Technische Universität München
TUM School of Natural Sciences

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Transition Metal-Catalyzed Functionalizations of C–H Bonds Utilizing Chiral Bifunctional Ligands

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Vollständiger Abdruck der von der TUM School of Natural Sciences der Technischen Universität München zur Erlangung einer

Doktorin der Naturwissenschaften (Dr. rer. nat.)

genehmigten Dissertation.

Vorsitz: Prof. Dr. Cathleen Zeymer

Prüfende der Dissertation:

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Die Dissertation wurde am 27.05.2024 bei der Technischen Universität München eingereicht und durch die TUM School of Natural Sciences am 13.06.2024 angenommen.

The presented Ph.D work was carried out at the chair for Organic Chemistry I at the Technical University of Munich between June 2020 and June 2024. The thesis was supervised by Prof. Dr. Thorsten Bach.

In this thesis, the relative configuration of racemates is represented by straight lines (bold or hahed). The absolute configuration of enantiomerically pure or enriched compounds is represented by wedge-shaped lines (bold or hashed).
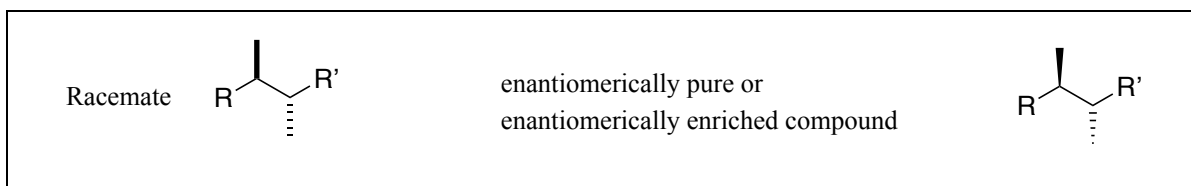
Conference contributions:

Orchem **2022**, Münster, Deutschland: *Bifunctional phenanthroline ligands with a hydrogen binding site in asymmetric catalysis* (poster presentation).

ACS **2023** (Harnessing the Power of Data), San Francisco, USA*: Enantioselective desymmetrization of hydantoins via iridium-catalyzed borylation utilizing a bifunctional bipyridine ligand with a hydrogen bonding site* (poster presentation).

Abstract:

Phenanthroline and bipyridine scaffolds, with their strong affinity to a wide range of (transition)metals, are among the most widely applied chelating ligands in organic synthesis. Their structure, with two closely spaced nitrogen atoms, enables the formation of strong, entropically favored complexes. In this Ph.D. thesis, new chiral ligands were developed, combining the favorable properties of these dinitrogen compounds with a chiral backbone exhibiting a lactam motif, which serves as a two-point binding site for hydrogen bonds. The applicability of these ligands in the activation of C–H bonds was investigated, examining the utilization of hydrogen bonding as a control element for the coordination of substrates and the selective transfer of reagents. In this context, a novel bipyridine ligand was developed and successfully applied in the iridium-catalyzed borylation of hydantoins, achieving yields up to 83%.

Kurzzusammenfassung

Phenanthrolin- und Bipyridin-Gerüste, die eine starke Affinität zu einer Vielzahl von (Übergangs)metallen aufweisen, gehören zu den am Häufigsten genutzten chelatisierenden Liganden in der organischen Synthese. Ihre Struktur mit zwei nah beieinanderliegenden Stickstoffatomen ermöglicht die Bildung starker, entropisch begünstigter Komplexe. In dieser Dissertation wurden neue, chirale Liganden entwickelt, die die vorteilhaften Eigenschaften dieser Stickstoff-Verbindungen mit einem chiralen Rückgrat kombinieren, das eine Bindungsstelle für Wasserstoffatome aufweist. Die Anwendbarkeit dieser Liganden wurde im Bereich der C–H Aktivierung untersucht und es wurde getestet, inwieweit Wasserstoffbrückenbindungen als zentrales Kontrollelement für die Koordination von Substraten und die selektive Übertragung von Reagenzien eingesetzt werden können. In diesem Zusammenhang wurde ein neuer Bipyridin-Ligand entwickelt und erfolgreich in der Iridium-katalysierten Borylierung von Hydantoinen eingesetzt, wobei Ausbeuten bis zu 83% erzielt wurden.

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I. Theory

1. Introduction

The fundamental building blocks of life, like amino acids in proteins and sugars such as deoxyribose in DNA, are chiral units characterized both by unique homochirality as well as by chiral purity. Two essential processes in organisms – protein synthesis mediated by DNA and RNA and the replication of DNA for the transmission of genetic information – rely on precise molecular interactions between enantiomers.[1] Two enantiomers of the same compound can display significantly different biological activity. One prominent example is carvone: While the (*S*)-enantiomer smells of caraway, its mirror image, (*R*)-carvone smells of mint (Figure 1). The reason why humans can distinguish between the two, is because our nasal receptors consists of chiral compounds as well, which are able to recognize the difference due to the concept of complementary.[2]

(*R*)-carvone   mirror plane   (*S*)-carvone

1   **2**
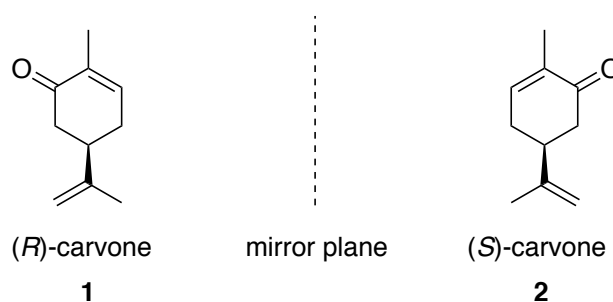
Figure 1: Differentiation of smell demonstrated on the example of carvone.

The same concept of recognition applies to drugs and their respective receptors in the cell, demonstrating that the need for methods to obtain enantiomerically pure compounds remains as crucial as ever for organic chemists. In addition, both financial and even more so environmental reasons create pressure to develop sustainable chemical processes, which reduce waste and increase efficiency. In this context, asymmetric catalysis is a valuable tool in organic chemistry as it only requires a small quantity of chiral material to achieve significant enantioenrichment in products. The application of rationally designed catalysts in sub-stochiometric amounts provide the necessary efficiency.[3]

2. Transition metal catalysis

One highly enantioselective example of asymmetric catalysis is the ruthenium-catalyzed asymmetric hydrogenation of β-keto-esters employing chiral 2,2′-*bis*(diphenylphosphino)-1,1′-binaphthyl (BINAP) ligands, which earned *Noyori* the Nobel prize in 2001 (Scheme 1).[4]
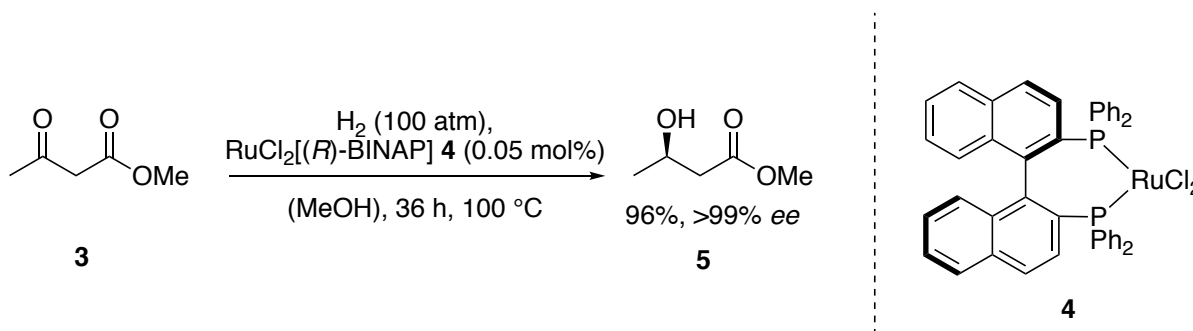
Scheme 1: Catalytic asymmetric hydrogenation of β-keto-esters using a chiral ruthenium-BINAP complex.

Synthetic efficiency can be divided into the two subcategories selectivity and atom economy, while selectivity can be divided into the five subgroups of chemoselectivity, site-selectivity, regioselectivity, diast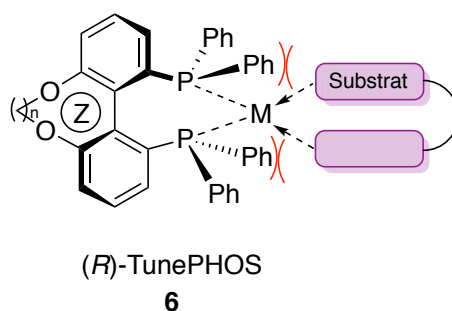ereoselectivity and enantioselectivity.[5] While selectivity is crucial to ensure minimal by-products that need to be separated and disposed of, atom economy deals with the amount of the reagents that actually ends up in the product.[6] The ultimate goal of a new synthetic strategy therefore involves maximizing selectivity, enhancing atom economy as well as simplification of the overall process. One of the most powerful approaches to simultaneously tackle these issues is to make use of transition metal complexes with their inherent ability to catalyze a plethora of organic reactions. Due to the abundance of transition metals with variable oxidation states and diverse coordination geometries, development of highly efficient catalysts is made possible. These metals can be combined with rationally designed ligands tailored to the requirements of the respective transformation.[7] Looking at the example of *Noyori* (*vide supra*), numerous modifications of biaryl diphosphane ligands have been synthesized, aiming to further enhance catalytic quality and broaden the scope of application. For example, the concept of dihedral angle control has been used to improve enantioselectivities. The *ortho,ortho*-bridged TunePhos diphosphane ligands were designed to enable easy adjustments corresponding to the steric demands of the respective substrates (Table 1) .

Regarding the asymmetric hydrogenation of β-keto esters, C4-TunePhos ligand (**6d**) with a dihedral angle of 88° performed best when using methyl acetoacetate as the substrate, surpassing the enantiomeric excess obtained with BINAP (98.5% vs. 99.1% *ee*, respectively, Table 1).[8]

(*R*)-TunePHOS
6

Table 1: Influence of the dihedral angle α on the enantioselectivity of the asymmetric hydrogenation of **3**.[8]
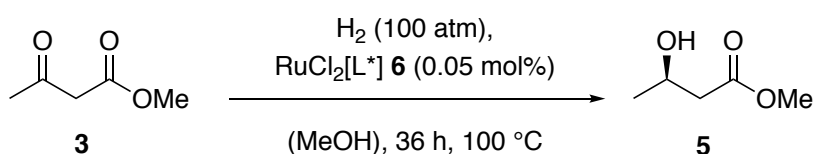
		TunePHOS					BINAP
#	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**4**
n	1	2	3	4	5	6	-
Z	7	8	9	10	11	12	-
Dihedral angle [°]	60	74	77	88	94	106	87
ee [%]	90.9	90.8	97.7	99.1	97.1	96.5	98.5

2.1. Supramolecular Catalysis

2.1.1. Organocatalysis

The ultimate compound class for asymmetric catalysis are represented by enzymes, since they efficiently combine molecular recognition and catalytic processes. A key element of enzyme catalysis is the use of attractive non-covalent interactions (NCIs). Therefore, in an attempt to mimic these natural concepts, organocatalysis has emerged as a rapidly expanding area of research. The goal is to imitate nature by *inter alia* implementing NCIs such as hydrophobic interactions, electrostatic effects, solvent reorganization and intermolecular hydrogen bonding in an enzyme-substrate-like fashion.[9],[10]

In 1998, *Miller et al.* presented an enantioselective, kinetic resolution of secondary alcohols inspired by enzyme catalysis. In their work, a chiral peptide (**8**) containing an *N*-methylimidazole substructure served as a catalyst for the acylation of alcohols with acetic anhydride, making use of hydrogen bonding between the substrate-amide and peptide backbone. Due to the chiral environment of the peptide created by hydrogen bond-assisted folding, acylation occurs enantioselectively, giving the acylated products **9** with up to 84% *ee* (Scheme 2).[11]
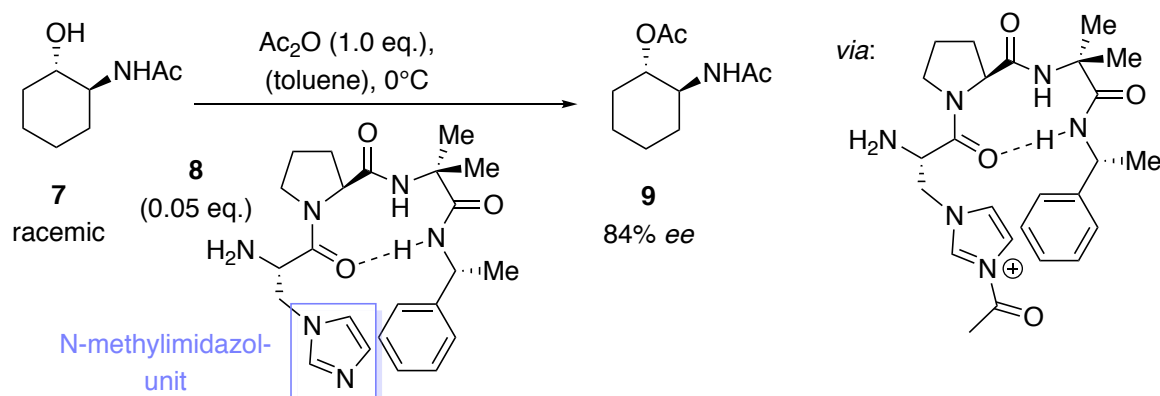
Scheme 2: Millers kinetic resolution of secondary alcohols.[11]

Another class of organocatalysts that use hydrogen bonding as an integral component of catalysis, are (thio)urea compounds and derivatives of bisamides of squaric acid (square amides), which non-covalently coordinate substrates *via* two hydrogen bonds.[12],[13],[14] One example is the *Friedel-Crafts*/substitution cascade reaction of naphthol **10** and (*Z*)-bromo nitroalkene **11** catalyzed by chiral square amide catalyst **12** containing a third hydrogen bonding site for the reagent leading to enantiomeric excesses of up to 98% *ee* (Scheme 3).[15]
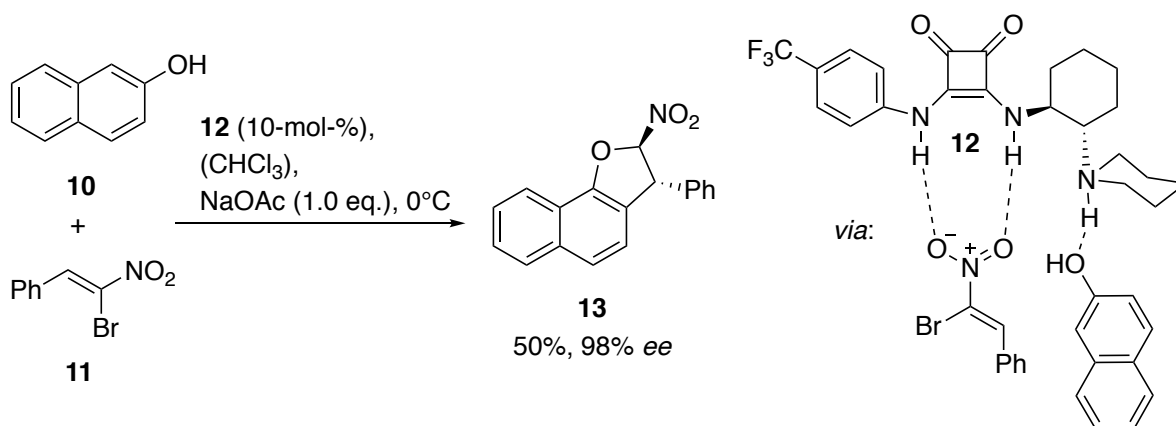

Scheme 3: *Friedel-Crafts*/substitution cascade reaction catalyzed by a square amide organocatalyst.[15]

2.1.2. Hydrogen bond-mediated transition metal catalysis

Despite these remarkable developments, there are some drawbacks to organocatalysts, like the need for high catalyst loading or a limited scope of reaction types or substrate classes. A key ability of transition metals is their redox capability and their ability to coordinate a plethora of different compounds, which provides the possibility to explore and develop a broad range of different organic transformations.[7]

By combining this prerequisite with the possibility of rationally designing ligands that employ enzyme-like non-covalent binding sites, it combines the best of both worlds as it allows to control both reactivity and selectivity. It has been shown that simple hydrogen bonding interactions between substrates and functional groups of catalysts significantly improve the selectivity of the catalyzed transformation.[16],[17],[18],[19]

In traditional asymmetric catalysis, repulsive interactions are used to induce enantioselectivity by employing steric bulk in order to increase the energy of one of the diastereomeric transition states compared to the other.[20] Using attractive forces to control selectivity can be an alternative control element for the same transformation, as demonstrated by *Zhou* and *Li* in their 1,3-dipolar cycloaddition of (*E*)-2-(ethylideneamino)acetate **15** on dimethyl maleates such as compound **14** (Scheme 4). They showed, that switching the dimethylamino- to an amino group on their ligand (**16/17**) enables the ability to form hydrogen bonds and completely reverses the enantioselectivity.[21]
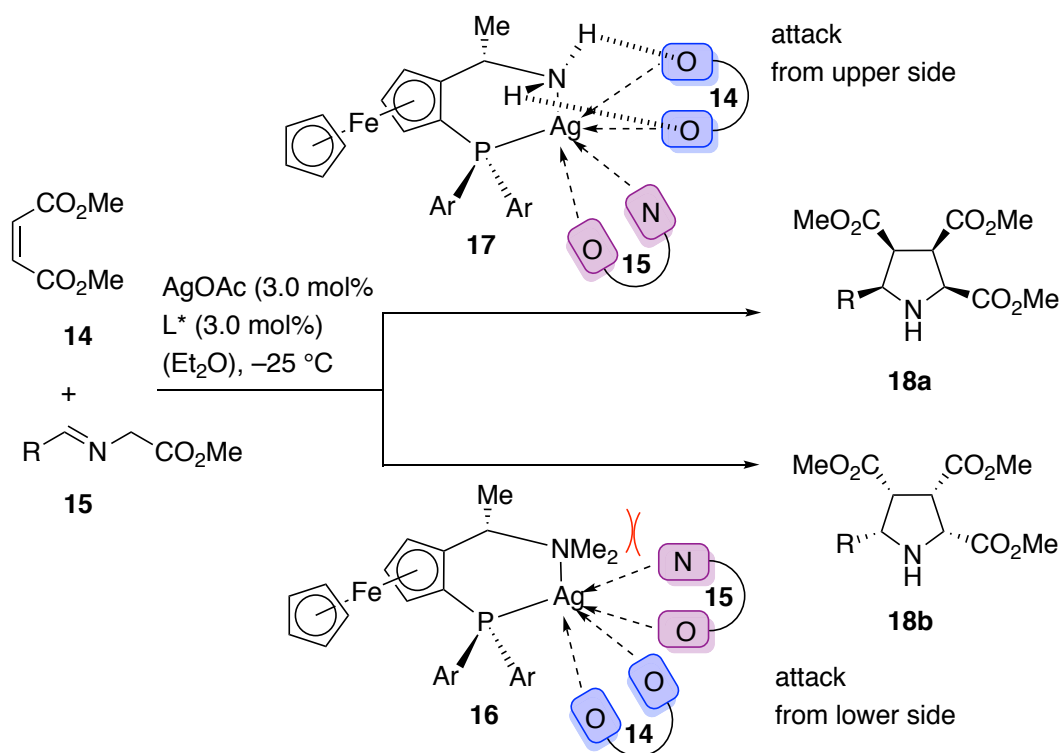
Scheme 4: Hydrogen bond-directed reversal of enantioselectivity in a 1,3-dipolar cycloaddition.[21]

Breit et al. developed a rhodium-based catalyst system with a ligand containing an acyl-guanidine-group (**20**), that can coordinate substrates *via* two-point hydrogen bonding for hydroformylation and hydration reactions. Fixation of the substrate *via* hydrogen bonding ensures its optimal positioning for high regio- and chemoselectivities, as they showed in transformations like their tandem hydroformylation-hydration cascade on internal alkynes such as compound **19** (Scheme **5**).[9]
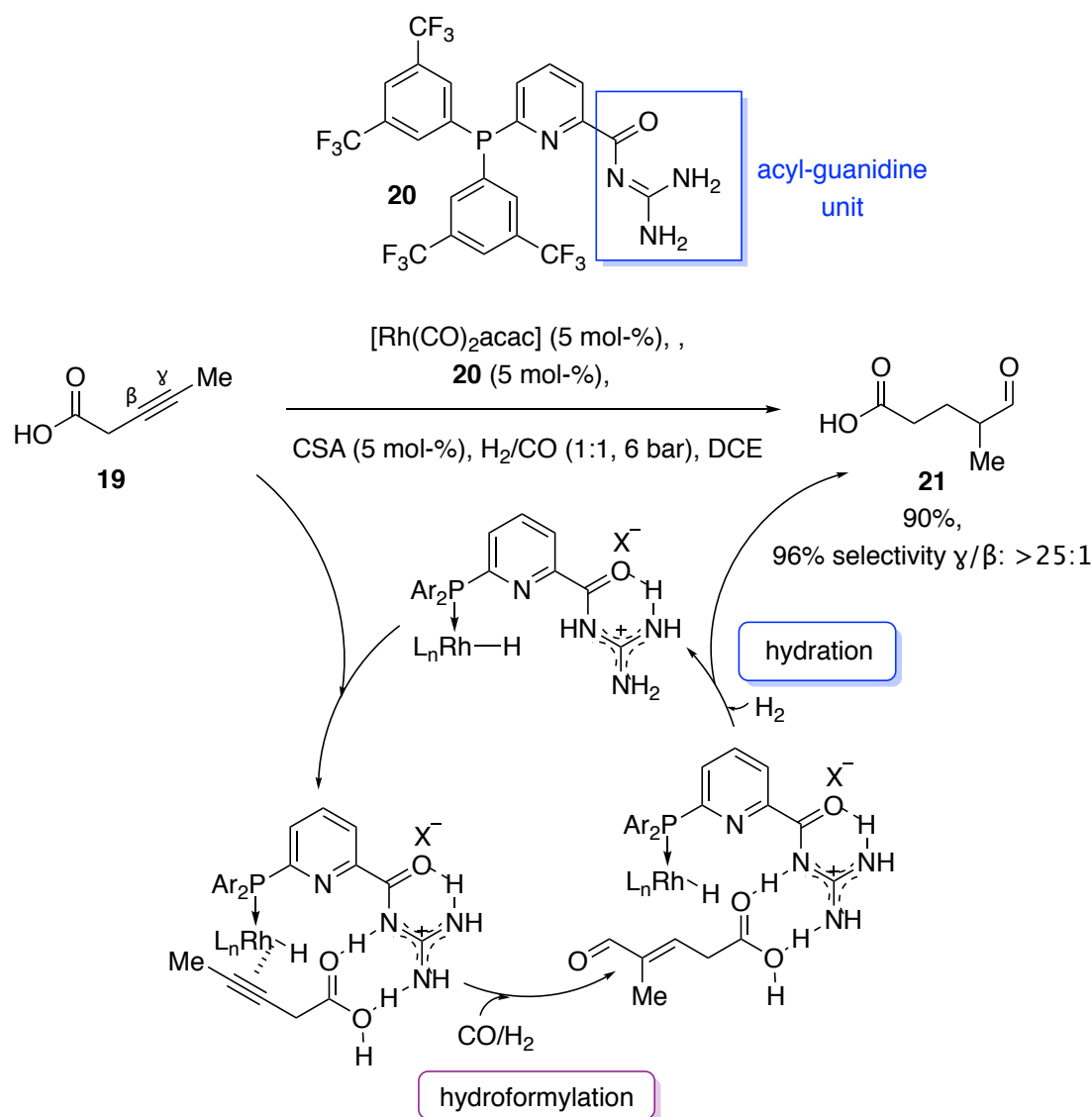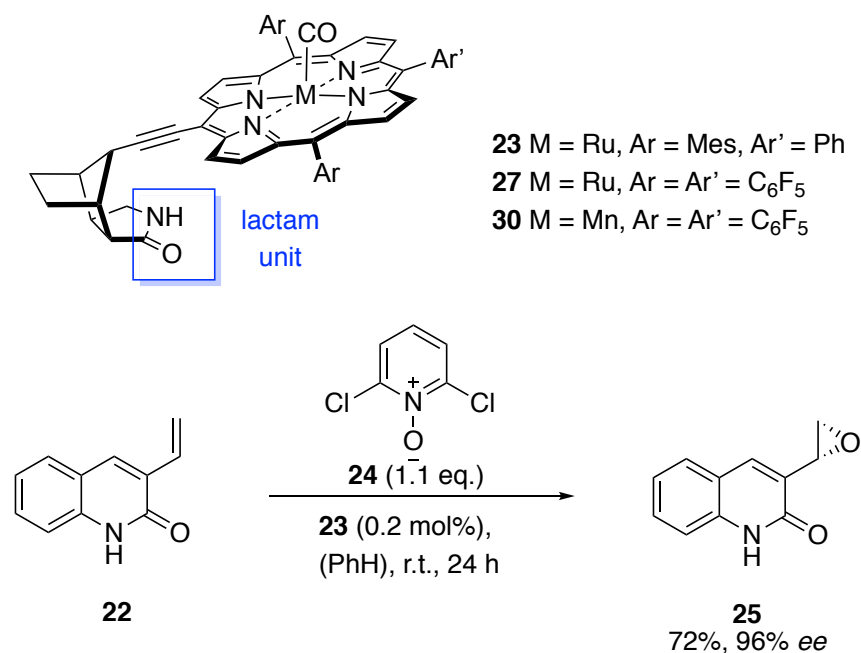

Scheme 5: Hydrogen bond-mediated hydroformylation/hydration cascade reaction by Breit.[9]

Another powerful hydrogen bond recognition site are amide units, which pose the central element in the ligands developed in our group. The ligands used in transition metal catalysis are based on the chiral octahydro-1*H*-4,7-methano-*iso*-indol-1-one skeleton and contain a lactam binding site, which coordinates substrates and acts as a control element to induce diastereo-or enantioselectivity *via* two-point hydrogen bonding. The respective metals are coordinated *via* specifically tailored binding sites connected to the backbone *via* an alkynyl linker.[22]

One of the first reactions that were explored, was the enantioselective epoxidation of vinyl-quinolones using a ruthenium porphyrin complex (**23**) developed by *Fackler*, where the epoxide products were obtained in good yields and excellent enantioselectivities. It was shown that both hydrogen bonds were crucial for achieving high enantioenrichment. Furthermore it was demonstrated that position control of the substrate was strong enough to obtain site-selectivity in substrates with competing alkenes such as quinolone **22** (Scheme 6).[23]

23 M = Ru, Ar = Mes, Ar' = Ph
27 M = Ru, Ar = Ar' = C$_6$F$_5$
30 M = Mn, Ar = Ar' = C$_6$F$_5$

24 (1.1 eq.)

**23** (0.2 mol%),
(PhH), r.t., 24 h

22

25
72%, 96% *ee*

Scheme 6: Enantioselective epoxidation of vinylquinolones catalyzed by a chiral porphyrin complex.[23]

This catalyst system was successfully applied to the epoxidation of vinyl-quinolones, alkenylpyridone and amides[24] as well as the enantioselective oxygenation of aliphatic C–H bonds imitating cytochrome P450 enzyme catalysis. The latter was demonstrated in the desymmetrization of spirocyclic compounds such as oxindole **26**, where the modified porphyrin catalyst **27** gave the best results (Scheme 7).[25]

24 (2.2 eq.)

27 (1.0 mol%),
(DCM), 50 °C, 20 h

26

28
69%, 98% *ee*
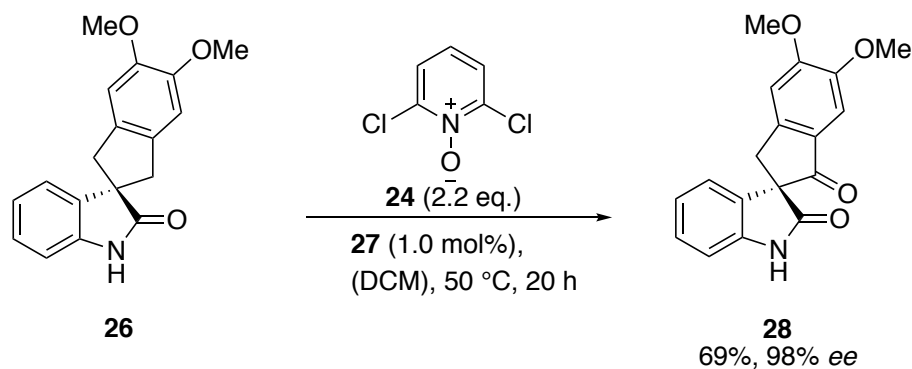
Scheme 7: Desymmetrization of spirocyclic oxindoles catalyzed by a chiral porphyrin complex.[25]

Since overoxidation was a challenging issue which prevented obtaining the respective chiral secondary alcohols, a change of metal was envisioned. By using manganese (**30**) in the C–H oxidation of dihydroquinolone substrates like **29**, the desired alcohols were obtained in good yields and once again excellent enantioselectivites (Scheme 8).[26]
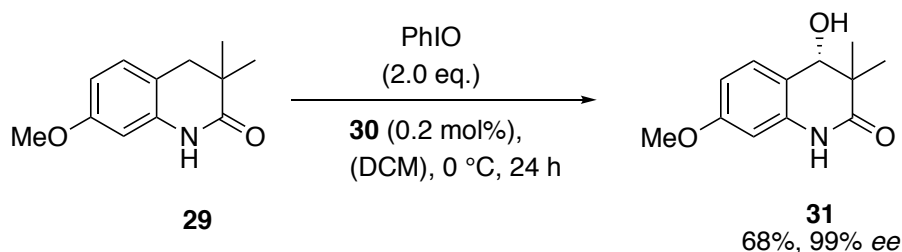


Scheme 8: C–H oxidation of dihydroquinolones by a chiral porphyrin complex.[26]

In analogy to oxidations, the direct amination of C–H bonds is a desirable transformation, since C–N bonds are important functional groups in natural products. In our group, a modified version of the *Du Bois* catalyst $Rh_2(esp)_2$ [27] was developed (**33**), which is known to effectively catalyze intermolecular, aliphatic C–H amination of quinolones (Scheme 9). In this catalyst, the robust rhodium scaffold is combined with the lactam-containing template to target enantioselective amination[28] and aziridination reactions[29] mediated by hydrogen bonding.


33
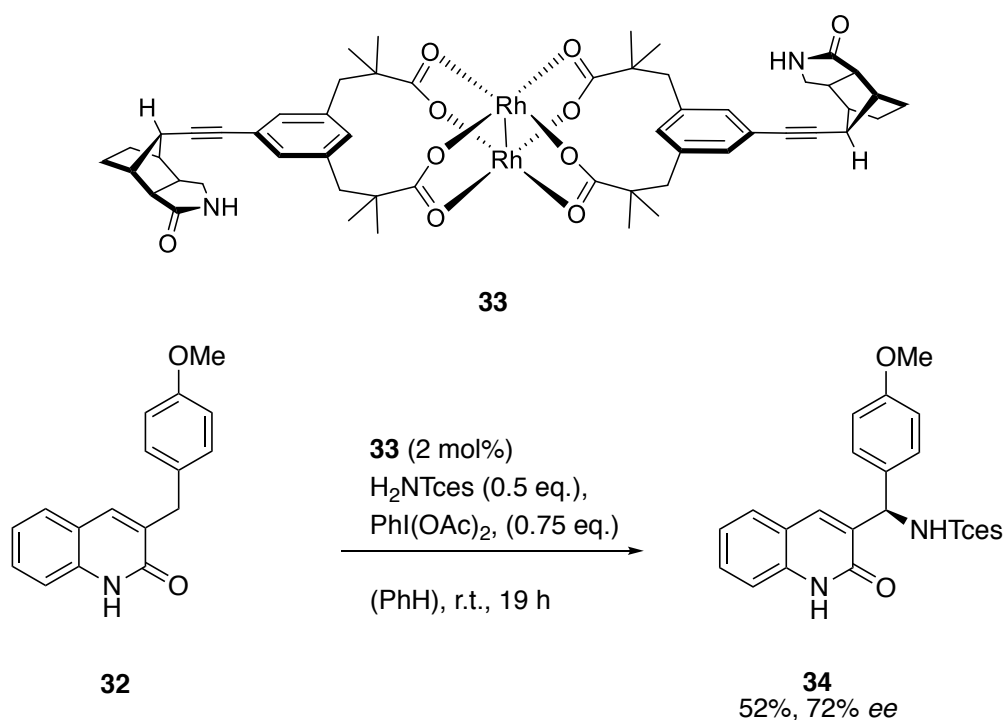
Scheme 9: Enantioselective C–H amination of quinolone **32** with a modified *Du Bois* catalyst.[28]

Next to rhodium, other metals proved to be useful in C–H aminations, with silver shown to be most effective by the groups of *Shi*,[30] *Perez*[31] and *Schomaker*.[32] In our group, a chiral phenanthroline ligand based on the chiral template employing a lactam unit ((+)-**36**) was developed and successfully applied in the silver-catalyzed, enantioselective amination of methylene groups with a nitrene source. As mentioned before, two-point hydrogen bonding between substrates and the chiral ligand allow for the correct positioning of the substrates for the efficient amination. The active silver species is a heteroleptic complex with one chiral as well as one achiral phenanthroline molecule bound to the metal. Using this catalyst complex, the enantioselective amination of pyridones and quinolone substrates like compound **35** proceeds with high yields and high enantioselectivity up to 94% *ee* as well as high site-selectivity (Scheme 10).[33]
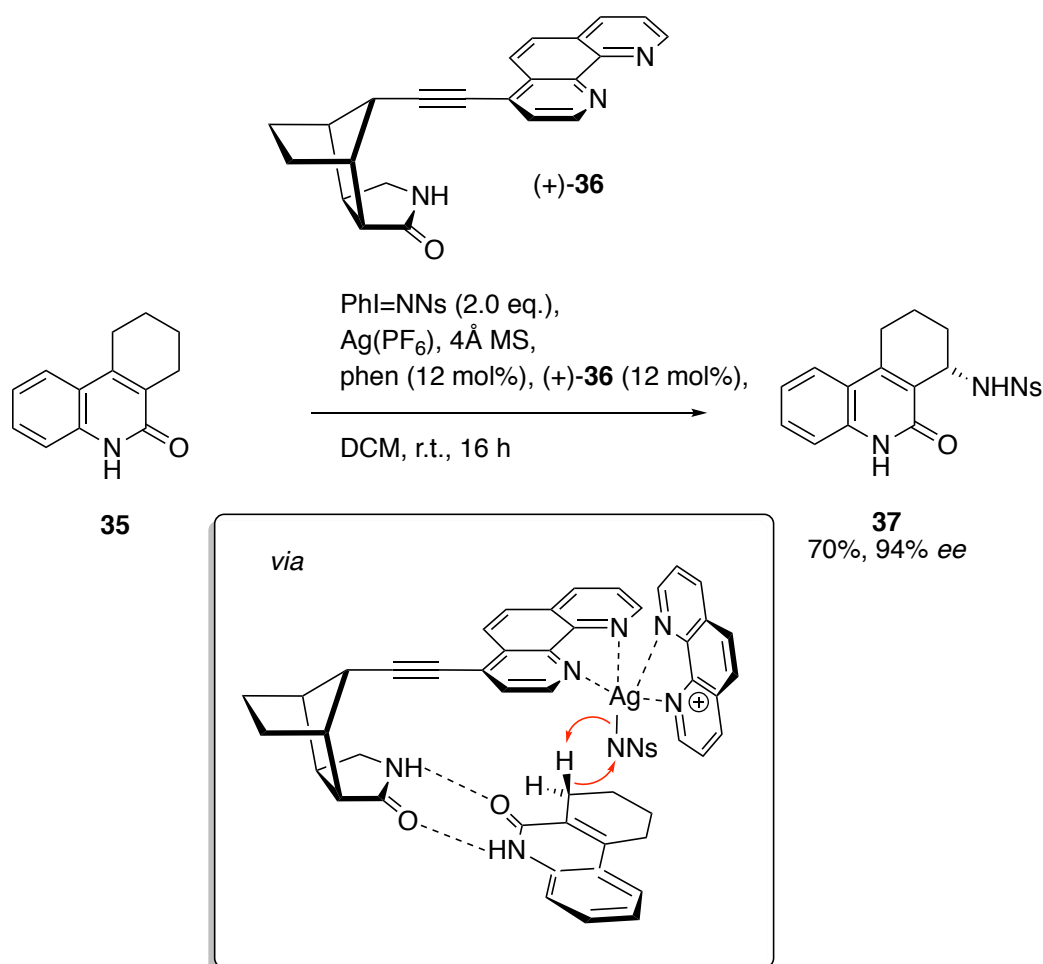
Scheme 10: Enantioselective C–H amination of quinolones with a chiral heteroleptic silver catalyst.[33]

The same catalyst system was successfully applied to the enantioselective sulfimidation of 3-thiosubstituted 2-quinolones and 2-pyridones, giving products in up to 97% yield and 97% *ee* (Scheme 11).[34]
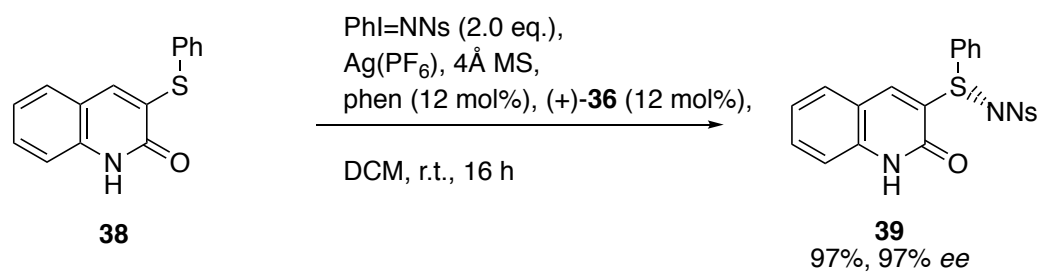
Scheme 11: Enantioselective sulfimidation of quinolone **38** with a chiral heteroleptic silver catalyst. [34]

3. Chiral bifunctional ligands with a hydrogen bonding site

3.1. Objective

The 1,10-phenanthroline backbone with its strong affinity to a wide range of (transition)metal ions, is one of the most widely applied chelating reagents in organic synthesis.[35] Its rigid and planar structure, containing two *cis*-oriented nitrogen atoms, enables the formation of strong, entropically favored complexes. Due to these characteristics, phenanthroline can be employed as an effective ligand in various reactions catalyzed by a lot of (transition)metal catalysts.[35],[36] In the past, it has been utilized as a ligand in non-asymmetric as well as in asymmetric trans-formations.[37]

Given the ubiquity of the 1,10-phenanthroline ligands in transition metal catalysis and the con-stant search for new chiral catalysts, the combination of the phenanthroline scaffold with our chiral template employing a lactam unit was expected to apply to other important reaction clas-ses next to the examples mentioned above.[38] Aim of this work was therefore to explore the area of application of this novel chiral ligand based on the chiral template developed by *Berthold*.[39] As in the previous studies mentioned above, the idea was to provide an enzyme-like, non-covalent binding site for prochiral substrates to fix their position and bring them in close proximity to the respective catalytically active metal center. The covalently bound phe-nanthroline unit should act as a binding site for the respective metal, which should enable a regio-and/or enantioselective transfer of a reagent onto the substrates (Scheme 12).
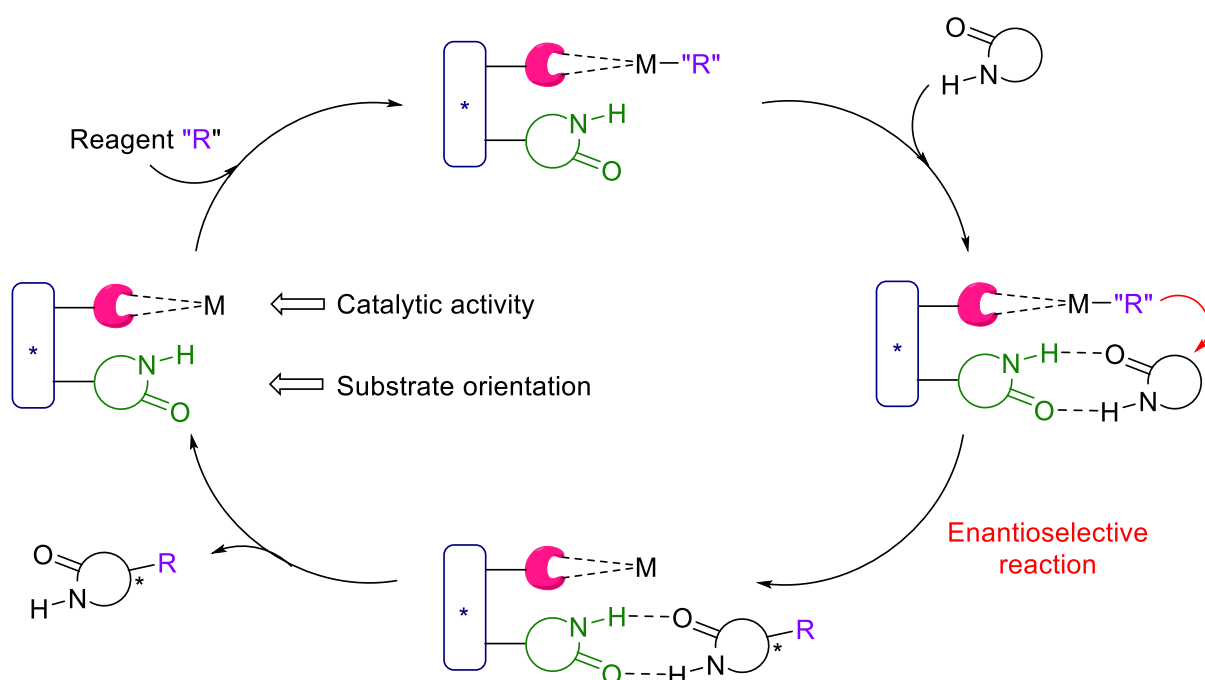

Scheme 12: Concept of enantioinduction *via* two-point hydrogen bonding in transition metal catalysis.[22]

3.2.   Synthesis of the chiral bifunctional ligands

The template scaffold was developed based on the work of *Deslongchamps*[40],[41] and proved to be efficient to bind both spatially demanding transition metal catalysts and provide the optimal distance between the metal and the respective substrates (*vide supra*).

The synthesis of the alkyne **61**, based on the work of *Berthold*[39], started with a *Knoevenagel* condensation of acetone and cyclopentadiene (cp, **50**) and gave 6,6-dimethylfulvene (**51**) in 93% yield. It reacted with maleic anhydride in a *Diels-Alder*-reaction and provided the bicyclic product **52** in 52% yield and an *exo:endo* ratio of >99:1. Hydrogenation of the more accessible double bond as well as the following transformation of the anhydride **53** to the respective imide **54** proceeded in quantitative yield. The subsequent introduction of a chiral 1-(–)phenylethyl protecting group allowed for the separation of the two diastereomers which formed upon the following non-stereoselective reduction of compound **54**. The two-step reduction to the amide started with the formation of a hemiaminal with sodium borohydride, which was then immediately reduced with triethylsilane and trifluoroacetic acid. The diastereoisomers (–)-**55a** and (–)-**55b** were obtained in 53% and 29% yield, respectively (Scheme 13).
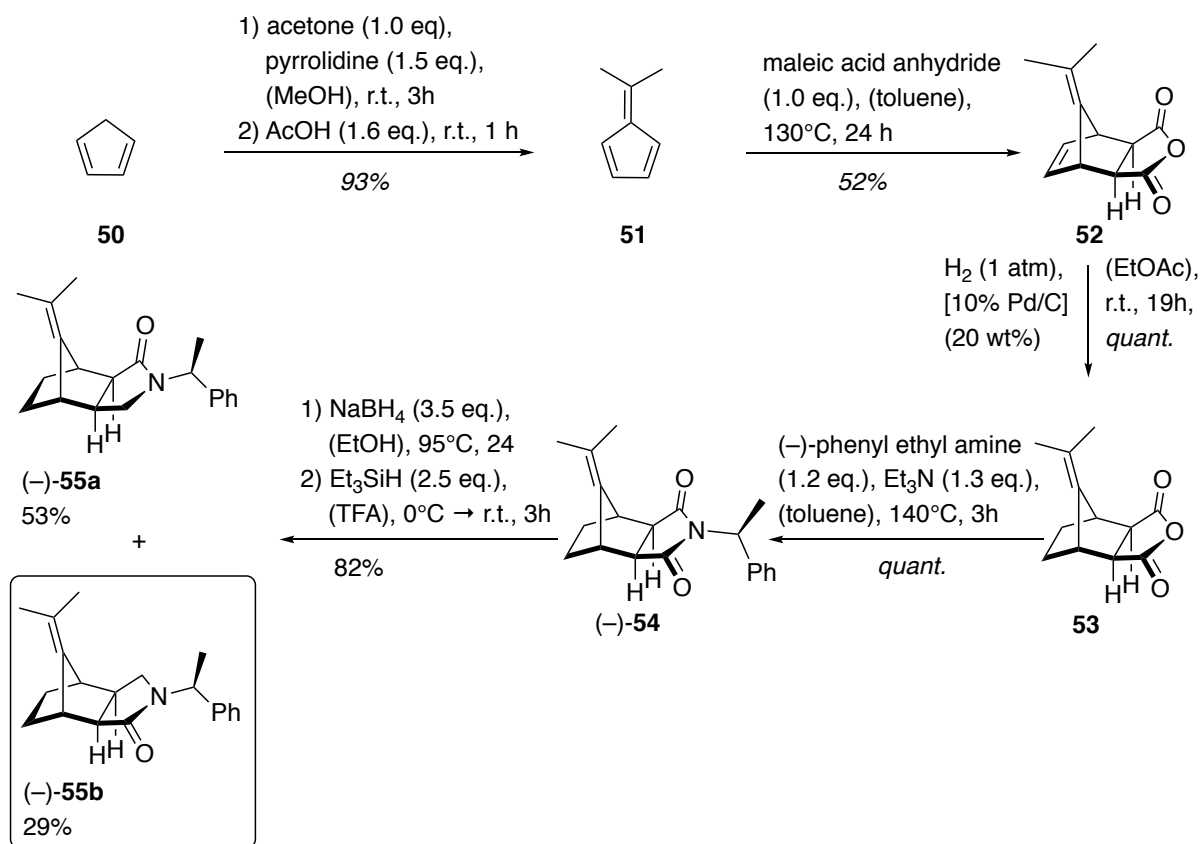

Scheme 13: Synthesis of diastereoisomers **55a** and **55b**.

