H, Ar-*H*), 5.19 (s, 1H, O*H*), 5.00 (s, 1H, ArOC*H*CO_2Et), 4.89 (s, 1H, ArC*H*Ar), 4.10 – 3.95 (m, 2H, $CO_2CH_2$$CH_3$), 3.88 (s, 3H, ArOC$H_3$), 1.61 (s, 9H, $NCO_2C(CH_3)_3$), 1.38 (s, 9H, $ArC(CH_3)_3$), 1.04 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.94 (s, 9H, $ArC(CH_3)_3$) ppm.

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

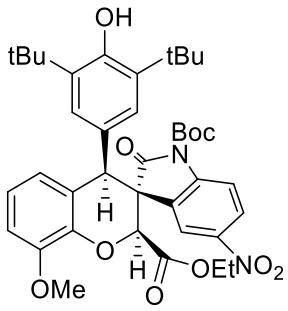
δ = 174.2 (N*C*O), 166.4 (*C*O_2Et), 160.0 (C_{Ar}), 153.8 (C_{Ar}), 153.1 (C_{Ar}), 148.2 (N*C*O_2), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 135.3 (C_{Ar}), 135.1 (C_{Ar}), 130.5 (C_{Ar}), 127.2 (C_{Ar}), 127.1 (C_{Ar}), 125.8 (C_{Ar}), 125.1 (C_{Ar}), 124.9 (C_{Ar}), 120.9 (C_{Ar}), 114.2 (C_{Ar}), 113.8 (C_{Ar}), 110.2 (C_{Ar}), 101.4 (C_{Ar}), 85.4 ($NCO_2C(CH_3)_3$), 77.6 (ArO*C*HCO$_2$Et), 62.2 (C_{spiro}), 55.5 (ArO*C*H_3), 53.4 ($CO_2CH_2CH_3$), 50.8 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.7 ($ArC(CH_3)_3$), 30.2 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3623, 2958, 2632, 2281, 2195, 2107, 2007, 1931, 1735, 1617, 1521, 1441, 1343, 1256, 1200, 1148, 1021, 939, 838, 753, 684 cm^{-1}.

MS (ESI): *m/z* = 725.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{46}N_2O_{10}Na^+$: 725.3045; found 725.3046.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-8-metho-xy-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162x)



According to **GP4**, **162x** was obtained as a light yellow solid (0.143 g, 51% yield).

TLC: R_f = 0.40 (n-petane:Et_2O = 4:1)

Melting Point: 116-118 ºC.

$[\alpha]_D^{25}$ = +37.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRACEL OD; *n*-heptane/iPrOH = 9/1; flow rate 0.7 mL/min; T= 30 ºC; retention time: 10.83 min (major), 15.32 min (minor), ee: 95%.

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

δ = 8.06 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.90 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.71 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 6.97 – 6.90 (m, 2H, Ar-*H*), 6.61 – 6.57 (m, 1H, Ar-*H*), 6.03 (s, 1H, Ar-*H*), 5.20 (s, 1H, O*H*), 5.00 (s, 1H, ArOC*H*CO_2Et), 4.98 (s, 1H, ArC*H*Ar), 4.13 – 4.07 (m, 1H, CO_2C*H*CHCH_3), 4.06 (s, 3H, ArOC*H*$_3$), 4.03 – 3.97 (m, 1H, CO_2CHC*H*CH_3), 1.61 (s, 9H, $NCO_2C(CH_3)_3$), 1.38 (s, 9H, $ArC(CH_3)_3$), 1.05 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.94 (s, 9H, $ArC(CH_3)_3$) ppm.