Minor diastereoisomer (–)-**55b**, which was obtained in >99% *de*, was then deprotected under *Birch* conditions to give the enantiomerically pure amide (+)-**56** in 93% yield. To introduce the alkynyl linker for the phenanthroline core, the second double bond was cleaved in an ozonolysis to give the diketone (+)-**57** in 82% yield. Compound **57** was then transformed into the enolether **58** in a *Wittig* reaction optimized by *Frost* [42] in 76% yield and an *E/Z*-ratio of 62:38. Acid-catalyzed hydrolysis of **58** with (+)-camphorsulphonic acid (CSA) gave epimerisation-prone *endo*-aldehyde (+)-**59** in 71% yield. Alkyne (–)-**61** was obtained *via Seyferth-Gilbert* homologisation in 90% yield (Scheme 14).
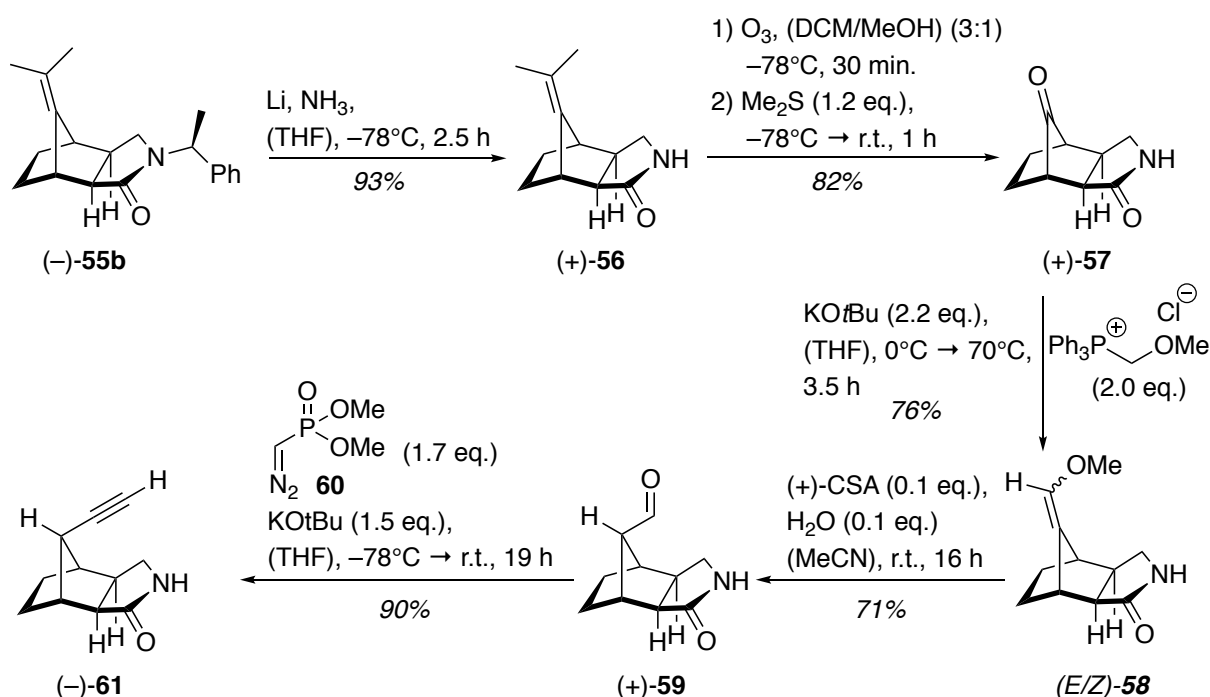

Scheme 14: Synthesis of template-alkyne **61**.

To obtain phenanthroline ligand (+)-**36**, terminal alkyne (–)-**61** was to be coupled with the respective bromophenanthroline in a *Sonogashira*-reaction optimized by *Annapureddy*[43]. To obtain the necessary 4-bromo-1,10-phenanthroline **65**, Meldrum's acid was coupled with 8-aminoquinoline (**62**) to give compound **63** in 82% yield. **63** was then cyclized to 4-hydroxy-1,10-phenanthroline (**64**) by refluxing at high temperatures, followed by bromination with phosphoryl chloride to give 4-bromo-1,10-phenanthroline **65** in 19% yield.
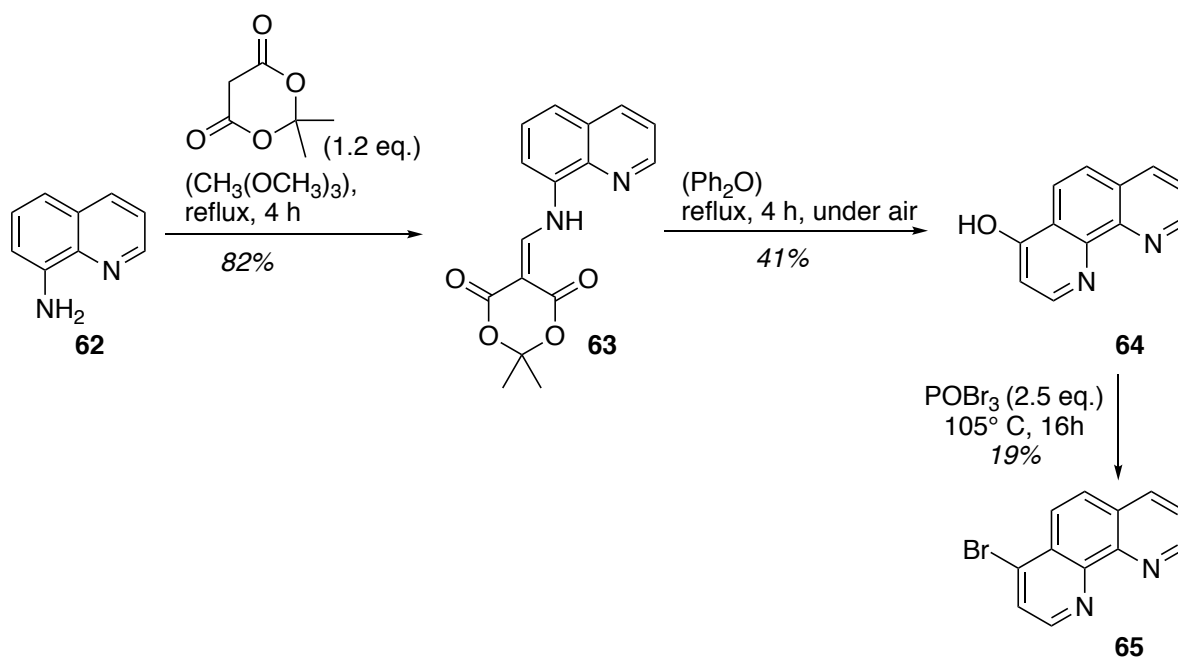
Scheme 15: Synthesis of 4-bromo-1,10-phenanthroline **65**.

The final phenanthroline ligand (+)-**36** was obtained *via* a *Sonogashira* cross-coupling of the template alkyne (–)-**61** with **65** in 85% yield (Scheme 16).
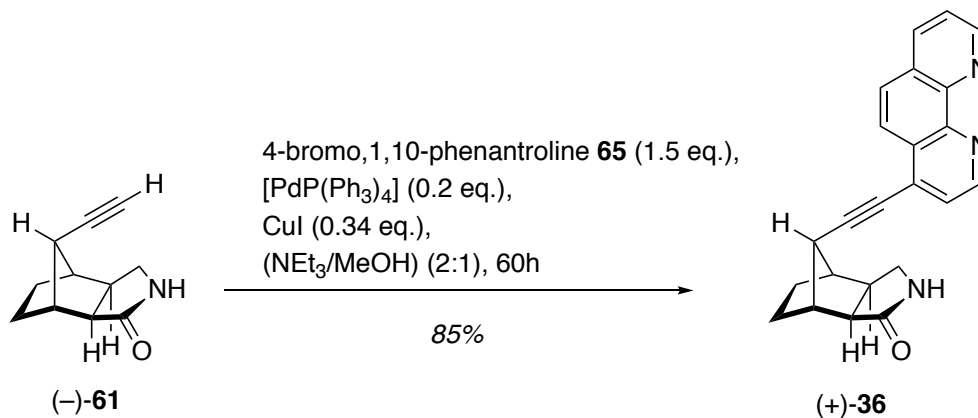
**Scheme 16:** Synthesis of ligand (+)-**36** *via Sonogashira* coupling.

4. Catalytic borylations

4.1. State of the art

A long-standing challenge for synthetic chemists is the direct and selective functionalization of unactivated alkyl-, alkenyl- and aryl C–H bonds. Extensive progress has been made in selectively transforming C–H bonds into C–C, C–N, C–O and C–halogen bonds, since they are important reactions for the synthesis and late-stage modification of natural products and pharmaceutical agents.[44],[45],[46] Today, a wide array of site- and stereoselective procedures for C–H functionalization are available, offering the precision and predictability necessary for assembling complex molecules. These procedures simplify former multi-step processes by eliminating functional group manipulations. Due to the numerous contributions from research groups focusing on this topic, the C–H bond can now be considered a building block for both C–C and C–heteroatom functionalities.[46],[47]

During the past two decades, the conversion of C–H into C–B bonds has gained increasing attention, since organoboron compounds are versatile building blocks for material science, agrochemistry and pharmaceutical chemistry.[48],[49],[50],[51]
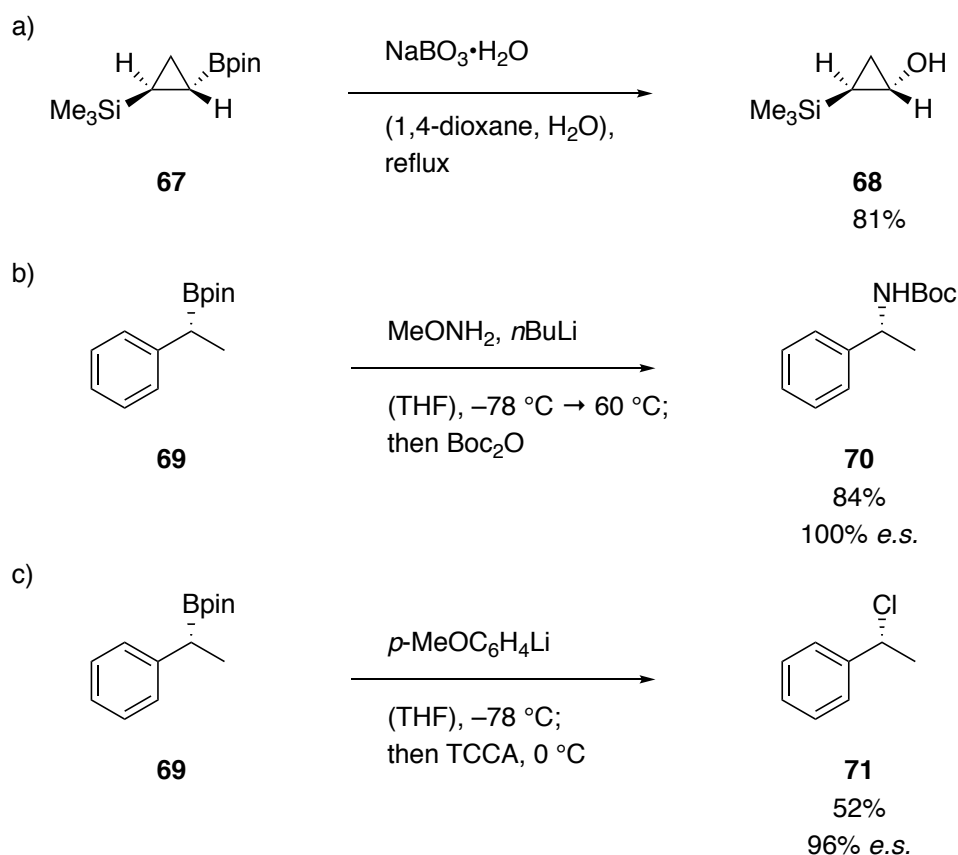

Scheme 17: a) Stereoretentive oxidation of boronic ester **67**[52]; b) Enantiospecific amination of boronic esters **69**[53]; c) Enantiospecific halogenation of boronic esters **69**.[54]

It is known that boronic esters undergo oxidation to form alcohols (Scheme 17a)[52], aminations (Scheme 17b)[53] to give amines and reactions with halogen electrophiles to organohalides (Scheme 17c)[54] without losing stereoinformation.[55],[56] Furthermore, they enable easy cross-coupling reactions with carbon-electrophiles to form new C–C bonds, which was used in the synthesis of natural products like *Niraparib*.[57] In addition, the direct C–H borylation reactions often exhibit high functional group tolerance, proceed under mild conditions and pose an orthogonal approach compared to conventional methods. [58]
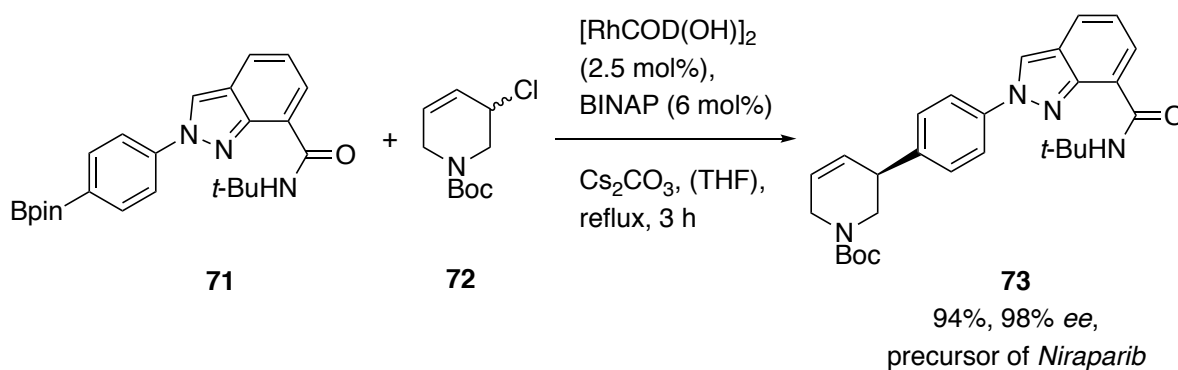
**Scheme 18:** Dynamic kinetic Suzuki coupling of a boronic ester in the synthesis of Niraparib.[57]

The first catalysts reported for the direct borylation of arenes were pentamethylcyclopentadienyl (Cp*) iridium complexes.[59] Since then, a plethora of different combinations of iridium precursors and ligands were reported that generated more active catalysts, especially catalyst systems with phosphane- and nitrogen-based ligands.[47] *Ishiyama, Miyaura* and *Hartwig* reported the successful and efficient borylation of arenes with iridium complexes containing bipyridine derivatives in combination with bis(pinacolato)diboron (B_2pin_2) in 2002, which catalyzed the reaction with higher turnover numbers (TON) as well as at lower temperatures compared to previous reports on C–H borylations.[60] In optimization studies they found that among the most efficient precatalysts, the (1,5-cyclooctadiene)-(methoxy)iridium(I)dimer ([Ir(COD)(OMe)]$_2$) proved to be the most active.[61] In their recent papers, *Hartwig* and co-workers reported the bidentate 3,4,7,8-tetramethylphenanthroline ligand to be one of the most active and effective ligands used in the iridium catalyzed borylation of aromatic C–H bonds due to its rigid and planar structure containing two *cis*-oriented nitrogen atoms and its high electron density.[59],[62]
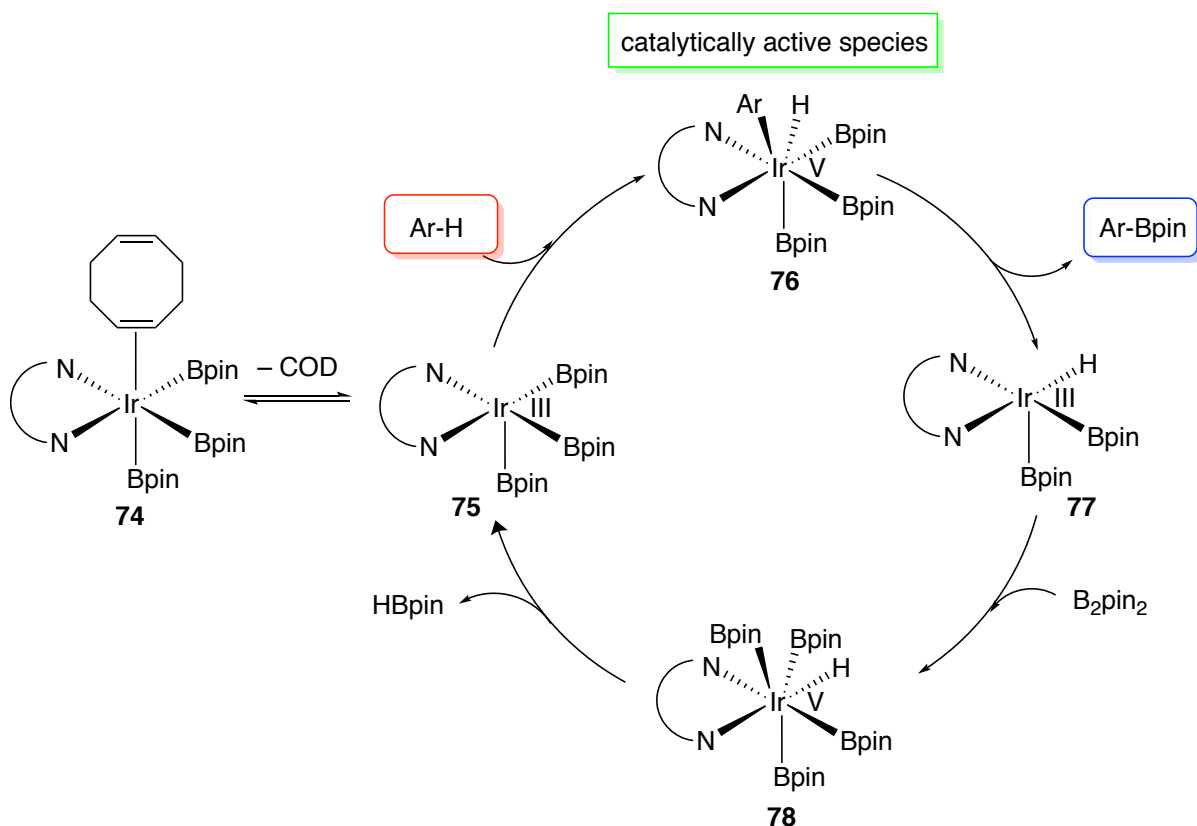
Scheme 19: General catalytic cycle of the iridium catalyzed arene C–H borylation.[63]

A general catalytic cycle for the borylation of aryl C–H bonds with an iridium catalyst bearing a tetramethyl phenanthroline ligand (tmphen), based on DFT calculations reported by *Sakaki et al*.,[64] is depicted in Scheme 19.[63] Starting from the [Ir(COD)(OMe)]$_2$, precatalyst [Ir(tmphen)-(Bpin)$_3$(cod)] (**74**) is formed upon addition of tmphen and boronate reagent B$_2$pin$_2$. Reversible dissociation of cyclooctadiene (cod) leads to the active 16-electron iridium(III)-species **75**, which then reacts with the aryl C–H bond to afford the catalytically active iridium(V) intermediate [Ir(tmphen)(Bpin)$_3$(H)Ar] (**76**) *via* oxidative addition. The borylated product dissociates from this complex *via* reductive elimination, leading to the Ir(III) hydride species **77**, which then reacts with B$_2$pin$_2$ to generate pinacol borane (HBpin) and regenerates the 16-electron triboryl-iridium intermediate **75**.[63]

One pioneering group of iridium-catalyzed, undirected borylation of sp^2- [65] as well as sp^3-carbon atoms[59] is the group of *Hartwig*. They showed, that due to the sterically crowded nature of the catalytically active species **76**, where iridium has seven coordination partners, regioselectivity is generally dominated by steric effects, while electronic factors are of minor significance. As demonstrated on the examples a) and b) in Scheme 20, borylation occurs at the most accessible position in simple arenes like **78** and **79**, regardless of their different electronic properties.[60]
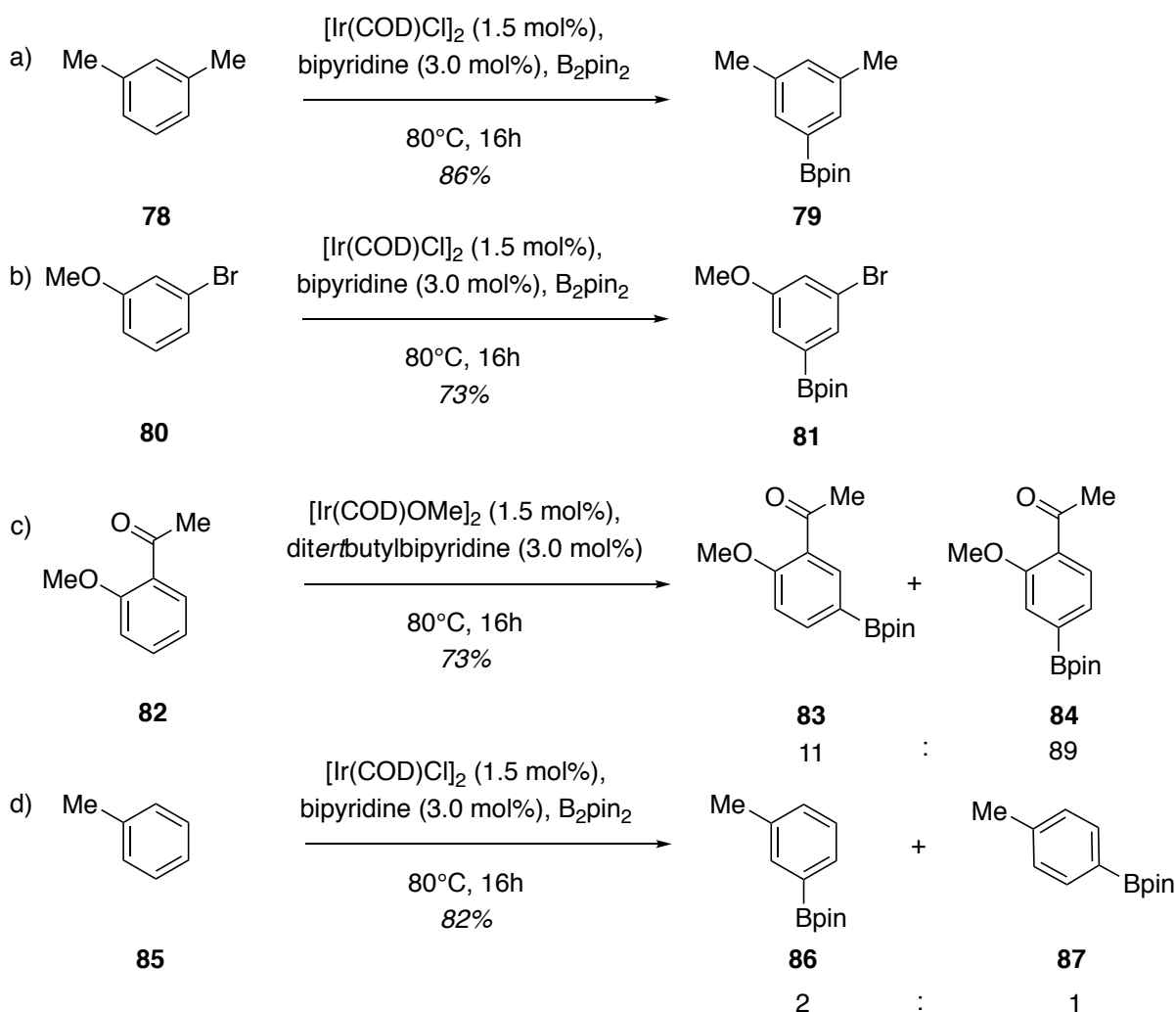
Scheme 20: Regioselectivity in the iridium catalyzed arene C–H borylation.[60]

While steric effects are exclusively dominating at higher temperatures, electronic influences have a bigger impact at lower temperatures. In general, π-electron acceptors like the ester group in compound **82** lead to *para*-borylation, while π-donor substituents like the methoxy group in compound **82** favor *meta*-borylation (Scheme 20c). In mono-substituted arenes, for example compound **85**, borylation will occur statistically at the most accessible positions *meta* and *para* to the substituent (Scheme 20d).[60] This preference of regioselectivity is complementary to traditional functionalization strategies of arenes, e.g., *Friedel-Crafts* reactions, making it a useful, orthogonal approach for functionalizing aromatic compounds.[47]

In heteroarenes, electronics play a bigger role in site-selectivity, which is why borylations occur with higher regioselectivity at the most acidic positions and rarely adjacent to nitrogen atoms (Scheme 21).[66],[67]
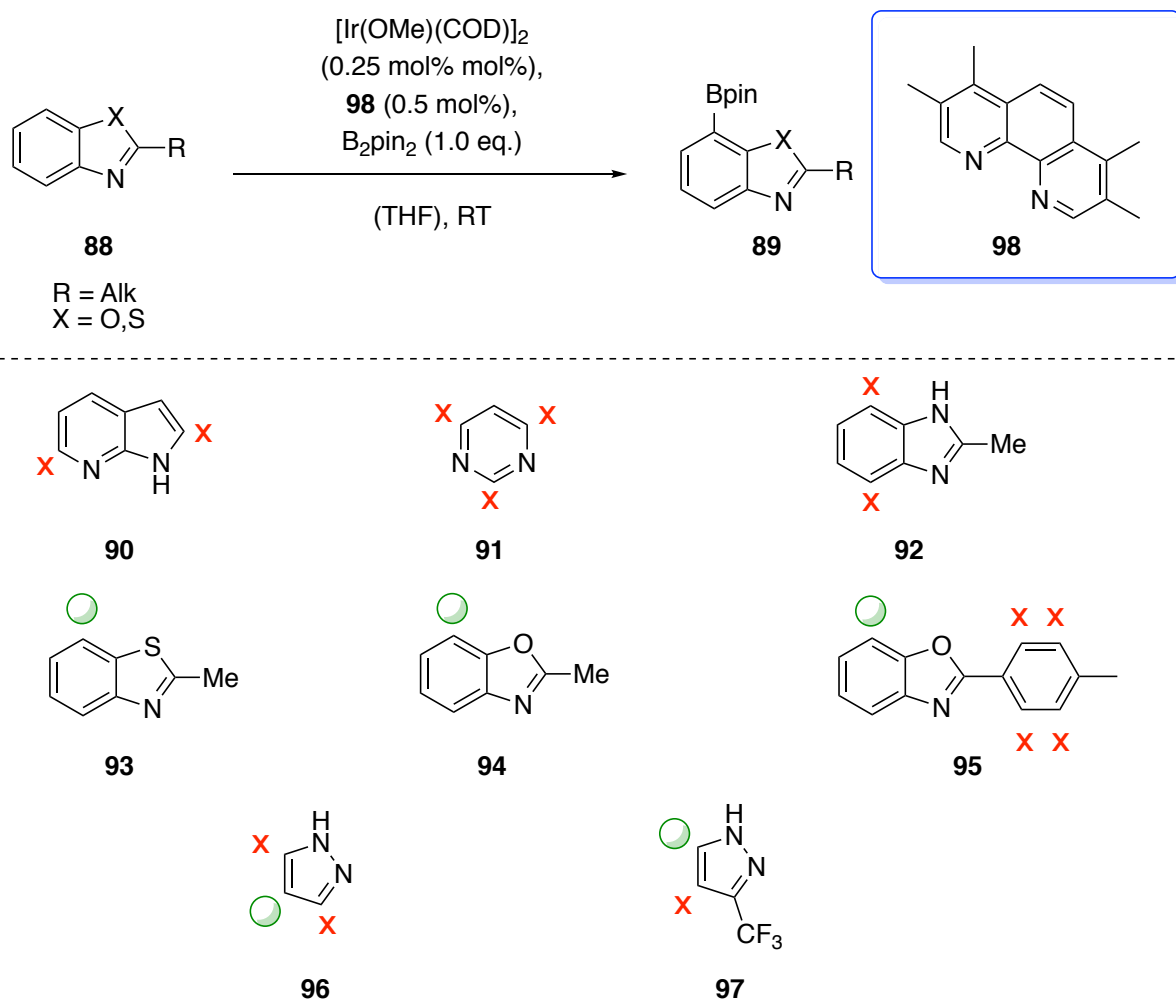
**Scheme 21:** Favoured and disfavoured sites of borylation on a variety of different heteroarens.

To tackle the issue of regioselectivity, a lot of research has been done on borylations with implemented directing groups on the substrates. One example is the silyl-directed regioselective borylation of arenes published by *Boebel et al.*, where a silyl group attached to the arene substrate **99** replaces one of the boryl groups on the iridium catalyst upon addition, which brings the substrate in closer proximity to the catalytically active center, and borylation occurs selectively on the *ortho*-position (Scheme 22a).[68]

In 2013, the group of *Hartwig* demonstrated the successful application of this method to the functionalization of sp³-carbon atoms, where they regioselectively borylated C–H bonds in benzylic positions (Scheme 22b).[69] The group of *Kanai* showed that next to covalently bound directing groups, hydrogen bonds can be utilized to efficiently control regioselectivity in their borylation of benzamides **105**, where a urea moiety on the ligand coordinates the carbonyl group of the substrate amide leading to *meta*-products exclusively (Scheme 22c).[70]

a)

b)

c)

	Yield	*meta: para*
dtbpy	49%	1.5
107	44%	27
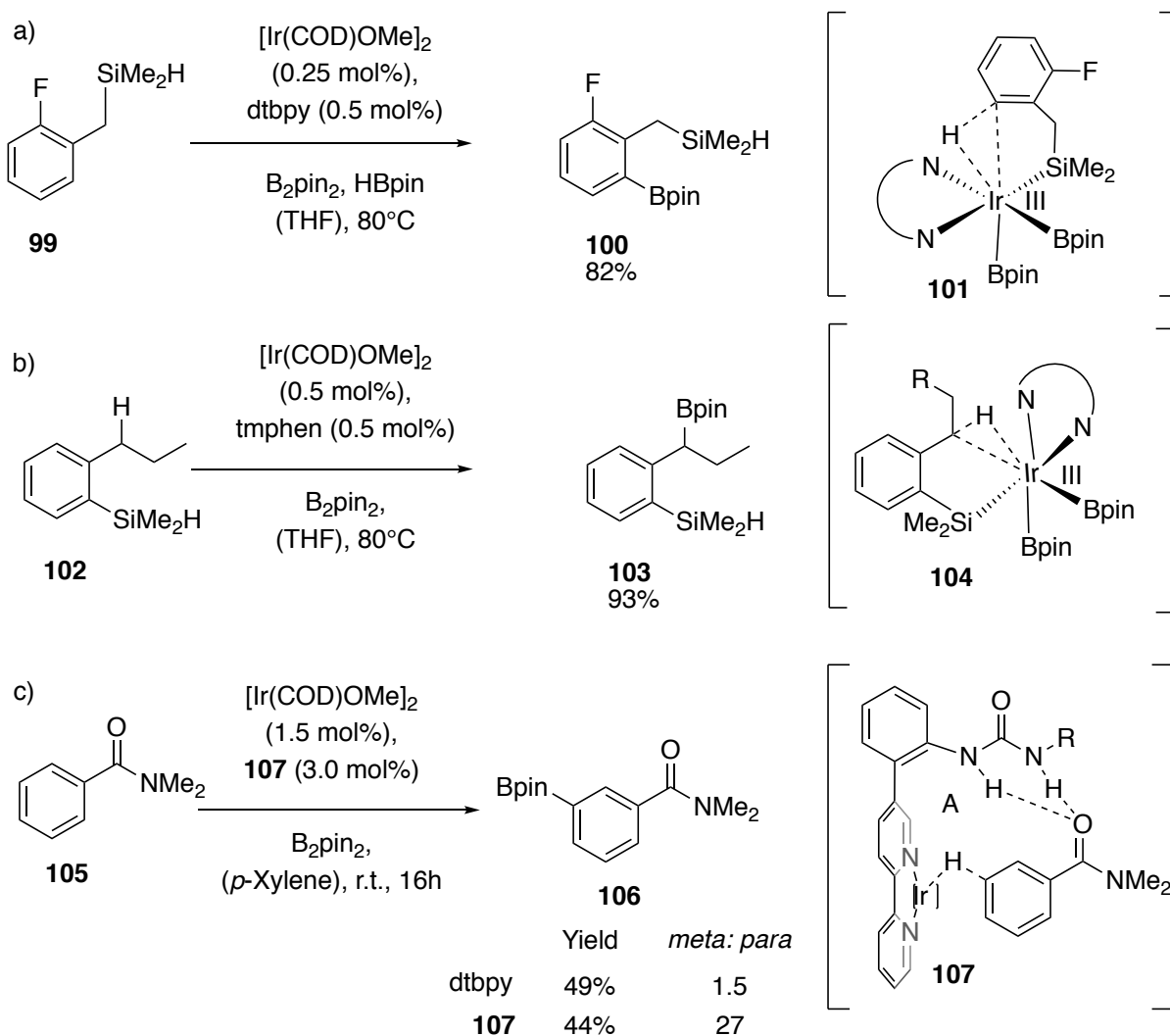
Scheme 22: Regioselective borylations mediated by silyl-[69] and amide[70] directing groups.

Despite the ubiquity of metal catalysts for the borylation of C–H bonds[47],[51], methods for enantioselective transformations were not known until 2013. One of the biggest tasks was to find suitable ligands that exhibit the necessary steric and electronic properties to generate active catalysts.[71] One of the first chiral ligands employed in a enantioselective borylation was the tetrahydroquinolyl oxazoline ligand **110**, which was designed initially for enantioselective silylation reactions[72] of C–H bonds. The group of *Hartwig* successfully applied this ligand in the silyl-group directed desymmetrization of diarylmethyl silanes **108**, affording borylated products with up to 92% *ee* (Scheme 23).[73]
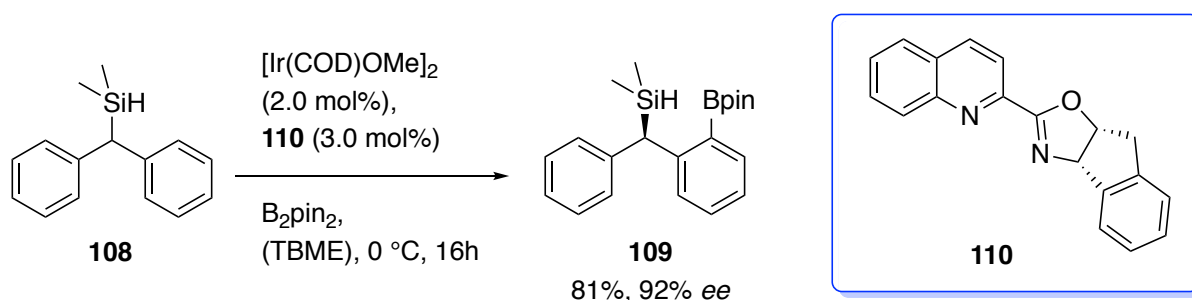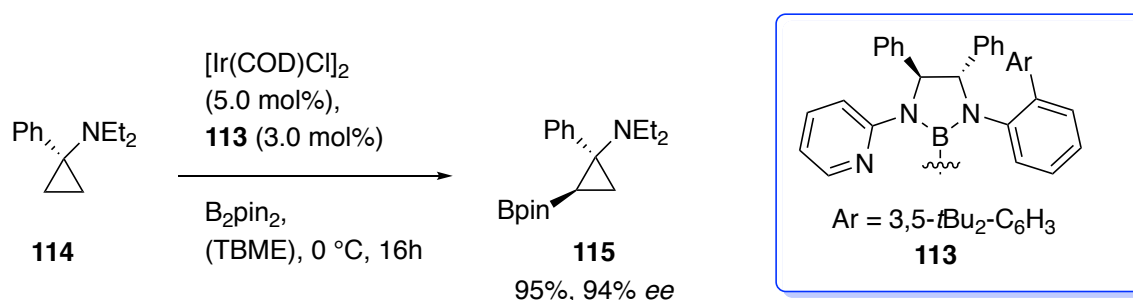
Scheme 23: Silyl group directed enantioselective desymmetrization of diarylmethyl silanes **108**.[73]

In 2017, the group of *Li* published the *ortho*-selective C–H borylation of arenes with a bidentate N,B-ligand containing a pyridyl- and a silylborane-moiety.[74] Inspired by this work, *Xu* and co-workers developed a N,B-ligand exhibiting a chiral boron-containing five-membered ring (**113**) and applied this catalyst system to the desymmetrization of diarylmethylamines such as **111** by iridium-catalyzed borylation leading to enantioenriched products with up to 95% *ee*.[75]
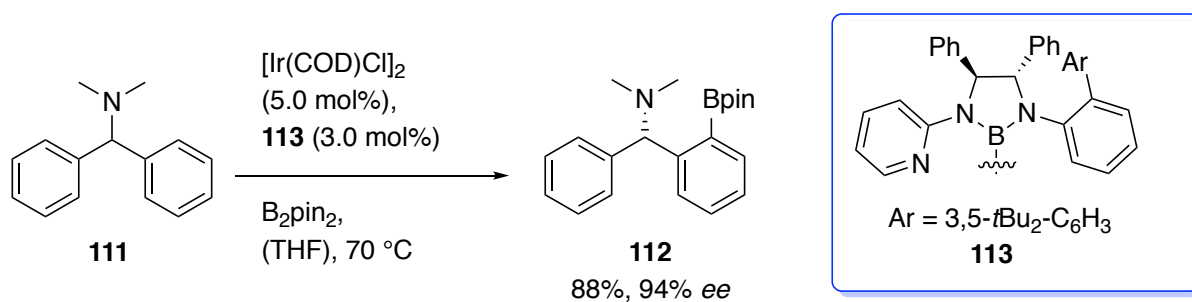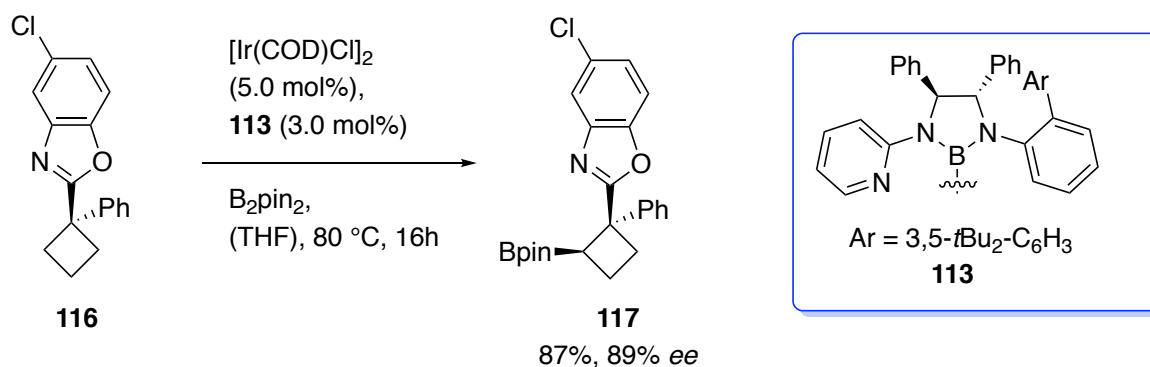

Scheme 24: Amine group directed enantioselective desymmetrization of diarylmethylamines.[75]
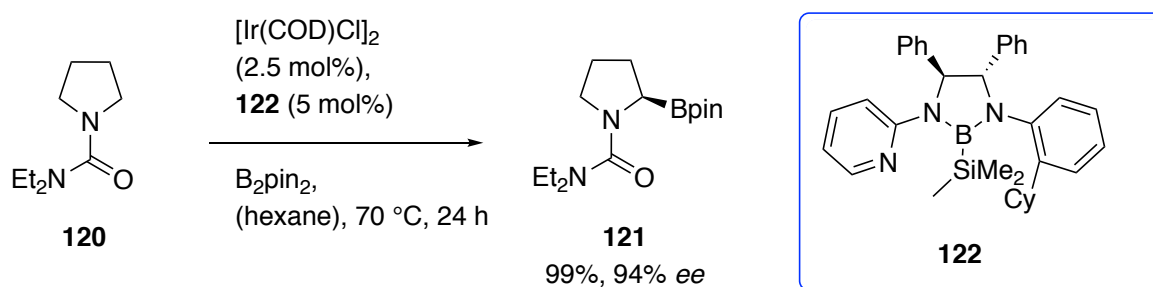
By optimizing the N,B-ligand, they were able to extend their substrate scope to the sp³-C–H borylation of cyclopropanes (Scheme 25)[76], cyclobutanes (Scheme 26)[77] and azacycles (Scheme 27).[78]

**Scheme 25:** Amine group directed enantioselective borylation of cyclopropanes **114**.[76]

Scheme 26: Oxazole-directed enantioselective borylation of cyclobutene **116**.[77]

Scheme 27: Amide group directed enantioselective borylation of azacyle **120**.[78]

Since dinitrogen donor compounds proved to be among the most efficient ligands due to their high functional group tolerance and activity, recent research also explored the development of chiral analogues of bipyridines and phenanthrolines for the iridium-mediated, enantioselective borylation of C–H bonds. An example which highlights the enantioselective borylation of substrates using hydrogen bonding as control element, is the *meta*-selective desymmetrization of geminal diaryl amides **123** published by the *Phipps* group. In their work, they developed a catalyst system containing an anionic bipyridine ligand with negatively charged sulfonate group, that interacts with a chiral dihydroquinine cation *via* electrostatic effects (**L•C**), giving highly enantioenriched alcohols after subsequent oxidation of the borylated products. Regioselectivity is controlled by the sulfonate group which coordinates the amide of the substrate *via* hydrogen bonding, while the chiral cationic counter ion enables enantioselectivity by creating a chiral environment (Scheme 28).[79]
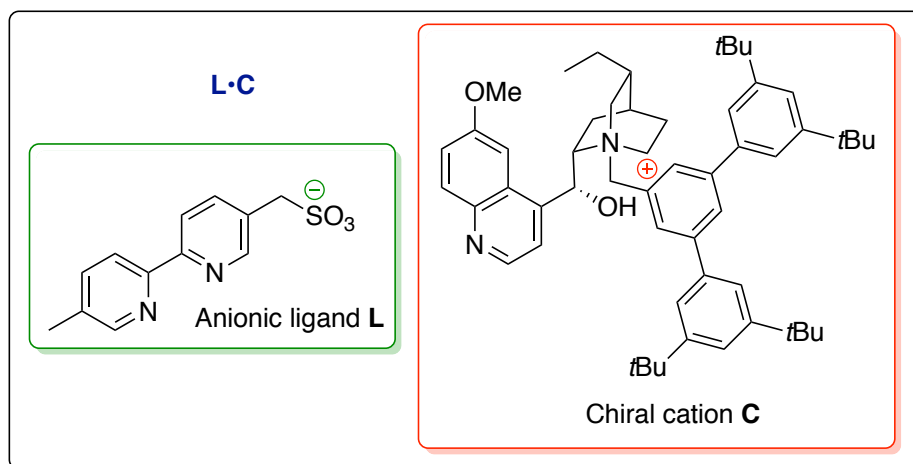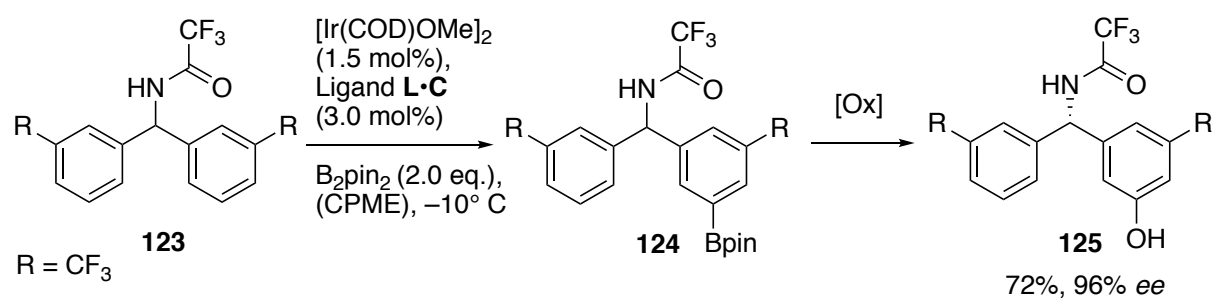
**Scheme 28:** Hydrogen bond-mediated, enantioselective borylation of diaryl amides.[79]

4.2. Objective

Based on the insights on hydrogen bond-mediated supramolecular catalysis and inspired by the previous work of *Hartwig*[59], *Phipps*[79] and *Xu*[75], the aim of this work was to develop new template-bound C–H borylation catalysts. Based on previous research on C–H borylations, [Ir(COD)(OMe)]$_2$ was chosen as a precatalyst and B$_2$pin$_2$ as boron source, since the combination of the two with bidentate nitrogen donors like bipyridine- or phenanthroline ligands proved to be most effective in terms of turn-over number and stability.[80]

Motivated by the undirected borylation of strong primary and secondary C-H -bonds by *Hartwig*[59], the iridium-catalyzed, undirected borylation of sp^3-carbon atoms should be investigated. A problem that needed to be tackled, was the high temperature required for this borylation reaction.[58] Since hydrogen bonds, which are an integral component of the catalytic system envisaged in this work, are weak non-covalent interactions, they exhibit high sensitivity to temperature.[81] To initiate borylations at lower reaction temperatures, the aim was to choose substrates with weaker C–H bonds. Therefore, prochiral quinolone- (**126**, **128** and **129**) and dihydroqiuinolones or oxindoles (**127**) exhibiting benzylic C–H bonds as well as a suitable lactam binding site were chosen as test substrates.


| **126** | **127** | **128** | **129** |

via

selective C–H bond activation
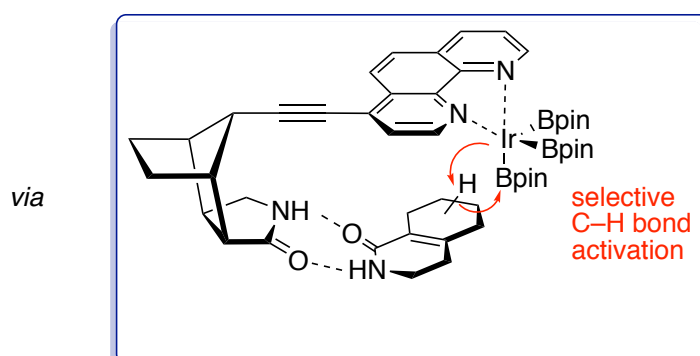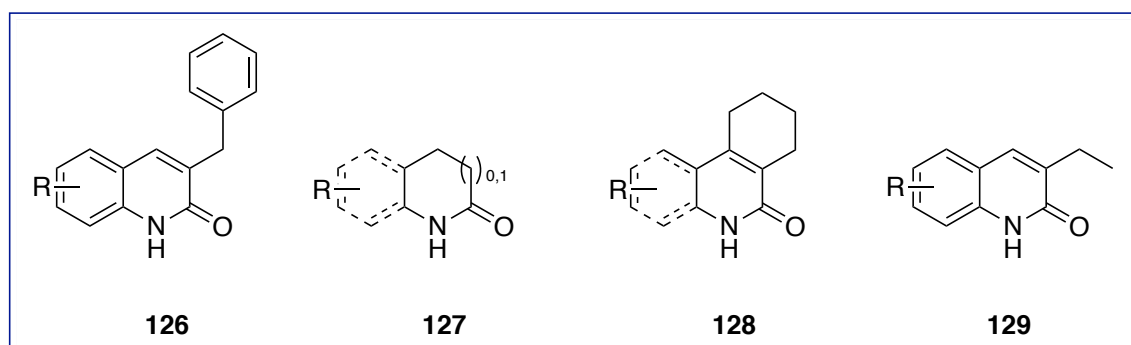
Since borylation of aromatic and heteroaromatic C–H bonds already occurs at room tempera-ture[60],[65], a variety of prochiral *bis*-phenyl-bearing compounds like oxindoles **130**, piperidi-nones **131**, acetamides **132** and hydantoins **133** were selected as test substrates for a possible desymmetrization *via* C–H borylation.


via
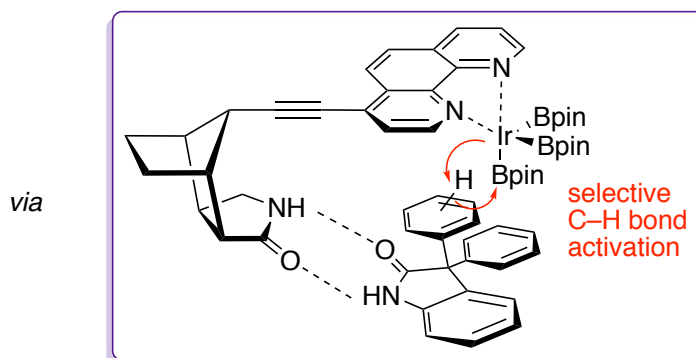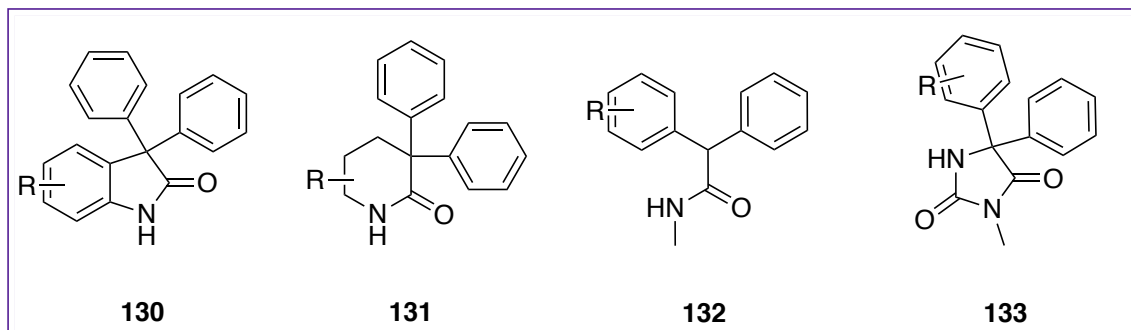
4.3.   Studies to catalytic borylations with bifunctional phenanthroline ligands

Depicted in Figure 2 are the substrates that were investigated first. While ∂-valerolactam (**140**) and 3,4-dihydroquinolin-2(1*H*)-one (**142**) are commercially available, compounds **134**[82],**135a**[83], **135b**[83], **136**[84], **137**[85], **138**[86], **139**[43], **141**[43] and **143**[86] were synthesized by literature-known procedures.
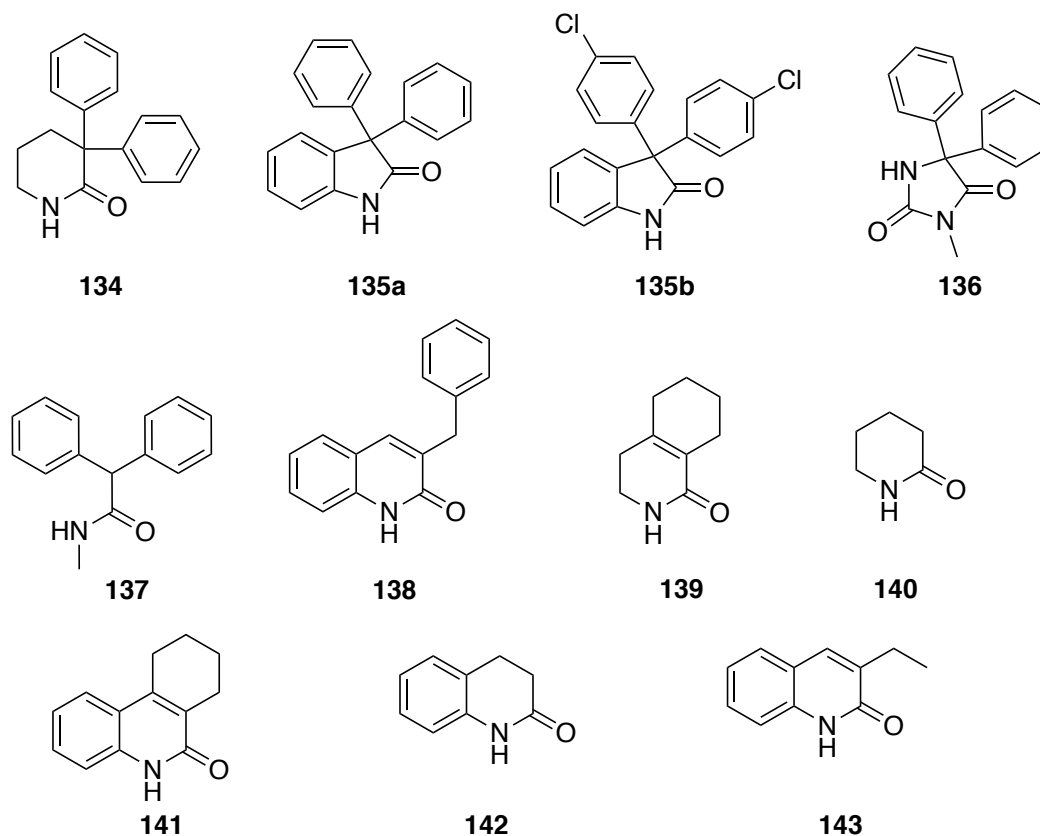
Figure 2: Test substrates exhibiting am lactam binding site and benzylic protons.

To test the general activity of phenanthroline ligand (+)-**36**, it was employed in the borylation reaction under standard conditions established in the literature using [Ir(COD)(OMe)]$_2$ as a precatalyst, B$_2$pin$_2$ as boron source and THF as solvent. First, piperidinone **134** was tested, running the reaction overnight at room temperature (r.t.) since it is known that arene borylation already occurs at low temperatures compared to sp^3-C–H borylation (Table 2, entry 1). Because no reactivity was observed, the reaction was run at higher temperatures, longer reaction times and the solvent was exchanged for cyclopentyl methylether (CPME). The latter was reported to be efficient in hydrogen bond-mediated borylation of sp^2-C–H bonds (Table 2, entries 2-4).[79] Given the lack of reactivity and the poor solubility of substrate **134**, oxindole **135a** and 3-benzylquinolone **138** were tested in combination with different solvents, temperatures and reaction times, but still no reactivity was observed (Table 2, entries 5-10).
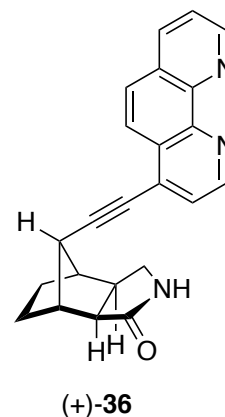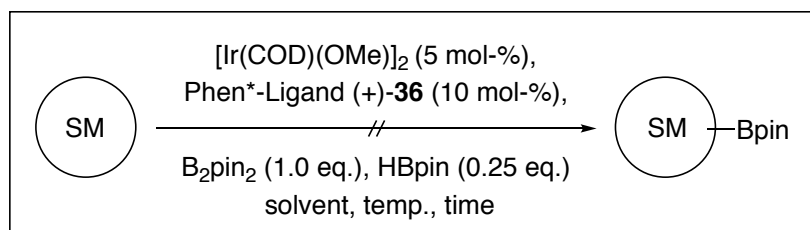
(+)-**36**
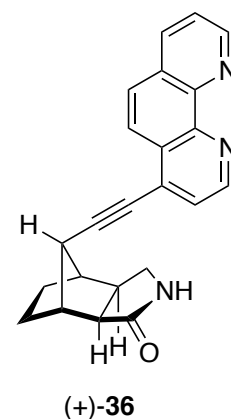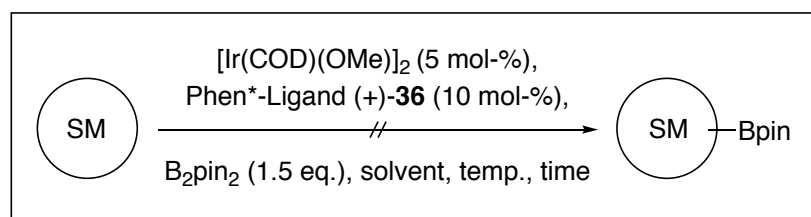
Table 2: Screening of reaction parameters for the iridium catalyzed borylation of different substrates.

Entry	Substrate	Solvent	Solubility	Temp.	Time
1	**134**	THF	poor	r.t.	17 h
2	**134**	THF	poor	60 °C	15 h
3	**134**	CPME	poor	60 °C	15 h
4	**134**	CPME	poor	80 °C	17 h-53 h
5	**135a**	cyclooctane	very poor	r.t.	15 h
6	**135a**	THF	moderate	r.t.	17 h
7	**135a**	THF	moderate	60 °C	17 h-53 h
8	**135a**	CPME	moderate	r.t.	17 h-53 h
9	**138**	cyclooctane	very poor	r.t.	15h
10	**138**	CPME	moderate	80 °C	17 h-53 h

Given the prevalence of cyclooctane in the literature, which should also be beneficial to the formation of hydrogen bonding[11] owing to its non-polar and non-protic properties[87], it was also tested as a solvent (Table 2, entries 5 and 9). [88],[59],[89] Unfortunately, all substrates **134-143** were insoluble in cyclooctane.

Considering the lack of reactivity in the previous solvents, *p*-xylene was tested, as it was reported in the literature to be an efficient solvent in iridium-catalyzed borylations.[3] Next to this, DCM was tested due to the good solubility of all substrates in this solvent. Although the solubility of the substrates was better in both solvents, still no reactivity was observed. Higher temperatures did not seem to induce reactivity either, which is why another approach was investigated. In the literature it was suggested that borylation with B$_2$pin$_2$ as boron source can exhibit

induction periods upon forming the catalytically active complex, which can be eliminated by addition of catalytic amounts of pinacolborane (HBpin).[90] Thus, 0.25 equivalents of HBpin were added in addition to 1.0 equivalents of B$_2$pin$_2$ in the following screening of substrates **134-141** (Table 3). Unfortunately, still no discernible reaction occurred.


(+)-**36**

Table 3: Screening of different substrates for the iridium catalyzed borylation with catalytic amounts of HBpin.

Entry	Substrate	Solvent	Solubility	Temp.	Time
1	**135a**	*p*-xylene	good	40 °C	17 h-29 h
2	**138**	*p*-xylene	good	40 °C	17 h-29 h
3	**134**	*p*-xylene	moderate	r.t.	17 h-29 h
4	**134**	*p*-xylene	moderate	40 °C	17 h-29 h
5	**137**	*p*-xylene	good	40 °C	17 h-29 h
6	**141**	*p*-xylene	poor	40 °C	17 h-29 h
7	**141**	DCM	moderate	40 °C	17 h-29 h
8	**135b**	DCM	good	40 °C	17 h-29 h

Next, a 1:1 mixture of CPME and toluene was investigated in an extensive substrate screen of compounds **134-142** (Table 4), since this solvent system was suggested in the literature to support effective enantioselective C–H borylations.[91]

While there was no observable reactivity at room temperature, reactions that were run at 80 °C led to borylation of the aromatic C–H bonds of toluene (Table 4, entries 6, 8, 9, 11).
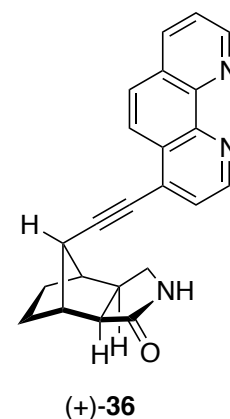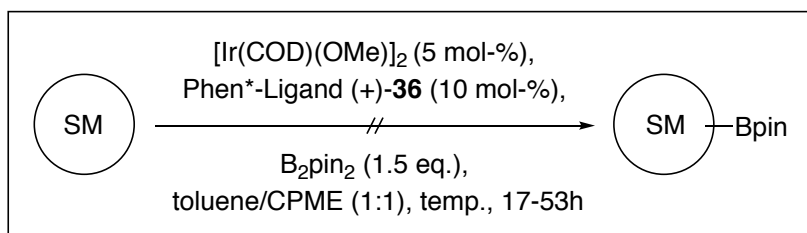
Table 4: Substrate screen in combination with a toluene/CPME solvent system.

Entry	Substrate	Solubility	Temp.	Yield
1	**142**	good	r.t.	-
2	**142**	good	80 °C	-
3	**141**	moderate	r.t.	-
4	**141**	moderate	80 °C	-
5	**140**	good	r.t.	-
6	**140**	good	80 °C	solvent borylation
7	**137**	moderate	r.t.	-
8	**138**	moderate	80 °C	solvent borylation
9	**135a**	good	80 °C	solvent borylation
10	**140**	good	80 °C	-
11	**136**	good	80 °C	solvent borylation
12	**136**	good	r.t.	-
13	**134**	moderate	r.t.	-
14	**134**	moderate	40°C	-
15	**136**	good	80°C	solvent borylation

However, when substrate **135b** was exposed to these reaction conditions, additional traces of new, low field shifted signals were observed in the ¹H-NMR. To avoid borylation of the solvent, different substituted aromatic solvents like trifluorotoluene, pentafluorotoluene and mesitylene were examined in a 1:1 solvent system with CPME in the borylation of **135b** (Table 5).

First, B$_2$pin$_2$ (1.5 eq.) was employed as the single boron source. With trifluorotoluene, borylation of the solvent was observed (Table 5, entry 1), while there were no indications of reactivity with pentafluorotoluene and mesitylene (Table 5, entries 2 and 3).
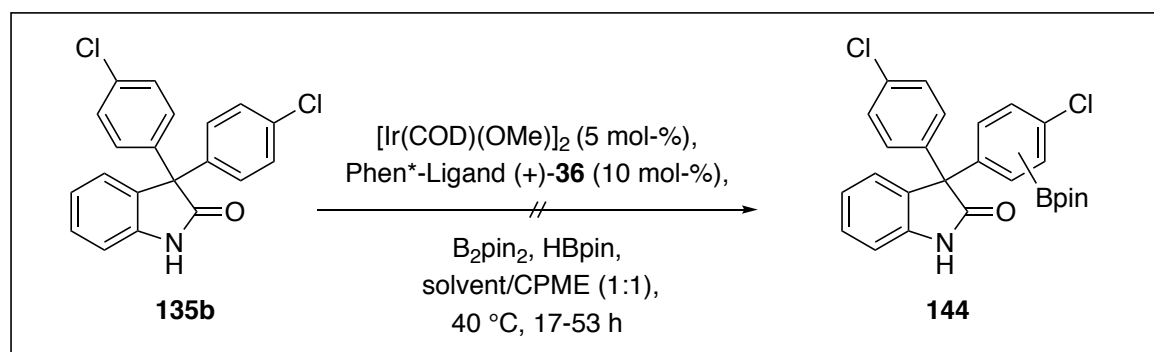
Table 5: Solvent screening of the C–H borylation of oxindole **135b**.

| Entry	Solvent	Solubility	B$_2$pin$_2$/ HBpin [eq.]	Yield
1	trifluorotoluene	good	1.5/-	solvent borylation
2	mesitylene	good	1.5/-	-
3	trifluorotoluene	good	1.5/-	-
4	pentaflurotoluene	poor	1.0/0.25	-
5	mesitylene	good	1.0/0.25	traces of low field shifted signals
6	trifluorotoluene	good	1.0/0.25	solvent borylation
7	DCM	good	1.0/0.25	traces of low field shifted signals
8	trifluorotoluene	good	1.0/0.25	solvent borylation

Next, a combination of B$_2$pin$_2$ (1.0 eq.) and HBpin (0.25 eq.) was investigated, which led to traces of borylated products when mesitylene or DCM were used (Table 5, entries 5 and 7), while no borylation of the solvent was detected.

Since changing reaction parameters like solvent, temperature and reaction time did not lead to significant improvement of the yields, a change of the ligand structure was envisioned.

Figure 3: Optimisation of the ligand structure by changing the linker position on the phenanthroline core.

Considering that both angle as well as distance between substrate and catalytically active center are two very important factors for reactivity, efficiency and selectivity of a given catalytic system[22], it was aimed to change both parameters by shifting the position of the linker between the chiral backbone and the phenanthroline core (Figure 3).

Scheme 29: Synthesis of the new phenanthroline ligands (+)-**145** and (+)-**146.**

Using the same reaction conditions as mentioned above (see section 3.2), phenanthroline ligands (+)-**145** and (+)-**146** were synthesized by *Sonogashira* coupling with 5- and 2-bromo-1,10-phenanthroline in 47% and 28% yield, respectively (Scheme 29).

A small screen with oxindole substrates **135a** and **135b** was conducted, varying solvent, temperature and borylation agents (Table 6).

(+)-**145**

135

[Ir(COD)(OMe)]$_2$ (5 mol-%),
(+)-**145** (10 mol-%),

B$_2$pin$_2$, HBpin, solvent,
temp., 15 h

147
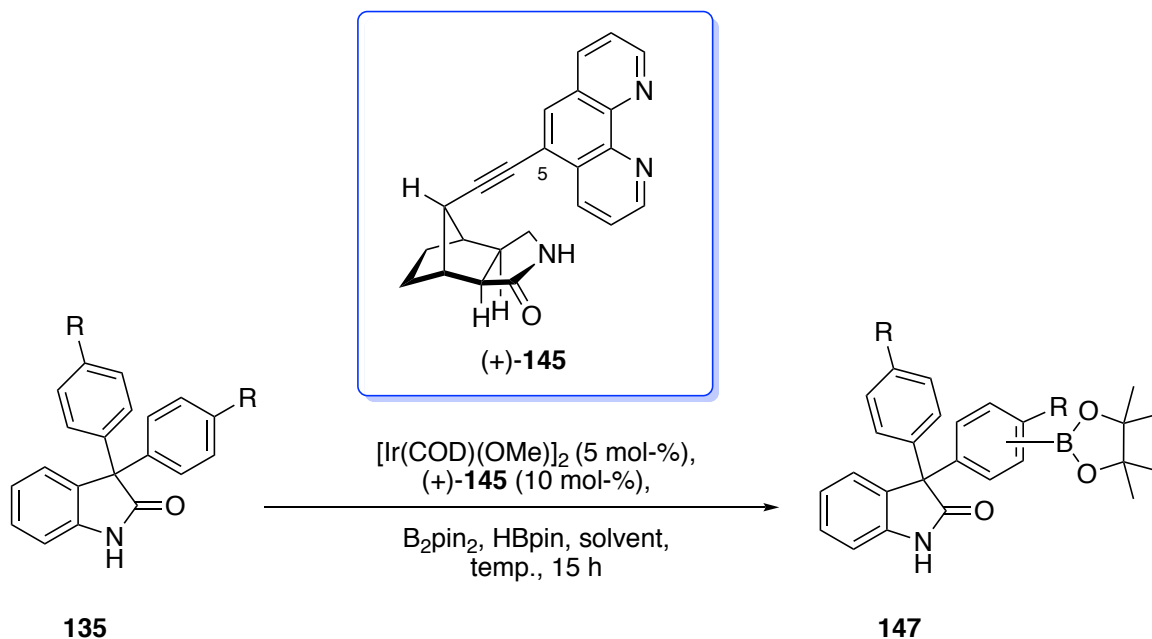
Table 6: Reaction parameter screen with oxindoles **135**.

Entry	#	Solvent	B$_2$pin$_2$/ HBpin [eq.]	Temp.	Product
1	**135b** R = Cl	THF	1.5/-	40 °C	-
2	**135a** R = H	THF	1.5 eq/-	preforming: 1 h at 80 °C, then r.t.	-
3	**135a** R = H	*p*-xylene	1/0.2	40 °C	mixture of borylated species
4	**135a** R = H	*p*-xylene	1/0.2	r.t.	-

While ligand (+)-**146** did not show any reactivity, ligand (+)-**145** led to a mixture of borylated products with substrate **135a** in combination with 1.0 equivalents of B$_2$pin$_2$ and 0.2 equivalents of HBpin, when the reaction was conducted in *p*-xylene at 40 °C for 15 hours (Table 6, entry 3). No reactivity was observed when no HBpin was added.

Given the challenging purification and analysis of the mixture of borylated products **147**, a new oxindole substrate **135c** was synthesized following a literature known procedure.[83] After subjecting it to the established borylation conditions, borylated product **147c** was isolated as the main product in 25% yield. NMR-analysis proved that borylation occurred at the C6-position. Borylation using achiral tetramethylphenanthroline (tmphen, **98**) as ligand gave the same compound **147c** in 20% yield, which indicated that no regioselectivity was achieved by using the chiral ligand (+)-**145** and that borylation occurred on the oxindole core instead on the phenyl rings (Scheme 30).
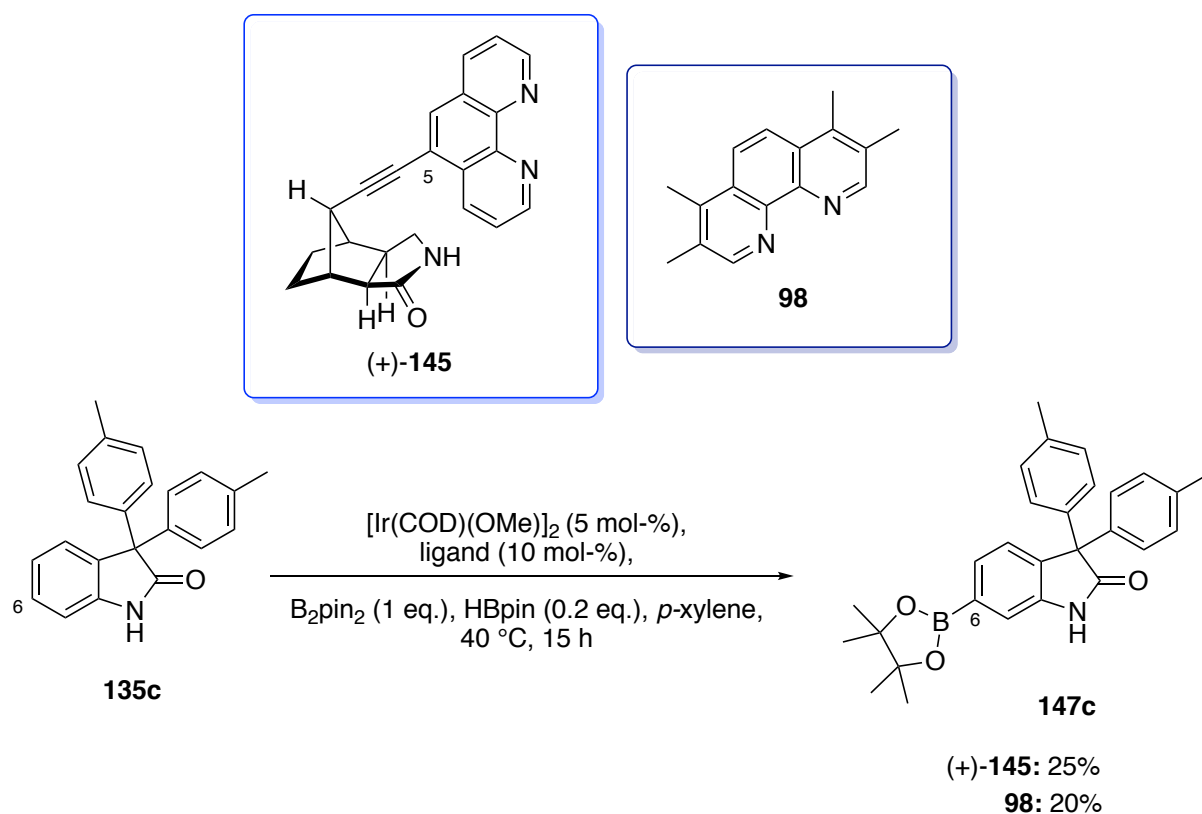
Scheme 30: Borylation at C6 position of oxindole **135c** with phenanthroline ligands **98** and (+)-**145.**

After a substrate screen of compounds **134-143** and commercially available acetamide **148** with the new ligand (+)-**145**, it became apparent that the desired borylation only occurred on hydantoin **136** and acetamides **137** and **148**.
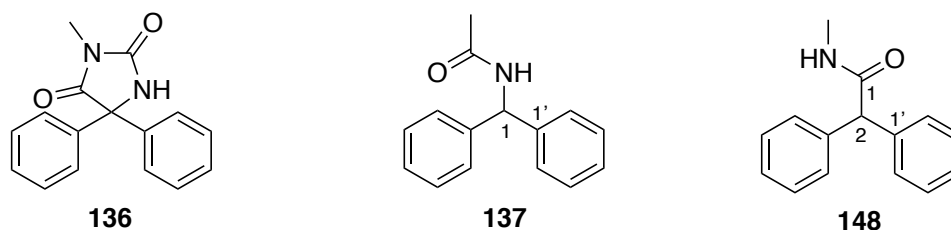
Figure 4: Reactive substrates in the catalytic C–H borylation with ligand (+)-**145**.

Since acetamides **137** and **148** exhibit a fairly high flexibility due to their free rotation around the C1–N-bond bond and the C1–C2 bond, which is unfavorable considering the desired enantioselective induction, hydantoin **136** was chosen for further investigation and optimization. After an extensive effort to purify the obtained borylated products, it became apparent by NMR and GC-MS analysis, that both the *meta*- as well as the *para*-borylated hydantoins were formed. A problem that needed to be tackled was the impossibility of separating the products from the starting material and the remaining B2pin2, which is a reported issue in iridium catalyzed C–H borylations in literature[79] as well as in previous work of our group.[92] To allow for the isolation of the products and determination of their enantiomeric excess (*ee*), the borylated products were oxidized to the corresponding alcohols with hydrogen peroxide following a literature-known procedure[79], giving the inseparable phenols **150a** and **150b** in an overall yield of 20% over two steps (Scheme 31). Subjecting the same starting material to the borylation reaction using tetramethylphenanthroline **98** gave alcohols **150a** and **150b** in an overall yield of 42%.
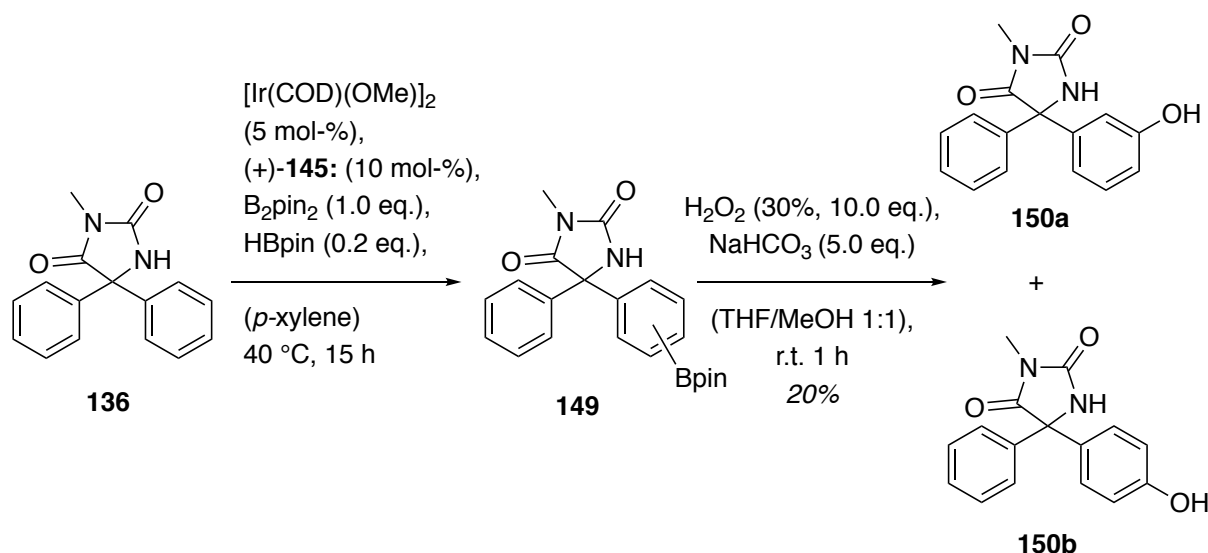
Scheme 31: C–H borylatio-oxidation sequence of hydantoin **136** with chiral ligand (+)-**145**.

Analysis by chiral HPLC indicated that the products **150a** and **150b** were obtained as racemic mixtures and ligand (+)-**145** did not lead to the desired enantioenrichment. Due to the difficulty of separating the two regioisomers by column chromatography, an exploration of substituted analogues of hydantoin **136** was envisaged to limit potential C–H borylation sites and to increase steric bulk for the induction of enantioselectivity. Therefore, *ortho*-fluoro-, *meta*-fluoro- and *meta*-chloro-substituted hydantoins **160-162** were synthesized by benzoin condensation of the respective aldehydes to the benzoins **154-156**, followed by oxidation to the benzils and subsequent *Biltz* reaction[93] to the desired substituted hydantoins (Scheme 32).
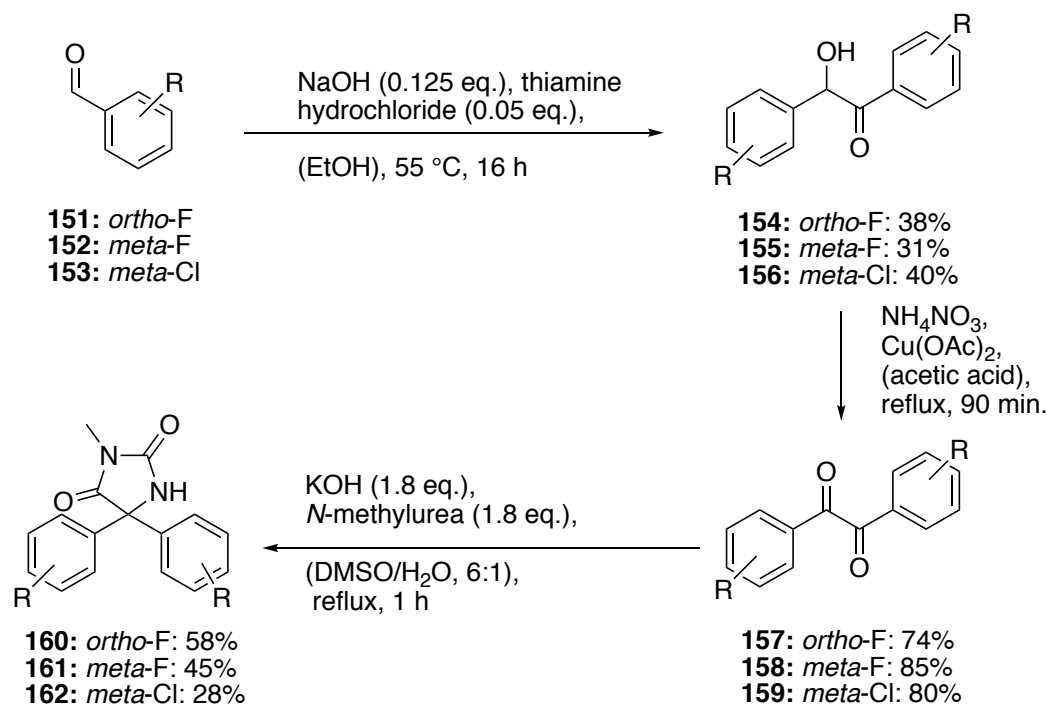
Scheme 32: Synthesis of *ortho*-fluoro hydantoin **160** *meta*-fluoro hydantoin **161** and *meta*-chloro hydantoin **162**.

Furthermore, a more rigid hydantoin, spiro-compound **165** was synthesized by a *Bucherer-Bergs* reaction, followed by protecting of nitrogen atom N3 by nucleophilic substitution using methyl iodide. Hydantoin **165** was obtained in 55% yield (Scheme 33).
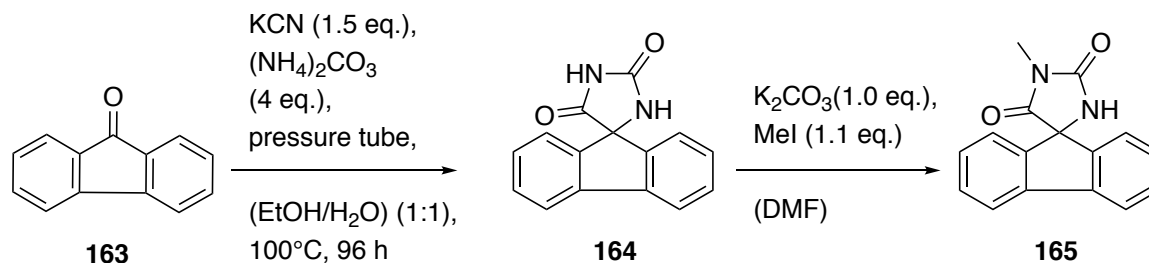

Scheme 33: Synthesis of spiro-hydantoin **165** *via Bucherer-Bergs* reaction.

When subjecting the newly synthesized, substituted hydantoins to the borylation reaction using chiral ligand (+)-**145**, borylation of *ortho*-fluoro hydantoin **160** gave a mixture of three regioisomers in an overall yield of 50% yield, in comparison to the yield of 64% using achiral ligand **98**. Analysis by HPLC indicated that the products were obtained as racemic mixtures.

Hydantoins **161**, **162** and **165** did not show any reactivity using ligand (+)-**145**, while they gave moderately good yields using achiral ligand tmphen (Figure 5). To make sure the previous results could be reproduced, hydantoin **136** was subjected to the same reaction conditions with ligand (+)-**145** again, which also did not lead to product formation. After inspection of the chemicals and consulting of literature, it was found that, although being stored under an argon

atmosphere at 6 °C, HBpin seemed to be instable and formed B_2pin_3 and BH_3[94],[95] which appeared to either inhibit the formation of the catalytically active species necessary to yield the borylated products or the catalytically active species did not form due to the lack of HBpin in the reaction mixture. As the previous studies showed (Table 4), the reaction did not proceed without catalytic amounts of HBpin in the reaction mixture.

	150	**166**	**167**
achiral **98**:	42%	64%	17%
(+)-**145**:	20%	50%	-

	168	**169**
achiral **98**:	72%	64%
(+)-**145**:	-	-
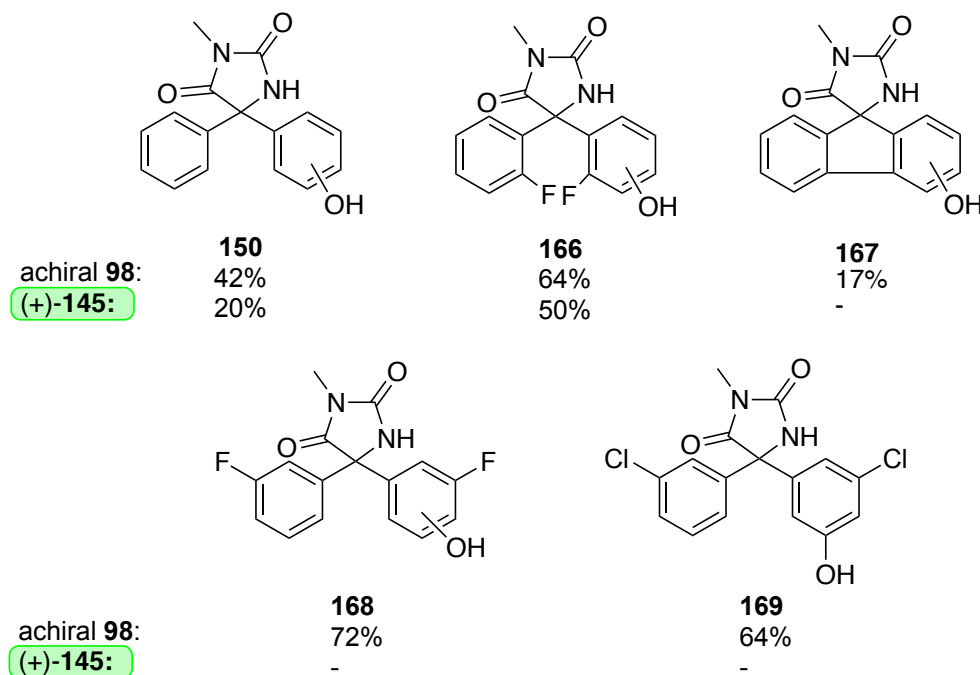
Figure 5: Catalytic borylations with chiral ligand **(+)-145** *versus* achiral ligand tmphen **98**.

Since the results indicated no stereoinduction by ligand (+)-**145**, further optimisation was necessary. To provide more flexibility for the formation of the sterically crowded catalytic complex, reduction of the alkyne linker was performed by addition of hydrogen under palladium catalysis yielding chiral ligand (+)-**170** in 73% yield (Scheme 34).
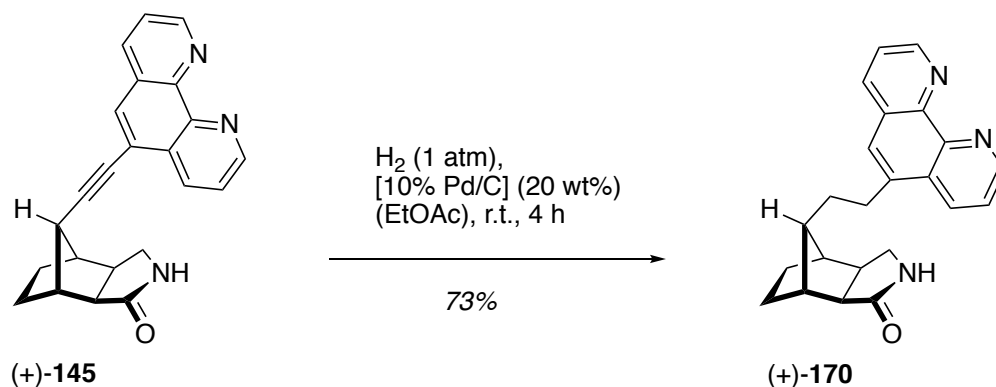
Scheme 34: Hydrogenation of the alkyne linker in ligand **(+)-145**.

Studies of *Hartwig* and co-workers suggested, that phenanthrolines with higher electron density are more effective than their unsubstituted analogues. They stated, that variation of the 4,7-substituents on the phenanthroline core can significantly change the electron-donating attributes of the ligand and rates of borylation are faster for the electron-rich iridium catalysts than for the electron-poor equivalents. While substitution on the 3,8-position does not seem to have a big influence on the electron-donating abilities of phenanthroline ligands, it can still have an effect on the rate of borylation. At the same time they argued that it is highly dependent on the substrate which ligand shows the highest efficiency.[62]

While they showed that a 3,4,7,8-tetra-donorsubstituted phenanthroline exhibits very high rates in the borylation of THF[62] they demonstrated that the single-substituted 2-methylphenanthroline (2-mphen) leads to the highest rates for borylation at primary C–H bonds and secondary C–H bonds beta to an oxygen atom in linear and cyclic ethers[59],[89]. In borylation of arenes however, the 3,4,7,8-tetramethylphenanthroline (tmphen) proves to be two orders of magnitudes more active than 2-mphen.[59]
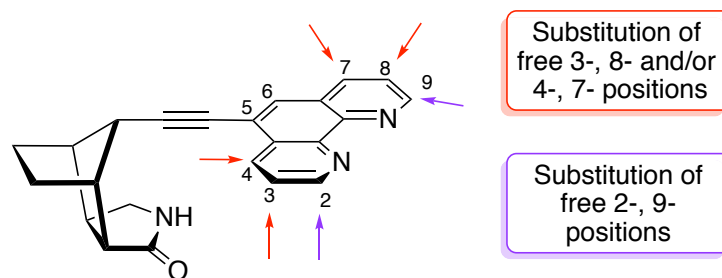
Figure 6: Varying the phenanthroline core by substitution of the phenanthroline core.

Therefore, it was planned to synthesize novel ligands featuring substituents on the phenanthroline core as depicted in Figure 6.

The first ligand which was attempted to be synthesized was compound **172**. To obtain the final ligand, the template alkyne needed to be coupled with the respective 5-bromo-3,4,7,8-tetramethylphenanthroline (**171**). There are no literature-known procedures to obtain **171** and bromination on the sterically hindered 3,4,7,8-tetramethylphenanthroline **98** turned out to be very challenging. After some less successful attempts, **171** was finally obtained in 10% yield by using a combination of bromine and fuming sulfuric acid. Unfortunately, the *Sonogashira* coupling with template alkyne (–)-**61** with the final ligand **172** was unsuccessful, which can be attributed to the pronounced steric hindrance induced by the four methyl groups in close proximity to the reactive C–H bond (Scheme 35).
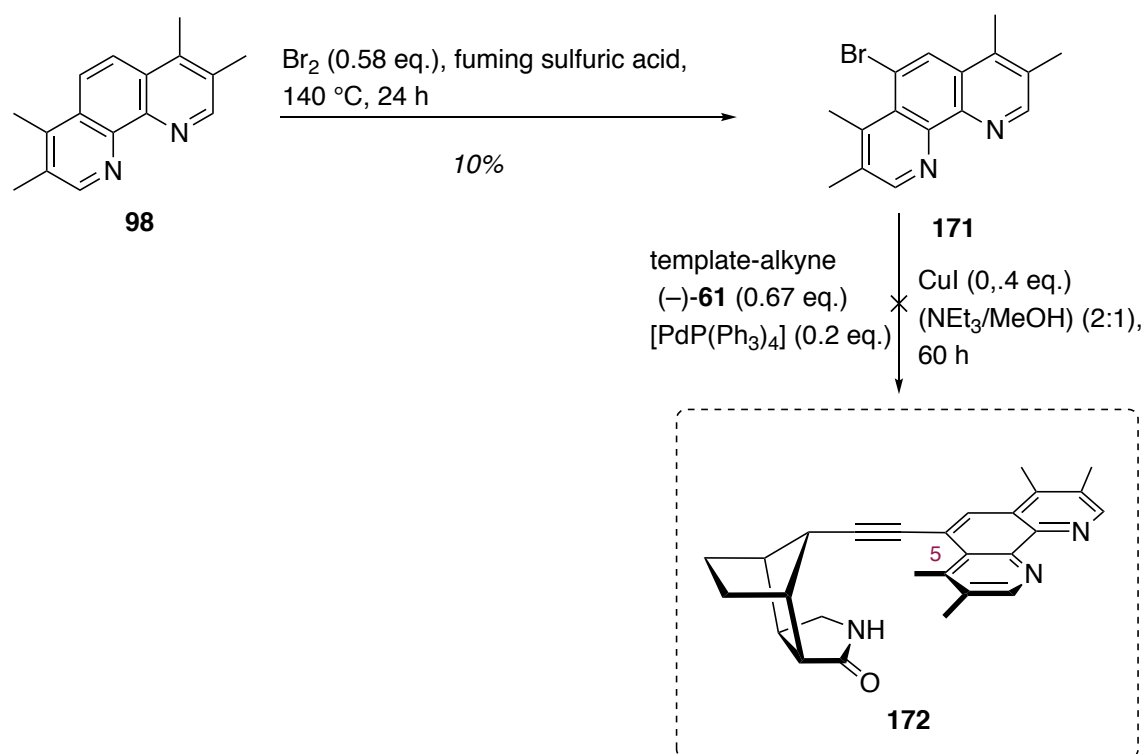
**Scheme 35:** Attempted synthesis of ligand **172.**

Bromination of 2,9-dimethylphenanthroline **174** was similarly cumbersome due to the formation of several inseparable brominated side products. This issue was overcome by using substochiometric amounts of bromine to avoid the formation of brominated regioisomers and dibrominated species. 5-Bromo-2,9-dimethylphenanthroline (**174**) was isolated in 23% yield together with unreacted starting material, which was subjected as a mixture to the final *Sonograshira* coupling to ligand (+)-**175**, since compound **173** was expected to be unreactive in the reaction. Ligand (+)-**175** was obtained in 82% yield (Scheme 36).
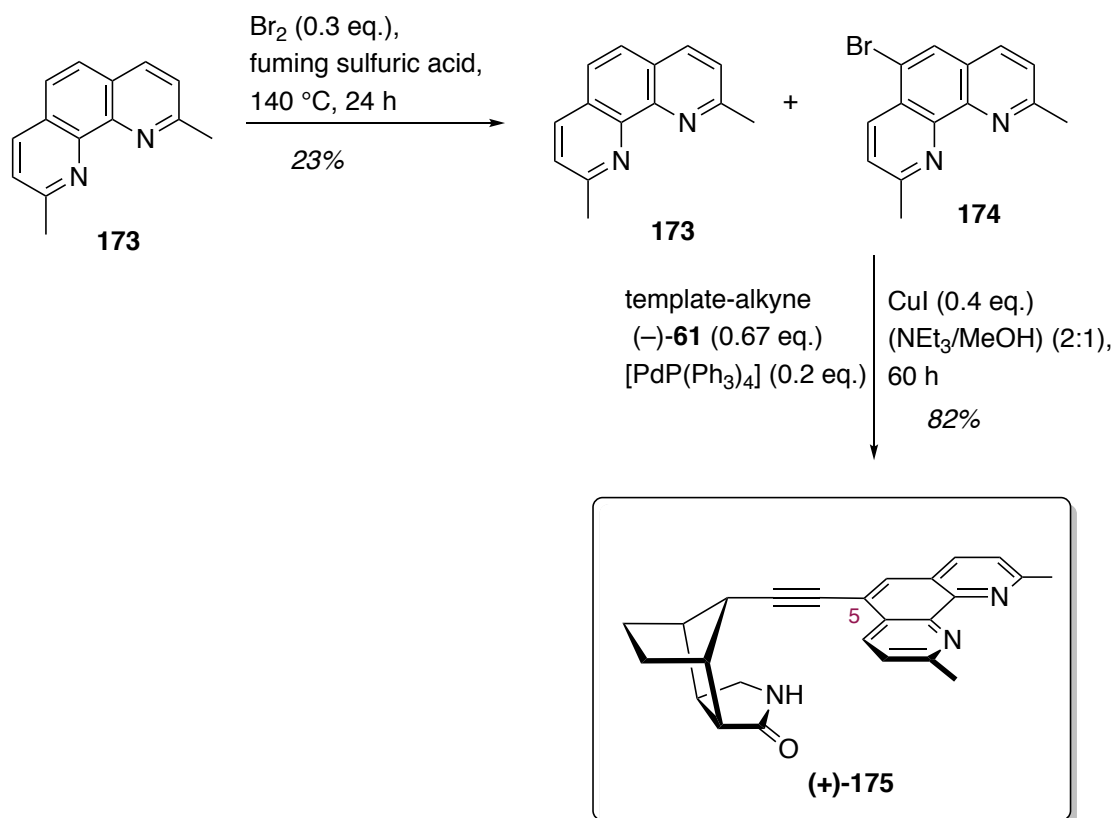
Scheme 36: Synthesis of dimethyl-substituted ligand (+)-**175**

Disappointingly, both ligands (+)-**170** as well as (+)-**175** were ineffective in the borylation of substrates **136, 160, 161** and **162** under the optimized reaction conditions using fresh HBpin (Scheme 37).

R = H, *m*-F, *o*-F, *m*-Cl,
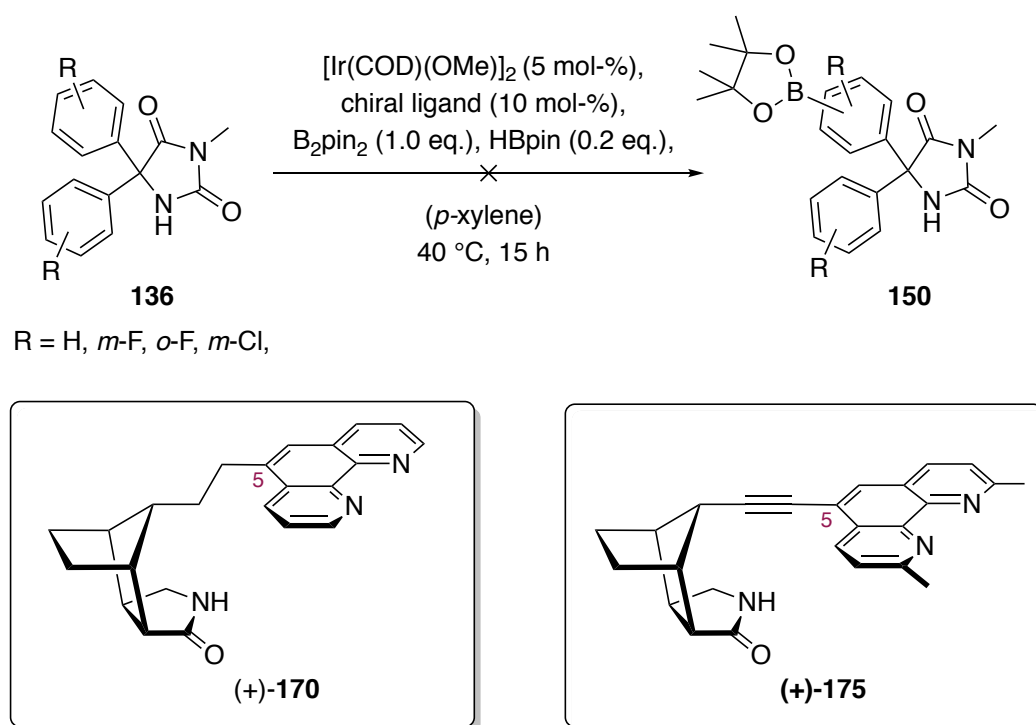
Scheme 37: Unsuccessful borylation attempts with the new chiral ligands.