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

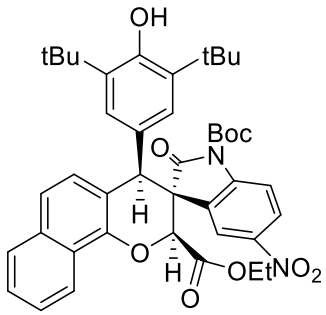
δ = 174.2 (N*C*O), 166.3 (*C*O_2Et), 153.1 (C_{Ar}), 148.5 (N*C*O_2), 148.3 (C_{Ar}), 145.4 (C_{Ar}), 144.2 (C_{Ar}), 142.9 (C_{Ar}), 135.2 (C_{Ar}), 135.1 (C_{Ar}), 127.2 (C_{Ar}), 127.1 (C_{Ar}), 125.7 (C_{Ar}), 125.4 (C_{Ar}), 124.9 (C_{Ar}), 123.2 (C_{Ar}), 121.9 (C_{Ar}), 121.2 (C_{Ar}), 121.0 (C_{Ar}), 114.3 (C_{Ar}), 111.0 (C_{Ar}), 85.4 ($NCO_2C(CH_3)_3$), 77.9 (ArO*C*HCO_2Et), 62.3 (C_{spiro}), 56.3 (ArO*C*H_3), 53.3 ($CO_2CH_2CH_3$), 51.1 (Ar*C*HAr), 34.1 ($ArC(CH_3)_3$), 33.7 ($ArC(CH_3)_3$), 30.2 (3C, $ArC(CH_3)_3$), 29.9 (3C, $ArC(CH_3)_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3616, 2955, 2629, 2300, 2088, 1749, 1460, 1139, 859, 734 cm^{-1}.

MS (ESI): *m/z* = 725.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{39}H_{46}N_2O_{10}Na^+$: 725.3045; found 725.3046.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-nitro-2'-oxo-2,4-dihydrospiro[benzo[h]chromene-3,3'-indoline]-1',2-dicarboxylate (162y)



According to **GP4**, **162y** was obtained as a light yellow solid (0.274 g, 92% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 5:1)

Melting Point: 161-164 °C.

$[\alpha]_D^{25}$ = +113.8 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/iPrOH = 9/1; flow rate 0.5 mL/min; T= 30 °C; retention time: 9.20 min (major), 10.30 min (minor), ee: 78%.

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

δ = 8.19 – 8.13 (m, 2H, Ar-*H*), 7.91 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.80 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.53 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.47 (d, *J* = 1.8 Hz, 1H, Ar-*H*), 7.41 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.31 – 7.26 (m, 2H, Ar-*H*), 6.83 (s, 2H, Ar-*H*), 5.31 (s, 1H, O*H*), 5.15 (s, 1H, ArOC*H*CO_2Et), 4.45 (s, 1H, ArC*H*Ar), 4.08 – 3.94 (m, 2H, $CO_2CH_2CH_3$), 1.66 (s, 9H, $NCO_2C(CH_3)_3$), 1.35 (s, 18H, 2*ArC(CH_3)$_3$), 1.07 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$) ppm.

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

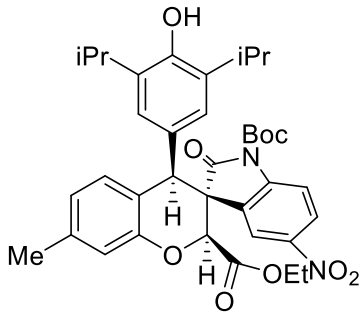
δ = 171.0 (N*C*O), 167.1 (*C*O_2Et), 153.4 (C_{Ar}), 150.7 (C_{Ar}), 149.2 (N*C*O_2), 144.6 (C_{Ar}), 144.2 (C_{Ar}), 135.3 (2C), 132.0 (C_{Ar}), 130.6 (C_{Ar}), 130.1 (C_{Ar}), 129.9 (C_{Ar}), 128.8 (C_{Ar}), 128.2 (C_{Ar}), 127.0 (C_{Ar}), 126.5 (2C), 125.0 (C_{Ar}), 124.0 (C_{Ar}), 122.5 (C_{Ar}), 119.5 (C_{Ar}), 117.6 (C_{Ar}), 114.8 (C_{Ar}), 112.4 (C_{Ar}), 85.5 ($NCO_2C(CH_3)_3$), 73.9 (ArO*C*HCO_2Et), 62.3 (C_{spiro}), 51.3 (Ar*C*HAr), 48.2 ($CO_2CH_2CH_3$), 34.3 (2C, 2*Ar*C*(CH_3)$_3$), 30.2 (6C, 2*ArC(CH_3)$_3$), 28.1 (3C, $NCO_2C(CH_3)_3$), 13.6 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3632, 2960, 2648, 2323, 2092, 1993, 1919, 1745, 1612, 1524, 1460, 1343, 1215, 1149, 1018, 906, 851, 803, 730 cm^{-1}.