4.4. Studies to catalytic borylations with bifunctional bipyridine ligands

Given the reproducibility issues and lack of enantioselectivity with the present catalyst system employing phenanthroline ligands, exploring another ligand type seemed appropriate. Next to phenanthroline, bipyridine-ligands are known to be active ligands in iridium-catalyzed C–H bond borylation reactions.[60],[96],[79] As mentioned above (see section 4.1), the catalytically active species in the catalytic cycle of iridium-mediated C–H borylation is the sterically very crowded iridium(V) species **76** as envisioned in complex **176**, which forms a capped trigonal prism with its seven coordination partners (Figure 7).[63]
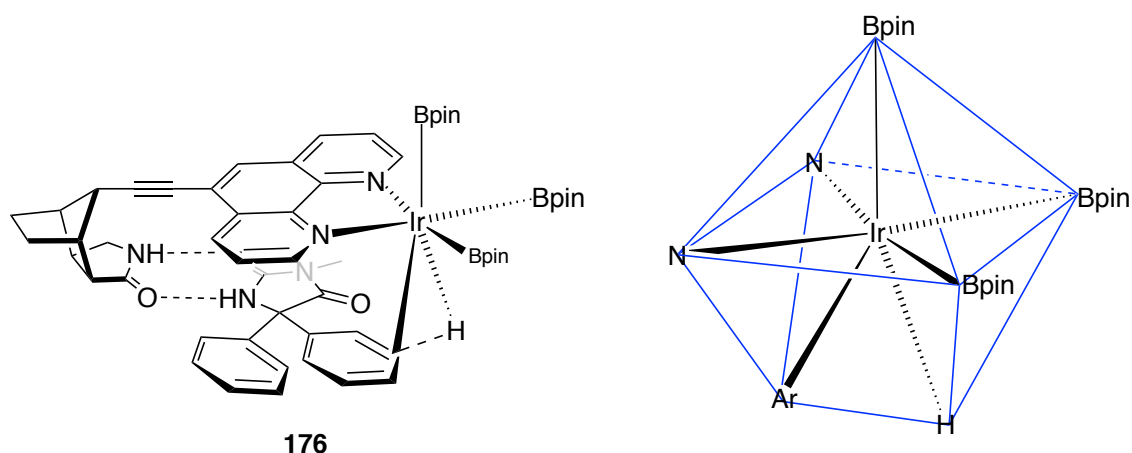
Figure 7: Sterically crowded iridium(V) species, featuring chiral phenanthroline ligand (+)-**145**.

Given this fact, it becomes evident that steric aspects exert a significant influence on the outcome of the reaction. Consequently, the structure of the employed ligand might have a high influence on reaction's selectivity and efficiency. Therefore, the adoption of a more slender ligand was considered to offer advantages. Due to their reduced steric bulk, bipyridine ligands like **177** (Figure 8) may facilitate substrate accessibility of the catalyst, thereby promoting a more favorable reaction pathway and potentially leading to improved reaction yields and selectivites.
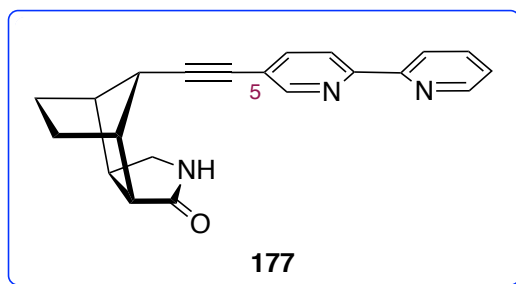
Figure 8: Chiral, bifunctional bipyridine ligand **177**.

Therefore, ligands (+)-**177**, (+)-**178** and (+)-**179** were synthesized by *Sonogashira*-coupling optimized by *Voss*[97]. For this, the commercially available 4-, 5- and 2-bromo-2,2-bipyridines respectively were coupled to the template alkyne (–)-**61** (Scheme 38).
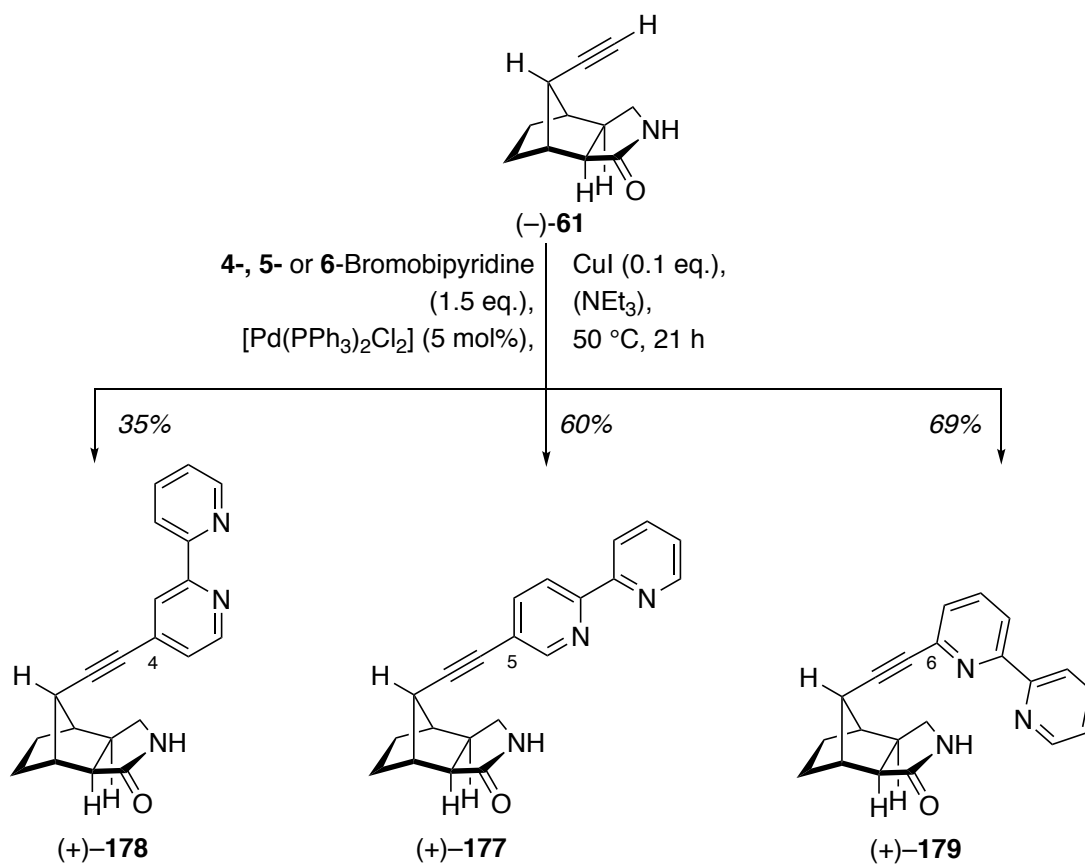
Scheme 38: Synthesis of the new chiral bipyridine ligands (+)-**178**, (+)-**177** and (+)-**179**.

The three new ligands (+)-**177**, (+)-**178** and (+)-**179** were tested in the iridium-catalyzed borylation of hydantoin substrates **136**, **160, 161, 162** and **165** and piperidinone **134** under HBpin-free conditions and it was discovered that both ligand (+)-**177**, as well as ligand (+)-**178** led to the desired borylated products. While the borylation of *meta*-chlorinated hydantoin **161** led to a single product, the other products were obtained as mixtures of *meta*- and *para*-hydroxy substituted regioisomers in good yields (Table 7). While ligand (+)-**177** generated higher yields compared to (+)-**178**, initial analysis *via* chiral HPLC suggested, that (+)-**177** seemed to lead to higher enantiomeric excesses. Analysis by chiral HPLC indicated slight enantiomeric excesses for all products except for the single regioisomer of *meta*-chlorinated compound **169**. Since all other compounds were obtained as regioisomers and separation by column chromatography as well as by chiral HPLC was challenging, further investigation on the reliability of these results had to be done. Subsequent optimisation studies were done on *meta*-fluoro substituted hydantoin **161**, since its hydroxylated product **168** initially showed the highest *ee* of 9%.
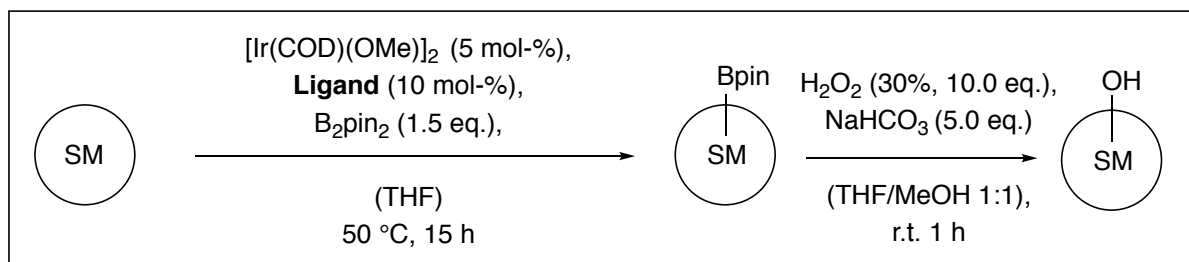
Table 7: Yields of the C–H borylations with the new ligands (+)-**177**, (+)-**178** and (+)-**179** of diverse substrates.

Ligand	150	166	167
mphen	42%[1]	64%[1]	17%[1]
(+)-**177**	64%[1]	77%[1]	83%[1]
(+)-**178**	-	-	-

Ligand	168	169	180
mphen	59%[1]	64%	29%[1]
(+)-**177**	80%[1]	68%	62%[1]
(+)-**178**	76%[1]	82%	79%[1]

To ensure the reproducibility of the enantiomeric excesses, borylation of *meta*-substituted hydantoin **161** was repeated and the separation of the products by column chromatography was executed with meticulous attention.

Given that the isolated *meta*-regioisomer was obtained as a racemic mixture and the *ee* couldn't be reproduced, it is likely that the presumed enantiomeric excesses resulted from the overlap of

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[1] Yields are reported as combined yields of *meta*- and *para*-regioisomers due to the inability to achieve complete separation.

the peaks of the *meta*-regioisomer with those of residual *para*-regiosisomer, which are not discernible in the corresponding NMR spectra.
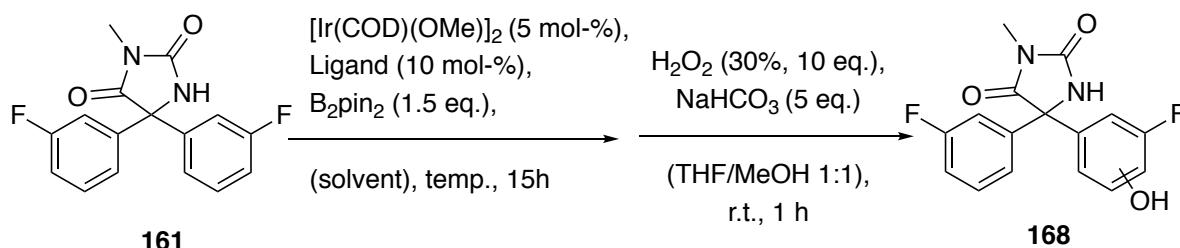
Table 8: Temperature and solvent screen for the C–H borylation of hydantoin **161.**

Entry	Ligand	Solvent	Temp.	Overall Yield (%)[2]	*ee* (%)[3]
1	tmphen	THF	50 °C	76	-
2	(+)-**177**	THF	50 °C	80	9, not reproducible
3	(+)-**177**	THF	r.t.	53	racemic
4	(+)-**177**	THF	40 °C	77	racemic
5	(+)-**177**	*p*-xylene	50 °C	50	racemic
6	(+)-**177**	1,4-dioxane	50 °C	74	racemic
7	(+)-**177**[4]	THF	50 °C	63	racemic
8	(+)-**178**	THF	50 °C	76	3

The influence of the reaction parameters, specifically solvent and temperature, on the borylation of hydantoin **161** mediated by ligand (+)-**177** was systematically investigated. As summarized in Table 8, the borylation yields increased with higher reaction temperatures. Among the solvents tested, THF was identified as the most efficient, outperforming *p*-xylene and 1,4-dioxane. Importantly, none of the examined reaction conditions induced enantioselectivity.

The present study used catalysts that were generated *in situ*, as this is the typical procedure reported in the literature.[98] Given that it was demonstrated that the order of addition of precatalyst, ligand and boron reagent could have a significant effect on the borylation efficiency[98], the effect of the order of addition on hydantoin **161** was investigated as well. Since THF proved

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[2] Yields are reported as combined yields of *meta*- and *para*-regioisomers due to the inability to achieve complete separation.
[3] Determined only for the *meta*-regioisomer, since the *para*-regioisomer always contained traces of the *meta*-product.
[4] Different order of addition.

to be the most efficient solvent for this substrate, it remained the solvent of choice for this investigation. As shown in entry 7 (Table 8), the yield significantly dropped from 80% to 63%, when the order of addition changed from the addition sequence iridium precatalyst, ligand and B_2pin_2, followed by addition of the starting material after one hour of preformation of the catalsyst, to the sequence of iridium precatalyst, ligand and starting material, followed by the addition of the boron reagent after one hour of stirring.

Although moderate to good yields of the hydroxylated products were obtained over two steps, no enantioenrichment was achieved with the current catalytic system. Therefore, a change of substrates was envisioned. To investigate, whether the protecting group on the nitrogen atom N3 on the hydantoins had an influence on the enantioselectivity, different substrates were synthesized.
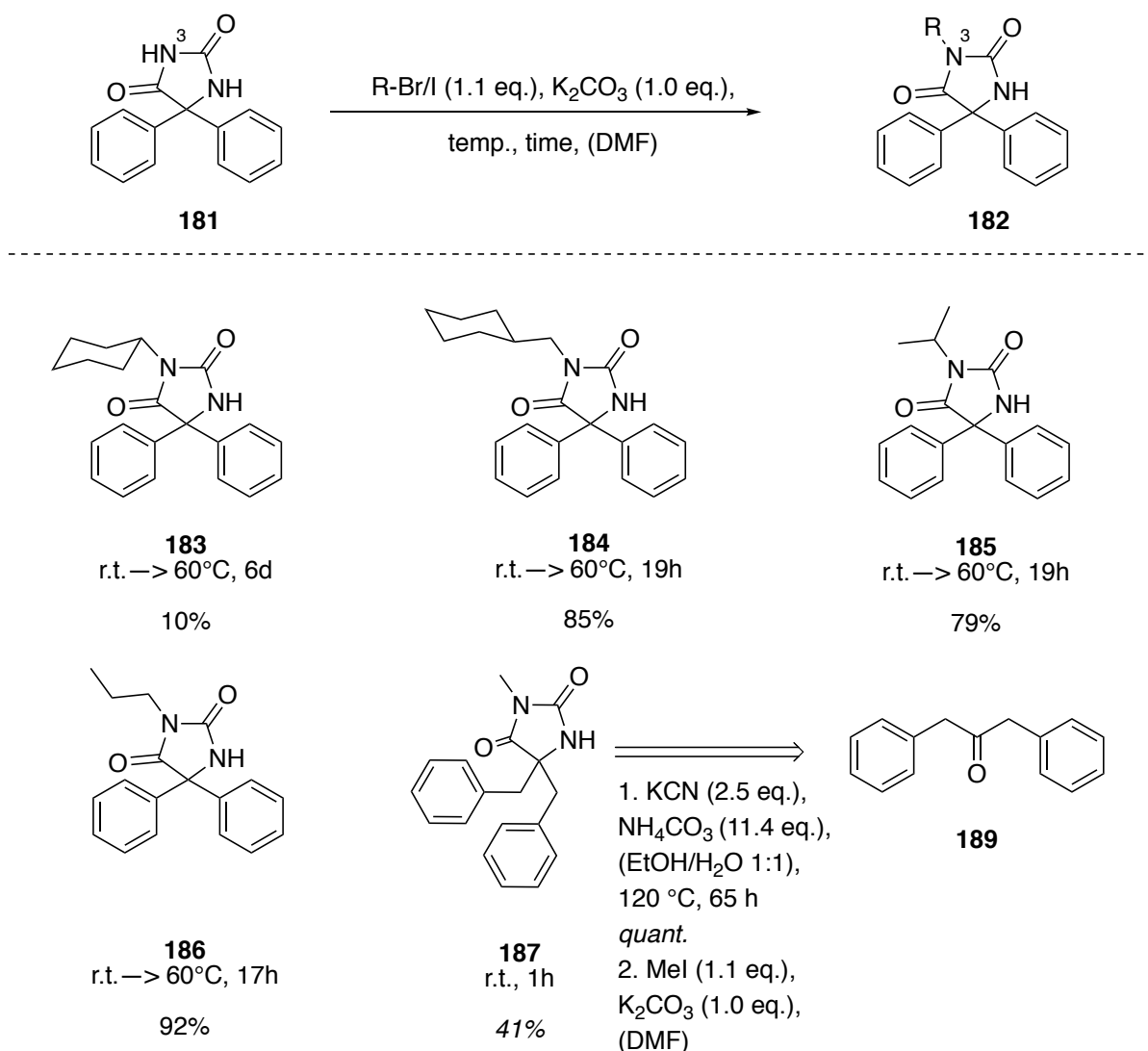
Scheme 39: Synthesis of hydantoin substrates with different aliphatic protecting groups at N3.

First, different acyclic and cyclic carbon chains were installed to examine their influence on the reaction outcome. Hydantoins **181-187** were synthesized *via* nucleophilic substitution with the respective bromides. The reactions proceeded with good yields for the respective primary halides and were less successful for substitution at secondary halides, as it was expected (Scheme 39). To investigate the potential impact of increased distance between the lactam unit and the enantiotopic phenyl groups on enantioinduction, the C5-dibenzyl substituted hydantoin **187** was synthesized *via Bucherer-Bergs* reaction and subsequent protection of N3 with methyl iodide.

To investigate the influence of various functional groups such as halides and silanes on the alkyl chain, substrates **193-195** were synthesized *via* nucleophilic substitution (Scheme 40). These functional groups are known to impact steric and electronic environments in some cases,[99] thereby potentially affecting the degree of enantioinduction observed in the reaction.
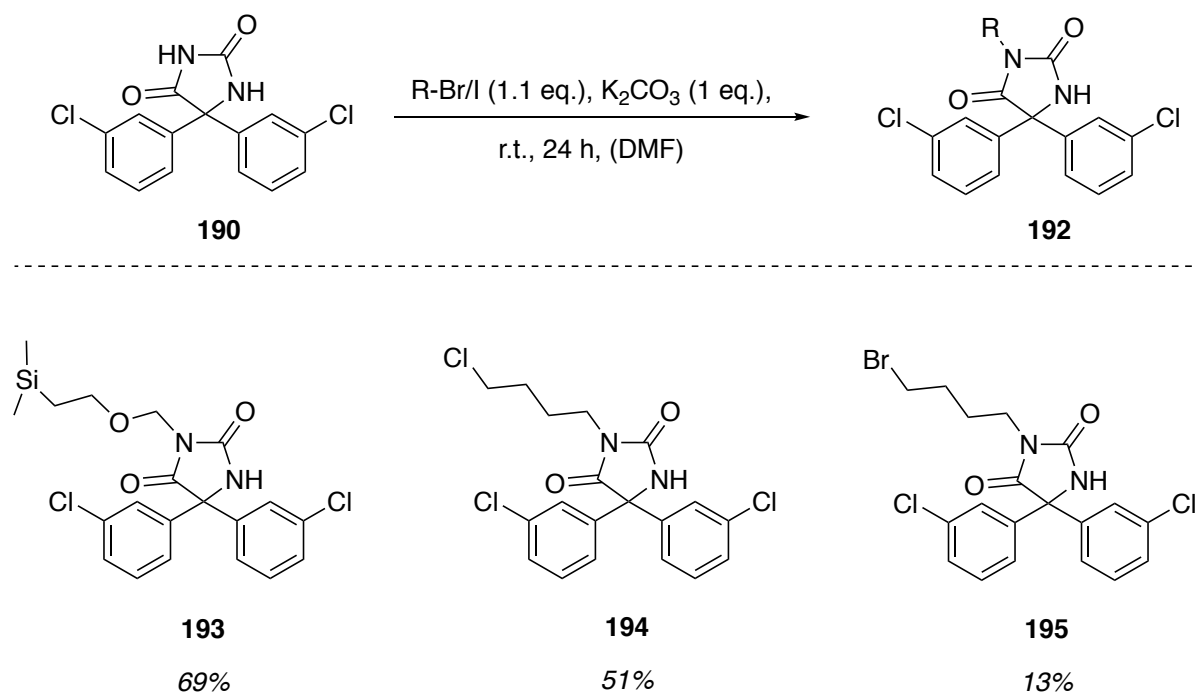
Scheme 40: Synthesis of hydantoin substrates with functionalized aliphatic protecting groups at N3.

To explore the potential influence of π-stacking interactions on enantioselectivity, arene-substituted hydantoins **196-199** were synthesized using copper-catalyzed coupling reactions. These substrates were obtained in good yields (Scheme 41). π-Stacking can significantly impact molecular interactions and spatial arrangements[100], which in turn may enhance enantioselectivity in the resulting products.
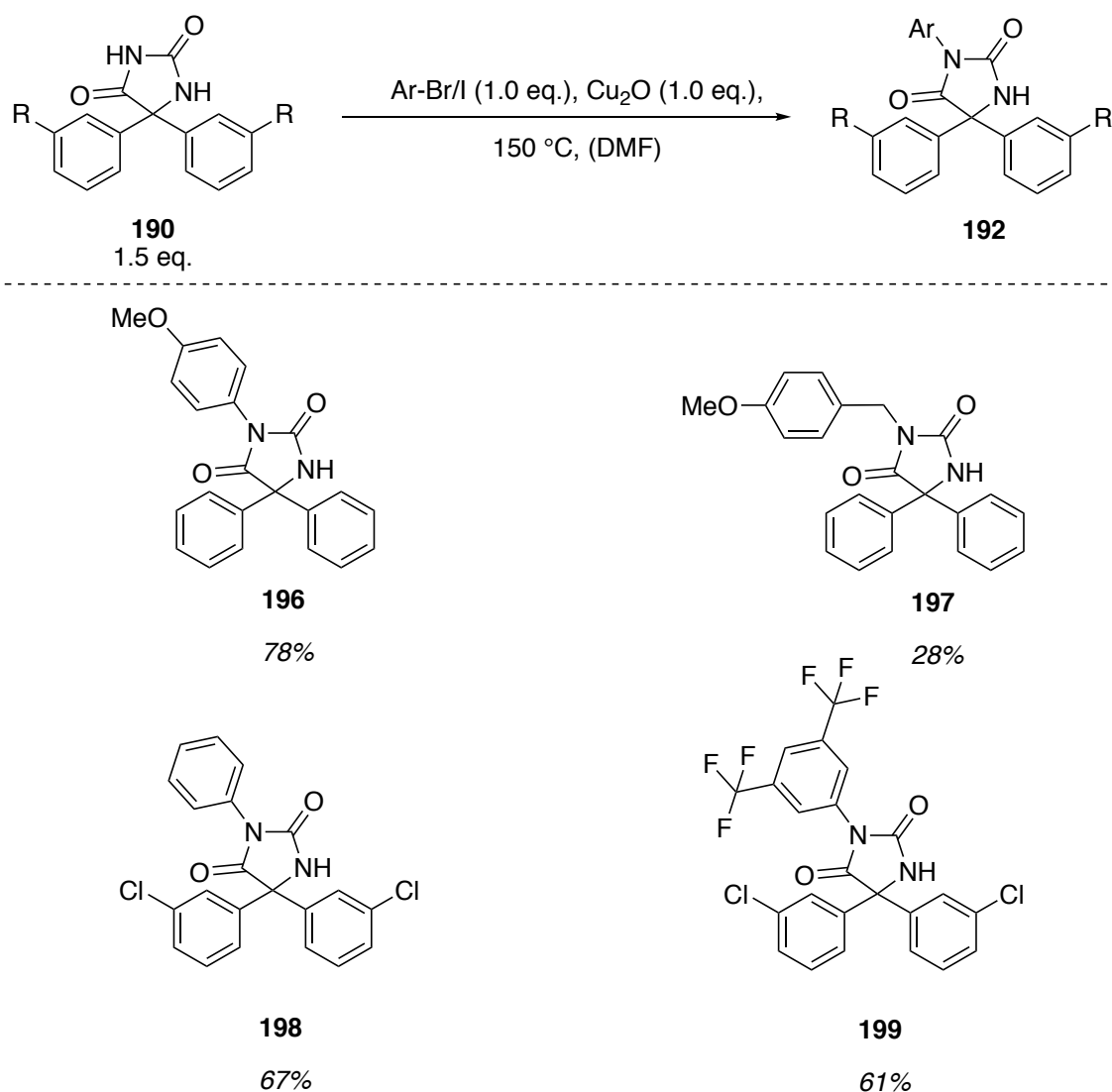
Scheme 41: Synthesis of hydantoins with aromatic protecting groups at N3.

The new substrates were then subjected to the borylation reaction with ligand (+)-**177**, which achieved moderate to good yields (64-80%). As shown inTable 9, the yields of the borylation of all substrates were higher with the chiral ligand (+)-**177** than with the achiral 3,4,7,8-tetra-methylphenanthroline, which is known to be one of the most effective ligands in iridium-cata-lyzed C–H borylation of arenes[59] and heteroarenes[65]. The highest yields were achieved with *n*-propyl-substituted substrate **186** (Table 9, entry 10) and the C5-benzyl-substituted hydantoin **187** (Table 9, entry 12) with 79% and 80% overall yield, respectively, over two steps. Isopropyl-substituted substrate **185** gave the lowest overall yield of 57% and 48% both with the chiral ligand (+)-**177** as well as with the achiral ligand tmphen (Table 9, entries 7 and 8), presumably due to steric reasons. It is surprising, that the cyclohexyl-substituted hydantoin **183** gave a higher yield in both the asymmetric as well as the non-asymmetric reaction, since both the isopropyl- as well as the cyclohexyl group exhibit an A-value of around 2.2 kcal/mol.[101]

Although good yields were achieved with all the substrates, either no significant enantioselectivity was observed, or the enantiomers were not separable on chiral HPLC.
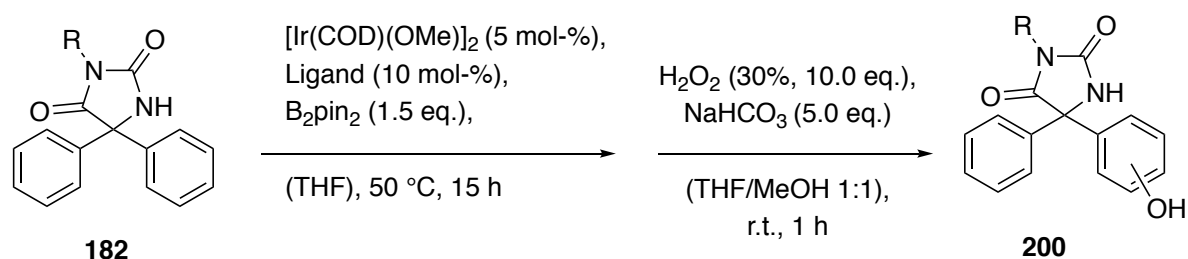
Table 9: C–H borylations of hydantoins with various N3-protecting groups with chiral ligand **(+)-177.**

Entry	SM #	R	Ligand	Product #	Yield (%)	RSM (%)	*ee (%) meta/para*
1	**136**	Me	tmphen	**150**	42	-	-
2			(+)-**177**		64	-	7/ -
3	**183**		tmphen	**183b**	52	43	-
4			(+)-**177**		76	24	racemic
5	**184**		tmphen	**184b**	62	20	-
6			(+)-**177**		75	25	racemic
7	**185**		tmphen	**185b**	48	34	-
8			(+)-**177**		57	21	4/5
9	**186**		tmphen	**186b**	21	46	-
10			(+)-**177**		79	20	racemic
11	**187**		tmphen	**187b**	46	6	-
12			(+)-**177**		80	20	4/8

A similar effect was observed for hydantoins with functionalized hydrocarbon protecting groups on the N3 position, as well as for arene-substituted hydantoins **198-199**. In all cases, the use of the chiral ligand (+)-**177** resulted in significantly higher yields compared to tmphen, reaching up to 52% with the silyl-substituted hydantoin **193** (Table 10). Substrate **198** exhibiting N3-phenyl substitution gave a mixture of regioisomers, attributed to the abundance of reactive arene C–H bonds (Table 10 , entry 7 and 8). However, no significant enantioselectivity was observed under these conditions (Table 10).
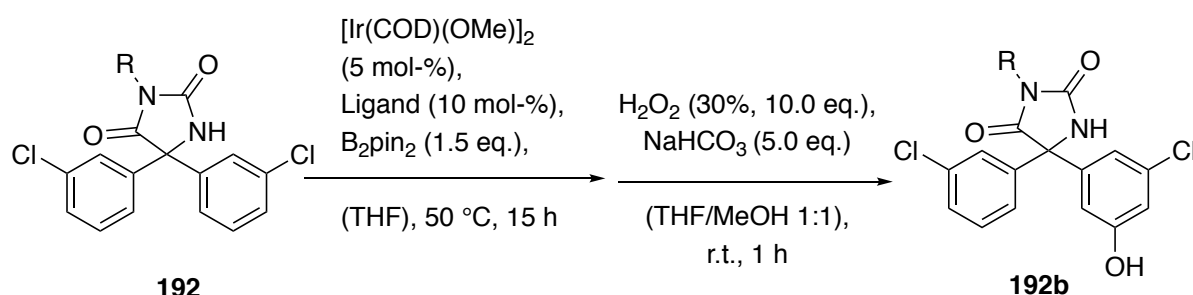
Table 10: C–H borylations of hydantoins with various functionalized N3-protecting groups with ligand (+)-**177.**

Entry	SM #	R	Ligand	Products #	Yield (%)	*ee (%)*
1	**136**		tmphen	**150**	64	-
2		Me	(+)-**177**		68	racemic
3	**193**		tmphen	**193b**	27	-
4			(+)-**177**		52	racemic
5	**194**		tmphen	**194b**	7	-
6			(+)-**177**		40	racemic
7	**198**		tmphen	**198b**	24 (+ 7 *meta* / 4 *para* on PG)	-
8			(+)-**177**		23 (+ 36 *para* on PG)	racemic
9	**199**		tmphen	**199b**	27	not separable on HPLC
10			(+)-**177**		55	-

The last class of substrates that were explored in the catalytic borylation with chiral ligand (+)-**177** were acetamides **137** and **148**. Despite their more flexible nature due to free rotation between C1–C2 and C1–NH, respectively, they showed significantly lower yields with achiral ligand tmphen than the hydantoin substrates. Substrate **137** gave a comparable yield of 73% with ligand (+)-**177**, while acetamide **148** gave the hydroxylated products in 43% yield (Table 11). After analysis via chiral HPLC, it became apparent, that no enantioselectivity was observable with these substrates either.
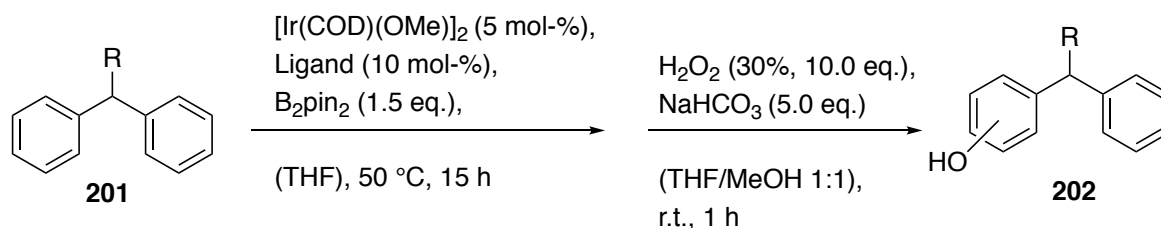
Table 11: C–H borylations of acetamides with ligand **(+)-177.**

Entry	SM #	R	Ligand	Products #	Yield (%)	*ee (%)*
1	**137**		tmphen	**137b**	40	-
2			(+)-**177**		73	racemic
3	**148**		tmphen	**148b**	28	-
4			(+)-**177**		43	racemic

Since the research results did not indicate any significant enantioinduction of the chiral ligands (+)-**177** and (+)-**178**, ligands (+)-**203**, (+)-**204,** (+)-**205** and (+)-**206** were synthesized via palladium-catalyzed hydration of the alkynyl linker (Scheme 42). While alkenyl-linked ligands (+)-**203** and (+)-**204** did not show reactivity in the borylation reaction, (+)-**205** and (+)-**206** gave good yields in the borylation of substrate **161** with a maximum yield of 82% for ligand (+)-**206** (Table 12 , entry 3). However, once again, no enantioselectivity was observed in these experiments, indicating that the modifications to the reaction conditions and substrates did not influence the chiral induction process.
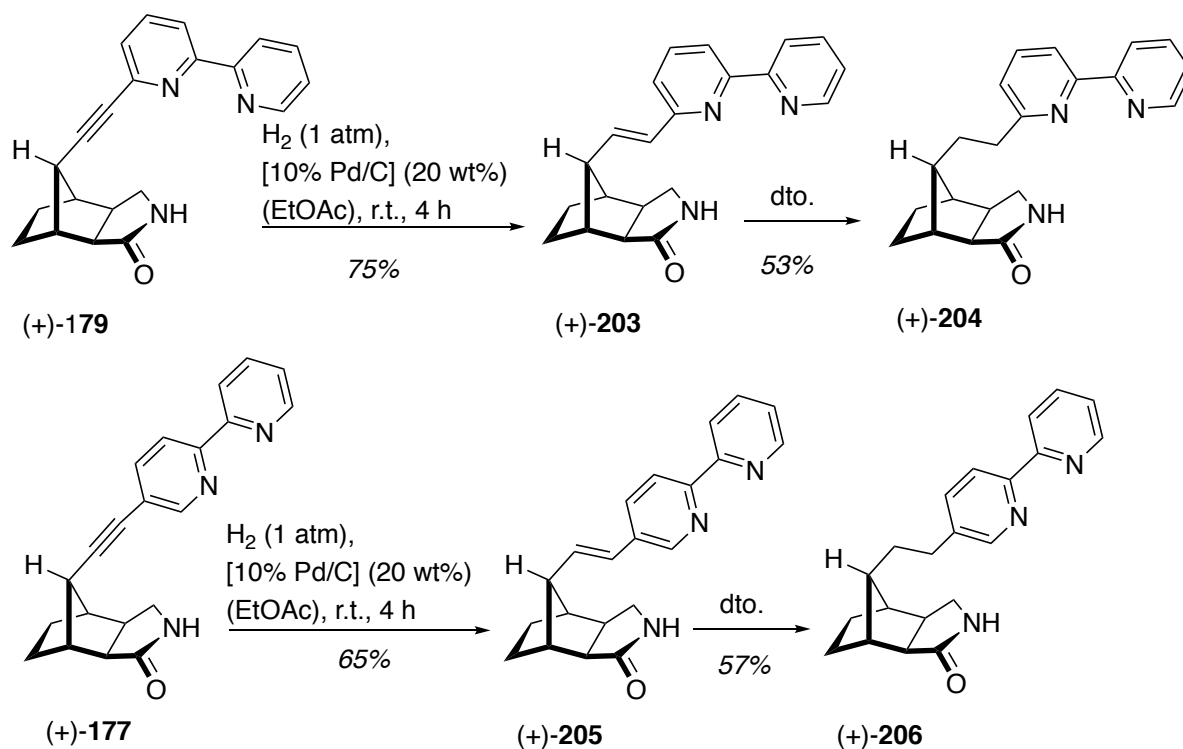
Scheme 42: Synthesis of ligands (+)-**204** and (+)-**206** by palladium-catalyzed hydrogenation of the alkynyl linker.
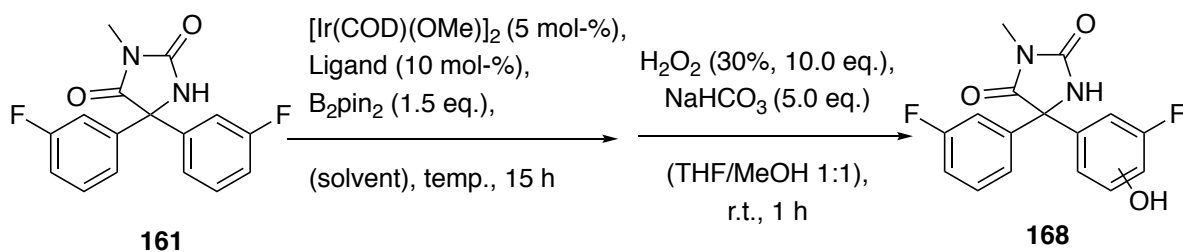
Table 12: Borylation of hydantoin **161** with the new chiral bipyridine ligands (+)-**204** and (+)-**206**.

Entry	Ligand	Yield (%)	*ee* (%)
1	(+)-**203**	-	-
2	(+)-**204**	-	-
3	(+)-**205**	61	racemic
4	(+)-**206**	82	racemic

Finally, an alternative ligand was proposed to enhance the proximity of substrates to the catalytic center. The strategy involved modification of the linker between the chiral template backbone and the bidentate ligand. Specifically, the alkyne linker was to be replaced with a phenyl group, positioning the bipyridine ligand at the *meta*-position. This modification aimed to create an enzyme-like chiral pocket, potentially increasing enantioselectivity by bringing substrates closer to the catalytic site.
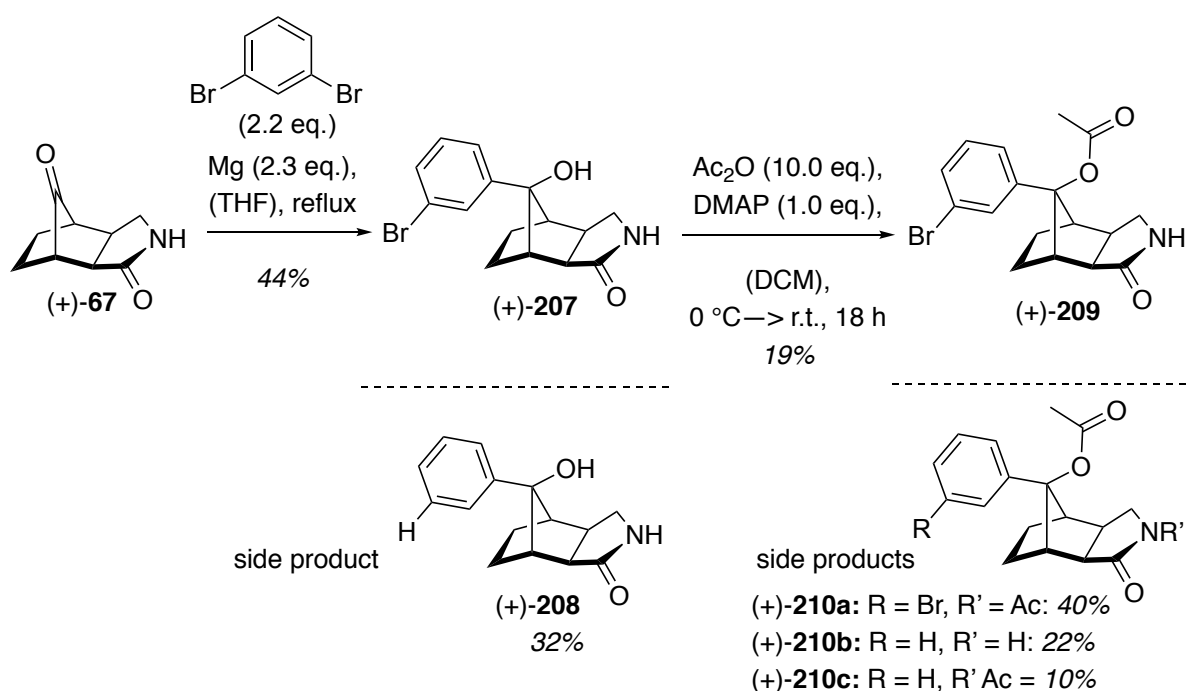
Scheme 43: Synthesis of meta-bromophenyl substituted amide (+)-**209**.

Similar to the reported reaction sequence by *Berthold*[39], starting point for the synthesis was ketone (+)-**67**, which was synthesized *via* the pathway described in section 3.2. A *meta*-bromophenyl group was introduced by *Grignard*-addition, followed by acetylation of the resulting alcohol to facilitate the formation of the benzylic cation in the subsequent epimerization to compound (+)-**210**. Subsequent cross coupling of brominated compound (+)-**210** with the respective boronic ester **211** in a *Suzuki* coupling led to ligand (+)-**215**.

Alcohol (+)-**207** was obtained in 44% yield as a mixture with the inseparable hydrodebrominated side product (+)-**208** in 32% yield. The selective acetylation of the hydroxy group turned out to be cumbersome due to simultaneous acetylation of the nitrogen atom of the amide. When using lower temperatures or less equivalents of acetylating agent, no reaction was observed. Monoacetyl compound (+)-**209** was finally obtained in 19% yield using 10 equivalents of acetic anhydride and 50 equivalents of triethyl amine as a mixture with its dehydrobrominated side product (Scheme 43). In addition, side products (+)-**210a**–(+)-**210c** included the double-

acetylated compound and its hydrodebrominated equivalent. These side products arose from over-acetylation as well as dehalogenation reactions, respectively.
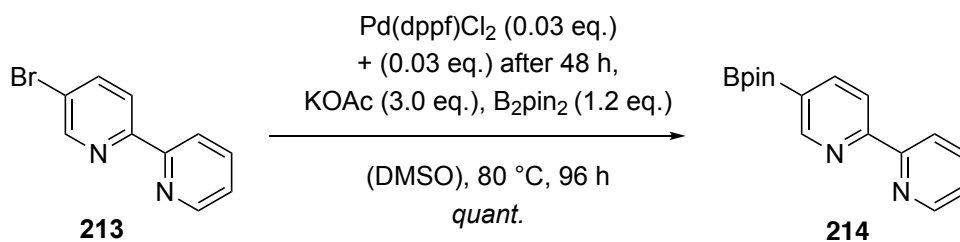
Scheme 44: Synthesis of boronic ester **214** *via Miyaura* borylation.

For the final *Suzuki* coupling, boronic ester **214** was prepared via a *Miyaura*-borylation of **213**. To get complete conversion to product **214**, addition of additional amounts of palladium catalyst after 48 hours, as well as increasing the reaction time to 72 hours was needed. Due to its instability on silica, the crude material of **214** was employed in the reaction (Scheme 44).
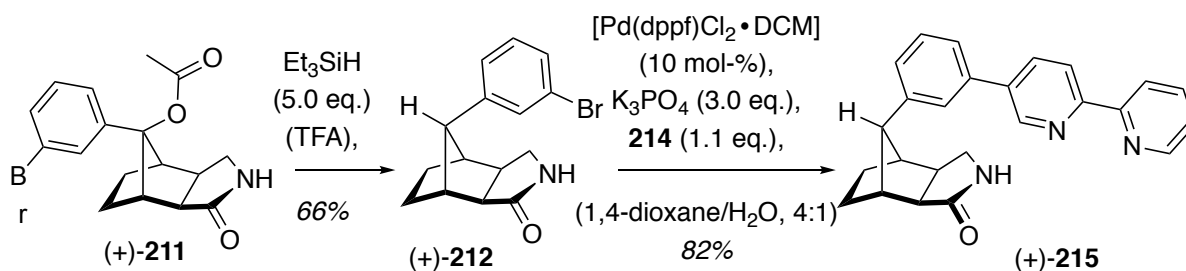
Scheme 45: Reduction of (+)-**211** and subsequent *Suzuki* coupling to phenyl-linked ligand **(+)-215.**

Reduction with triethyl silane and subsequent *Suzuki* coupling of (+)-**212** with boronic ester **214** yielded the final phenyl-linked ligand (+)-**215** in 82% yield (Scheme 45).

Upon using this new ligand in the iridium-catalyzed borylation of hydantoins **161** and **162** under the established reaction conditions, only trace amounts of the desired product were obtained. Consequently, analysis via chiral HPLC was not feasible. These results indicate that further optimization is required to identify the optimal ligand for the iridium-catalyzed, enantioselective C–H borylation mediated by chiral ligands utilizing hydrogen bonding as control elements.