MS (ESI): *m/z* = 745.3 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{42}H_{46}N_2O_9Na^+$: 745.3096; found 745.3095.

(2*S*,3*R*,4*R*)-1'-Tert-butyl 2-ethyl 4-(4-hydroxy-3,5-diisopropylphenyl)-7-methyl-5'-nitro-2'-oxospiro[chroman-3,3'-indoline]-1',2-dicarboxylate (162z)



According to **GP4**, **162z** was obtained as a light yellow solid (0.113 g, 43% yield).

TLC: R_f = 0.50 (n-petane:Et_2O = 4:1)

Melting Point: 147-149 °C.

$[\alpha]_D^{25}$ = +42.0 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IA; *n*-heptane/EtOH = 9/1; flow rate 0.7 mL/min; T= 30 °C; retention time: 9.16 min (major), 11.39 min (minor), ee: 93%.

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

δ = 8.08 (dd, *J* = 9.0, 2.4 Hz, 1H, Ar-*H*), 7.95 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.72 (d, *J* = 9.0 Hz, 1H, Ar-*H*), 7.10 (s, 1H, Ar-*H*), 6.90 (s, 1H, Ar-*H*), 6.77 (s, 2H, Ar-*H*), 5.88 (s, 1H, Ar-*H*), 5.16 (s, 1H, O*H*), 4.91 (s, 1H, ArOC*H*CO_2Et), 4.65 (s, 1H, ArC*H*Ar), 4.09 – 3.97 (m, 2H, $CO_2CH_2CH_3$), 3.07 – 3.00 (m, 1H, ArC*H*$(CH_3)_2$), 2.78 – 2.72 (m, 1H, ArC*H*$(CH_3)_2$), 2.40 (s, 3H, ArCH_3), 1.58 (s, 9H, $NCO_2C(CH_3)_3$), 1.23 (d, *J* = 6.6 Hz, 3H, ArCHCH_3), 1.20 (d, *J* = 6.6 Hz, 3H, ArCHCH_3), 1.04 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.84 (d, *J* = 6.6 Hz, 3H, ArCHCH_3), 0.53 (d, *J* = 6.6 Hz, 3H, ArCHCH_3) ppm.

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

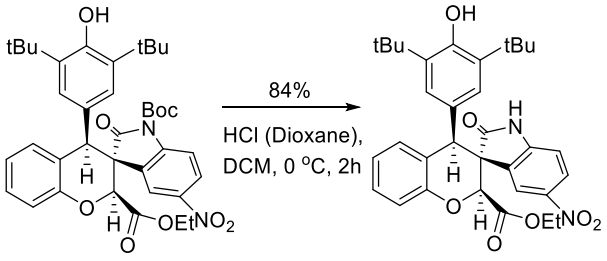
δ = 174.1 (N*C*O), 166.5 (*C*O_2Et), 152.8 (C_{Ar}), 149.0 (C_{Ar}), 148.3 (N*C*O_2), 145.5 (C_{Ar}), 144.2 (C_{Ar}), 139.2 (C_{Ar}), 133.1 (2C), 129.4 (C_{Ar}), 127.2 (C_{Ar}), 127.1 (C_{Ar}), 126.1 (C_{Ar}), 125.0 (C_{Ar}), 123.8 (C_{Ar}), 123.5 (C_{Ar}), 121.0 (C_{Ar}), 119.2 (C_{Ar}), 117.7 (C_{Ar}), 114.5 (C_{Ar}),

85.3 ($NCO_2C(CH_3)_3$), 77.7 (ArO*C*HCO$_2$Et), 62.1 (C_{spiro}), 53.3 ($CO_2CH_2CH_3$), 50.8 (Ar*C*HAr), 28.0 (3C, $NCO_2C(CH_3)_3$), 26.9 (Ar*C*H$(CH_3)_2$), 26.5 (Ar*C*H$(CH_3)_2$), 23.0 (ArCH_3), 22.7 (ArCH*C*H$_3$), 22.5 (ArCH*C*H$_3$), 22.2 (ArCH*C*H$_3$), 21.2 (ArCH*C*H$_3$), 13.7 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3856, 3748, 3525, 2963, 2871, 2323, 2073, 1941, 1737, 1616, 1525, 1468, 1342, 1301, 1252, 1216, 1144, 1022, 939, 839, 752, 693 cm^{-1}.

MS (ESI): *m/z* = 681.3 $[M+Na]^+$.

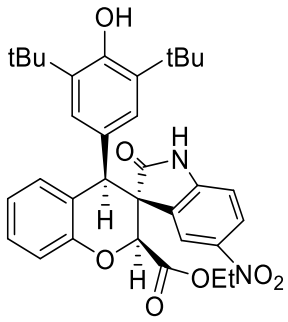
HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{37}H_{42}N_2O_9Na^+$: 681.2783; found 681.2792.



162h **183**

To a vial containing a solution of **162h** (0.067 g, 0.1 mmol, 1.0 equiv) in DCM (2.0 mL) was added 4N HCl in dioxane (0.5 mL, 2.0 mmol, 20.0 equiv) slowly at 0 oC. The mixture was stirred at the same temperature for 2 h, and then saturated NaHCO3 solution (1.0 mL) was added to quench the reaction. The resulting solution was extracted with EtOAc (3×5.0 mL). The organic layers were combined, washed with brine and dried over anhydrous Na2SO4. The solvent was removed on a rotary evaporator and the residue was purified by flash column chromatography (DCM/MeOH = 50/1 to 20/1) to afford the desired product **183** as a light yellow solid (0.048 g, 84% yield).

(2*S*,3*R*,4*R*)-Ethyl 4-(3,5-di-tert-butyl-4-hydroxyphenyl)-5'-nitro-2'-oxospiro[chro -man-3,3'-indoline]-2-carboxylate (183)



TLC: R_f = 0.30 (DCM:MeOH = 30:1)

Melting Point: 114-116 °C.

$[\alpha]_D^{25}$ = +62.6 (c = 1.0, $CHCl_3$).

HPLC: CHIRALPAK IC; *n*-heptane/EtOH = 97/3; flow rate 1.0 mL/min; T= 30 °C; retention time: 7.12 min (major), 8.85 min (minor), ee: 98%.

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

δ = 8.06 (dd, *J* = 8.4, 2.4 Hz, 1H, Ar-*H*), 7.91 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.80 (s, 1H, Ar-*H*), 7.34 – 7.32 (m, 1H, Ar-*H*), 7.24 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.10 (s, 1H, Ar-*H*), 6.99 – 6.90 (m, 2H, Ar-*H*), 6.65 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 5.99 (s, 1H, Ar-*H*), 5.21 (s, 1H, O*H*), 5.04 (s, 1H, ArOC*H*CO_2Et), 4.89 (s, 1H, ArC*H*Ar), 4.12 – 3.98 (m, 2H, $CO_2CH_2CH_3$), 1.40 (s, 9H, ArC(CH_3)$_3$), 1.06 (t, *J* = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 0.94 (s, 9H, ArC(CH_3)$_3$) ppm.