5. Catalytic chlorinations

5.1. State of the art

One of the most central functional groups in organic chemistry is the carbon-halogen bond. Organohalides are both part of a wide variety of natural products[102] as well as synthetic precursors for targets in pharmaceutical,[103], agrochemical[104] and material science.[105] For instance, the axially chiral, chloride containing glycopeptide vancomycin is used as an antibiotic against penicillin-resistant bacteria (Figure 9).[102] The versatility of the organohalide functionality relies on its reactivity in a variety of different synthetic transformations, while exhibiting stability under a range of different reaction conditions. Due to their ubiquity as a synthon in synthesis, novel methods for the simple, cost-effective and environmentally friendly installation of carbon–halogen bonds with improved levels of reactivity and selectivity bonds are highly sought after.[106]
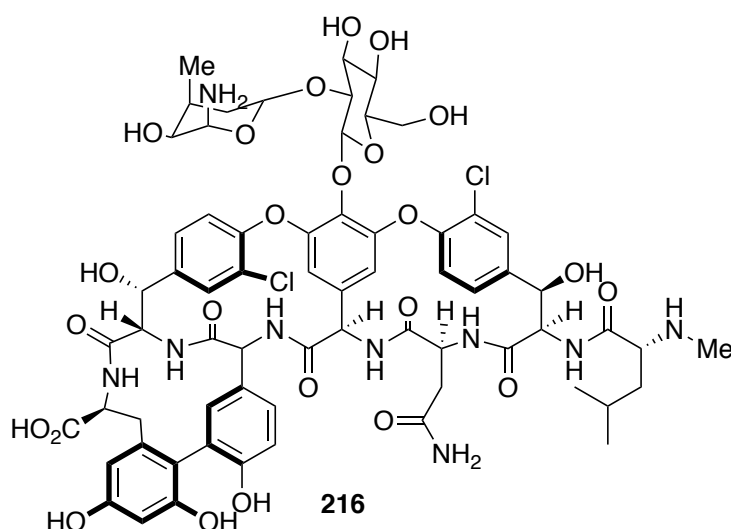
Figure 9: Axially chiral, chloride containing antibiotic agent Vancomycin.[102]

While aryl halides are versatile building blocks in chemical synthesis to install aromatic cores, alkyl halides are a diverse class of compounds which can be used as synthetic equivalents for alkyl cations, chlorinating reagents, key functional groups in natural product synthesis as well as solvents. In traditional approaches, the sp^3-C-halogen bond is often generated by substitution of the respective alcohol or other useful leaving groups with reagents like hydrohalic acids, thionyl chloride or phosphorous tribromide. Other methods include hydrohalogenation, halohydration and dihalogenation of olefins or radical pathways. Drawbacks to these techniques include the use of toxic reagents, harsh reaction conditions, lack of functional group tolerance and the limited possibility of regio-, chemo- and enantioselectivity.[107]

Consequently, approaches that address these challenges often involve transition metal catalysis, which has become increasingly prevalent in the synthesis of organohalides. These methods offer a more refined and versatile framework for achieving desired reaction outcomes, thereby enhancing the efficiency and selectivity of the synthetic process.[108],[109]

One example of an enantioselective halogenation is the palladium catalyzed 1,1-arylhalogenation of allylic amines **217** with arylboronic acid nucleophiles **218** by *Toste* and co-workers. The racemic arylfluorination proceeded with a catalytic system containing bipyridine ligand **219** in combination with *Selectfluor®* as halogenating agent. For their enantioselective version, they used chiral bisoxazoline ligand **220**, achieving moderate yields and good enantioselectivities (Scheme 46). [110]
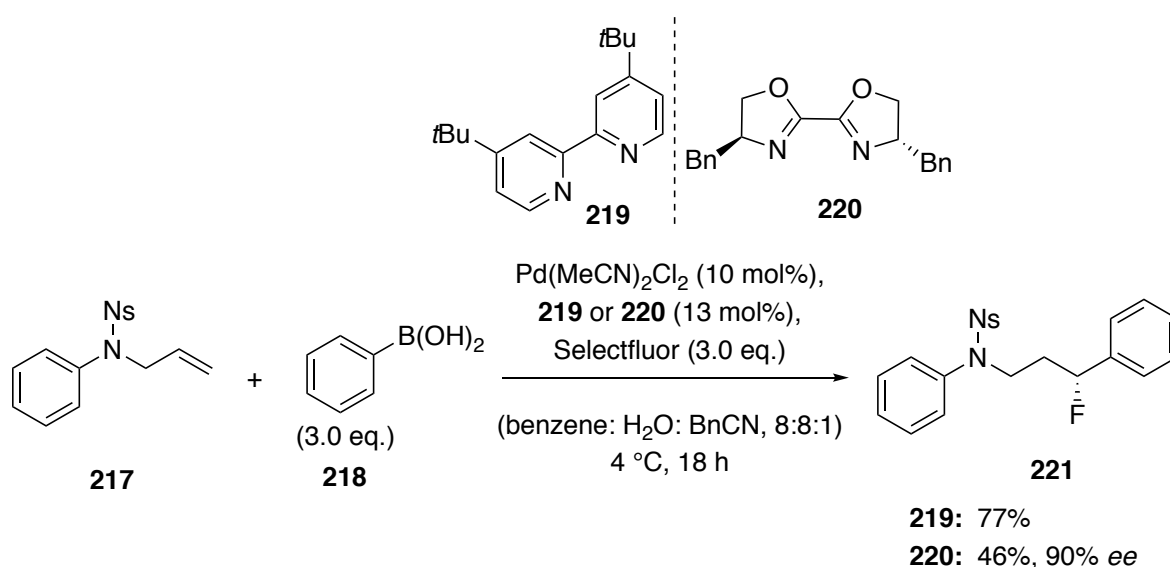
Scheme 46: Enantioselective 1,1-arylhalogenation of allylic amines with arylboronic acid nucleophiles.[110]

A more straightforward approach to synthesizing organohalides is through direct C–H halogenation, which removes the need for pre-functionalization of substrates. However, methods that are applicable to the synthesis of more complex molecules are limited and the direct halogenation of unactivated sp^3-C–H bonds is particularly challenging. While direct C–H halogenation can be efficient and straightforward for simpler substrates, developing robust and generalizable methods that can be applied to intricate and multifunctional molecules is a challenging frontier in the field[111]. While common procedures utilize *N*-halosuccinimides without the use of a catalyst for the halogenation of benzylic, allylic and activated C–H bonds, there are less examples for the direct C–H halogenation of strong sp^3-C–H bonds in substrates containing competing sp^2-C–H bonds and most procedures can only proceed at high temperatures.[112]

One example of a direct C–H bond chlorination catalyzed by a palladium catalyst was published by the group of *Sanford*. Their method was originally developed for the aerobic oxidation of

sp³-C–H bonds of 2-*tert*-butylpyridines, but they demonstrate that it can be utilized for chlorination reactions of primary C–H bonds by adding the simple reagent NaCl to their reaction mixture (Scheme 47).[113]
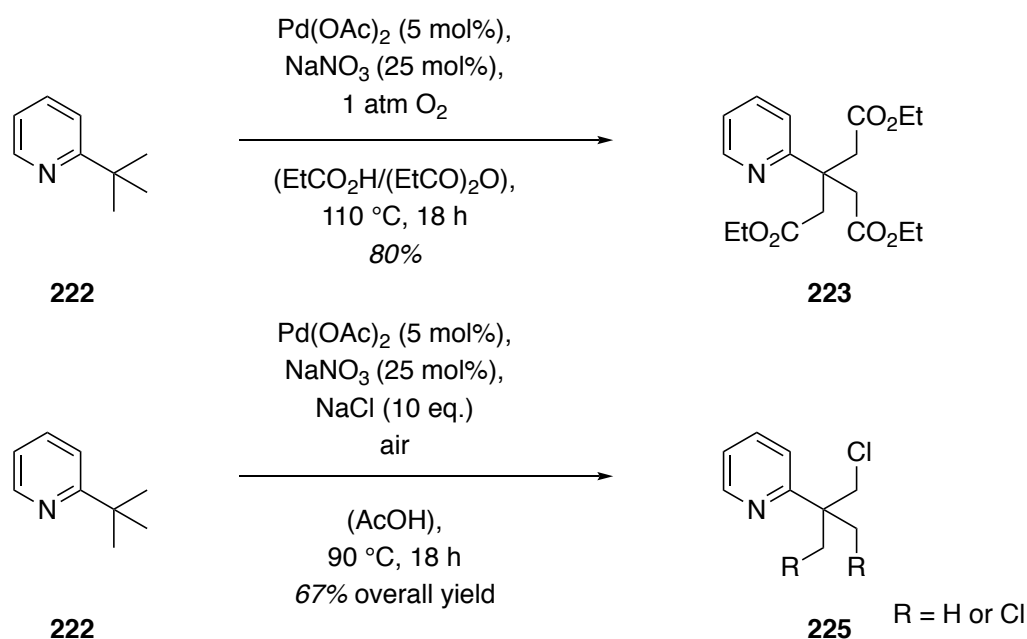
Scheme 47: Sanford's Pd-catalyzed oxidation and chlorination of primary C–H bonds.[113]

Inspired by the work of *Sanford, Rao* and co-workers reported an auxilliary-assisted palladium-catalyzed chlorination of amides like compound **226**, where the β-position of amides was selectively activated by a palladium catalyst. They employed 8-aminoquinoline-substrates such as **226**, in which the quinoline moiety acts as a bifunctional directing group (Scheme 48).[114]
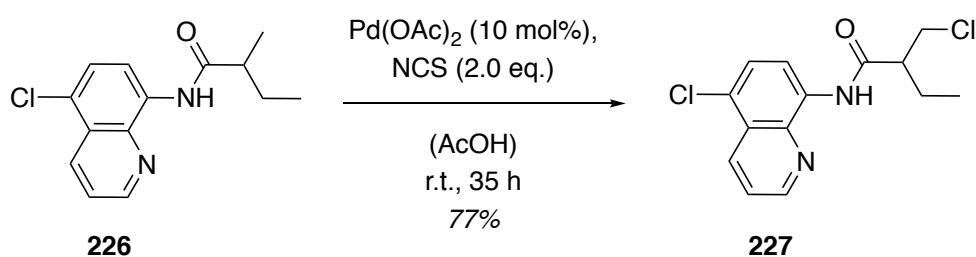
Scheme 48: Chlorination of primary C–H bonds of amides mediated by a quinoline directing group.[114]

Groves and co-workers reported a new strategy for constructing sp^3-C–halogen bonds utilizing the manganese-porphyrin complex **229**. They state that the method relies on the generation of long-lived substrate radicals by selective C–H abstraction of a reactive Mn(V)=O species, which can undergo a heteroatom (F, Cl or Br) rebound step to form the halogenated products. With this method, they were able to selectively chlorinate the natural product sclareolide in 42% (Scheme 49).[115]
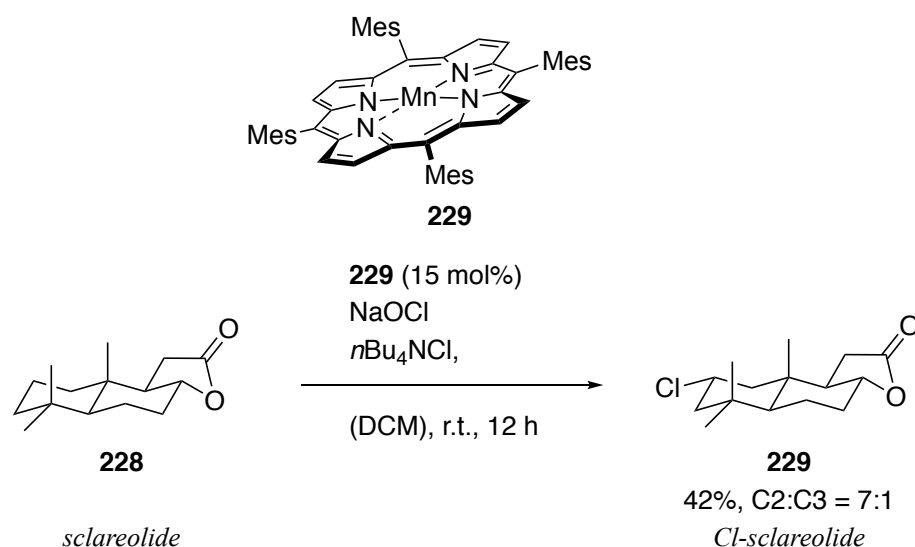
Scheme 49: Selective chlorination of sclareolide via Mn-porphyrin catalysis.[115]

Hartwig and co-workers reported a method utilizing a copper-phenanthroline catalyst for the chlorination of tertiary as well as benzylic sp^3-C–H bonds, that proceeds with high site-selectivity and functional group tolerance. They showed that *Zhdankin*'s azidoiodinane **231** reagent can be used to generate a *o*-iodobenzoyloxy radical, which is highly selective for H-abstraction. They demonstrated that their method proceeds with high yield and high site-selectivity on an array of complex molecules containing reactive functional groups like ketones, esters, amines and amides (Scheme 50).[116]

Scheme 50: Chlorination of sp³-C–H bods with a (phen)CuCl₂ catalyst. [116]

Inspired by the silver-catalyzed decarboxylative chlorination reported by *Li*,[117] the group of *Kanai* reported a sp³-C–H chlorination reaction with a Ag(phen)₂OTf-catalyst system using *tert*-butyl hypochlorite (*t*BuOCl) as chloride-source. They showed that benzylic, tertiary and secondary sp³-C–H were chlorinated under mild conditions and with high functional group tolerance (Scheme 51).[118]

Scheme 51: Chlorination of sp³-C–H bonds with a Ag(phen)₂OTf catalyst. [118]

To gain insight into the reaction mechanism, they conducted a series of experiments. Exposing an enantiomerically pure substrate containing a chiral tertiary stereogenic center to the reaction conditions led to the respective racemic chlorinated product, which suggested the possible involvement of a tertiary carbon radical intermediate. By subjecting a separately generated *tert*-butoxy radical *via* photoirradiation to the reaction conditions, they examined whether a free *tert*-butoxy radical was involved in the C–H cleavage step. Since the yields obtained with that method were significantly lower, they concluded that this radical was not an active species in the process. Based on these preliminary results and the proposed mechanism for the decarboxylative chlorination by *Li*[117], they suggested a mechanism for the catalytic cycle, which is shown in Scheme 52.
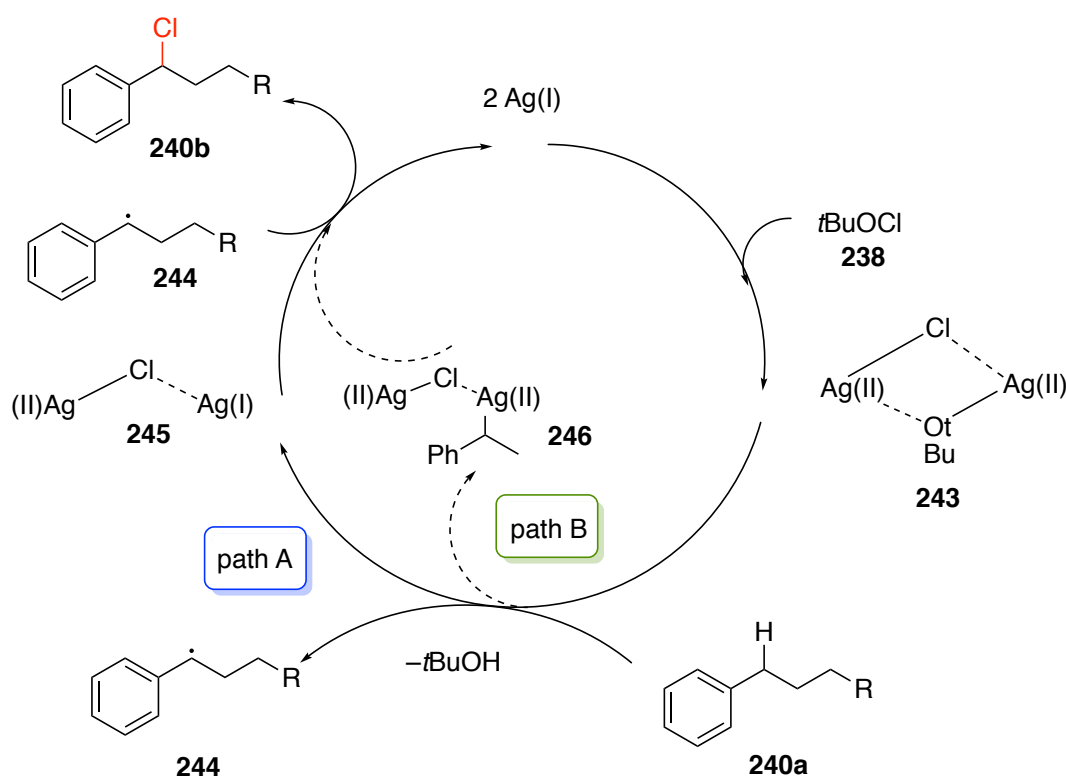
Scheme 52: Suggested catalytic cycle of the silver-catalyzed sp^3-C–H chlorination. [118]

According to the authors, there are two possible pathways. They stated, that first, binuclear Ag(II)-complex **243** is formed by combining Ag(phen)$_2$OTf and *tert*-butyl hypochlorite **238**. Upon addition of the substrate, the C–H bond is cleaved homolytically mediated by complex **243**, leading to carbon radical **244** and *tert*-butanol (pathway A). Radical **244** is trapped by the resulting Ag(II)-species **245** leading to chlorinated product **240b**. An alternative pathway would be the formation of alkylsilver species **246**, which could form upon cleavage of the C–H bond and subsequent reductive elimination of the chlorinated product **240b** (path B).

5.2. Objective

Ag(I) has emerged as an important and versatile metal for catalysts for a variety of organic transformations.[119] Silver has proved to be efficient in the enantioselective amination reaction of pyridones and quinolones [33], as well as in the enantioselective sulfimidation of 3-thiosubstituted 2-quinolones and 2-pyridones.[34] By employing a bifunctional phenanthroline ligand reported by our group (see section 2.1.2), an enantioselective, silver catalyzed chlorination employing the developed chiral phenanthroline ligands (+)-**36**, (+)-**145** and (+)-**146** was envisioned (Figure 10). As described in section 3.1, the objective was to control site- and enantioselectivity via two-point hydrogen bonding between the prochiral substrates and the lactam unit on the chiral ligands, by bringing them closer to the catalytically active metal center. The covalently bound phenanthroline unit was intended to act as a coordination site for the silver metal, facilitating regio- and/or enantioselective transfer of the reagent onto the substrates.
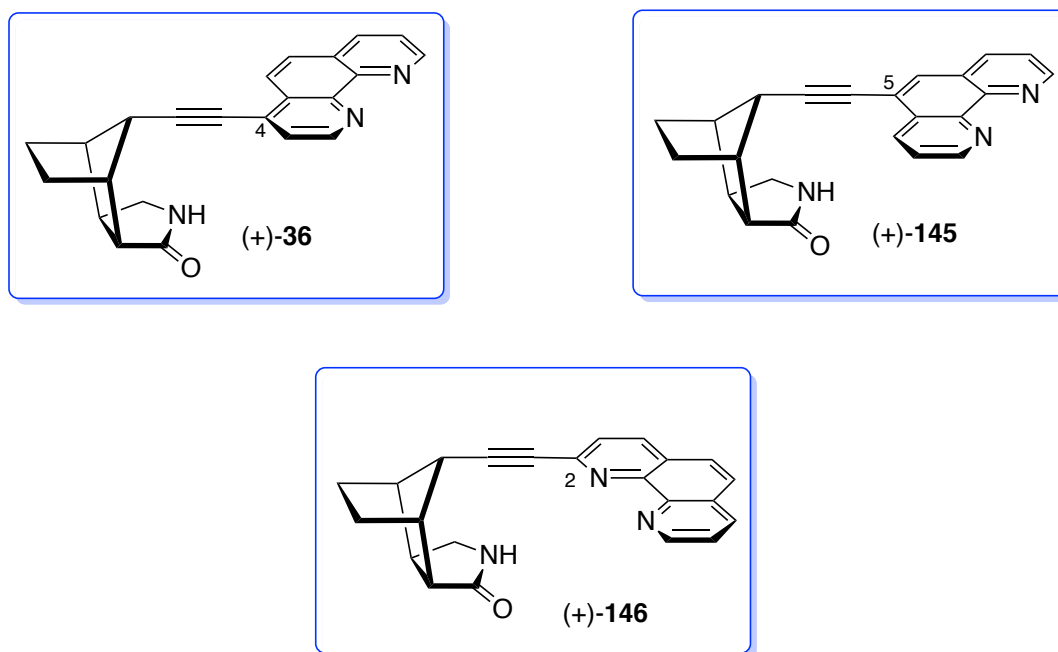
Figure 10: Chiral bifunctional phenanthroline ligands developed in the course of this work.

Inspired by the work of *Kanai* and co-workers, *tert*-butyl hypochlorite (*t*BuOCl) was tested as chlorinating agent in the chlorination reaction of sp³-C–H bonds of quinolone-, dihydroquinolone- and oxindole substrates depicted in Figure 11. These substrate classes were chosen, since they exhibit both a lactam unit for the formation of two-point hydrogen bonds, as well as containing benzylic C–H bonds, which are known to be weaker than other sp³-C–H bonds and therefore easier to functionalize.[120]
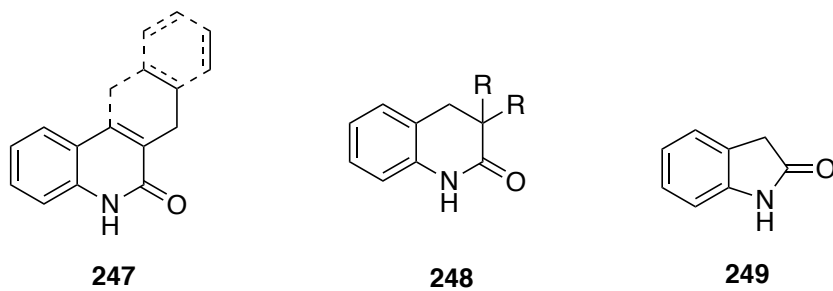
Figure 11: Substrates for the silver catalyzed chlorination, exhibiting a lactam unit and benzylic C–H bonds.

5.3. Results

First, [*bis*(1,10-phenanthroline)]silvertrifluoromethanesulfonate (Ag(phen)₂OTf) **251** was pre-pared from silver trifluoromethanesulfonate (AgOTf) according to a literature known procedure (Scheme 53).[118]
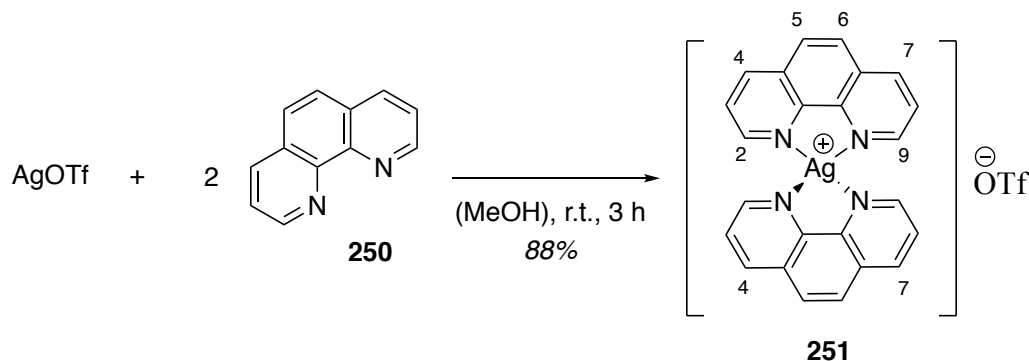
Scheme 53: Synthesis of Ag(phen)₂OTf by a literature-known procedure. [118]

To determine whether the silver catalyst needed to be preassembled to be effective in the chlo-rination reaction, substrates **252** and **253** were tested under the reported reaction conditions which were featured in the work of *Kanai* and co-workers (Figure 12).
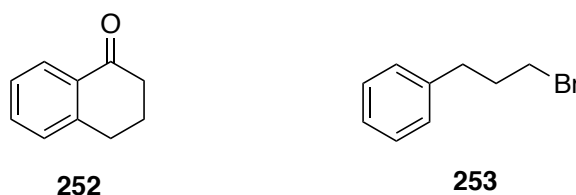
Figure 12: Reported substrates in the silver-catalyzed chlorination.

The reaction was performed using the preassembled catalyst **251** and compared with a sepa-rately employed 1:2 mixture of AgOTf and 1,10-phenanthroline (phen). The two catalyst sys-tems were tested under the reported conditions of 0.2 mol% catalyst in acetonitrile and two equivalents of *t*BuOCl. As evident from Table 13, the yield for substrate **252** were lower than the reported yield of 61% in the literature[118], but the obtained yield for the preassembled cat-alyst **251** compared to the separately employed catalyst mixture were very similar and gave the products in 40% or 35% yield, respectively (Table 13, entry 1 and 2). To investigate another example, reported substrate **253** was tested as well. The obtained yield of 71% with catalyst **251** was almost identical with the yields achieved with the non-assembled catalyst system, and was higher compared to the literature yield of 50%[118] (Table 13, entries 3 and 4).
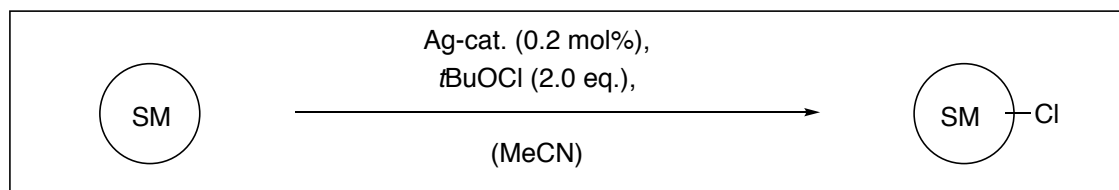
Table 13: Silver-catalyzed chlorinations with *t*BuOCl.

Entry	Substrate	Catalyst	Product	Yield [%]
1	**252**	Ag(phen)₂OTf	**241**	40 Lit.[118]: 61
2	**252**	AgOTf + phen 1:2	as above	35
3	**253**	Ag(phen)₂OTf	**240b**	71 Lit.[118]: 50
4	**253**	AgOTf + phen 1:2	as above	70

Next, quinolones **143, 141, 138** (for synthesis see section 4.3) and dihydroquinolone **142** were investigated (Figure 13).
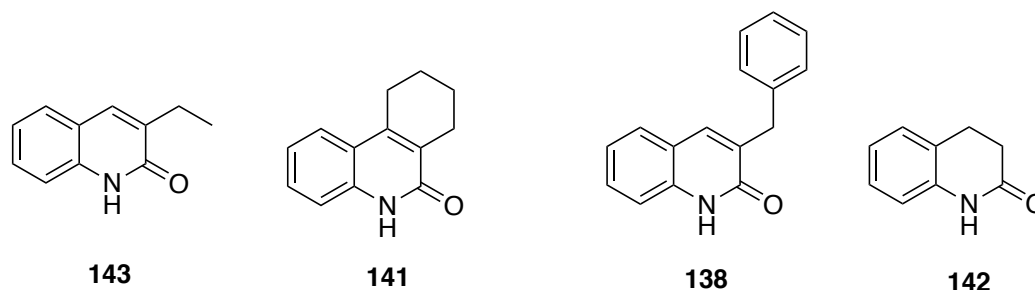
Figure 13: Investigated substrates for the silver catalyzed chlorination reaction.

When these substrates were exposed to the reaction conditions mentioned above, full conversion to a mixture of new species was observed. To gain insight into the details of the transformations, substrate **143** was examined in closer detail.

When dihydroquinolone substrate **143** was employed under the reaction conditions with catalyst **251** and the separate catalyst mixture, two products were formed in both cases. Evident from the NMR-spectra it was found that the main product was compound **254**, which is chlorinated both at the amide-nitrogen atoms as well as at the C6 atom on the arene core. The minor product **255**, obtained in 14% and 15% yield, respectively, showed chlorination at the desired sp³-C4-position of the molecule, but also at the amide-nitrogen atom. It eventually eliminated

to 6-chloro-quinolone **256** (Table 14, entries 1 and 2)**.** To avoid elimination of the chlorinated species **255** to **256**, dimethyl dihydroquonolone **257** was synthesized by a literature known procedure[26] and tested under the same reaction conditions (Figure 14).

256 **257**
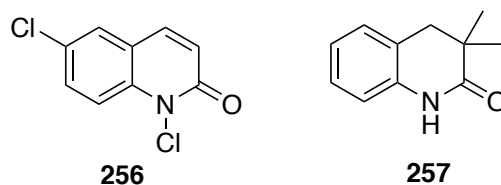
Figure 14: Quinolone **256** resulting from elimination from dihydroquinolone **255** and new substrate **257**.
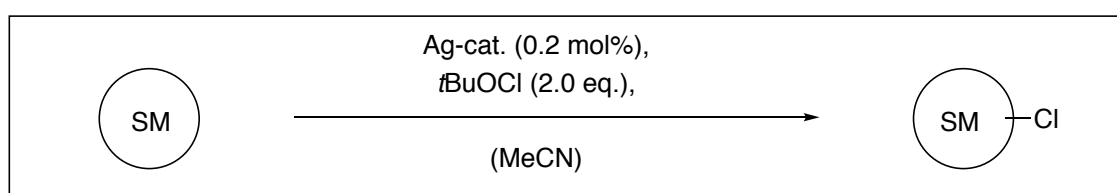
Table 14: Chlorination of dihydroquinolones **142** and **257**.

Entry	Substrate	Catalyst	Main product	Minor product	Yield [%]
1	**142**	Ag(phen)$_2$OTf	**254**	**255**[5]	15[6]
2	**142**	AgOTf + phen 1:2	as above	as above	14[1]
3	**257**	Ag(phen)$_2$OTf	**258**	**259**	36[1]
4	**257**	AgOTf + phen 1:2	as above	as above	33[1]

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[5] Eliminated to compound **256.**
[6] Determined with CH$_2$Br$_2$ as internal NMR-standard.

When dimethyl dihydroquonolone **257** was subjected to the same reaction conditions, similar observations were made as with substrate **142**. Instead of just chlorination at the sp³-C4-position, the two products **258** and **259** were obtained with both catalyst systems (Table 14, entries 3 and 4), while **259** was obtained in 36 and 33% yield, respectively.

Notably, the NMR spectra of the same compound exhibited substantial differences when measured on the day of the workup compared to those obtained the following day. This observation suggests that the products chlorinated at the nitrogen atom are not stable, leading to the eventual loss of chlorine over time. This effect results in the signals shifting upfield and at the same time revealing the N-H protons that were not initially observed (Scheme 54).
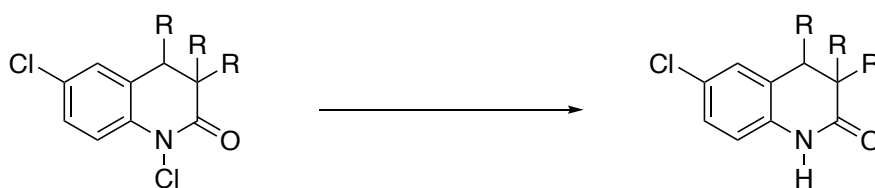
Scheme 54: Loss of the *N*-chlorine over time.

It is hypothesized that initially, chlorination occurs at the nitrogen atom, followed by an *Orton* rearrangement[121], where the chloride migrates *via* a radical pathway to position C6 on the arene core of the molecule, upon which the nitrogen atom gets chlorinated again (Scheme 55). This sequence results in the formation of the main product **258**, where both the nitrogen atom and the aromatic ring are chlorinated.
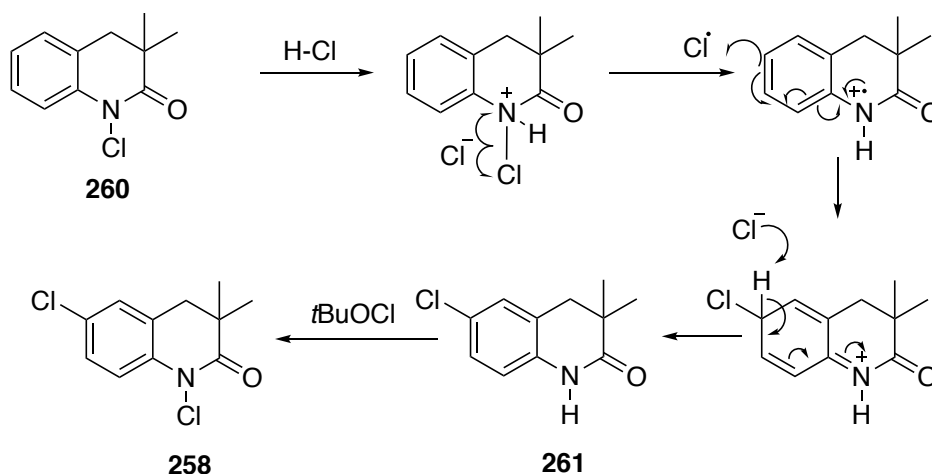
Scheme 55: *Orton* rearrangement of compound **260**.

To investigate the influence of different parameters on the reaction outcome, solvents and amounts of chlorinating agent were varied in the following experiments. Since the obtained products seemed to be unstable and therefore isolation was impossible, the ratio of products was determined by ^{1}H-NMR analysis instead.

First, substrate **142** was tested in the solvents DCM, DCE, CCl$_4$, benzene, toluene and THF combined with different amounts of *t*BuOCl. While benzene, toluene and THF did not lead to any chlorination at the desired sp^3-C4-position, DCE in combination with the separately employed silver catalyst and phenanthroline ligand gave a ratio of 1:10 of products **254** to **255**, presenting a significant improvement to the reaction in acetonitrile (Table 14, entry 1 *versus* Table 15, entry 4). Decreasing the amount of chlorinating agent from two to one equivalent generally led to a higher ratio of **254** to **255**, indicating that chloride-rearrangement from the nitrogen atom to position C6 on the arene core occurs prior to sp^3-C4 chlorination (Table 15).
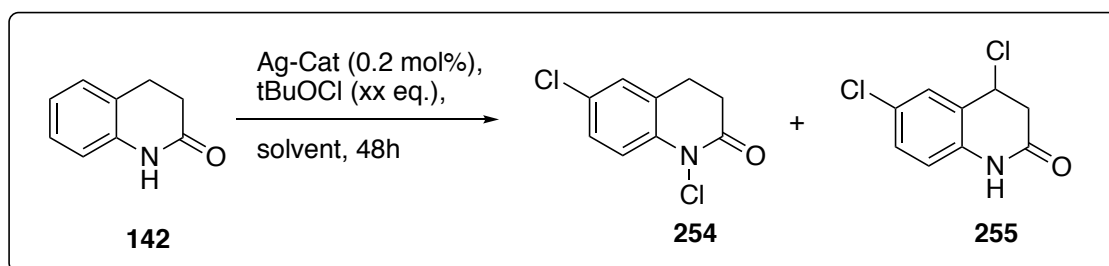
Table 15: Parameter screen of chlorination of substrate **142**.

Entry	Catalyst	*t*BuOCl (eq.)	Solvent	Ratio 254:255[7]
1	Ag(phen)$_2$OTf	2	DCM	20:1
2	AgOTf + phen 1:2	2	DCM	18:1
3	Ag(phen)$_2$OTf	2	DCE	11:1
4	AgOTf + phen 1:2	2	DCE	1:10
5	Ag(phen)$_2$OTf	1	DCM	43:1
6	Ag(phen)$_2$OTf	1.5	DCM	8:1
7	Ag(phen)$_2$OTf	2	CCl$_4$	36:1
8	Ag(phen)$_2$OTf	2	benzene	100:0
9	Ag(phen)$_2$OTf	2	toluene	100:0
10	Ag(phen)$_2$OTf	2	THF	100:0

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[7] Compound **255** was obtained as a mixture with the respective *N*-chlorinated compound.

Similar results were obtained with substrate **257**, in the case of which DCM seemed to give the best ratio of **258** to **259** (Table 16, entry 2). When the amount of chlorinating agent was lowered to one equivalent, only traces of chlorination at the desired sp^3-C4-position were observed (Table 16, entry 5). It was noted again that the solvents benzene, toluene and THF did not lead to any chlorination at the desired sp^3-C4-position.
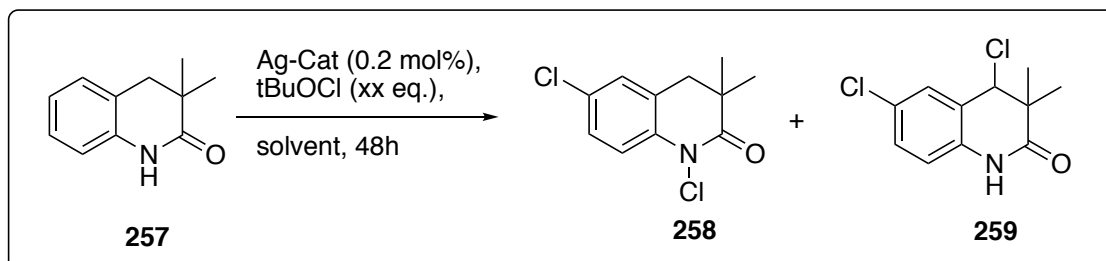
Table 16: Parameter screen of chlorination of substrate **257**.

Entry	Catalyst	tBuOCl (eq.)	Solvent	Ratio **258:259**[8]
1	Ag(phen)$_2$OTf	2	DCM	12:1
2	AgOTf + phen 1:2	2	DCM	6:1
3	Ag(phen)$_2$OTf	2	DCE	16:1
4	AgOTf + phen 1:2	2	DCE	12:1
5	Ag(phen)$_2$OTf	1	DCM	100:1
6	Ag(phen)$_2$OTf	1.5	DCM	76:1
7	Ag(phen)$_2$OTf	2	CCl$_4$	85:1
8	Ag(phen)$_2$OTf	2	benzene	100:0
9	Ag(phen)$_2$OTf	2	toluene	100:0
10	Ag(phen)$_2$OTf	2	THF	100:0

To assess the impact of the developed chiral phenanthroline ligands on the reaction outcome, ligands (+)-**36**, (+)-**145** and (+)-**146** (Figure 15) were utilized in the chlorination of dihydroquinolones **142** and **247**, using DCE as the solvent.

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[8] Compound **259** was obtained as a mixture with the respective *N*-chlorinated compound.
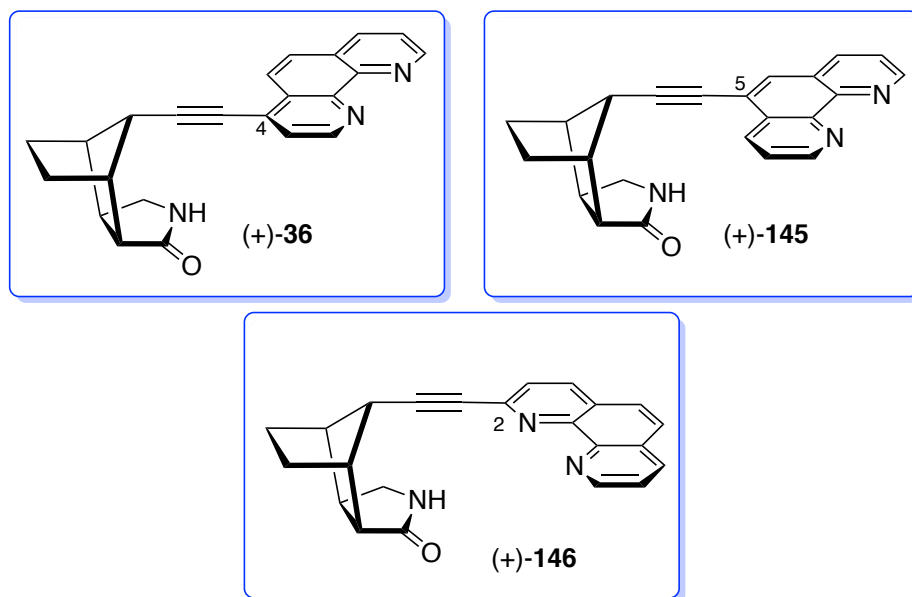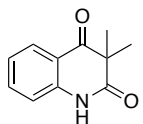
Figure 15: Chiral phenanthroline ligands tested in the silver catalyzed chlorination of dihydroquinolones.

When ligand (+)-**145** was employed, formation of the same products **254** and **254** (Table 17, entry 1) or **258** and **259** (Table 17, entry 3) was observed, respectively. Additionally, to determine the influence of catalyst loading on the reaction, 5 mol% of AgOTf and 10 mol% of the ligand were used in the next experiments. With both substrates **142** and **247** this led to a higher ratio of **254** to **254**, or **258** to **259**, indicating that more catalyst was disadvantageous for the chlorination at the desired C4 position (Table 17, entries 2 and 4).

Given that silver is known to form heteroleptic complexes and can coordinate two different phenanthroline ligands, the effect of using 10 mol% of AgOTf in combination with 10 mol% of the achiral 1,10-phenanthroline and 10 mol% of the chiral phenanthroline ligands (+)-**36**, as reported in the literature[33], was explored (Table 17, entry 6). The same experiments were repeated with chiral ligand (+)-**146** (Table 17, entry 7) as well as with 20 mol% of the achiral 1,10-phenanthroline ligand (Table 17, entry 5). In all experiments, a complex mixture including oxidized product **262** was obtained.
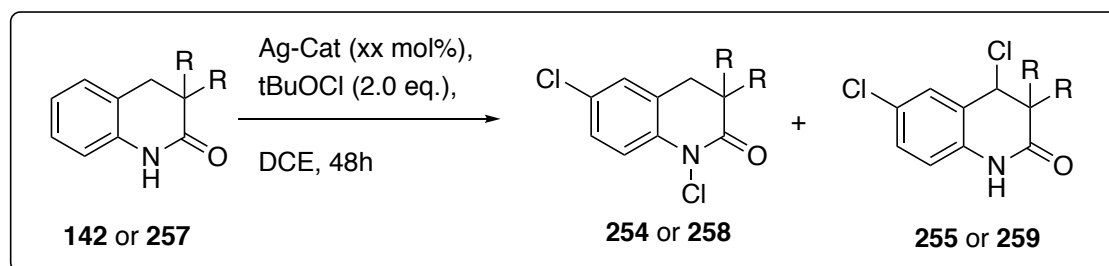
Table 17: Silver-catalyzed chlorination with the chiral ligands (+)-36, (+)-**145** and (+)-**146**.

Entry	Substrate	Catalyst	Equiv. [mol%]	Ligand	Equiv. [mol%]	Products[9]
1	**142** R = H	AgOTf	0.2	(+)-**145**	0.4	**254:255** 9:1
2	**142** R = H	AgOTf	5.0	(+)-**145**	10	**254:255** 32:1
3	**257** R = Me	AgOTf	0.2	(+)-**145**	0.4	**258:259** 8:1
4	**257** R = Me	AgOTf	5.0	5-L*	10	**258:259** 27:1
5	**257** R = Me	AgOTf	10	1,10-phenan-throline	20	**262** + SM
6	**257** R = Me	AgOTf	10	(+)-**36** plus 1,10-phen	10 +10	Complex mix + **262**
7	**257** R = Me	AgOTf	10	(+)-**146** plus 1,10-phen	10 +10	Complex mix + **262**

Since chlorination occurred on the arene C6-position of the dihydroquinolone substrates, 6-bromodihydroquinolone **263** was tested as a substrate to block the reactive position on the arene core, but unfortunately no reactivity with this compound was observed (Scheme 56).

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[9] Compounds **255** and **259** were obtained as mixtures with the respective *N*-chlorinated compounds.
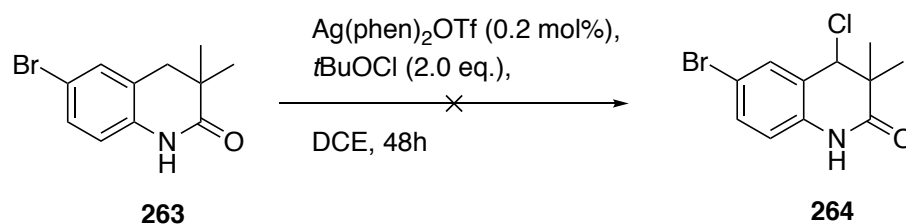
Scheme 56: Testing 6-bromo-substituted substrate in the silver-catalyzed chlorination reaction.

Finally, to investigate the actual impact of the silver catalyst on the reaction, the reaction was performed without catalyst and ligand. Surprisingly it was found, that the same products **258** and **259** were obtained.

Therefore, it was concluded, that the C–H-chlorination of the sp^3-C4 position may result from another rearrangement reaction, which is slower that the rearrangement to position C6, but does not require a silver catalyst. It was concluded, that the chlorination at the amide nitrogen atom and subsequent *Orton*-rearrangement must be much faster than the desired silver-catalyzed C–H-chlorination of the C4 position.

6. Summary

The objective of this work was to functionalize C–H bonds of substrates exhibiting an amide unit for hydrogen bonding by means of a catalytic system utilizing chiral phenanthroline or bipyridine ligands based on the chiral octahydro-template containing a lactam site. The aim was to use two-point hydrogen bonding as a control element to induce regioselectivity and or enantioselectivity.
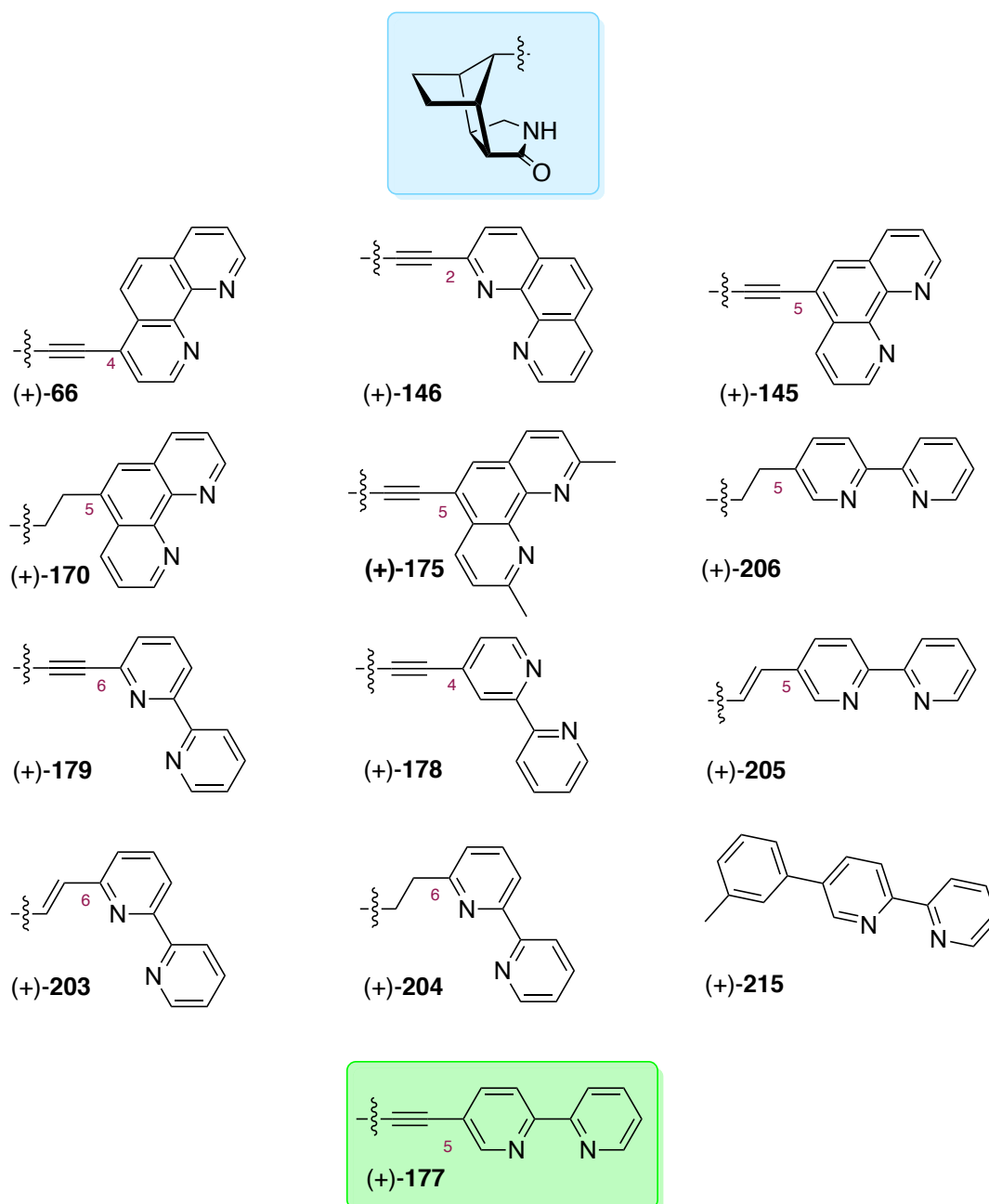
Figure 16: Summary of all synthesized chiral, bifunctional phenanthroline- and bipyridine ligands.

To investigate the enantioselectivity, a variety of different chiral phenanthroline and bipyridine ligands were synthesized, differing in the linker between the chiral backbone and the dinitrogen donor ligand as well as the linker position on the phenanthroline or bipyridine core (Figure 16). It was found that compounds (+)-**145**, (+)-**177**, (+)-**178**, (+)-**205**, (+)-**206** were effective ligands in the established iridium-catalyzed C–H borylation of hydantoins, with ligand (+)-**177**, giving the most reliable results.

Therefore, different hydantoins varying in substitution at the arene core and with different protecting groups at the nitrogen atom N3 were transformed into the respective alcohols by an iridium-catalyzed C–H bond borylation utilizing ligand (+)-**177**. This was followed by the oxidation of the borylated products with hydrogen peroxide to enable purification and analysis of the products. The hydroxylated products were obtained in moderate to good yields exceeding the yields obtained with the commercially available, achiral 3,4,7,8-tetramethylphenanthroline (tmphen) in most cases, which is known to be one of the most active and effective ligands used in the iridium catalyzed borylation of aromatic C–H bonds (Scheme 57, Scheme 58).[59],[62]

However, no enantioselectivity was induced with the present catalytic system, probably due to the suboptimal chiral environment created by the utilized chiral ligands. Successful examples for enantioselective iridium catalyzed C–H borylation utilizing hydrogen bonding are still very rare in the literature. In fact, most highly enantioselective borylations are based on directing groups such as silyl groups or amino groups on the respective substrates which directly bind to the iridium metal, enabling a close proximity between substrate and catalytic center.[73],[75],[76],[77],[78]The only case reported so far based solely on hydrogen bonding to induce enantioselectivity is the desymmetrization of biarylamides by *Phipps* and co-workers, which use a very large and complex catalytic system consisting of an achiral anionic bipyridine ligand that interacts with a chiral cation through electrostatic interactions.[79] In their recent paper on the interactions in their catalytic systems, they display the complex interactions between cation, ligand and substrate. In an extensive computational study exploring mechanism, involving all non-covalent interactions and points of potential origin of selectivity they have demonstrated the high complexity of the reaction. They state, that each substrate participated in a unique combination of different interactions and several hydrogen bonds, proving the difficulty of developing an efficient, simplistic catalytic system for an iridium catalyzed, enantioselective C–H borylation mediated by hydrogen bonding[122]
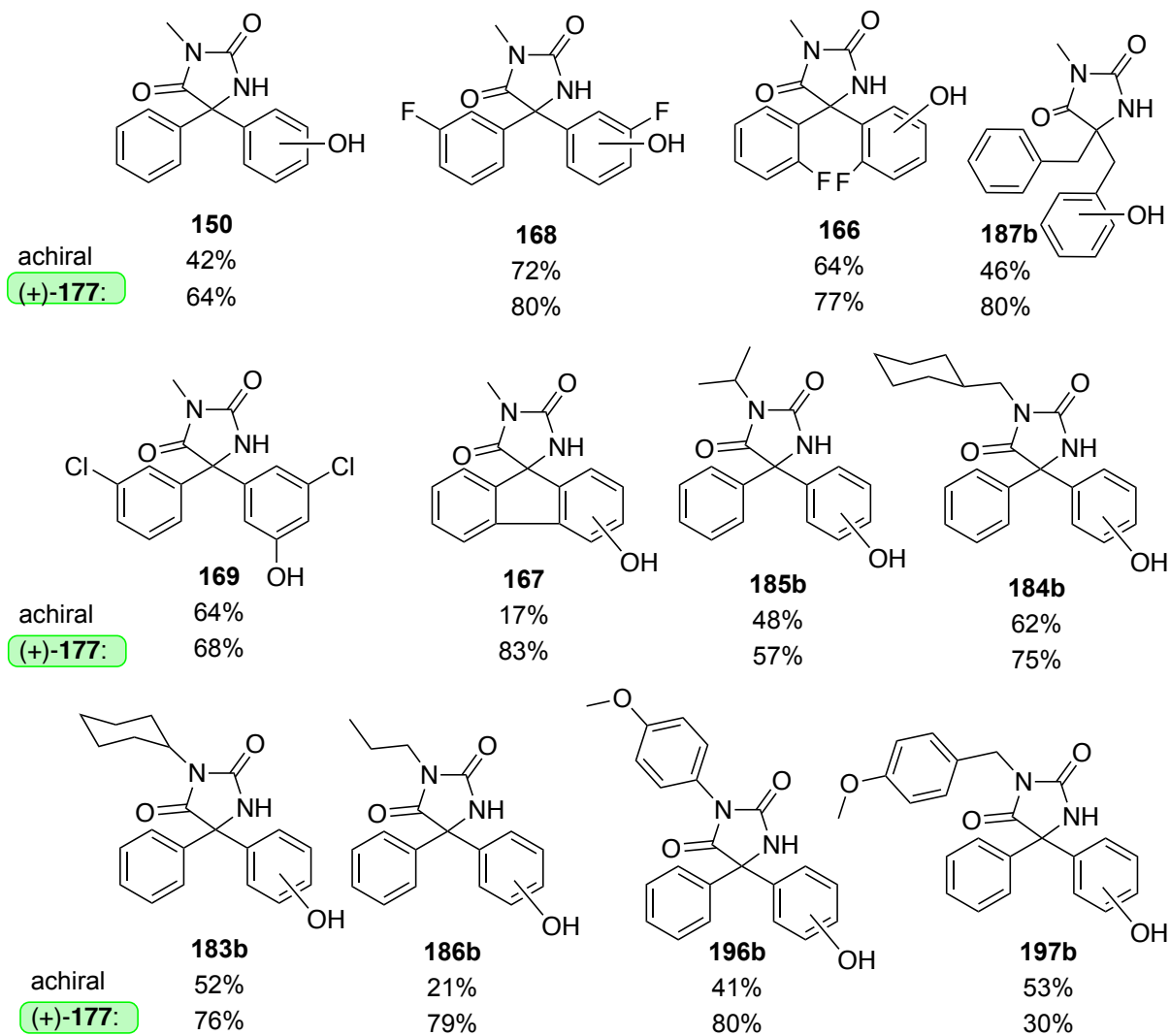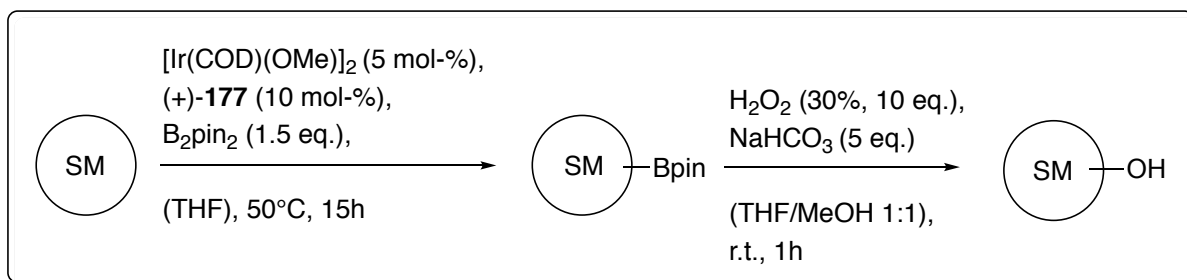
Scheme 57: Substrate scope of the iridium-catalyzed borylation/oxidation utilizing chiral ligand **(+)-177**.

Scheme 58: Substrate scope of the iridium-catalyzed borylation/oxidation utilizing chiral ligand **(+)-177**.

In the second project, the aim was to develop a silver-catalyzed, enantioselective chlorination reaction of dihydroquinolones such as **142** and **257,** utilizing chiral, bifunctional phenanthroline ligands with a lactam unit (Figure 17). The covalently bound phenanthroline unit was intended to act as a coordination site for the silver metal, facilitating regio- and/or enantioselective transfer of the chlorinating reagent *tert*butyl hypochlorite onto the substrates.
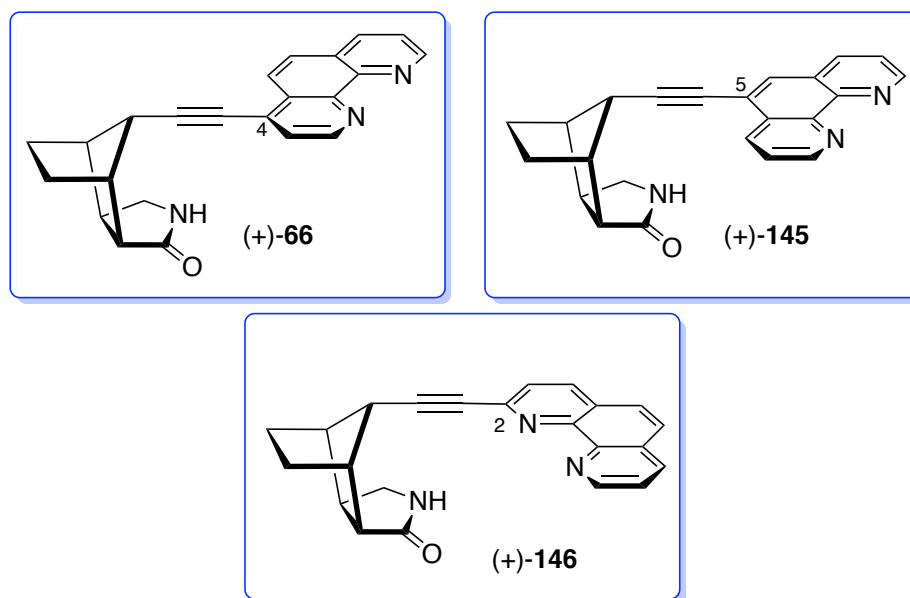
Figure 17: Chiral, bifunctional phenanthroline ligands with a lactam unit.
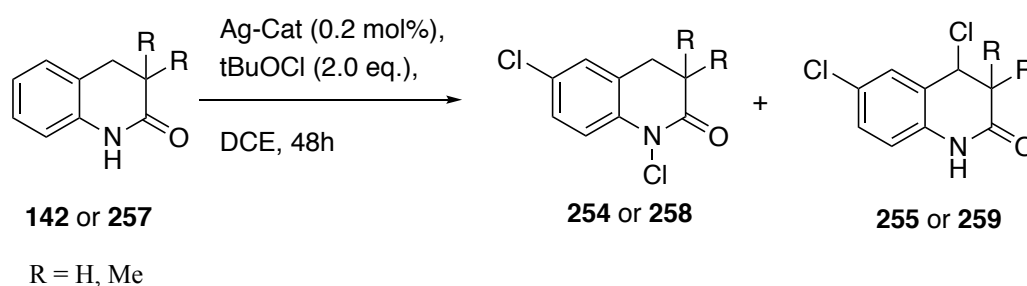
Scheme 59: Silver-catalyzed chlorination of dihydroquinolines.

It was observed that instead of the desired silver-catalyzed chlorination of the sp^3-C4 position of the molecules, chlorination mainly occurred on the amide nitrogen atom and on the C6-position of the arene core, leading to products **254** and **258**. Consequently, it was hypothesized that initially, chlorination occurs at the nitrogen atom, followed by an *Orton* rearrangement[121], where the chloride migrates *via* a radical pathway to position C6 on the arene core of the molecule, upon which the nitrogen atom gets chlorinated again (Scheme 60). Based on catalyst-free experiments, where it was found that the same products were formed, it was suggested that chlorination also occurs at the sp^3-C4 position *via* another rearrangement leading to product **255** and **259**, which are formed without the need for the silver-catalyst.
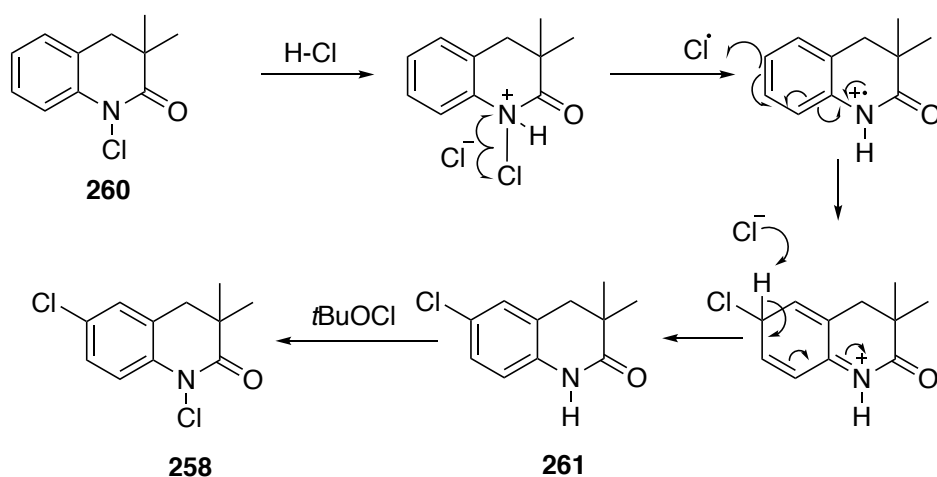
Scheme 60: *Orton*-rearrangement to chlorinated product **258.**

Based on the experimental results, it was concluded, that chlorination of dihydroquinolone substrate occurs at the amide nitrogen atom, followed by the rearrangement of the chloride to the C6-position of the arene core must be much faster than the desired silver-catalyzed C–H-chlorination of the C4 position. Since *N*-chlorination caused the loss of hydrogen bonding and no significant chlorination of the desired C4 position was achieved with the silver-catalyst complex, this method is not suitable for the desired transformation.

II. Experimental

1. General methods

1.1. General remarks

Procedures using oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents (*vide infra*) under an atmosphere of anhydrous argon in flame-dried flasks, using standard *Schlenk*-techniques. Reagents and solvents were added dropwise by using plastic syringes (B. Braun Melsungen AG).

1.2. Solvents and reagents

Dichloromethane, diethyl ether and tetrahydrofuran were obtained *via* a solvent purification system from *MBraun*, type MB-SPS-800, which is operated with argon gas. Residual water is removed using the following purification columns:

Dichloromethane: 2 × MB-KOL-A (aluminum oxide),

Diethyl ether: 1 × MB-KOL-A (aluminum oxide), 1 × MB-KOL-M type 2 (molecular sieve 3Å),

Tetrahydrofuran: 2 × MB-KOL-M type 2 (molecular sieve 3 Å).

Other dry solvents (methanol, ethanol, acetonitrile, pyridine, toluene, dimethyl sulfoxide) were purchased from *Fluka®*, *Sigma-Aldrich®* and *Acros Organics®* in the highest stated available purity and used without further purification:

Acetonitrile: extra dry, over molecular sieve, Acros Organics®, 99.9% (≤ 0.005% water),

Benzene: *Sigma-Aldrich®* puriss. 99.8%, (≤ 0.005% water),

N,N-Dimethylformamide: extra dry, over molecular sieve, *Acros Organics®*, 99.8%,

Dimethyl sulfoxide: extra dry, via molecular sieve, *Acros Organics®*, 99.7+%,

Ethanol: absolute reag., *Sigma-Aldrich®*, ≥99.8%, (< 0.005% water),

Methanol: extra dry, over molecular sieve, *Acros Organics®*, 99.8% (≤ 0.005% water),

Octane: *Sigma-Aldrich®*, dry (≥99%),

Pyridine: extra dry, over molecular sieve, *Acros Organics®*, 99.5%,

Toluene: extra dry, over molecular sieve, *Acros Organics®*, 99.5% (< 0.005% water),

p-Xylene: *Sigma-Aldrich®*, dry (≥99%).

For air-sensitive reactions, solvents were degassed using at least three *freeze-pump-thaw* cycles and stored under argon over molecular sieves (4Å).

For column chromatography and work up of reaction mixtures distilled technical solvents (acetone, dichloromethane, diethyl ether, ethyl acetate, methanol, n-pentane, i-propanol) were used. Solvent mixtures refer to the ratio of volumes.

Percentage values (%) always refer to mass percent. Saturated aqueous salt solutions were used to purify mixtures of substances. Unless otherwise stated, saturated and x% solutions are solutions in water.

The content of *n*-butyllithium, *t*-butyllithium and methyllithium was determined by titration against menthol (indicator 1,10-phenantroline).

Reagents not explicitly mentioned were purchased commercially and used without further purification.

Styrene was purified via distillation in a Büchi GKR-50 spherical tube furnace.

To measure pH values, universal indicator paper from *Merck* (pH 1-14) and indicator strips from *Machery-Nagel* were used.

1.3.   Analytical methods

A Laborota 4000 and Hei-VAP from *Heidolph* were used to evaporate solutions to dryness. Reaction vessels were cooled with baths of ice water (0 °C), an acetone/dry ice (−78 °C) or acetonitrile/dry ice mixture (−40 °C). Alternatively, a ThermoHaake EK90 cryostat was used. Reaction vessels were heated with a paraffin or silicone oil bath under temperature control using a contact thermometer.

Ozonolysis

Ozone was generated using an ozone generator type 502 from *FisherTechnology*.

Flash and thin layer chromatography

Qualitative thin-layer chromatograms were performed on prefabricated plates (glass) from *Merck* (0.25 mm silica gel 60, F254) containing a fluorescence indicator. Substances were visualized using UV light ($\lambda = 254$ nm and $\lambda = 366$ nm), aqueous ceric ammonium molybdate (CAM) or aqueous basic potassium permanganate ($KMnO_4$) stains. silica gel with a grain size of 40-63 μm (Si 60) from *Merck* was used for flash chromatography. Both the filling height and the diameter of the columns used were based on the amount of substance and separation difficulty.

Gas chromatography with Mass spectrometry coupling (GC/MS)

Gas chromatography coupled with mass spectrometry (GC/MS) was carried out on a 5973 Network Mass Selective Detector (EI, 70 eV) [flame ionization detector, hydrogen carrier gas, HP-

5 column (30 m × 0.25 mm)] or on an *Agilent* 7890 B [mass detector Agilent 5977 MS, helium as carrier gas, HP-5ms UI column (30 m × 0.25 mm × 0.25 μm), flow rate = 1.8 mL/min] from *Agilent*. Standard temperature program was STDLT (30 min) (50 °C 3 min, 10 °C/min → 250 °C, 250 °C 5 min) or STD (20 min) (60 °C 3 min, 15 °C/min → 250 °C, 250 °C 5min).

Gas chromatography (GC)

For analytical achiral gas chromatography, measurements were carried out on an *HP* 6890 Series GC system [flame ionization detector, hydrogen carrier gas, pressure = 160 kPa, HP-5 column (poly-dimethyl/diphenyl-siloxane, 95/5)]. An *Agilent* 7890 B [flame ionization detector, nitrogen as carrier gas, flow rate = 0.7 mL/min, Cyclosil-B (β-cyclodextrinic acid), (30 m × 0.25 m × 0.25 μm)] from *Agilent* was used for chiral measurements. The temperature programs are specified for the corresponding compounds.

High performance liquid chromatography (HPLC)

Analytical HPLC separations were carried out using chiral stationary phases *Daicel ChiralPak* AD−H (250 × 4.6 mm), *Daicel ChiralPak* AS−H (250 × 4.6 mm) and *Daicel ChiralPak* AS-RH (150 × 4.6 mm). The apparatus was operated with a P580 pump, an ASI-100 utomated Sample Injector and a UVD 340 U photodiode array detector. A mixture of *n*-hexane (*Merck*, LiChrosolv) or *n*-heptane and *i*-propanol or acetonitrile/water (all *VWR*, HiPersolv CHROMA-NORM) served as the mobile phase. Solvent ratios and flow rates are specified in the respective experimental procedure.

Nuclear magnetic resonance spectroscopy

Nuclear magnetic resonance spectra were recorded in deuterated solvents on a *Bruker* AV-500cr (^{1}H [500.36 MHz], ^{13}C [125.83 MHz]), AVHD300 (^{1}H [300.13 MHz], ^{13}C [75.48 MHz]), AVHD400 (^{1}H [400.13 MHz], ^{13}C [100.62 MHz]), and AVHD500 (^{1}H [500.36 MHz], ^{13}C [125.83 MHz]) at 300 K.

Chemical shifts are reported in parts per million (ppm) from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). *MestReNova* was used for evaluation of all spectra. In ^{13}C NMR spectra, the deuterium-coupled multiplets of the solvents serve as a reference. Samples were measured in chloroform [CDCl$_3$: δ (^{1}H) = 7.26 ppm, δ (^{13}C) = 77.16 ppm], methanol [CD$_3$OD: δ (^{1}H) = 3.31 ppm, δ (^{13}C) = 49.0 ppm], dimethyl sulfoxide [DMSO-d6: δ (^{1}H) = 2.50 ppm, δ (^{13}C) = 39.52 ppm], benzene [C$_6$D$_6$: δ (^{1}H) = 7.16 ppm, δ (^{13}C) = 128.06 ppm], dichloromethane [CD$_2$Cl$_2$: δ (^{1}H) = 5.32 ppm, δ (^{13}C) = 53.84 ppm] and acetone [CD$_3$CO: δ (^{1}H) = 2.09 ppm, δ (^{13}C) = 205.87 ppm]. The following abbreviations were used: s - singlet, br s – broad singlet, d - doublet, t - triplet, q - quartet, quint

- quintet, sept - septet, sx - sextet, m – multiplet, b – broad. Signal multriplicities for magnetically non-equivalent protons with a random equivalence of coupling constants are marked as virtual (virt.) Coupling constants J are given as mean values of the respective experimentally determinded values. Diastereotopic protons were described using the indices a and b. Protons at terminal double bonds were labeled E/Z according to IUPAC. For all signals that could not be assigned unequivocally, all feasable atoms were listed and separated with a dash (/). Signals were assigned *via* $^1H/^1H$–COSY, $^1H/^{13}C$–HSQC, and $^1H/^{13}C$–HMBC 2D NMR experiments.

Infrared spectroscopy

The infrared spectra were measured using total internal reflection (ATR) on a *JASCO* IR-4100 or *Perkin-Elmer* 1600 FT-IR spectrometer. Band signals are given in reciprocal wavelength (cm^{-1}) and their intensity using the following abbreviations: w - weak, m - medium, s - strong, br - broad. If the same assignments were made for different bands, they are separated from each other with a semicolon (;).

Mass spectrometry

The mass spectrometric data were obtained using a *Agilent* GC-MS coupling [GC system: Agilent 6890 with an HP-5MS column (dimethylpolysiloxane, 30 m), carrier gas helium; Mass detection: Agilent 5973 Network Mass Selective Detector (EI, 70 eV)] or a *Finnigan* MAT 8200 (EI, 70 eV).

High-resolution masses (HRMS) were obtained on a *Finnigan* MAT 8200 or a Thermo Scientific DFS-HRMS Spectrometer (ESI) or a *Thermo Finnigan* LTQ FT Ultra (ESI). The concentration of the sample solutions was approximately 1 mg/mL.

Melting points

Melting points of solids were measured using a *Kofler* apparatus ("Thermopan", Reichert, Vienna) or on an IA9100 melting point measuring device from Electrothermal and were not corrected.

Specific optical rotation

Specific optical rotation values were measured with a *Perkin-Elmer* 241 MC polarimeter in a 1 dm cuvette at $\lambda = 589$ nm (Na-D line) at 20 °C. The rotation values are given in 10^{-1} degrees $cm^2 \, g^{-1}$ and concentration c is given in g/100 mL. The optical purity of the sample is given as enantiomeric excess in % *ee* and was taken into account when calculating the specific rotation.

Elemental analysis

The elemental analyses were carried out by the microanalytical laboratory of the Technical University of Munich. Carbon (C), hydrogen (H) and nitrogen (N) were analyzed after oxidative combustion at high temperatures (approx. 1000 °C) using a EuroEA elemental analyzer from *HEKAtech* GmbH. After alkali digestion (Na_2O_2) using a micronickel bomb (according to *Merz* and *Pfab*), chlorine (Cl) was determined potentiometrically using a silver nitrate solution. Manganese (Mn) was determined after acidic wet digestion (e.g. H_2SO_4/HNO_3, H_2SO_4/H_2O_2, $HNO_3/3HCl$) and subsequent atomic absorption spectroscopy (AAS) using an FS280 AA from *Agilent Technologies*. Nickel (Ni) was also digested with acid and then determined photometrically on a *Shimadzu* UV-160 (λ = 436 nm) [reference electrode: dimethylglyoxym (1% in MeOH)].

2. General procedures

GP 1: Synthesis of chiral phenanthroline ligands

(3aR,4S,7R,7aS,8S)-8-Ethynyloctahydro-1H-4,7-methano-iso-indol-1-one [(–)-**61**] (30.0 mg, 171 µmol, 1.0 eq.), Pd(PPh₃)₄ (39.6 mg, 3.40 µmol, 0.20 eq.), CuI (11.2 mg, 6.00 µmol, 0.34 eq.) and the respective bromo-phenanthroline (66.1 mg, 257 µmol, 1.5 eq.) were added to a heatgun-dried *Schlenk*-flask purged with argon and dissolved in a 2:1 mixture of degassed NEt₃/MeOH (4.8 mL). The reaction mixture was degassed by three *freeze-pump-thaw* cycles and subsequently sonicated for a specified time (*vide infra*), whereas the sonication bath temperature remained at 60 °C throughout the reaction. After the reaction was allowed to cool to r.t., MeOH (3.2 mL) and satd., aq. KCN-solution (6 mL) was added and the reaction mixture was stirred for 1 h at r.t. The aqueous layer was extracted with DCM (3 × 15 mL) and the combined organic layers were dried over MgSO₄. After the solvent was removed *in vacuo*, the excess of NEt₃ was removed via co-evaporation with toluene (3 × 30 mL). Purification by column chromatography (silica, dry load, 15 × 1.5 cm, DCM/MeOH, 100:0 → 95:5; then 1% NEt₃ + DCM/MeOH +, 100:0 → 95:5) gave the desired ligand as a triethyl amine hydrochloride salt adduct. To remove the impurity, the adduct was dissolved in DCM (15 mL) washed with aq. K₂CO₃-solution (10%, 15 mL) and H₂O (10 mL) and the combined organic phases were dried over Na₂SO₄. After removal of the solvent *in vacuo* and trituration of the resulting solid with petroleum ether (PE 40-60, 5 mL), the pure product was obtained as a pale-yellow solid. Any variation of these reaction conditions is listed for individual entries (*vide infra*).

GP 2: Synthesis of chiral bipyridine ligands

(3aR,4S,7R,7aS,8S)-8-ethynyloctahydro-1H-4,7-methano-iso-indol-1-one [(–)-**61**] (25 mg, 143 µmol, 1.0 eq.), the respective bromo-bipyridine (37.0 mg, 157 µmol, 1.5 eq.) and THF (3 mL) were added to a heatgun-dried *Schlenk*-flask purged with argon and the solution was degassed by three *freeze-pump-thaw* cycles. Pd(PPh₃)₄ (5.00 mg, 7.00 µmol, 5.0 mol%), CuI (2.75 mg, 14.0 µmol, 0.10 eq.) and NEt₃ (376 µL, 274 µg, 2.71 µmol, 19 eq.) were added, the reaction mixture was degassed by three *freeze-pump-thaw* cycles again and subsequently stirred for 21 h at 50°C. After the reaction was allowed to cool to r.t., satd. aq. NH₄Cl-solution (10 mL) was added, the aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers were washed with satd. NaCl-solution (15 mL) and dried over MgSO₄. After the solvent was removed *in vacuo*, the excess of NEt₃ was removed via co-evaporation with toluene

(3 × 30 mL). Purification by column chromatography (silica, dry load, 15 × 1.5 cm, DCM/MeOH, 100:0 → 95:5) gave the desired ligand as a pale-yellow solid.

GP 3: Iridium-catalyzed borylations

[IrCOD(OMe)]$_2$ (1.00 mg, 1.50 mmol, 5.0 mol%), B$_2$pin$_2$ (11.4 mg, 45.0 µmol, 1.5 eq.) and the respective chiral ligand (10 mol%) were added to a heatgun-dried *Schlenk* tube purged with argon. They were dissolved in the respective solvent and heated to 50°C for 1 h. After cooling to r.t., the respective substrate (30 µmol, 1.0 eq.) was added and the reaction mixture was stirred for 16 h at the specified temperature (*vide infra*). The flask was then opened, and the solvents were removed *in vacuo* to give the crude borylated products.

GP 4: Oxidation of the borylated products

The crude products obtained from **GP 3** were dissolved in THF/MeOH (1:1, 1 mL, 0.03 M). NaHCO$_3$ (12.6 mg, 151 µmol, 5.0 eq.) was added in one portion followed by dropwise addition of H$_2$O$_2$ (35%, 25.8 µL, 300 µmol, 10 eq.). The reaction mixture was stirred at r.t. for 1 h and the solvents were then removed *in vacuo*. H$_2$O (3 mL) and DCM (3 mL) were added and the aqueous layer was extracted with DCM (3 × 3 mL). The combined organic phases were dried over MgSO$_4$ and the crude alcohol products were purified by column chromatography (silica, dry load, 10 × 1.5 cm, pentane/acetone, 10:1 → 4:1). The borylated products were obtained as colorless solids. Any variation of these reaction conditions is listed for individual entries (*vide infra*).

GP 5: Silver-catalyzed chlorinations, method A

A stock solution of Ag(phen)$_2$OTf (2.10 mg, 3.00 µmol) in the respective solvent (5.4 mL) was prepared in a *Schlenk*-tube under an argon atmosphere. 100 µL of stock solution containing Ag(phen)$_2$OTf (34.3 µg, 0.06 µmol, 0.2 mol%) were added to the respective substrate (30 µmol, 1.0 eq.) in a *Schlenk*-tube purged with argon. Subsequently, *t*BuOCl (7.00 µL, 60.0 µmol, 2.0 eq.) was added and the reaction mixture was stirred for 48 h at r.t. The reaction mixture was then filtered through a pad of silica to remove the silver catalyst and the solvent was removed *in vacuo* to give the crude products. Purification by column chromatography (silica, dry load, 15 × 1.5 cm, DCM/MeOH, hexane/EtOAc) gave the desired products.

GP 6: Silver catalyzed chlorinations, method B

A stock solution of AgOTf (8.6 mg, 33.0 µmol) and the respective phenanthroline ligand (66.0 µmol) in in the respective solvent (54 mL) was prepared in a *Schlenk*-tube under an argon atmosphere and the reaction mixture was stirred for 10 mins. 100 µL of stock solution containing Ag(phen)$_2$OTf (0.06 µmol, 0.2 mol%) were added to the respective substrate (30 µmol, 1.0 eq.) in a *Schlenk*-tube purged with argon. Subsequently, *t*BuOCl (7.00 µL, 60.0 µmol, 2.0 eq.) was added and the reaction mixture was stirred for 48 h at r.t. The reaction mixture was then filtered through a pad of silica to remove the silver catalyst and the solvent was removed *in vacuo* to give the crude products. The yields were assessed by ^{1}H-NMR with CH$_2$Br$_2$ as internal standard.

3. Synthesis of the chiral bifunctional ligands

3.1. Synthesis of the template backbone

6,6-Dimethylfulvene (50)
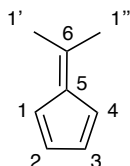
$$C_8H_{10}$$
$$M = 106.17 \text{ g/mol}$$

Acetone (44.4 mL, 34.6 g, 596 mmol, 1.0 eq.) was added to a solution of freshly distilled cyclopentadiene (127 mL, 1.53 mol, 2.6 eq.) in dry MeOH (440 mL). Pyrrolidine (74.6 mL, 64.2 g, 903 mmol 1.5 eq.) was added dropwise over a period of 60 mins. at 0 °C. The reaction mixture was stirred for 3 h at r.t. and subsequently neutralized by dropwise addition of concentrated (conc.) acetic acid (55.4 mL, 58.2 g, 970 mmol, 1.6 eq.) at 0 °C. Water (100 mL) and pentane (200 mL) were added, the layers were separated and the aqueous layer was extracted with pentane (4 × 200 mL). The combined organic layers were washed with brine (100 mL) and dried over MgSO4. After removal of the solvent *in vacuo,* 6,6-dimethylfulvene (57.8 g, 544 mmol, 93%) was obtained as a yellow oil.

TLC: R_f (pentane) = 0.54 [UV, KMnO4].

^{1}H-NMR (500 MHz, CDCl3): δ [ppm] = 6.55-6.54 (m, 4H, C1–H, C2–H, C3–H, C4–H), 2.24 (s, 6H, 1′–H, 1"–H).

^{13}C-NMR (101 MHz, CDCl3): δ [ppm] = 150.3 (s, C6), 142.6 (s, C5), 130.9 (d, C1, C2), 120.7 (d, C3, C4), 23.2 (q, C1′, C1′′).

The analytical data are consistent with those in the literature.[39]

(3a*R*,4*R*,7*S*,7a*S*)-8-(Propan-2´-yliden)-3a,4,7,7a-tetrahydro-4,7-methano-*iso*-benzofu-ran- 1,3-dione (52)

$C_{12}H_{12}O_3$

$M = 204.23$ g/mol
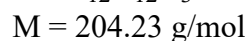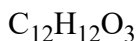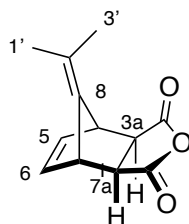
Dimethylfulvene (57.8 g, 544 mmol, 1.0 eq.) was dissolved in dry toluene (650 mL) and maleic anhydride (53.4 g, 544 mmol, 1.0 eq.) was added in one portion. The reaction mixture was stirred over night at 130 °C. After cooling to r.t. the solvent was removed *in vacuo* and the crude material was purified by recrystallisation (pentane/EtOAc 2:3). The dione **52** (58.0 g, 284 mmol, 52%) was obtained as a colourless crystalline solid.

TLC: R_f (pentane/Et$_2$O) = 0.51 [UV, KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 6.45 (dd, ^3J = 2.5 Hz, ^4J = 1.8 Hz, 2H, C5–H, C6–H), 3.87 (dd, ^3J = 2.5 Hz, ^4J = 1.8 Hz, 2H, C3a–H, C7a–H), 3.04 (s, 2H, C4–H, C7–H), 1.59 (s, 6H, C1´–H$_3$, C3´–H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 171.2 (s, C1, C3), 139.7 (s, C8), 138.1 (s, C2´), 117.3 (d, C5, C6), 49.3 (d, C3a, C7a), 46.9 (d, C4, C7), 19.8 (q, C1´, C3´).

The analytical data are consistent with those in the literature.[39]

(4*R*,7*S*,7a*S*)-8-(Propan-2´-yliden)hexahydro-4,7-methano-*iso*-benzofuran-1,3-dione (53)

$$C_{12}H_{14}O_3$$
$$M = 206.24 \text{ g/mol}$$
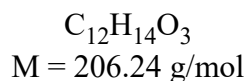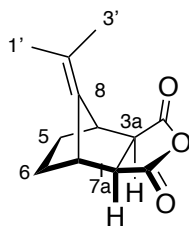
*Iso*benzofurane **53** (58.0 g, 284 mmol, 1.0 eq.), Pd/C (10%, 10.8 g, 20 wt%) and EtOAc (710 mL) were added to a heatgun-dried round bottom flask purged with argon. The reaction mixture was carefully evacuated and backfilled with hydrogen (3 ×) and stirred for 21 h at r.t. Subsequently, the reaction mixture was filtered over Celite® and washed with EtOAc (5 × 100 mL). After removal of the solvent *in vacuo*, the reduced *iso*benzofurane (**53,** 58.0 g, 281 mmol, 99%) was obtained as a colourless crystalline solid.

TLC: R_f (pentane/Et$_2$O) = 0.54 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 3.20 (*virt.* t, $^3J = {}^4J \approx 2.2$ Hz, 2H, C3a–H, C7a–H), 2.96 (s, 2H, C4H, C7–H), 1.78 – 1.70 (m, 2H, C5–H$_{ax}$, C6– H$_{ax}$), 1.66 (s, 6H, C1´–H$_3$, C3´–H$_3$), 1.49 – 1.42 (m, 2H, C5–H$_{eq}$, C6– H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 172.8 (s, C1, C3), 133.5 (s, C8), 123.5 (s, C2´), 117.3 (d, C5, C6), 48.8 (d, C3a, C7a), 40.7 (d, C4, C7), 27.1 (t, C5, C6), 20.8 (q, C1´, C3´).

The analytical data are consistent with those in the literature.[39]

(3a*R*,4*R*,7*S*,7a*S*)-2-[(*S*)-1´´-Phenylethyl]-8-(propan-2´-yliden)hexahydro-1*H*-4,7-methano-*iso*-indol-1,3(2*H*)-dione [(−)-54]

C$_{20}$H$_{23}$NO$_3$
M = 309.41 g/mol
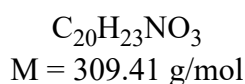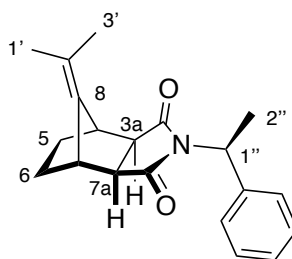
Triethylamine (51.0 mL, 37.0 g, 366 mmol, 1.3 eq.) and (*S*)-(–)- phenylethylamine (42.4 mL, 40.9 g, 338 mmol, 1.2 eq.) were added dropwise to a solution of *Iso*benzofurane **53** (58.0 g, 281 mmol, 1.0 eq.) in toluene (530 mL). The reaction mixture was stirred for 3 h at 140 °C. After cooling to r.t. H$_2$O (180 mL) was added to the reaction mixture and its layers were separated. The organic layer was washed with 2 M HCl (2 × 360 mL) and the aqueous layer was extracted with EtOAc (3 × 300 mL). The combined organic layers were dried over MgSO4. After removal of the solvent *in vacuo* diketo*iso*indole **(−)-54** (83.3 g, 269 mmol, 96%) was obtained as a colourless crystalline solid.

TLC: R_f (pentane/Et$_2$O 1:3) = 0.68 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.41-7.38 (m, 2H, CPh−H), 7.32-7.22 (m, 3H, CPh−H), 5.30 (q, ^3J = 7.3 Hz, 1H, C1´´−H), 3.03 (d, ^3J = 2.2 Hz, 1H, C3a−H/C7a−H), 2.98 (d, ^3J = 2.2 Hz, 1H, C3a−H/C7a−H), 2.60 (s, 2H, C4−H, C7−H), 1.71 (d, ^3J = 7.3 Hz, 3H, C2´´−H$_3$), 1.68–1.63 (m, 2H, C5–H$_{ax}$, C6– H$_{ax}$), 1.44 (s, 3H, C1´−H$_3$), 1.45–1.39 (m, 2H, C5–H$_{eq}$, C6– H$_{eq}$), 1.29 (s, 3H, C3´−H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 178.7 (s, C1/C3), 178.6 (s, C1/C3), 139.8 (s, CPh), 134.6 (s, C8), 128.4 (d, 2 × CPh), 127.9 (d, 2 × CPh), 127.6 (d, CPh), 121.6 (s, C2´), 50.1 (d, C1´´), 47.9 (d, C3a, C7a), 40.1 (d, C4, C7), 27.6 (t, C5, C6), 20.6 (q, C1´/C3´), 20.4 (q, C1´/C3´), 16.5 (q, C2´´).

The analytical data are consistent with those in the literature.[39]

(3a*S*,4*S*,7*R*,7a*R*)-2-[(*S*)-1´´-phenylethyl]-8-(propan-2´-yliden)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(−)-55a]

(3a*R*,4*R*,7*S*,7a*S*)-2-[(*S*)-1´´-Phenylethyl]-8-(propan-2´-yliden)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(−)-55b]

$$C_{20}H_{25}NO$$
$$M = 295.43 \text{ g/mol}$$
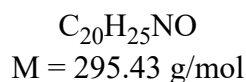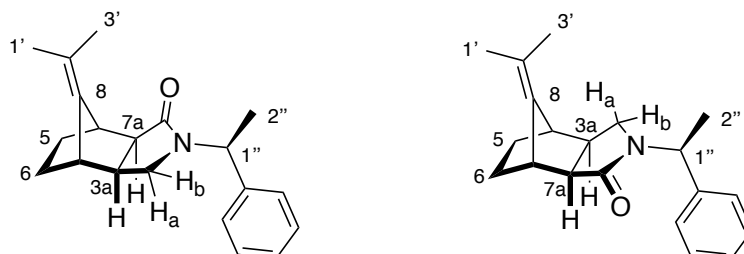
A solution of diketo*iso*indole **(−)-54** (20 g, 64.7 mmol, 1.0 eq.) in dry ethanol (200 mL) was cooled to 0 °C and sodium borohydride (8.56g, 226 mmol, 3.5 eq.) was added portionwise over a period of 20 min. The reaction mixture was allowed to warm to r.t. and heated to reflux for 24 h. After cooling to r.t. 1 M HCl (130 mL) was added, the resulting precipitate was filtered off and washed with EtOAc (90 mL). Subsequently, EtOAc was removed *in vacuo* and the resulting aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were dried over MgSO$_4$ and the crude amino alcohol was obtained by removing the solvent *in vacuo* as a yellow oil. The crude material was used in the next step without further purification.

The amino alcohol was dissolved in trifluoroacetic acid (TFA, 110 mL) and triethylsilane (25.8 mL 18.8 g, , 80.8 mmol, 2.5 eq.) was added dropwise at 0 °C over a period of 30 mins. The reaction mixture was allowed to warm to r.t. and stirred for another 3 h at r.t. After removal of the solvent *in vacuo* H$_2$O (70 mL) and EtOAc (70 mL) were added. The two layers were seperated and the organic layer was washed with a satd. sodium hydrogencarbonate solution (6 × 70 mL) and 1 M aq. NaOH (2 × 45 mL). The aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried over MgSO4, filtrated and the solvent was removed *in vacuo*. After purification by column chromatography (silica, dry load, 22 × 8 cm, P/Et2O 3:2 → 1:4), major compound (–)-**55a** (10.2 g, 34.5 mmol, 53%, *de* ≥98%) and minor compound (–)-**55b** (5.49 g, 18.6 mmol, 29%, *de* ≥98%) were obtained as colourless crystalline solids.

Major diastereomere [(–)-55a]:

TLC: R_f (pentane/Et$_2$O 1:3) = 0.50 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.36–7.23 (m, 5H, CPh−H), 5.38 (q, ^3J = 7.0 Hz, 1H, C1′′−H), 3.02 (d, ^3J = 4.3 Hz, 1H, C7−H), 2.98 (dd, ^2J = 9.7 Hz, ^3J = 9.4 Hz, 1H, C3−H$_a$), 2.69 (dd, ^2J = 9.7 Hz, ^3J = 3.1 Hz, 1H, C3−H$_b$), 2.52 (d, ^3J = 8.6 Hz, 1H, C7a−H), 2.48 (d, ^3J = 4.3 Hz, 1H, C4−H), 2.17 (ddd, ^3J = 9.4 Hz, 8.6 Hz, 3.1 Hz, 1H, C3a−H), 1.69 (s, 3H, C1′−H$_3$/C3′−H$_3$), 1.68 (s, 3H, C1′−H$_3$/C3′−H$_3$), 1.66–1.52 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.37 (d, ^3J = 7.2 Hz, 3H, C2′′−H$_3$), 1.44–1.25 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 174.7 (s, C1), 139.8 (s, C8), 137.9 (s, CPh), 128.5 (d, CPh), 127.5 (d, CPh), 119.0 (s, C2′), 51.1 (t, C3), 48.9 (d, C1′′), 47.5 (d, C4), 43.0 (d, C3a), 40.1 (d, C7), 37.3 (d, C7a), 27.8 (t, C5/C6), 27.1 (t, C5/C6), 21.3 (q, C1′/C3′), 21.0 (q, C1′/C3′), 15.7 (q, C2′′).

The analytical data are consistent with those in the literature.[39]

Minor diastereomere [(–)-55b]:

TLC: R_f (pentane/Et$_2$O 1:3) = 0.30 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.34–7.28 (m, 2H, CPh−H), 7.25–7.20 (m, 3H, CPh−H), 5.44 (q, ^3J = 7.2 Hz, 1H, C1′′−H), 3.43 (dd, ^2J = 9.6 Hz, ^3J = 9.2 Hz, 1H, C3−H$_a$), 2.98 (d, ^3J = 4.4 Hz, 1H, C7−H), 2.52 (d, ^3J = 8.7 Hz, 1H, C7a−H), 2.42 (dd, ^2J = 9.6 Hz, ^3J = 3.8 Hz, 1H, C3−H$_b$), 2.35 (d, ^3J = 4.4 Hz, 1H, C4−H), 2.27 (ddd, ^3J = 9.2 Hz, 8.7 Hz, 3.1 Hz, 1H, C3a−H), 1.57 (s, 3H, C1′−H/C3′−H), 1.62–1.48 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.46 (d, ^3J = 7.2 Hz, 3H, C2′′−H$_3$), 1.41–1.25 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$), 1.24 (s, 3H, C1′−H$_3$/C3′−H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 174.7 (s, C1), 140.3 (s, C8), 137.5 (s, CPh), 128.4 (d, CPh), 127.4 (d, CPh), 127.3 (d, CPh), 119.3 (s, C2′), 51.3 (t, C3), 48.8 (d, C1′′), 47.1 (d, C4), 42.5 (d, C3a), 39.8 (d, C7), 37.5 (d, C7a), 28.0 (t, C5/C6), 27.1 (t, C5/C6), 20.9 (q, C1′/C3′), 20.8 (q, C1′/C3′), 15.8 (q, C2′′).

The analytical data are consistent with those in the literature.[39]

(3aR,4R,7S,7aS)-8-(Propan-2´-ylidene)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-56]

$$C_{12}H_{17}NO$$
$$M = 191.27 \text{ g/mol}$$
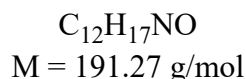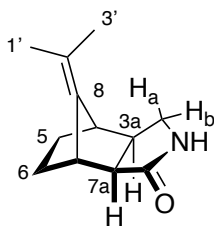
Ammonia (200 mL) was condensed in a three-neck flask at –78 °C and lithium was added in portions until the solution turned deep blue. A solution of compound (–)-**55b** (6.71 g, 22.7 mmol, 1.0 eq.) in THF (60 mL) was added dropwise. When the reaction solution became discolored during this process more lithium was added. The reaction mixture was stirred for 4 h at –78 °C and subsequently quenched with solid NH₄Cl until the blue color disappeared. Ammonia was removed slowly by allowing the reaction mixture to warm to r.t. over night. Water (100 mL) and EtOAc (250 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combindes organic layers were washed with brine and dried over NaSO₄. After the solvent was removed *in vacuo*, compound (+)-**56** (4.04 g, 21.1 mmol, 93%) was obtained as a colourless solid.

TLC: R_f (EtOAc) = 0.10 [KMnO₄].

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 5.34 (br s, 1H, NH), 3.46 (*virt.* t, $^2J = {}^3J \approx 9.4$ Hz, 1H, 3–Hₐ), 2.98 (d, $^3J = 4.0$ Hz, 1H, C7−H), 2.80 (dd, $^2J = 9.4$ Hz, $^3J = 3.6$ Hz, 1H, C3−H_b), 2.54 (d, $^3J = 4.0$ Hz, 1H, C4−H), 2.46 (*virt.* td, $^3J \approx 8.8$ Hz, 3.6 Hz, 1H, C3a–H), 2.38 (d, $^3J = 8.8$ Hz, 1H, C7a−H), 1.69 (s, 3H, C1´−H₃/C3´−H₃), 1.67 (s, 3H, C1´−H₃/C3´−H₃), 1.62–1.53 (m, 2H, C5−Hₐₓ, C6−Hₐₓ), 1.44–1.25 (m, 2H, C5−H_eq, C6−H_eq).

¹³C-NMR (91 MHz, CDCl₃): δ [ppm] = 179.2 (s, C1), 137.1 (s, C8), 119.4 (s, C2´), 49.4 (d, C4), 47.0 (t, C3), 42.8 (d, C3a), 41.0 (d, C7), 39.7 (d, C7a), 28.0 (t, C5/C6), 27.1 (t, C5/C6), 21.3 (q, C1´/C3´), 20.9 (q, C1´/C3´).

The analytical data are consistent with those in the literature.[39]

(3aR,4R,7S,7aR)-Octahydro-1H-4,7-methano-*iso*-indol-1,8-dione [(+)-57]

$C_9H_{11}NO_2$
M = 165.19 g/mol
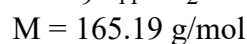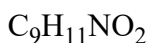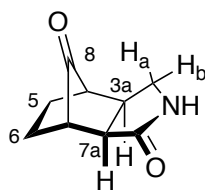
A solution of (+)-**56** (4.04 g, 21.1 mmol, 1.0 eq.) in MeOH (61 mL) and DCM (180 mL) was cooled to –78 °C and purged with oxygen for 15 mins. Subsequently, the solution was saturated with ozone for 40 mins. until it turned blue. After removal of excess ozone by purging the reaction solution with argon for 15 mins. (discoloriation), dimethyl sulphide (1.85 mL, 1.57 g, 25.6 mmol, 1.2 eq.) was added. The reaction mixture was then allowed to warm to r.t. over a period of 60 mins. And the solvent was removed *in vacuo.* Purification by column chromatography (silica, dry load, 22 × 3 cm, DCM/MeOH, 19:1→9:1) provided the diketone (+)-**57** (2.86 g, 17.3 mmol, 82%) as a colorless solid.

TLC: R_f (DMC/MeOH, 10:1) = 0.40 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 5.76 (br s, 1H, NH), 3.66 (dd, ^2J = 10.7 Hz, ^3J = 9.4 Hz, 1H, C3−H$_a$), 3.12 (dd, ^2J = 10.5 Hz, ^3J = 3.5 Hz, 1H, C3−H$_b$), 2.76 (ddd, ^3J = 10.2 Hz, 9.8 Hz, 3.5 Hz, 1H, C3a−H), 2.69 (d, ^3J = 9.9 Hz, 1H, C7a−H), 2.31 (d, ^3J = 4.2 Hz, 1H, C7−H), 2.06–1.94 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.93 (d, ^3J = 4.4 Hz, 1H, C4−H), 1.72–1.59 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 213.3 (s, C8), 176.6 (s, C1), 46.3 (t, C3), 45.2 (d, C3a), 44.9 (d, C7), 41.6 (d, C7a), 37.2 (d, C4), 22.7 (t, C5/C6), 22.4 (t, C5/C6).