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

δ = 177.5 (N*C*O), 166.9 (*C*O_2Et), 153.1 (C_{Ar}), 153.0 (C_{Ar}), 147.1 (C_{Ar}), 143.1 (C_{Ar}), 135.1 (C_{Ar}), 135.0 (C_{Ar}), 129.8 (C_{Ar}), 129.0 (C_{Ar}), 128.2 (C_{Ar}), 128.1 (C_{Ar}), 125.7 (C_{Ar}), 125.5 (C_{Ar}), 125.0 (C_{Ar}), 122.5 (C_{Ar}), 122.3 (C_{Ar}), 121.9 (C_{Ar}), 117.2 (C_{Ar}), 108.7 (C_{Ar}), 77.6 (ArO*C*HCO$_2$Et), 62.0 (C_{spiro}), 53.6 ($CO_2CH_2CH_3$), 50.6 (Ar*C*HAr), 34.1 (Ar*C*(CH_3)$_3$), 33.8 (Ar*C*(CH_3)$_3$), 30.3 (3C, ArC(*C*H_3)$_3$), 29.9 (3C, ArC(*C*H_3)$_3$), 13.8 ($CO_2C_2CH_3$) ppm.

IR (ATR): 3620, 3306, 2952, 2268, 1929, 1735, 1613, 1451, 1330, 1217, 1103, 864, 752 cm^{-1}.

MS (ESI): *m/z* = 595.2 $[M+Na]^+$.

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{33}H_{36}N_2O_7Na^+$: 595.2415; found 595.2413.

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7. Abbreviations

Å	Ångström
Ac	Acetyl
Ar-	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
cat.	Catalyst
CDI	Carbonyldiimidazole
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	N,N-Diisopropylethylamine
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DPE	1,2-Di(pyrrolidinyl)ethane
d	day
d.r.	diastereomeric ratio
E	Electrophile
ee	enantiomeric excess
EI	Electron Ionization
equiv.	equivalent
ESI	Electron Spray Ionization
Et	Ethyl
EWG	Electro-withdrawing groups
e.r.	enantiomeric ratio
h	hour
HRMS	High Resolution Mass Spectrometry

Hz	Hertz
i-Pr	iso-Propyl
J	coupling constant (in NMR spectroscopy)
m-CPBA	*meta*-Chloroperoxybenzoic acid
MATHs	Malonic acids half thioesters
Me	Methyl
Mes	2,4,6-Trimethylphenyl
MS	Molecular Sieve
MTBE	Methyl *tert*-butyl ether
NHC	N-Heterocyclic Carbene
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
n.r.	no reaction
Nu	Nucleophile
PG	Protecting Group
Ph	Phenyl
rt	room temperature
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl

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9. Curriculum Vitae of Kun Zhao

PERSONAL DATA

Name: Kun Zhao
Gender: Male
Date of Birth: 10. 01. 1986
Place of Birth: Qingzhou, P. R. China
Nationality: P. R. China
Marital Status: Married

EDUCATION:

RWTH Aachen University, Aachen, Germany (2013.02-present).
• Advisor: *Prof. Dieter Enders.*

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China (2008.9-2011.7)
• M.S. in Medicinal Chemistry. • Advisor: *Prof. Lihong Hu*.

Shandong University of Traditional Chinese Medicine, Jinan, China (2003.9-2007.7)
• B.S. in Chinese Material Medica. • Advisor: *Prof. Yuanyin Jia*

PROFESSIONAL EXPERIENCE:

Tsinghua University, Beijing, China (2011.07- 2012.11)
• Research Assistant working on total synthesis of natural products.
• Advisor: *Prof. Yefeng Tang*
Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai, China
• Research Assistant working on isolation of bioactive natural products.
• Advisor: *Prof. Lihong Hu*

HONORS AND AWARDS:

2006 Scholarship of Luxin Pharmaceutical.
2003-2007 First Prize Scholarship (four times) in Shandong University of Traditional Chinese Medicine.

PUBLICATIONS:

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