The analytical data are consistent with those in the literature.[39]

(3aR,4R,7S,7aS)-8-(Methoxymethylene)octahydro-1H-4,7-methano-iso-indol-1-one [(E/Z)-58]

$$C_{11}H_{15}NO_2$$
$$M = 193.25 \text{ g/mol}$$
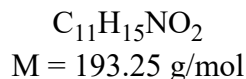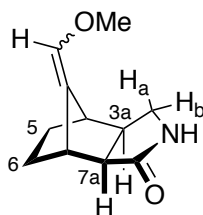
At 0°C, potassium *tert*-butanolate (3.74 g, 33.3 mmol, 2.3 eq.) was added portionwise to a solution of (methoxymethyl)triphenylphosphonium chloride (10.3 g, 29.1 mmol, 2.1 eq.) in THF (160 mL) and the solution was stirred for 45 mins. at 0 °C. Subsequently, compound (+)-**57** (2.40 g, 14.5 mmol, 1.0 eq.) was added portionwise and the reaction mixture was allowed to warm to r.t. The reaction mixture was then heated to reflux for 4 h at 70 °C. Water (120 mL) and EtOAc (120 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 60 mL) and the combined organic layers were dried over MgSO4. After removal of the solvent *in vacuo*, purification of the crude material by column chromatography (silica, dry load, 22 × 3 cm, DCM/MeOH 99:1 → 96:4) yielded compound (E/Z)-**58** (2.12 g, 11.0 mmol, 76%) as a colorless solid. The product was obtained as a mixture of diastereoisomers (d.r. = 62:38).

TLC: R_f (DMC/MeOH, 10:1) = 0.43 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 5.91 (s, 1H, C1′−H), 5.90 (s, 1H, C1′−H), 5.30 (br s, 2H, 2 × NH), 3.53 (s, 6H, 2 × OCH$_3$), 3.43–3.51 (m, 2H, C3−H), 3.29 (d, ^3J = 4.3 Hz, 1H, C7−H), 2.91–2.82 (m, 3H, C3−H, 2 × C7a−H), 2.73 (d, ^3J = 4.1 Hz, 1H, C7−H), 2.53–2.38 (m, 4H, C3−H, 2 × C3a−H, C4−H), 2.24 (d, ^3J = 4.2 Hz, 1H, C4−H), 1.76–1.55 (m, 4H, 2 × C5−H$_{ax}$, 2 × C6−H$_{ax}$), 1.46–1.23 (m, 4H, 2 × C5−H$_{eq}$, 2 × C6−H$_{eq}$).

Major diastereoisomer: **[(E)-58]**

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 27.9 (t, C5/C6), 28.2 (t, C5/C6), 38.3 (d, C7), 40.6 (d, C3a), 44.6 (d, C4), 46.9 (d, C7a), 50.5 (t, C3), 59.5 (q, CH$_3$), 121.9 (s, C8), 135.2 (d, C1′), 180.0 (s, C1).

Minor diastereoisomer [(Z)-58]:

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 27.0 (t, C5/C6), 28.9 (t, C5/C6), 40.9 (d, C7), 41.1 (d, C3a), 41.2 (d, C4), 47.0 (d, C7a), 50.1 (t, C3), 59.7 (q, CH$_3$), 121.8 (s, C8), 135.8 (d, C1′), 179.0 (s, C1).

The analytical data are consistent with those in the literature.[39]

(3aR,4R,7S,7aS,8S)-1-oxooctahydro-1*H*-4,7-methano-*iso*-indol-8-carbaldehyde [(+)-59]

C$_{10}$H$_{13}$NO$_2$
M = 179.22 g/mol
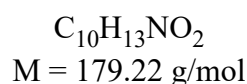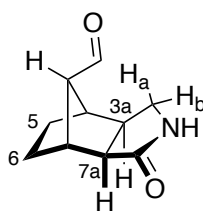
(+)-Camphorsulphonic acid (98.6 mg, 424 µmol, 0.1 eq.) and H$_2$O (20 µL) were added to a solution of (E/Z)-**58** (820 mg, 4.24 mmol, 1.0 eq.) in acetonitrile (14 mL). The reaction mixture was stirred for 16 h at r.t. After removal of the solvent *in vacuo*, the crude material was purified by column chromatography (silica, dry load, 15 × 2 cm, EtOAc/acetone 9:1). Aldehyde (+)-**59** (494 mg, 2.76 mmol, 65%) was obtained as a colourless crystalline solid.

TLC: R_f (DMC/MeOH, 10:1) = 0.42 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 9.86 (s, 1H, CHO), 5.42 (br s, 1H, NH), 3.49 (*virt*. t, $^2J = {}^3J ≈ 10.1$ Hz, 1H, C3−H$_a$), 3.12 (d, $^3J = 4.0$ Hz, 1 H, C7−H), 3.09 (d, $^3J = 3.2$ Hz, 1 H, C3−H$_b$), 2.77 (d, $^3J = 4.0$ Hz, C4−H), 2.53 (d, $^3J = 9.1$ Hz, C7a−H), 2.46 (*virt*. td, $^3J = {}^3J ≈ 9.1$ Hz, $^3J = 3.2$ Hz, 1H, C3a−H), 2.34 (s, 1H, C8−H), 1.79–1.58 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.40–1.23 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 201.3 (s, CHO), 178.0 (s, C1), 61.9 (d, C8), 49.8 (d, C7a), 45.9 (t, C3), 42.9 (d, C4), 41.2 (d, C7), 39.1 (d, C3a), 28.7 (t, C5/C6), 28.6 (t, C6/C5).

The analytical data are consistent with those in the literature.[39]

Dimethyl (diazomethyl)phosphonate (*Seyferth-Gilbert*-reagent, 60)

$$C_3H_7N_2O_3P$$
$$M = 150.07 \text{ g/mol}$$
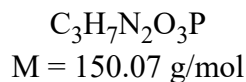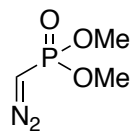
Methansulfonyl chloride (1.60 mL, 2.36 g, 20.5 mmol, 1.5 eq.) was added dropwise to a solution of sodium azide (1.34 g, 20.6 mmol, 1.5 eq.) in acetonitrile (25 mL) over a period of 10 mins. The reaction mixture was stirred for 30 mins. at r.t. Dimethyl (2-oxopropyl)phosphonate (2.28 g, 13.7 mmol, 1.0 eq.) was then added portionwise over a period of 10 mins. and the reaction mixture was stirred for 6 h at r.t. Subsequently, Cs_2CO_3 (6.7 g, 20.5 mmol, 1.5 eq.) was added portionwise and the reaction mixture was stirred at r.t. for another 16 h. Methanol (21.5 mL) was then added and the reaction mixture was stirred for 1 h. The reaction was stopped by adding aq. satd. NH_4Cl solution (12.5 mL), the aqueous phase was extracted with EtOAc (5 × 50 mL) and the combined organic phases were dried over $MgSO_4$. The crude material was purified by column chromatography (silica, dry load, 15 × 2 cm, EtOAc) and the *Seyferth-Gilbert*-reagent (**60**, 1.09 g, 7.26 mmol, 90%) was obtained as a yellow oil.

TLC: R_f (EtOAc) = 0.29 [$KMnO_4$].

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.76 (d, $^2J_{P-H}$ = 11.0 Hz, 1H, CHN_2).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 53.1, 53.0.

The analytical data are consistent with those in the literature.[123]

(3aR,4S,7*R*,7a*S*,8*S*)-8-Ethynyloctahydro-1*H*-4,7-methano-*iso*-indol-1-one [(–)-61]

$C_{11}H_{13}NO$

M = 175.23 g/mol
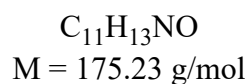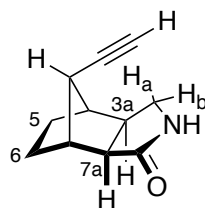
Potassium *tert*-butanolate (119 mg, 1.06 mmol, 1.5 eq.) was added portionwise to a solution of the *Seyferth-Gilbert*-reagent (**60**, 150 µL, 180 mg, 1.20 mmol, 1.7 eq.) in dry THF (2.3 mL) at –78 °C and the reaction mixture was stirred for 10 mins. Subsequently, a solution of the aldehyde (+)-**59** (127 mg, 709 µmol, 1.0 eq.) in THF (3.3 mL) was added dropwise. The reaction mixture was allowed to warm to r.t. over night. After addition of aq. satd. NH$_4$Cl solution (1.9 mL) was added, the aqueous phase was extracted with EtOAc (7 × 10 mL). The combined organic layers were dried over MgSO$_4$ and the solvent was removed *in vacuo*. After purification by column chromatography (silica, dry load, 15 × 2 cm, DCM/MeOH 50:1→19:1) the alkyne (–)-**61** (102 mg, 581 µmol, 82%) was obtained as a colorless solid.

TLC: R_f (DMC/MeOH, 10:1) = 0.46 [KMnO$_4$].

¹H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 5.21 (br s, 1H, NH), 3.66–3.55 (m, 2H, C3−H$_a$, C4−H), 2.83 (d, ^3J = 3.8 Hz, C7−H), 2.52 (*virt.* td, ^3J = ^3J ≈ 9.1 Hz, ^3J = 5.2 Hz, 1H, C3a−H), 2.47 (d, ^3J = 9.1 Hz, 1H, C7a−H), 2.44–2.40 (m, 2H, C3−H$_b$, C8−H), 1.98 (d, ^4J = 2.6 Hz, C2′−H), 1.74–1.51 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.29-1.13–1.23 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

¹³C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 178.3 (s, C1), 82.6 (s, C1′), 71.3 (d, C2′), 50.3 (d, C7a), 46.4 (t, C3), 46.2 (d, C4), 44.1 (d, C7), 41.9 (d, C3a), 38.2 (d, C8), 28.7 (t, C5/C6), 28.6 (t, C6/C5).

The analytical data are consistent with those in the literature.[23]

2,2-Dimethyl-5-(quinolin-8′-ylaminomethylene)-1,3-dioxane-4,6-dione (63)

$$C_{16}H_{14}N_2O_4$$
$$M = 298.30 \text{ g/mol}$$
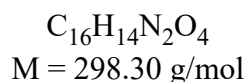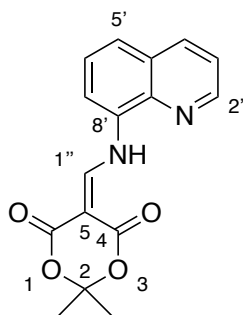
In a heatgun-dried flask purged with argon, Meldrum′s acid (3.20 g, 22.2 mmol, 1.2 eq.) was dissolved in trimethyl orthoformate (34 mL) and heated up to reflux for 2 h. After the solution was allowed to cool to r.t., 8-aminoquinoline (2.66 g, 18.5 mmol, 1.0 eq.) was added and the reaction mixture was heated to reflux for another 90 mins. After cooling to r.t. and removing the solvent *in vacuo*, the resulting precipitate was recrystallizied from ethanol (45 mL). Compound **63** (4.69 g, 15.7 mmol, 85%) was obtained as a yellow solid.

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 12.86 (br d, ^3J = 15.0 Hz, 1H, NH), 9.00 (dd, ^3J = 4.2 Hz, 1.7 Hz, 1H, C2′–H), 8.93 (d, ^3J = 15.0 Hz,1H, C1′′–H), 8.21 (dd, ^3J = 8.3, 1.7 Hz, 1H, C4′-H), 7.74 – 7.65 (m, 2H, C5′–H, C7′–H), 7.61 (d, ^3J =7.8 Hz, 1H, C6′–H), 7.54 (dd, ^3J = 8.3, 4.2 Hz, 1H, C3′–H), 1.78 (s, 6H, C2–H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 165.2 (s, C=O), 164.4 (s, C=O), 150.5 (d, C2′, C1′′), 139.2 (s, C8a′), 136.5 (d, C4′), 135.0 (s, C8′), 129.1 (s, C4a′), 126.9 (s, C6′), 125.2 (s, C5′/C7′), 123.0 (s, C3′), 112.5 (s, C7′/C5′), 105.4 (s, C5), 88.9 (s, C2), 27.6 (q, 2 × *C*H$_3$)

The analytical data are consistent with those in the literature. [124]

4-Hydroxy-1,10-phenanthroline (64)

$$C_{12}H_8N_2O$$
$$M = 196.21 \text{ g/mol}$$
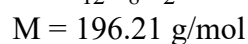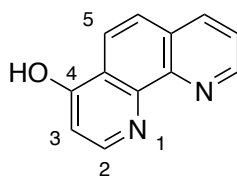
Compound **63** (2.37 g, 7.95 mmol, 1.0 eq.) was refluxed in diphenyl ether (40 mL) under vigorous stirring for 4 h. After the reaction mixture was allowed to cool to r.t., petroleum ether (PE 40-60 °C, 20 mL) was added and the resulting precipitate was filtered, washed with PE and dried *in vacuo* at 90 °C. 4-Hydroxy-1,10-phenanthroline (**64**, 805 mg, 4.10 mmol, 52%) was obtained as a brown solid.

^{1}H-NMR (300 MHz, CDCl$_3$): δ [ppm] = 8.93 (d, ^3J = 4.5 Hz, 1H, C9–H), 8.40 (d, ^3J = 8.9 Hz,1H, C5–H), 8.28 (d, ^3J = 8.1 Hz, 1H, C7-H), 7.96 (d, ^3J = 7.4 Hz, 1H, C2-H), 7.68 (d, ^3J = 9.2 Hz, 1H, C6-H), 7.66-7.59 (m, 1H, C8–H), 6.74 (d, ^3J =7.4 Hz, 1H, C3–H).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 149.3 (d, C9), 136.82 (d, C2/C7), 136.7 (d, C7/C2), 129.5 (s, C4), 124.1 (d, C8), 123.8 (d, C5), 122.3 (d, C6), 113.9 (d, C3). Quarternary carbon atoms were not detected due to low solubility of the compound.

The analytical data are consistent with those in the literature. [124]

4-Bromo-1,10-phenanthroline (65)

$$C_{12}H_7BrN_2$$
$$M = 259.11 \text{ g/mol}$$
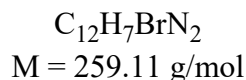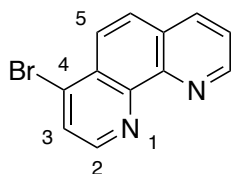
Compound **64** (650 mg, 3.31 mmol, 1.0 eq.) and $POCl_3$ (2.57 g, 8.28 mmol, 2.5 eq.) were heated to 110 °C in a heatgun-dried flask purged with argon for 15 h. After the reaction mixture was allowed to cool to r.t., aq. NH_3-solution (15 mL) was slowly added until pH 13 was reached. The resulting precipitate was filtered, washed with H_2O (3 × 50 mL), redissolved in warm $CHCl_3$ and washed again with H_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, dry load, 15 × 2.5 cm, DCM/MeOH, DCM/MeOH, 100:0 → 95:5, then DCM/MeOH + 1% NEt_3, 100:0 → 95:5) provided 4-bromo-1,10-phenanthroline (**65**, 166 mg, 0.75 mmol, 19%) as a colorless solid.

TLC: R_f (DCM/MeOH/NEt_3, 10:1:1) = 0.61 [$KMnO_4$].

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 9.22 (dd, ^3J = 4.5, 1.7 Hz, 1H, C9–H), 8.94 (d, ^3J = 4.8 Hz,1H, C2–H), 8.28 (dd, ^3J = 8.1, 1.7 Hz, 1H, C7-H), 8.21 (d, ^3J = 9.1 Hz, 1H, C5-H), 7.92 (d, ^3J = 4.8 Hz, 1H, C6-H), 7.89 (d, ^3J = 9.1 Hz, 1H, C3-H), 7.67 (dd, ^3J =8.1, 4.4 Hz, 1H, C8–H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 151.0 (d, C9), 149.9 (d, C2), 147.3 (s, C10b), 145.8 (s, C10a), 136.3 (d, C7), 134.2 (s, C4), 128.8 (s, C6a), 128.3 (s, C4a), 127.9 (d, C6), 127.3 (d, C8), 125.1 (d, C3), 123.8 (d, C5).

The analytical data are consistent with those in the literature. [125]

5-bromo-2,9-dimethyl-1,10-phenanthroline (171)

$C_{14}H_{11}BrN_2$
M = 287.16 g/mol
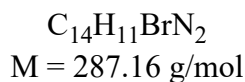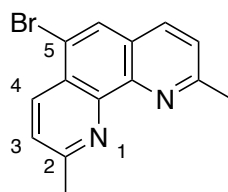
Neocuproine (2.08 g, 10.0 mmol, 1.0 eq.) was dissolved in fuming H_2SO_4 (6 mL). After cooling the solution to 0 °C, Br_2 (150 μL, 479 mg, 0.3 eq.) was slowly added and the reaction mixture was then heated to 140 °C for 24 h. The reaction mixture was allowed to cool to r.t. and ice (80 g) was added. Subsequently, NaOH-pellets were added, until the pH of the solution was 7. $CHCl_3$ (80 mL) was added, the aqueous phase was extracted with $CHCl_3$ (2 × 80 mL) and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (silica, dry load, 15 × 4 cm, 1% NEt_3 + DCM/MeOH, 0% → 0.5%) and subsequent recrystallisation from toluene (10 mL) provided 5-bromo-2,9-dimethyl-1,10-phenanthroline (**171**, 409 mg, 1.42 mmol, 14%) as a yellow solid.

TLC: R_f (DCM/MeOH/NEt$_3$, 19:1:1) = 0.11 [KMnO$_4$].

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 8.51 (d, ^3J = 8.5 Hz, 1H, C4–H), 8.05 – 7.97 (m, 2H, C7–H, C6–H), 7.56 (d, J = 8.5 Hz, 1H, C3–H), 7.47 (d, J = 8.2 Hz, 1H, C8–H), 2.95 (s, 3H, C2–CH$_3$), 2.91 (s, 3H, C9–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 160.3 (s, C2), 160.0 (s, C9), 145.9 (s, C10b), 144.8 (s, C10a), 136.2 (s, C5), 135.5 (d, C7), 128.7 (d, C6), 127.2 (s, C4a), 126.2 (s, C6a), 124.4 (C3), 124.2 (d, C8), 119.8 (d, C4), 26.0 (q, C9–CH$_3$), 25.7 (q, C2–CH$_3$).

The analytical data are consistent with those in the literature. [126]

3.2.   Synthesis of the chiral phenanthroline ligands

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-((1,10-Phenanthrolin-4′′-yl)ethynyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-36]

$C_{23}H_{19}N_3O$
M = 353.43 g/mol
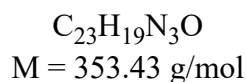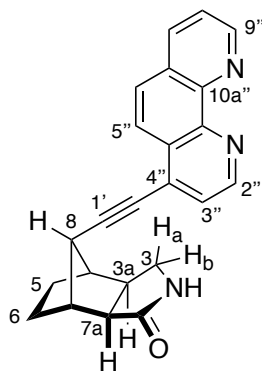
Compound (+)-**36** was synthesized according to general procedure **GP1** using 4-bromo-1,10-phenanthroline **65** (66.1 mg, 0.257 mmol, 1.5 eq.) and a reaction time of 70 h. The product (+)-**36** (51.3 mg, 145 µmol, 85%) was obtained as a pale-yellow solid.

TLC: R_f (DCM/MeOH/NEt$_3$, 10:1:1) = 0.61 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 9.12 (dd, ^3J = 4.3 Hz, ^4J =1.8 Hz, 1H, C9′′–H), 9.04 (d, ^3J = 4.6 Hz, 1H, C2′′–H), 7.89 (dd, ^3J = 8.2 Hz, ^4J =1.9 Hz, 1H, C7′′–H), 7.87 (d, ^3J = 9.0 Hz, 1H, C5′′–H), 7.62 (d, ^3J = 4.6 Hz, 1H, C6′′–H), 7.52 (dd, ^3J = 8.0, 4.3 Hz, 1H, C8′′–H), 7.34 (d, ^3J = 3.2 Hz, 1H, C3′′H), 7.16 (s, 1H, NH), 3.73-3.65 (m, 2H, C3–H$_a$, C3–H$_b$), 3.09 (d, ^3J = 4.1 Hz, 1H, C7–H), 2.81 (s, 1H, C8–H), 2.65 – 2.60 (m, 2H, C3a–H, C7a–H), 2.59 (d, ^3J = 4.2 Hz, 1H, C4–H), 1.84 – 1.70 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.41 – 1.26 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 179.0 (s, C=O), 151.8 (s, C10b′′), 150.4 (d, C9′′), 145.9 (d, C2′′), 144.4 (s, C10a′′), 138.1 (d, C6′′), 136.0 (s, C4a′′), 128.8 (s, C6a′′), 127.8 (s, C4′′), 127.1 (d, C5′′), 126.1 (d, C6′′), 123.1 (d, C3′′), 119.8 (d, C7′′), 93.7 (s, C1′), 79.8 (s, C2′), 50.4 (s, C7a), 46.9 (t, C3), 46.5 (d, C4), 44.6 (d, C7), 41.8 (d, C3a), 39.1 (s, C8), 28.8 (t, C5/C6), 28.6 (t, C6/C5).

The analytical data are consistent with those in the literature.[43]

(3a*R*,4S,7*R*,7a*S*,8*S*)-8-((1,10-Phenanthrolin-5´´-yl)ethynyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-145]

$C_{23}H_{19}N_3O$
M = 353.43 g/mol
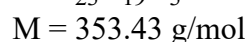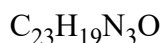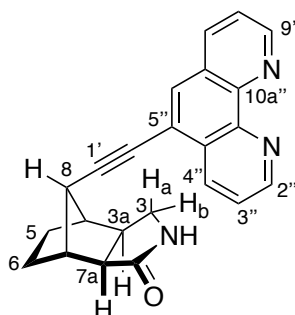
Compound (+)-**145** was synthesized according to general procedure **GP1** using 5-bromo-1,10-phenanthroline (66.1 mg, 257 µmol, 1.5 eq.) and a reaction time of 48 h. The product (+)-**145** (43.5 mg, 123 µmol, 72%) was obtained as a pale yellow solid.

TLC: R_f (DCM/MeOH/NEt₃, 10:1:1) = 0.61 [KMnO₄].

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 9.15 (td, ^3J = 4.3 Hz, ^4J =1.7 Hz, 2H, C2´´–H, C9´´–H), 8.66 (dd, ^3J = 8.2 Hz, ^4J =1.8 Hz, 1H, C4´´–H), 8.19 (dd, ^3J = 8.1 Hz, ^4J =1.8 Hz, 1H, C7´´–H), 7.90 (s, 1H, C6´´–H), 7.69 (dd, ^3J = 8.2, 4.3 Hz, 1H, C3´´–H), 7.60 (dd, ^3J = 8.1, 4.3 Hz, 1H, C8´´–H), 5.58 (s, 1H, NH), 3.64 (d, ^3J = 5.8 Hz, 2H, C3-H$_a$, C3-H$_b$), 3.06 (d, ^3J = 4.2 Hz, 1H, C7–H), 2.81 (s, 1H, C8–H), 2.64 – 2.60 (m, 3H, C3a–H, C7a–H, C4–H), 1.85 – 1.71 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.42 – 1.30 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 179.3 (s, C=O), 150.2 (d, C9´´), 150.1 (d, C2´´), 135.9 (s, C10b´´), 134.4 (s, C10a´´), 130.1 (d, C4´´), 128.9 (d, C7´´), 128.5 (s, C4a´´), 128.1 (s, C6a´´), 127.8 (d, C6´´), 123.3 (d, C8´´), 123.0 (d, C3´´), 119.8 (s, C5´´), 94.7 (s, C1´), 79.0 (s, C2´), 50.8 (s, C7a), 47.2 (t, C3), 46.9 (d, C4), 44.5 (d, C7), 41.8 (d, C3a), 39.1 (s, C8), 29.7 (t, C5/C6), 28.7 (t, C6/C5).

The analytical data are consistent with those in the literature.[43]

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-((1,10-Phenanthrolin-2´´-yl)ethynyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-146]

$C_{23}H_{19}N_3O$

M = 353.43 g/mol
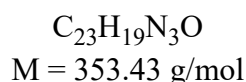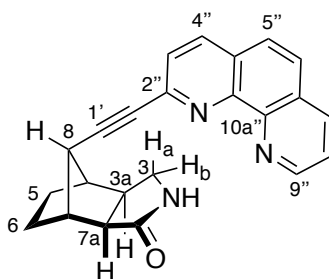
Compound (+)-**146** was synthesized according to general procedure **GP1** using 2-bromo-1,10-phenanthroline (66.1 mg, 257 µmol, 1.5 eq.) and a reaction time of 62 h. The product (+)-**146** (16.9 mg, 123 µmol, 28%) was obtained as a pale-yellow solid.

TLC: R_f (DCM/MeOH/NEt₃, 10:1:1) = 0.61 [KMnO₄].

Mp: >230 °C

Specific rotation: $[\alpha]_D^{20}$= +4.3 (c = 1.0, CHCl₃)

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3219 (w, NH), 2960 (m, sp³-CH), 2878 (w, sp³-CH), 2226 (w, C≡C), 1683 (s, C=O), 1699, (m, C=C), 1504 (m, C=C), 1261 (m), 855 (m), 798 (s, sp²-CH), 749 (s).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 9.16 (d, ³*J* = 4.4 Hz, 1H), 8.23 (d, ³*J* = 7.9 Hz, 1H, C7´´–H), 8.15 (d, ³*J* = 8.2 Hz, 1H, C4–H), 7.79 – 7.72 (m, 2H, C5´´-H, C6´´–H), 7.67 (d, ³*J* = 8.2 Hz, 1H, C3´´–H), 7.63 (dd, ³*J* = 8.1, 4.4 Hz, 1H, C8´´–H), 6.59 (s, 1H, NH), 3.86 – 3.80 (m, 1H, C3-Hₐ), 3.74 – 3.66 (m, 1H, C3-H_b), 3.03 (d, *J* = 4.1 Hz, 1H, C7–H), 2.64 (s, 1H, C8-H), 2.63 – 2.58 (m, 3H, C3a–H, C7a–H, C4–H), 1.81 – 1.68 (m, 2H, C5−Hₐₓ, C6−Hₐₓ), 1.38 – 1.29 (m, 2H, C5−H_eq, C6−H_eq).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 179.9 (s, C=O), 150.4 (d, C9´´), 145.9 (s, C2´´), 145.3 (s, C10b´´), 144.0 (s, C10a´´), 136.9 (d, C7´), 136.5 (d, C4´´), 129.2 (s, C4a´´), 127.8 (s, C6a´´), 126.9 (d, C5´´/C6´´), 126.7 (d, C6´´/C5´´), 126.4 (d, C3´´), 123.6 (s, C8´´), 91.8 (s, C1´), 83.4 (s, C2´), 51.2 (s, C7a), 47.3 (t, C3), 47.2 (d, C4), 44.5 (d, C7), 42.1 (d, C3a), 39.3 (s, C8), 29.71(t, C5/C6), 29.0 (t, C6/C5).

HRMS (ESI): $C_{23}H_{19}N_3O$ [(M+H)⁺] = calcd.: 354.1606, found: 354.1607.

(3a*R*,4S,7*R*,7a*S*,8*S*)-8-((2″,9″-Dimethyl-1,10-phenanthrolin-5″-yl)ethynyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-172]

$$C_{25}H_{23}N_3O$$
$$M = 381.48 \text{ g/mol}$$
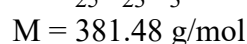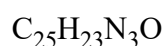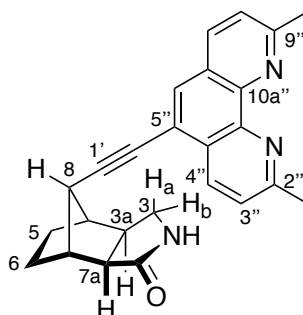
Compound (+)-**172** was synthesized according to general procedure **GP1** using 5-bromo-2,9-dimethyl-1,10-phenanthroline (**171**, 73.7 mg, 257 µmol, 1.5 eq.) and a reaction time of 72 h. The product (+)-**172** (41.7 mg, 109 µmol, 64%) was obtained as a pale-yellow solid.

TLC: R_f (DCM/MeOH/NEt$_3$, 10:1:1) = 0.10 [KMnO$_4$].

Mp: >230 °C

Specific rotation: $[\alpha]_D^{20}$ = +8.7 (c = 1.0, CHCl$_3$)

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3234 (w, NH), 2952 (w, sp^3-CH), 2919 (w, sp^3-CH), 2874 (w, sp^3-CH), 2217 (w, C≡C), 1678 (s, C=O), 1699 (m, C=C), 1369 (m), 890 (m), 722 (s).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.54 (d, ^3J = 8.3 Hz, 1H, C4–H), 8.11 (d, ^3J = 8.2 Hz, 1H, C7″–H), 7.84 (s, 1H, C6″–H), 7.54 (d, ^3J = 8.4 Hz, 1H, C3″–H), 7.44 (d, ^3J = 8.2 Hz, 1H, C8″–H), 5.87 (s, 1H, NH), 3.70 – 3.59 (m, 2H, C3-H$_a$, C3-H$_b$), 3.03 (d, J = 4.1 Hz, 1H, C7–H), 2.93 (s, 6H, C2″-H$_3$, C9″-H$_3$), 2.80 (s, 1H, C8–H), 2.67 – 2.57 (m, 3H, C3a–H, C7a–H, C4–H), 1.85 – 1.67 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.41 – 1.27 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 179.2 (s, C=O), 160.0 (s, C9″), 159.8 (s, C2″), 144.1 (s, 2 × C, C10a″, C10b″), 136.6 (d, C7″), 135.5 (d, C4″), 129.6 (d, C6″), 126.8 (s, C4a″), 126.4 (s, C6a″), 124.3 (d, C3″), 124.1 (d, C8″), 119.2 (s, C5″), 94.5 (s, C1′), 79.5 (s, C2′), 50.7 (s, C7a), 47.1 (t, C3), 46.8 (d, C4), 44.7 (d, C7), 41.9 (d, C3a), 39.3 (s, C8), 29.8 (t, C5/C6), 28.3 (t, C6/C5), 25.9 (q, 2″C-CH$_3$/9″C-CH$_3$), 25.7 (q, 9″C-CH$_3$/2″C-CH$_3$).

HRMS (ESI): C$_{25}$H$_{23}$N$_3$O [(M+H)$^+$] = calcd.: 382.1918, found: 382.1930

(3a*R*,4S,7*R*,7a*S*,8*S*)-8-(2-(1,10-Phenanthrolin-5´´-yl)ethyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-170]

$C_{23}H_{23}N_3O$
M = 357.46 g/mol
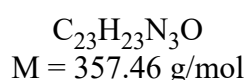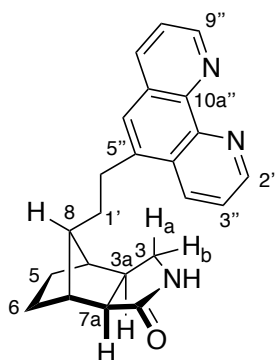
Compound (+)-**145** (6.00 mg, 15.7 µmol, 1.0 eq.), Pd/C (10%, 1.20 mg, 1.13 µmol, 0.08 eq.) and dry EtOAc (1 mL) were added to a heatgun-dried round bottom flask purged with argon. The reaction mixture was carefully evacuated and backfilled with hydrogen (3 ×) and stirred for 4 h at r.t. Subsequently, the reaction mixture was filtered over Celite®, washed with EtOAc (5 × 5 mL) and the solvent was removed *in vacuo*. Purification by column chromatography (silica, dry load, 10 × 1 cm, DCM/MeOH, 100:0 → 95:5, then DCM/MeOH + 1% NEt₃, 99:1 → 95:5) provided compound (+)-**170** (4.40 mg, 12.3 µmol, 73%) as a colorless solid.

TLC: R_f (DCM/MeOH/NEt₃, 10:1:1) = 0.23 [KMnO₄].

Mp: >230 °C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3247 (w, NH), 2932 (w, sp³-CH), 2869 (w, sp³-CH), 1668 (s, C=O), 1587 (m, C=C), 1255 (m), 890 (m), 723 (s).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 9.12 (ddd, ^3J = 8.9, 4.3 Hz, ^4J =1.7 Hz, 2H, C2´´–H, C9´´–H), 8.55 (dd, ^3J = 8.3 Hz, ^4J =1.8 Hz, 1H, C4´´–H), 8.17 (dd, ^3J = 8.1 Hz, ^4J =1.8 Hz, 1H, C7´´–H), 7.85 (s, 1H, C6´´–H), 7.63 (dd, ^3J = 8.2, 4.3 Hz, 1H, C3´´–H), 7.58 (dd, ^3J = 8.1 Hz, 4.3 Hz, 1H, C8´´–H), 6.14 (s, 1H, NH), 3.71 – 3.63 (m, 4H, C3-Hₐ, C3-H_b, C2´-H₂), 3.10 (q, ^3J = 7.6 Hz, 1H, C1´-Hₐ), 3.06 (d, ^3J = 4.2 Hz, 1H, C7–H), 2.79 (s, 1H, C8–H), 2.69 – 2.57 (m, 3H, C3a–H, C7a–H, C4–H), 1.87– 1.67 (m, 2H, C5−Hₐₓ, C6−Hₐₓ), 1.39 (t, J = 7.4 Hz, 2H, C1´–H_b), 1.36 - 1.27 (m, 2H, C5−H_eq, C6−H_eq).

13C-NMR (101 MHz, CDCl₃): δ [ppm] = 179.2 (s, C=O), 150.7 (d, C2´´/ C9´´), 150.6 (d, C2´´/ C2´´), 145.8 (s, C10b´´), 141.4 (s, C10a´´), 136.0 (d, C7´´), 134.8 (d, C4´´), 130.1 (d, C6´´), 128.4 (s, C4a´´), 128.1 (s, C6a´´), 123.5 (d, C3´´), 123.3 (d, C8´´), 120.3 (s, C5´´), 50.6 (d, C8), 47.3 (d, C7a), 46.9 (t, C3), 44.7 (d, C4), 42.0 (d, C3a), 39.3 (d, C7), 29.8 (t, C5/C6), 28.9 (C2´), 28.6 (t, C5/C6).

HRMS (ESI): $C_{23}H_{23}N_3O$ [(M+H)⁺] = calcd.: 358.1919, found: 358.1915.

3.3. Synthesis of the chiral bipyridine ligands

(3a*R*,4S,7*R*,7a*S*,8*S*)-8-([2´´,2´´´-Bipyridin]-5´´-ylethynyl)octahydro-1*H*-4,7-methano-*iso-*indol-1-one [(+)-177]

$$C_{21}H_{19}N_3O$$
$$M = 329.40 \text{ g/mol}$$
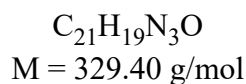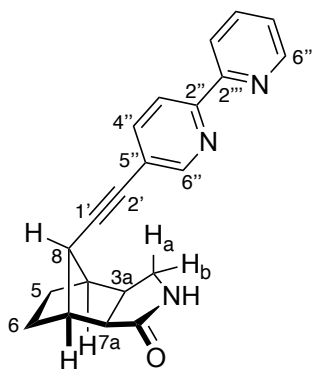
Compound (+)-**177** was synthesized according to general procedure **GP2** using 5-bromo-2,2´-bipyridine (37.0 mg, 157 µmol, 1.5 eq.). Ligand (+)-**177** (28.3 mg, 85.8 µmol, 60%) was obtained as a pale-yellow solid.

TLC: R_f (DCM/MeOH, 19:1) = 0.17 [UV, KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.71 (br d, ^3J = 4.9 Hz, 1H, C6´´´−H), 8.63 (s, 1H, C6´´−H), 8.42 (d, ^3J = 8.0 Hz, 1H, C3´´´−H), 8.39 (dd, ^3J = 8.2 Hz, 1H, C3´´−H), 7.88 (*virt.* td, ^3J = ^3J ≈ 7.8 Hz, ^4J = 1.8 Hz, 1H C4´´´−H), 7.80 (dd, ^3J = 8.2 Hz, ^4J = 2.1 Hz, 1H, C4´´−H), 7.37 (*virt.* t, ^3J = ^3J ≈ 7.5 Hz, 1H, C5´´´−H), 5.40 (br s, 1H, NH), 3.66–3.56 (m, 2H, C3−H$_a$, C3−H$_b$), 2.95 (d, ^3J = 4.1 Hz, C7−H), 2.66 (s, 1H, C8−H), 2.60 (*virt.* td, ^3J = ^3J ≈ 9.3 Hz, ^3J = 4.5 Hz, 1H, C3a−H), 2.57–2.52 (m, 2H, C4−H, C7a−H), 1.81–1.60 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.36–1.14 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 178.9 (s, C=O), 155.7 (s, C2´´/C2´´´), 154.9 (s, C2´´/C2´´´), 151.4 (d, C6´´), 148.6 (d, C6´´´), 139.6 (d, C4´´), 138.1 (d, C4´´´), 124.2 (d, C3´´), 121.1 (d, C3´´´), 120.9 (s, C5´´), 120.5 (d, C5´´´), 94.0 (s, C1´), 79.6 (s, C2´), 50.3 (d, C7a), 46.9 (t, C3), 46.5 (d, C4), 44.7 (d, C7), 41.9 (d, C3a), 39.2 (d, C8), 28.8 (t, C5/C6), 28.7 (t, C5/C6).

The analytical data are consistent with those in the literature.[127]

(3a*R*,4S,7*R*,7a*S*,8*S*)-8-([2´´,2´´´-Bipyridin]-4´´-ylethynyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-178]

$C_{21}H_{19}N_3O$

M = 329.40 g/mol
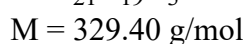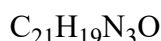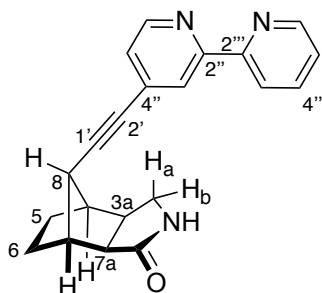
Compound (+)-**178** was synthesized according to general procedure **GP2** using 4-bromo-2,2´-bipyridine (37.0 mg, 157 µmol, 1.5 eq.). Ligand (+)-**178** (16.3 mg, 49.5 µmol, 35%) was obtained as a pale-yellow solid.

TLC: R_f (DCM/MeOH, 19:1) = 0.17 [UV, KMnO₄].

Mp: >230 °C

Specific rotation: $[\alpha]_D^{20}$= +2.3 (c = 1.0, CHCl₃)

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3216 (w, NH), 2954 (m, sp³-CH), 2924 (s, sp³-CH), 2875 (m, sp³-CH), 2854 (m, sp³-CH), 2227 (w, C≡C), 1688 (s, C=O), 1584, (m, C=C), 1459 (m, C=C), 794 (m, sp²-CH), 748 (m).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 8.67 (d, ^3J = 4.9 Hz, 1H, C3´´´−H), 8.58 (d, ^3J = 5.0 Hz, 1H, C6´´−H), 8.38 (d, ^3J = 8.0 Hz, 1H, C6´´´−H), 8.30 (s, 1H, C3´´−H), 7.86 (*virt.* td, $^3J = ^3J \approx$ 7.8 Hz, ^4J = 1.8 Hz, 1H, C5´´´−H), 7.35 (dd, ^3J = 7.5 Hz, 4.3 Hz, 1H, C4´´´−H), 7.29 (dd, ^3J = 5.0 Hz, ^4J = 1.8 Hz, 4.3 Hz, 1H, C5´´−H), 5.83 (br s, 1H, NH), 3.70–3.58 (m, 2H, C3−H$_a$, C3−H$_b$), 2.94 (d, ^3J = 4.1 Hz, C7−H), 2.65(s, 1H, C8−H), 2.62–2.50 (m, 3H, C3a−H, C4−H, C7a−H), 1.81–1.62 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.37–1.19 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 179.0 (s, C=O), 155.3 (s, C2´´/C2´´´), 155.1 (s, C2´´´/C2´´), 149.3 (d, C6´´), 148.7 (d, C3´´´), 137.9 (d, C5´´´), 133.1 (s, C4´´), 126.0 (d, C5´´), 124.3 (d, C4´´´), 123.2 (s, C3´´), 121.8 (d, C6´´´), 94.8 (s, C1´), 80.4 (s, C2´), 53.6 (d, C7a), 47.0 (t, C3), 46.5 (d, C4), 44.7 (d, C7), 41.8 (d, C3a), 39.1 (d, C8), 28.8 (t, C5/C6), 28.7 (t, C6/C5).

HRMS (ESI): $C_{21}H_{19}N_3O$ [(M+H)$^+$] = calcd.: 330.1601, found: 330.1605.

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-([2´´,2´´´-Bipyridin]-6´´-ylethynyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-179]
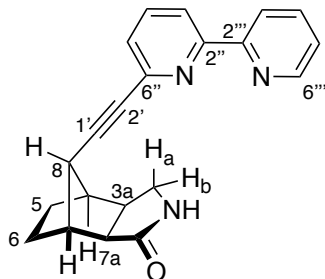
$C_{21}H_{19}N_3O$
M = 329.40 g/mol

Compound (+)-**179** was synthesized according to general procedure **GP2** using 6-Bromo-2,2´-bipyridine (37.0 mg, 157 µmolmmol, 1.5 eq.). Ligand (+)-**179** (32.2 mg, 98.1 µmol, 69%) was obtained as a pale-yellow solid.

TLC: R_f (DCM/MeOH, 19:1) = 0.17 [UV, KMnO$_4$].

Mp: >230 °C

Specific rotation: $[\alpha]_D^{20}$ = +2.6 (c = 1.0, CHCl$_3$)

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3220 (w, NH), 2957 (m, sp^3-CH), 2925 (w, sp^3-CH), 2879 (w, sp^3-CH), 2229 (w, C≡C), 1685 (s, C=O), 1580 (w, C=C), 1560 (m, C=C), 1428 (m), 745 (m).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.68 (d, ^3J = 5.0 Hz, 1H, C3´´´−H), 8.39 (d, ^3J = 8.0 Hz, 1H, C6´´´−H), 8.32 (d, ^3J = 7.9 Hz, 1H, C3´´−H), 7.85 (*virt.* td, ^3J = ^3J ≈ 7.8 Hz, ^4J =1.8 Hz, 1H), C5´´´−H), 7.75 (t, ^3J = 7.8 Hz, 1H, C4´´−H), 7.41 (d, ^3J = 7.7 Hz, 1H, C5´´−H), 7.35 (dd, ^3J = 6.9 Hz, 4.3 Hz, 1H, C4´´´−H), 5.83 (br s, 1H, NH), 3.78–3.57 (m, 2H, C3−H$_a$, C3−H$_b$), 2.98 (d, ^3J = 4.0 Hz, 1H, C7−H), 2.64 (s, 1H, C8−H), 2.62–2.54 (m, 3H, C3a−H, C4−H, C7a−H), 1.80–1.62 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.35–1.23 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 179.5 (s, C=O), 155.2 (s, C2´´/C2´´´), 155.1 (s, C2´´/C2´´´), 148.6 (d, C3 ´´´), 143.2 (s, C6´´), 137.9 (d, C5´´´), 137.5 (s, C4´´), 127.2 (d, C5´), 124.2 (d, C4´´´), 121.8 (s, C6´´´), 120.5 (d, C3´´), 106.5 (s, C1´), 89.7 (s, C2´), 50.5 (d, C7a), 47.1 (t, C3), 46.7 (d, C4), 45.0 (d, C7), 42.0 (d, C3a), 39.0 (d, C8), 28.8 (t, C5/C6), 28.7 (t, C5/C6).

HRMS (ESI): $C_{21}H_{19}N_3O$ [(M+H)$^+$] = calcd.: 330.1601, found: 330.1603.

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-(2′-([2′′,2′′′-Bipyridin]-5′′-yl(ethyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-204]

C$_{21}$H$_{23}$N$_3$O
M = 333.44 g/mol
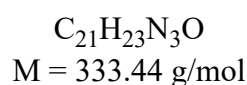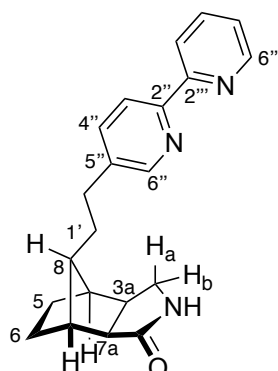
Compound (+)-**177** (20.0 mg, 60.7 µmol, 1.0 eq.), Pd/C (10%, 10.0 mg, 9.40 µmol, 0.08 eq.) and dry MeOH (1 mL) were added to a heatgun-dried round bottom flask purged with argon. The reaction mixture was carefully evacuated and backfilled with hydrogen (3 ×) and stirred for 4 h at r.t. Subsequently, the reaction mixture was filtered over Celite®, washed with EtOAc (5 × 10 mL) and the solvent was removed *in vacuo*. Purification by column chromatography (silica, dry load, 10 × 1 cm, DCM/MeOH, 100:0 → 95:5) provided ligand (+)-**204** (11.5 mg, 34.4 mmol, 57%) as a colorless product. Ligand (+)-**203** (*vide infra*, 8.00 mg, 42.1 µmol, 40%) was isolated as a side product.

Ligand (+)-**204:**

TLC: R_f (DCM/MeOH, 10:1) = 0.23 [KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.68 (d, ^3J = 4.0 Hz, 1H, C6′′′−H), 8.50 (s, 1H, C6′′−H), 8.39 (d, ^3J = 7.8 Hz, 1H, C3′′′−H), 8.32 (d, ^3J = 8.2 Hz, 1H, C3′′−H), 7.83 (*virt.* td, ^3J = ^3J ≈ 7.8 Hz, ^4J = 1.8 Hz, 1H C4′′′−H), 7.65 (dd, ^3J = 8.1 Hz, ^4J = 2.3 Hz, 1H, C4′′−H), 7.31 (*virt.* t, ^3J = ^3J ≈ 7.5 Hz, 1H, C5′′′−H), 5.55 (br s, 1H, NH), 3.63 (*virt.* t, ^2J = ^3J ≈ 9.7 Hz, 1H, C3−H$_a$), 3.20 − 3.15 (m, 1H, C3−H$_b$), 2.82 − 2.73 (m, 1H, C2′−H$_a$), 2.68 − 2.58 (m, 2H, C2′−H$_b$, C7−H), 2.53 − 2.42 (m, 2H, C3a−H, C7a−H), 2.16 (d, ^3J = 4.0 Hz, 1H, C4−H), 1.91 − 1.75

(m, 2H, C1′−H$_2$), 1.71 − 1.53 (m, 3H, C8−H, C5−H$_{ax}$, C6−H$_{ax}$), 1.23 − 1.12 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

13C-NMR (101 MHz, CDCl₃): δ [ppm] = 180.4 (s, C=O), 156.4 (s, C2''/C2'''), 154.2 (s, C2''/C2'''), 149.4 (d, C6''), 149.3 (d, C6'''), 137.79(s, C5''), 137.0 (d, C4'', C4'''), 123.6 (d, C5'''), 120.9 (d, C3'''), 120.7 (d, C3''), 50.9 (d, C8), 50.3 (d, C7a), 46.4 (t, C3), 44.7 (d, C4), 41.8 (d, C3a), 41.0 (d, C7), 33.1 (t, C2'), 29.8 (t, C5/C6), 29.5 (t, C5/C6), 29.0 (t, C1').

The analytical data are consistent with those in the literature.[127]

Side product ligand (+)-203:

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-((E)-2´-([2´´,2´´´-Bipyridin]-5´´-yl(vinyl)octahydro-1*H*-4,7-meth-ano-*iso*-indol-1-one [(+)-203]

C₂₁H₂₁N₃O
M = 331.44 g/mol
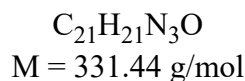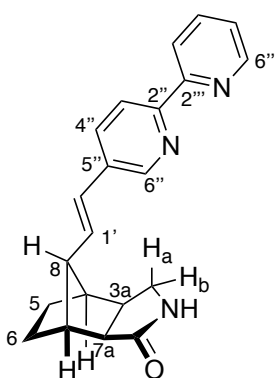
TLC: R_f (DCM/MeOH, 10:1) = 0.31 [KMnO₄].

1H-NMR (500 MHz, CDCl₃): δ [ppm] = 8.68 (dd, ^3J = 4.8 Hz, ^4J =1.8, 1H, C6'''−H), 8.64 (d, ^4J = 2.3 Hz, 1H, C6''−H), 8.37 (dd, ^3J = 8.1 Hz, 4.0 Hz, 2H, C3'''−H, C3''−H), 7.82 (*virt.* td, ^3J = ^3J ≈ 7.8 Hz, ^4J = 1.8 Hz, 1H C4'''−H), 7.73 (dd, ^3J = 8.3 Hz, ^4J = 2.3 Hz, 1H, C4''−H), 7.31 (dd, ^3J = 7.5 Hz, 4.8 Hz, 1H, C5'''−H), 6.37 (d, ^3J = 11.9 Hz, 1H, C2'−H), 6.11 (dd, ^3J = 11.9 Hz, 8.7 Hz, 1H, C1'−H), 5.75 (br s, 1H, NH), 3.63–3.56 (m, 1H, C3−Hₐ), 3.28–3.22 (m, 1H, C3−H_b), 2.80 (d, ^3J = 8.7 Hz, 1H, C8−H), 2.72 (s, 1H, C7−H), 2.57 − 2.51 (m, 2H, C3a–H, C7a–H), 2.42 (d, ^3J = 3.2 Hz, 1H, C4–H), 1.74 − 1.67 (m, 2H, C5−Hₐₓ, C6−Hₐₓ), 1.30 − 1.20 (m, 2H, C5−H_eq, C6−H_eq).

(3a*R*,4*R*,7*S*,7a*R*,8*S*)-8-((3´-Bromophenyl)-8-hydroxyoctahydro-1*H*-4,7-methano-*iso-*indol-1-one [(+)-207]

$$C_{15}H_{16}BrNO_2$$
$$M = 322.30 \text{ g/mol}$$
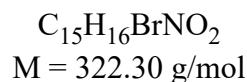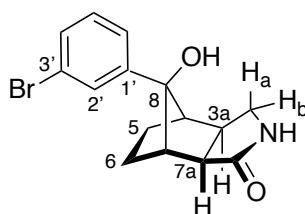
Magnesium (334 mg, 13.9 mmol, 2.3 eq.) was added to a heatgun-dried flask purged with argon. *m*-Dibromobenzene (1.61 mL, 3.14 g, 13.3 mmol, 2.2 eq.) was dissolved in THF (50 mL) and added dropwise over a period of 15 mins. The mixture was stirred for 1 h at r.t. until the magnesium was fully dissolved. Compound (+)-**67** (1.00 g, 6.05 mmol, 1.0 eq.) in THF (25 mL) was added dropwise over a period of 20 mins. and the the reaction mixture was heated up to reflux for 2 h. The reaction mixture was then allowed to cool to r.t. and stirred for another 62 h at r.t. Satd. aq. NH$_4$Cl-solution (45 mL) was added and the reaction mixture was acidified with 3M HCl to pH = 4. The aqueous phase was extracted with EtOAc (3 × 25 mL) and the combined organic layers were washed with a satd. aq. NH$_4$Cl-solution and dried over MgSO$_4$. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica, dry load, 15 × 3.5 cm, DCM/MeOH, 100:0 → 95:5) yielding (+)-**207** as colorless solid (860 mg, 2.68 mmol, 44%) in combination with the hydrodebrominated side product (471 mg, 1.94 mmol, 32%).

TLC: R_f (DCM/MeOH, 19:1) = 0.33 [KMnO$_4$].

Mp: 140 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3280 (m, br, NH, OH), 2957 (m, CH$_2$), 1683 (s, NC=O), 1450 (w, CH$_2$), 1287 (w, C-O), 1143 (w, C=O), 1068 (w, C-O), 910 (w, C=CH), 700 (w, Ar).

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.61 (t, ^4J = 1.8 Hz, 1H, C2′–H), 7.44 (m, 1H, C4′–H), 7.40 – 7.33 (m 1H, C6′–H), 7.23 (*virt*. t, $^3J = ^3J$ ≈ 7.8 Hz, 1H, C5′–H), 5.52 (s, 1H, NH), 3.61 (t, ^3J = 9.1 Hz, 1H, C3–H$_b$), 3.66 – 3.49 (m, 1H, C3–H$_a$), 2.95 (d, ^3J = 4.3 Hz, 1H, C4–H), 2.73-2.60 (m, 2H, C3a–H, C7a–H), 2.50 (d, ^3J = 4.1 Hz, 1H, C7–H), 2.03 (br s, 1H, OH), 1.60 – 1.48 (m, 1H, C5−H$_{ax}$/C6−H$_{ax}$), 1.45 – 1.32 (m, 1H, C6−H$_{ax}$/C5−H$_{ax}$), 1.32 – 1.09 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 180.8 (s, C=O), 144.8 (s, C1′), 131.0 (d, C4′), 130.6 (d, C5′), 130.2 (d, C2′), 125.4 (d, C6′), 122.9 (s, C3′), 88.4 (d, C8), 50.2 (d, C7a), 46.9 (t, C3), 46.8 (d, C4), 45.3 (d, C7), 42.0 (d, C3a), 26.3 (t, C5/C6), 26.3 (t, C6/C5).

HRMS (ESI): C₁₅H₁₆BrNO₂ [(M+H)⁺] = calcd.: 322.0442, found: 322.0443.

(3a*R*,4*R*,7*S*,7a*R*,8*S*)-8-((3′-Bromophenyl)-1′′-oxooctahydro-1*H*-4,7-methano-*iso*-indol-8-yl acetate [(+)-209]

C$_{17}$H$_{18}$BrNO$_3$

M = 364.24 g/mol
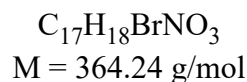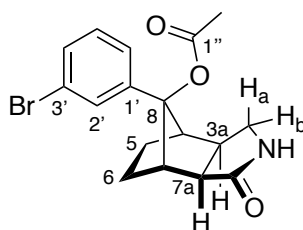
Compound (+)-**207** (100 mg, 310 µmol, 1.0 eq.) was added to a heatgun-dried flask purged with argon, dissolved in DCM (22.5 mL) and cooled to 0 °C. DMAP (38.0 mg, 310 µmol, 1.0 eq.), and NEt$_3$ (2.15 mL, 15.5 mmol, 50.0 eq.) were added. Subsequently, acetic anhydride (0.34 mL, 356 mg, 3.10 mmol, 10.0 eq.) was added dropwise over a period of 5 min. The reaction mixture was allowed to warm to r.t. over night. Water (45 mL) was added the aqueous phase was extracted with DCM (3 × 40 mL). The combined organic phases were washed with H$_2$O (40 mL), dried over MgSO$_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, dry load, 15 × 2 cm, DCM/MeOH, 100:0 → 90:10) yielded (+)-**209** as colorless solid (20.3 mg, 55.8 µmol, 18%) in combination with the hydrodebrominated byproduct (471 mg, 1.94 mmol, 22%).

TLC: R_f (DCM/MeOH = 19:1) = 0.25 [UV, KMnO$_4$]

Mp: decomp. >230 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3252 (w, br, NH), 2959, 2878 (w, CH$_2$), 1739 (s, CH$_3$C=OO), 1692 (s, NC=O), 1487 (m, CH$_2$), 1367 (m, COCH$_3$), 1238 (s, C-O), 1179, 1142 (m, C=O), 1036 (s, C-O), 796 (m, Ar).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.68 (*virt.* t, $^4J = {}^4J \approx 1.9$ Hz, 1 H, C2′–H), 7.49 (d, $^3J = 7.9$ Hz, 1H, C6′–H), 7.40 (d, $^3J = 8.9$ Hz, 1H, C4′–H), 7.20 (*virt.* t, $^3J = {}^3J \approx 7.9$ Hz, 1H, C5′–H), 6.13 (br s, 1 H, NH), 3.64 (*virt.* t, $^2J = {}^3J \approx 9.9$ Hz, 1 H, C3-H$_a$), 3.35 (d, $^3J = 2.2$ Hz 1 H, C4–H), 3.31 (dd, $^3J = 10.1$ Hz, 4.1 Hz 1 H, C3–H$_b$), 3.09 (s, 1 H, C7–H), 2.73 (*virt.* td, $^3J = {}^3J \approx 9.8$ Hz, 3.8 Hz, C3a-H), 2.69 (d, $^3J = 10.0$ Hz, 1 H, C7a–H), 1.83 (s, 3 H, OC=OC*H*$_3$), 1.53 – 1.48 (m, 2 H, C6–H$_{eq}$, C5–H$_{eq}$), 1.27 – 1.23 (m, 2 H, C6–H$_{ax}$, C5–H$_{ax}$).

^{13}C-NMR (101 MHz, CDCl$_3$, 300 K): δ [ppm] = 179.4 (s, C1=O), 169.9 (s, C1´´=O), 140.0 (s, C1´), 132.0 (d, C2´), 131.3 (d, C4´), 129.5 (d, C5´), 127.9 (d, C6), 122.0 (s, C3´), 92.6 (d, C8), 50.1 (d, C7a), 45.9 (t, C3), 45.4 (d, C4), 44.2 (d, C7), 41.6 (d, C3a), 26.5 (t, C5/C6), 25.0 (t, C5/C6), 21.7 (q, OCH$_3$).

HRMS (ESI): C$_{17}$H$_{18}$BrNO$_3$ [(M+H)$^+$] = calcd.: 364.0548, found: 364.0449.

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-((3´-Bromophenyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-212]

C₁₅H₁₆BrNO

M = 306.20 g/mol
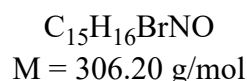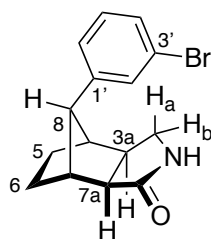
Compound (+)-**209** (15.0 mg, 41.2 µmol, 1.0 eq.) was added to a heatgun-dried flask purged with argon and dissolved in trifluoroacetic acid (TFA, 500 µL). Triethyl silane (32.9 µL, 23.9 mg, 206 µmol, 5.0 eq.) was added and the reaction mixture was stirred for 23 h at r.t. EtOAc (10 mL) was added and the organic phase was washed with H_2O (3 × 10 mL). The organic phase was neutralized with satd. aq. $NaHCO_3$-solution (7 mL) and the combined aqueous phases were reextracted with EtOAc (10 mL). The combined organic phases were then dried with $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification by column chromatography (silica, dry load, 10 × 1 cm, DCM/MeOH, 100:0 → 90:10) yielded (+)-**212** as colorless wax (6.22 mg, 20.2 µmol, 49%) in combination with the hydrodebrominated sideproduct (2.00 mg, 8.01 µmol, 21%).

TLC: R_f (DCM/MeOH = 19:1) = 0.32 [UV, KMnO₄]

Mp: 132°C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3240 (w, br, NH), 2950, 2914, 2869 (m, CH₂), 1782 (w), 1693, 1653 (s, NC=O), 1489 (m, CH₂), 1307 (m, C-O), 1189 (m, C=O), 1013 (m, C-O), 752 (m, Ar).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.55 (dd, ^4J = 1.9 Hz, 1.7 Hz, 1H, C2´–H), 7.35 (dd, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, C6´´–H), 7.30 – 7.26 (m, 1H, C4´–H), 7.09 (*virt.* t, ^3J = ^3J ≈ 7.8 Hz, 1H, C5´–H), 4.49 (br s, 1 H, NH, 3.28 (*virt.* t, ^3J = ^3J ≈ 9.8 Hz, 1H, C3–Hₐ), 3.23 (d, ^3J = 3.3 Hz, 1H, C4–H), 3.04 (s, 1H, C8–H), 2.83 – 2.75 (m, 2H, C7–H, C3–H_b), 2.54 – 2.45 (m, 2H, C3a H, C7a H), 1.84 – 1.72 (m, 2H, C5–H_ax, C6–H_ax), 1.38 – 1.29 (m, 2H, C5–H_eq, C6–H_eq).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 178.9 (s, C=O), 140.9 (s, C1´), 131.2 (d, C2´), 129.5 (d, C4´), 129.4 (d, C5´), 127.2 (d, C6´), 121.7 (s, C3´), 53.2 (d, C8), 50.1 (d, C7a), 45.8 (t, C3), 44.5 (d, C7), 42.1 (d, C3a), 40.1 (d, C4), 29.6 (t, C5/C6), 29.5 (t, C6/C5).

HRMS (ESI): C₁₇H₁₈BrNO₃ [(M)⁺] = calcd.: 305.0410, found: 305.0410.

5´-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-2´,2´´-Bipyridine (214)

$$C_{18}H_{21}BO_2$$
$$M = 282.15 \text{ g/mol}$$
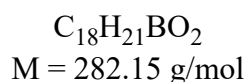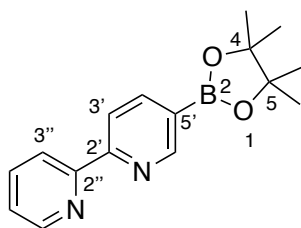
5-bromo-2,2´-bipyridine (495 mg, 2.11 mmol, 1.0 eq), bis(pinacolato)diboron (649 mg, 2.56 mmol, 1.2 eq.) and potassium acetate (632 mg, 6.44 mmol, 3.05 eq.) were added to a heat-gun-dried flask purged with argon. Dry, degassed DMSO (5 mL) was added, followed by [Pd(dppf)Cl$_2$] (77.0 mg, 105 µmol, 5 mol%). The reaction mixture was degassed by three *freeze-pump-thaw* cycles and subsequently stirred for 50 h at 105 °C. [Pd(dppf)Cl$_2$] (77.0 mg, 105 µmol, 5 mol%) was added again and the reaction mixture was stirred for another 19 h at 105 °C. After the reaction mixture was allowed to cool to r.t., the solvent was removed *in vacuo* and the crude product was redissolved in EtOAc (50 mL). Filtering over celite, washing with EtOAC (4 × 20 mL) and removing the solvent *in vacuo,* yielded compound **214** as a purple solid (562 mg, 2.00 mmol, 95%).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 9.01 (s, 1H, C6´–H), 8.69 (d, ^3J = 4.8 Hz, 1H, C6´´–H), 8.44 (d, ^3J = 7.8 Hz, 1H, C3´´–H), 8.37 (dd, ^3J = 7.9 Hz, ^5J = 0.8 Hz, 1H, C3´–H), 8.19 (dd, ^3J = 7.8 Hz, ^4J = 1.8 Hz, 1H, C4´–H), 7.82 (*virt.* td, ^3J = ^3J ≈ 7.8 Hz, ^4J = 1.8 Hz, 1H, C4´´–H), 7.32 (ddd, ^3J = 7.8 Hz, ^3J = 4.7 Hz, ^4J = 1.2 Hz, 1H, C5´´–H), 1.37 (s, 12 H, C4(CH_3)$_2$, C5(CH_3)$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 158.1 (s, C2´), 156.3 (s, C2´´), 155.2 (d, C6´), 149.4 (d, C6´´), 143.4 (d, C4´), 137.1 (d, C4´´), 124.1 (d, C5´´), 121.8 (d, C3´´), 120.4 (d, C3´), 83.2 (s, C4, C5), 24.7 (q, C4(CH$_3$)$_2$, C5(CH$_3$)$_2$,).

The carbon atom attached to the boron atom could not be detected due to quadrupolar relaxation.

The analytical data are consistent with those in the literature.[128]

(3a*R*,4*S*,7*R*,7a*S*,8*S*)-8-(3-[2″,2‴-Bipyridin]-5″-yl)phenyl)octahydro-1*H*-4,7-methano-*iso*-indol-1-one [(+)-215]

$C_{25}H_{23}N_3O$

M = 381.48 g/mol
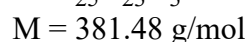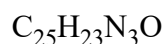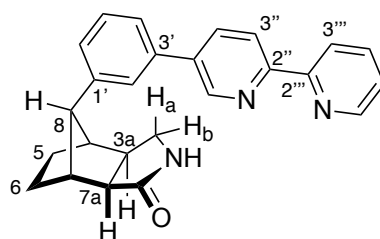
Compound **(+)-212** (5.00 mg, 16.3 µmol, 1.0 eq.) was added to a heatgun-dried *Schlenk*-flask purged with argon and dissolved in a mixture of dry dioxane (0.4 mL) and H_2O (0.1 mL). Subsequently, compound **214** (5.10 mg, 18.2 µmol, 1.1 eq.) and K_3PO_4 (10.2 mg, 48.0 µmol, 3.0 eq.) were added and the solution was degassed by bubbling argon through for 5 mins. [Pd(dppf)Cl$_2$*DCM] (1.30 mg, 1.60 µmol, 10.0 mol%) was then added and the reaction mixture was heated to 110 °C for 15 h. Purification by column chromatography (silica, dry load, 10 × 1 cm, DCM/MeOH, 100:0 → 95:5) yielded ligand **(+)-215** (5.10 mg, 13.4 µmol, 82%) as pale-orange solid.

Mp: >230°C

Specific rotation: $[\alpha]_D^{20}$ = +3.4 (c = 1.0, CHCl$_3$)

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3233 (w, NH), 2954 (m, sp^3-CH), 2924 (w, sp^3-CH), 2876 (w, sp^3-CH), 2854 (w, sp^3-CH), 1679 (s, C=O), 1588 (w, C=C), 1459 (m, C=C), 1019 (m), 749 (s).

TLC: R_f (DCM/MeOH, 10:1) = 0.43 [UV, KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.99 (s, 1H, C6″−H), 8.75 (d, ^3J = 5.4 Hz, 1H, C6‴−H), 8.57 – 8.50 (m, 2H, C3″−H, C3‴−H), 8.24 (d, ^3J = 7.0 Hz, 1H, C4″−H), 7.93 (*virt.* td, $^3J = ^3J \approx$ 8.2 Hz, ^4J = 1.8 Hz, 1H, C4‴−H), 7.70 (s, 1H, C2′–H), 7.47 (*virt.* t, $^3J = ^3J \approx$ 8.9 Hz, 2H, C6′−H, C4′−H), 7.44 – 7.38 (m, 1H, C5‴−H), 7.37 (*virt.* t, $^3J = ^3J \approx$ 7.6 Hz, 1H, C5′−H), 4.66 (br s, 1H, NH), 3.36 (d, ^3J = 3.9 Hz, 1H, C7–H), 3.34 – 3.27 (m, 1H, C3−H$_a$), 3.16 (s, 1H, C8–H), 2.91 (d, ^3J = 3.6 Hz, 1H, C4–H), 2.81 (d, ^2J = 10.9 Hz, 1H, C3−H$_b$), 2.57 – 2.51 (m, 2H, C3a–H, C7a–H), 1.88 – 1.81 (m, 2H, C5−H$_{ax}$, C6−H$_{ax}$), 1.46 – 1.29 (m, 2H, C5−H$_{eq}$, C6−H$_{eq}$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 179.4 (s, C=O), 155.7 (s, C2′′/C2′′′), 154.9 (s, C2′′/C2′′′), 148.8 (d, C6′′), 146.9 (d, C6′′′), 139.5 (s, C1′), 138.2 (d, C4′′′), 137.5 (d, C3′), 137.0 (d, C4′′), 136.2 (s, C3′), 128.6 (d, C5′ , C6′), 128.5 (s, C5′′), 127.5 (d, C2′), 125.0 (d, C4′), 124.4 (d, C5′′′), 122.02 (d, C3′′, C3′′′), 53.4 (d, C7a), 50.4 (t, C3), 46.0 (d, C4), 44.6 (d, C7), 42.2 (d, C3a), 41.2 (d, C8), 29.8 (t, C5/C6), 29.6 (t, C6/C5).

HRMS (ESI): C$_{25}$H$_{23}$N$_3$O [(M+H)$^+$] = calcd.: 382.1919, found: 382.1922.

4. Synthesis of the starting materials

3,3-Di-*p*-tolylindoline-2-one (135c)

$$C_{22}H_{19}NO$$
$$M = 313.40 \text{ g/mol}$$
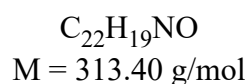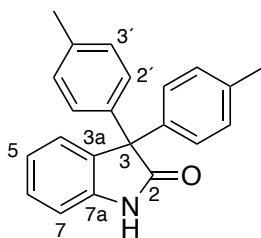
Isatin (100 mg, 680 µmol, 1.0 eq.) was dissolved in triflic acid (2 mL). Toluene (1.00 mL, 0.86 g, 9.36 mmol, 13.8 eq.) was added dropwise over a period of 5 mins. and the reaction mixture was stirred at r.t. for 18 h. The reaction mixture was then poured on ice (30 g), the phases were separated and the aqueous phase was extracted with $CHCl_3$ (3 × 10 mL). The combined organic phases were washed with H_2O (10 mL) and satd. NaCl-solution (10 mL) and dried over $MgSO_4$. Purification by column chromatography (silica, 10 × 2 cm, DCM/EtOAc, 20:1 → 10:1) provided Compound **135c** (200 mg, 637 µmol, 94%) as a colorless solid.

TLC: R_f (DCM/EtOAc, 10:1) = 0.69 [UV, KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.22 (s, 1H, NH), 7.25 – 7.19 (m, 2H, C5–H, C7–H), 7.17 (d, ^3J = 8.1 Hz, 4H, 2 × C3′–H, 2 × C5′–H), 7.10 (d, ^3J = 8.1 Hz, 4H, 2 × C2′–H, 2 × C6′–H), 7.04 (*virt.* td, ^3J = ^3J ≈ 7.5 Hz, ^4J = 1.1 Hz, 1H, C6–H), 6.94 (d, ^3J = 7.5 Hz, 1H, C4–H), 2.31 (s, 6H, 2 × C5′–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 180.0 (s, C=O), 140.2 (s, C3a), 138.9 (s, 2 × C1′), 137.2 (s, 2 × C4′), 134.6 (s, C7a), 129.3 (d, 2 × C2′, 2 × C6′), 128.4 (d, 2 × C3′, 2 × C5′), 128.3 (d, C5/C7), 126.4 (d, C5/C7), 123.0 (d, C6), 110.2 (d, C4), 62.5 (s, C3), 21.2 (2 × C5′–*C*H$_3$).

The analytical data are consistent with those in the literature.[129]

1,2-(3′-Chlorophenyl)-(3′′-chlorophenyl)-2-hydroxyethan-1-one (156)

$$C_{14}H_{10}Cl_2O_2$$
$$M = 281.13 \text{ g/mol}$$
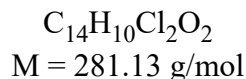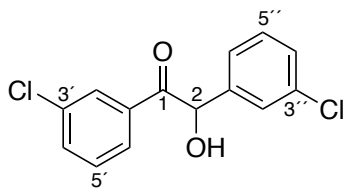
Finely grounded NaOH (236 mg, 4.72 mmol, 0.1 eq) and EtOH (15 mL) were added to a heat-gun-dried *Schlenk*-flask purged with argon and heated to 55 °C until dissolution. Subsequently, thiamine dichloride (795 mg, 2.35 mmol, 5 mol%) and 3-chloro-benzaldehyde (5.34 mL, 6.63 g, 47.2 mmol, 1.0 eq.) were added and the reaction mixture was stirred at 55 °C for 16 h. After the reaction mixture was allowed to cool to r.t., satd. aq. NaCl-solution (25 mL) was added, the phases were separated and the aqueous layer was extracted with DCM (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography (silica, 15 × 4 cm, petane/EtOAc, 20:1 → 15:1) to yield benzoin **156** (5.15 g, 18.3 mmol, 39%) as a yellow solid. Benzil **159** (*vide infra*, 1.80 g, 6.43 mmol, 14%) was obtained as a side product.

TLC: R_f (pentane/EtOAc, 10:1) = 0.42 [UV, $KMnO_4$].

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.90 (*virt.* t, $^4J = {}^4J \approx 2.0$ Hz, 1H, C2′–H), 7.74 (*virt.* dt, $^3J = {}^3J \approx 7.8$ Hz, $^4J = 2.0$ Hz, 1H, C6′–H), 7.51 (ddd, $^3J = 7.8$ Hz, $^4J = 2.0$ Hz, 1.1 Hz, 1H, C4′–H), 7.35 (*virt* t, $^3J = {}^3J \approx 7.8$ Hz, 1H, C5′–H), 7.33 – 7.24 (m, 3H, C2′′–H, C4′′–H, C5′′–H), 7.26 – 7.15 (m, 1H, C6′′–H), 5.88 (s, 1H, C2–H), 4.40 (s, 1H, OH).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 197.5 (s, C=O), 140.4 (s, C1′), 135.4 (s, C1′′), 135.2 (s, C3′′), 135.0 (s, C3′), 134.2 (d, C4′), 130.6 (d, C2′′, C4′′, C5′′), 130.2 (d, C5′), 129.2 (d, C2′), 129.2 (d, C2′′, C4′′, C5′′), 127.9 (d, C2′′, C4′′, C5′′), 127.3 (d, C6′), 126.0 (d, C6′′), 75.8 (d, C2).

The analytical data are consistent with those in the literature.[130]

1,2-*bis*(3′-Chlorophenyl)ethane-1,2-dione (159)

$$C_{14}H_8Cl_2O_2$$
$$M = 279.12 \text{ g/mol}$$
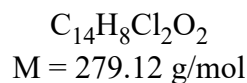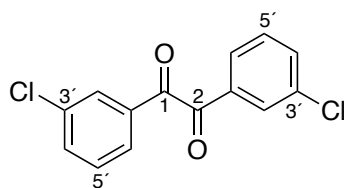
Benzoin **156** (5.15 g, 18.3 mmol, 1.0 eq.), NH_4NO_3 (1.80 g, 22.5 mmol, 1.3 eq.) and $Cu(OAc)_2 \cdot H_2O$ (35.9 mg, 180 µg, 1.0 mol%) were dissolved in a mixture of H_2O (3.6 mL) and AcOH (14.4 mL) and the reaction mixture was heated to reflux for 90 mins. The resulting precipitate was filtered and washed with H_2O (100 mL). Benzil **159** (2.28 g, 8.17 mmol, 45%) was obtained as yellow crystals.

TLC: R_f (pentane/EtOAc, 10:1) = 0.68 [UV, KMnO$_4$]

¹H-NMR (300 MHz, CDCl$_3$): δ [ppm] = 7.97 (*virt.* t, $^4J = {}^4J \approx 1.9$ Hz, 2H, 2 × C2′–H), 7.84 (*virt.* dt, $^3J = {}^3J \approx 7.8$ Hz, $^4J = 1.4$ Hz, 2H, 2 × C6′–H), 7.65 (ddd, $^3J = 8.0$ Hz, $^4J = 2.2$ Hz, 1.1 Hz, 2H, 2 × C4′–H), 7.47 (*virt* t, $^3J = {}^3J \approx 7.9$ Hz, 2H, 2 × C5′–H).

¹³C-NMR (75 MHz, CDCl$_3$): δ [ppm] = 192.2 (s, 2 × C=O), 135.7 (s, 2 × C1′), 135.2 (d, 2 × C4′), 134.3 (s, 2 × C3′), 130.6 (d, 2 × C5′), 129.8 (d, 2 × C2′), 128.3 (d, 2 × C6′).

The analytical data are consistent with those in the literature.[131]

5,5-*bis*(3′-Chlorophenyl)-3-methylimidazolidine-2,4-dione (162)

$$C_{16}H_{12}Cl_2N_2O_2$$
$$M = 335.18 \text{ g/mol}$$
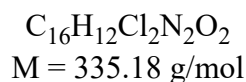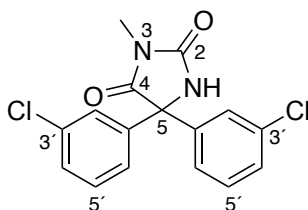
Benzil **159** (1.50 g, 5.37 mmol, 1.0 eq.) and *N*-methylurea (720 mg, 9.67 mmol, 1.8 eq.) were dissolved in a mixture of H_2O (4 mL) and DMSO (24 mL). KOH (540 mg, 9.67 mmol, 1.8 eq.) was added portionwise and the reaction mixture was heated to reflux for 45 mins. The reaction mixture was then allowed to cool to r.t., H_2O (30 mL) was added and it was acidified to pH ≠ 3 with conc. HCl. The resulting precipitate was filtered, washed with H_2O (50 mL) and recrystallized from EtOH (10 mL). Compound **162** (504 mg, 1.50 mmol, 28%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone, 4:1) = 0.40 [UV, KMnO$_4$].

Mp: 210 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3218 (w, NH), 1778 (w, C=O), 1720 (m, C=O), 1488 (m, C=C), 1450 (m, C=C), 1391 (m), 1189 (m), 759 (s, sp^2-CH).

^{1}H-NMR (300 MHz, CDCl$_3$): δ [ppm] = 7.35 (*virt.* t, $^4J = {}^4J \approx 1.9$ Hz, 2H, 2 × C2′–H), 7.32 (*virt.* dt, $^3J = {}^3J \approx 7.8$ Hz, $^4J = 1.4$ Hz, 2H, 2 × C4′–H), 7.28 (*virt* t, $^3J = {}^3J \approx 7.8$ Hz, 2H, 2 × C5′–H), 7.28 (*virt.* dt, $^3J = {}^3J \approx 7.3$ Hz, $^4J = 1.8$ Hz, 2H, 2 × C6′–H), 6.92 (s, 1H, NH), 3.07 (s, 3H, N3-CH$_3$).

^{13}C-NMR (75 MHz, CDCl$_3$): δ [ppm] = 172.5 (s, C4=O), 156.8 (C2=O), 140.6 (s, 2 × C1′), 135.2 (s, 2 × C3′), 130.4 (d, 2 × C5′), 129.3 (d, 2 × C4′), 127.0 (d, 2 × C2′), 125.2 (d, 2 × C6′), 69.5 (s, C5), 25.4 (N3-*C*H$_3$).

HRMS (ESI): $C_{16}H_{12}Cl_2N_2O_2$ [(M+H)$^+$] = calcd.: 335.0354, found: 335.0346.

5,5-*bis*(3′-Chlorophenyl)imidazolidine-2,4-dione (190)

$$C_{15}H_{10}Cl_2N_2O_2$$
$$M = 321.16 \text{ g/mol}$$
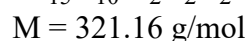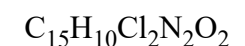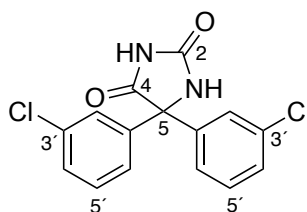
Benzil **159** (1.07 g, 3.83 mmol, 1.0 eq.), KOH (387 mg, 6.89 mmol, 1.8 eq.) and urea (300 mg, 4.98 mmol, 1.3 eq.) were dissolved dry EtOH (15 mL) and the reaction mixture was heated to 55°C for 24 h. The reaction mixture was then allowed to cool to r.t. and subsequently poured on ice (30 g). The resulting precipitate was filtered off and the filtrate was acidified to pH 3 with conc. HCl. The resulting precipitate was filtered and washed with H_2O (50 mL). Compound **190** (1.00 g, 3.11 mmol, 81%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone) = 0.73 [UV, $KMnO_4$].

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3282 (w, NH), 3198 (w, NH), 3068 (w, NH), 1773 (m, C=O), 1729 (m, C=O), 1713 (s, C=O), 1592 (w, Ar), 1397 (m), 1208 (m), 755 (s, sp^2-CH).

^{1}H-NMR (300 MHz, acetone-d$_6$): δ [ppm] = 10.90 (s, 1H, N3–H), 9.02 (s, 1H, N1–H), 7.04 – 7.00 (m, 4H, 2 × C2′–H, 2 × C6′–H), 6.92 – 6.87 (m, 4H, 2 × C4′–H, 2 × C5′–H).

^{13}C-NMR (75 MHz, acetone-d$_6$): δ [ppm] = 164.1 (s, C4=O), 146.0 (C2=O), 131.9 (s, 2 × C1′), 123.7 (s, 2 × C3′), 121.2 (d, 2 × C5′), 118.8 (d, 2 × C4′), 116.5 (d, 2 × C2′), 115.6 (d, 2 × C6′), 59.5 (s, C5).

HRMS (ESI): $C_{15}H_{10}Cl_2N_2O_2$ [(M+H)$^+$] = calcd.: 321.0197, found: 321.0198.

5,5-*bis*(3′-Chlorophenyl)-3-((2-(trimethylsilyl)ethoxy)methyl)imidazolidine-2,4-dione (193)

$$C_{21}H_{24}Cl_2N_2O_3Si$$
$$M = 451.42 \text{ g/mol}$$
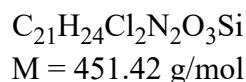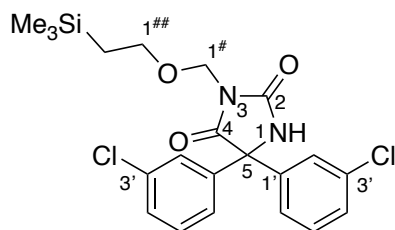
Compound **190** (100 mg, 311 µmol, 1.0 eq.) and K_2CO_3 (43.0 mg, 311 µmol, 1.0 eq.) were suspended in DMF (15 mL) and stirred at r.t. for 30 mins. Subsequently, (2-(chloromethoxy)ethyl)trimethylsilane (60.5 µL, 57.0 mg, 342 µmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 1 h. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 1.5 cm, pentane/acetone, 8:1 → 2:1) yielded compound **193** (97.3 mg, 215 µmol, 69%) as colorless crystals.

TLC: R_f (pentane/acetone, 4:1) = 0.54 [UV, $KMnO_4$].

Mp: 173 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3253 (w, NH), 2822 (m, sp^3-CH), 2810 (m, sp^3-CH), 1718 (w, C=O), 1700 (m, C=O), 1493 (m, C=C), 1447 (m, C=C), 1121 (m), 743 (s, sp^2-CH).

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.39 – 7.35 (m, 4H, 2 × C2′–H, 2 × C4′–H), 7.33 (*virt.* t, $^3J = {}^3J \approx 7.6$ Hz, 2H, 2 × C5′–H), 7.24 (*virt.* dt, $^3J = {}^3J \approx 7.6$ Hz, $^4J = 1.4$ Hz, 2H, 2 × C6′–H), 6.07 (s, 1H, NH), 5.02 (s, 2H, C1$^\#$–H$_2$), 3.61 (t, $^3J = 8.2$ Hz, 2H, C1$^{\#\#}$–H$_2$), 0.92 (t, $^3J = 8.2$ Hz, 2H, C2$^{\#\#}$–H$_2$), 0.04 (s, 9H, Si(CH$_3$)$_3$).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 172.2 (s, C4=O), 156.8 (C2=O), 140.6 (s, 2 × C1′), 135.2 (s, 2 × C3′), 130.4 (d, 2 × C5′), 129.3 (d, 2 × C4′), 127.0 (d, 2 × C2′), 125.2 (d, 2 × C6′), 69.5 (s, C5), 68.9 (t, C1$^\#$), 67.6 (t, C1$^{\#\#}$), 18.5 (t, C2$^{\#\#}$), −1.34 (q, Si(*C*H$_3$)$_3$).

HRMS (ESI): $C_{21}H_{24}Cl_2N_2O_3Si$ [(M+H)$^+$] = calcd.: 451.1011, found: 451.1010.

3-(4-Chlorobutyl)-5,5-bis(3′-chlorophenyl)imidazolidine-2,4-dione (194)

$$C_{19}H_{17}Cl_3N_2O_2$$
$$M = 411.71 \text{ g/mol}$$
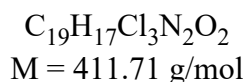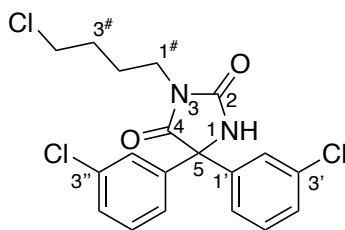
Compound **159** (100 mg, 311 µmol, 1.0 eq.) and K_2CO_3 (43.0 mg, 311 µmol, 1.0 eq.) were suspended in DMF (15 mL) and stirred at r.t. for 30 mins. Subsequently, 1-bromo-4-chlorobutane (39.4 µL, 58.6 mg, 342 µmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 1 h. Water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 1.5 cm, pentane/acetone, 8:1 → 2:1) yielded compound **194** (64.6 mg, 156 µmol, 50%) as colorless crystals. The brominated equivalent 3-(4-bromobutyl)-5,5-bis(3′-chlorophenyl)imidazolidine-2,4-dione (18.4 mg, 40.3 µmol, 13%) was obtained as a side product.

TLC: R_f (pentane/acetone, 4:1) = 0.56 [UV].

Mp: 222 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3253 (w, NH), 2924 (m, sp^3-CH), 2853 (m, sp^3-CH), 1771 (w, C=O), 1701 (m, C=O), 1592 (m, C=C), 1447 (m, C=C), 1138 (m), 745 (s, sp^2-CH).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.40 – 7.29 (m, 6H, 2 × C2′–H, 2 × C4′–H, 2 × C5′–H), 7.26 – 7.22 (m, 2H, 2 × C6′–H), 6.73 (s, 1H, NH), 3.62 (t, ^3J = 6.8 Hz, 2H, C1$^\#$–H$_2$), 3.54 (t, ^3J = 6.3 Hz, 2H, C4$^\#$–H$_2$), 1.88 – 1.71 (m, 4H, C2$^\#$–H$_2$, C3$^\#$–H$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.5 (s, C4=O), 156.9 (C2=O), 141.4 (s, 2 × C1′), 135.2 (s, 2 × C3′), 130.4 (d, 2 × C5′), 129.3 (d, 2 × C4′), 127.0 (d, 2 × C2′), 125.2 (d, 2 × C6′), 69.9 (s, C5), 44.4 (t, C4$^\#$), 38.8 (t, C1$^\#$), 29.6 (t, C3$^\#$), 25.8 (t, C2$^\#$).

HRMS (ESI): $C_{19}H_{17}Cl_3N_2O_2$ [(M+H)$^+$] = calcd.: 427.0383, found: 427.0379.

5,5-bis(3′-Chlorophenyl)-3-phenylimidazolidine-2,4-dione (198)

$$C_{21}H_{14}Cl_2N_2O_2$$
$$M = 397.26 \text{ g/mol}$$
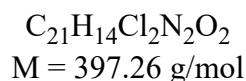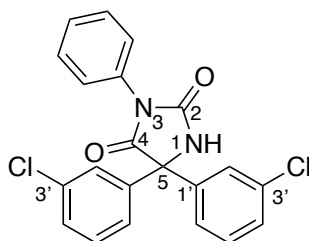
Compound **159** (200 mg, 620 µmol, 1.5 eq.), Cu$_2$O (59.4 mg, 420 µmol, 1.0 eq.) and Iodobenzene (47.0 µL, 85.7 mg, 420 µmol, 1.0 eq.) were dissolved in dry DMF (5 mL) and heated to 150 °C for 24 h. The reaction mixture was allowed to cool to r.t. and filtered over Celite® and washed with EtOAc. The filtrate was concentrated to 1/10th of the volume, poured on ice H$_2$O (10 mL) and stirred at r.t. for 30 mins. Aq. NH$_4$OH-solution (25%, 1 mL) was added and the solution was stirred at r.t. for additional 30 mins. The resulting precipitate was filtered and purified by column chromatography (silica, 15 × 1.5 cm, petane/EtOAc, 10:1 → 7:1) to yield Compound **198** (111 mg, 279 µmol, 45%) as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.87 [UV].

Mp: 195 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3279 (w, NH), 2932 (w, sp^3-CH), 2828 (w, sp^3-CH), 1716 (s, C=O), 1610 (m, C=C), 1582 (m, C=C), 1514 (s, C=C), 1417 (s, C=C), 758 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.52 – 7.38 (m, 9H, 2 × C2′–H, 2 × C4′–H, 5 × Ar$^\#$–H), 7.36 (*virt.* td, $^3J = {}^3J ≈ 7.7$ Hz, $^4J = 0.6$ Hz, 2H, 2 × C5′–H), 7.32 (*virt.* dt, $^3J = {}^3J ≈ 7.2$ Hz, $^4J = 1.9$ Hz, 2H, 2 × C6′–H), 6.20 (s, 1H, NH).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 171.2 (s, C4=O), 155.6 (s, C2=O), 140.5 (s, 2 × C1′), 135.2 (s, 2 × C3′), 131.1 (d, 2 × C5′), 130.0 (d, Ar$^\#$-C/Ar′-C), 129.9 (s, C1$^\#$), 129.8 (d, 2 × C6′), 128.7 (d, Ar$^\#$-C/Ar′-C), 127.8 (d, Ar$^\#$-C/Ar′-C), 127.0 (d, Ar$^\#$-C/Ar′-C), 126.5 (d, Ar$^\#$-C/Ar′-C), 125.9 (d, Ar$^\#$-C/Ar′-C), 125.7 (d, Ar$^\#$-C/Ar′-C), 124.6 (d, Ar$^\#$-C/Ar′-C), 69.1 (s, C5).

HRMS (ESI): C$_{21}$H$_{14}$Cl$_2$N$_2$O$_2$ [(M+H)$^+$] = calcd.: 397.0510, found: 397.0504.

3-(3#,5#-*bis*(Trifluoromethyl)phenyl)-5,5-bis(3´-chlorophenyl)imidazolidine-2,4-dione (199)

$$C_{23}H_{12}Cl_2F_6N_2O_2$$
$$M = 533.25 \text{ g/mol}$$
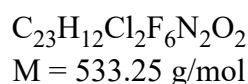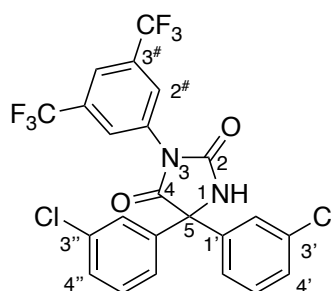
Compound **159** (200 mg, 620 µmol, 1.5 eq.), Cu$_2$O (59.4 mg, 420 µmol, 1.0 eq.) and 1-bromo-3,5-bis(trifluoromethyl)benzene (72.4 µL, 123 mg, 420 µmol, 1.0 eq.) were dissolved in dry DMF (5 mL) and heated to 150 °C for 24 h. The reaction mixture was allowed to cool to r.t., filtered over Celite® and washed with EtOAc. The filtrate was concentrated to 1/10th of the volume, poured on ice water (10 mL) and stirred at r.t. for 30 mins. Aq. NH$_4$OH-solution (25%, 1 mL) was added and the solution was stirred at r.t. for additional 30 mins. The resulting precipitate was filtered and purified by column chromatography (silica, 15 × 1.5 cm, petane/EtOAc, 10:1 → 7:1) to yield Compound **199** (148 mg, 279 µmol, 45%) as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.89 [UV].

Mp: 209 °C

IR (ATR, neat): $\tilde{v}$ [cm^{-1}] = 3224 (w, NH), 3116 (w), 2923 (w), 1784 (C=O), 1728 (s, C=O), 1592 (m, C=C), 1474 (m, C=C),1408 (s, C=C) 1275 (s, C-F), 1173 (s, C-F), 734 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 8.00 (s, 2H, C2#–H, C6#–H), 7.83 (s, 1H, C4#–H), 7.38 – 7.34 (m, 4H, 2 × C2´–H, 2 × C4´–H), 7.33 (*virt.* t, $^3J = {}^3J \approx 8.7$ Hz, 2H, 2 × C5´–H), 7.25 (*virt.* dt, $^3J = {}^3J \approx 7.1$ Hz, $^4J = 1.8$ Hz, 2H, 2 × C6´–H), 6.43 (s, 1H, NH).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 170.5 (s, C4=O), 153.7 (s, C2=O), 139.8 (s, 2 × C1´), 135.5 (s, 2 × C3´), 132.8 (q, $^1J = 34.1$ Hz, C3#-CF$_3$, C5#-CF$_3$), 131.4 (d, 2 × C5´), 130.5 (s, C1#), 130.1 (d, 2 × C6´), 129.2 (d, C4#), 127.7 (d, C2#), 126.6 (d, 2 × C2´), 126.4 (d, C6#), 125.8 (s, C3#), 125.2 (d, 2 × C4´), 124.5 (s, C5#), 69.2 (s, C5).

HRMS (ESI): C$_{23}$H$_{12}$Cl$_2$F$_2$N$_2$O$_2$ [(M+H)$^+$] = calcd.: 533.0258, found: 533.0260.

1,2-(3′-Fluorophenyl)-(3′′-fluorophenyl)-2-hydroxyethan-1-one (155)

$$C_{14}H_{10}F_2O_2$$
$$M = 248.23 \text{ g/mol}$$
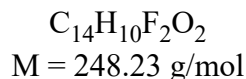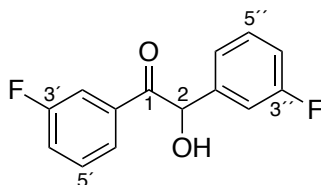
Finely grounded NaOH (227 mg, 5.68 mmol, 0.1 eq) and EtOH (15 mL) were added to a heat-gun-dried *Schlenk*-flask purged with argon and heated to 55 °C until dissolution. Subsequently, thiamine dichloride (795 mg, 2.35 mmol, 5 mol%) and 3-fluoro-benzaldehyde (5.00 mL, 5.85 g, 47.2 mmol, 1.0 eq.) were added and the reaction mixture was stirred at 55 °C for 16 h. After the reaction mixture was allowed to cool to r.t., satd. aq. NaCl-solution (25 mL) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography (silica, 15 × 4 cm, petane/EtOAc, 20:1 → 15:1) to yield benzoin **155** (3.60 g, 14.5 mmol, 31%) as a yellow solid. Benzil **158** (*vide infra*, 1.30 g, 5.28 mmol, 12%) was obtained as a side product.

TLC: R_f (pentane/EtOAc, 10:1) = 0.44 [UV, $KMnO_4$].

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.67 (d, ^3J = 7.9 Hz, 1H, C6′–H), 7.60 (ddd, $^3J_{H,F}$ = 9.2 Hz, ^4J =2.6 Hz, 1.6 Hz, 1H, C2′–H), 7.40 (*virt.* td, $^3J = {}^3J ≈ 8.1$ Hz, $^4J_{H,F}$ = 5.4 Hz, 1H, C5′–H), 7.31 (*virt.* td, $^3J = {}^3J ≈ 8.0$ Hz, $^4J_{H,F}$ = 5.8 Hz, 1H, C5′′–H), 7.25 (*virt.* tdd, $^3J_{H,F} = {}^3J ≈ 8.2$ Hz, ^4J =2.6 Hz, 1.0 Hz, 1H, C4′–H), 7.12 (d, ^3J = 7.7 Hz, 1H, C6′′–H), 7.02 (*virt.* dt, $^3J_{H,F}$ = 9.3 Hz, $^4J = {}^4J ≈ 2.1$ Hz, 1H, C2′′–H), 6.99 (*virt.* tdd, $^3J_{H,F} ≈ {}^3J ≈ 8.5$ Hz, ^4J = 2.6 Hz, 1.0 Hz, 1H C4′′–H), 5.90 (d, ^3J = 5.9 Hz, 1H, C2–H), 4.45 (d, ^3J = 5.9 Hz, 1H, OH).

^{13}C-NMR (101 MHz, $CDCl_3$): δ [ppm] = 197.5 (sd, $^4J_{F,C}$ = 2.2 Hz, C=O), 164.1 (d, $^1J_{F,C}$ = 21.3 Hz, C3′), 162.1 (d, $^1J_{F,C}$ = 23.1 Hz, C3′), 140.8 (d, $^3J_{F,C}$ = 6.8 Hz, C1′), 134.8 (d, $^3J_{F,C}$ = 6.5 Hz, C1′′), 130.9 (dd, $^3J_{F,C}$ = 8.2 Hz, C5′′), 130.6 (dd, $^3J_{F,C}$ = 7.7 Hz, C5), 124.9 (dd, $^4J_{F,C}$ = 3.2 Hz, C6′′), 123.6 (d, $^4J_{F,C}$ = 3.1 Hz, C6′), 121.4 (dd, $^2J_{F,C}$ = 21.5 Hz, C4′), 116.0 (dd, $^2J_{F,C}$ = 3.0 Hz, C2′′), 115.7 (d, $^2J_{F,C}$ = 4.5 Hz, C4′′), 114.8 (d, $^2J_{F,C}$ = 22.1 Hz, C2′), 75.8 (dd, $^4J_{F,C}$ = 6.8 Hz, C2).

¹⁹F-NMR (476 MHz, CDCl₃): δ [ppm] = –110.68 (s, 1F), –111.28 (s, 1F).

The analytical data are consistent with those in the literature.[132]

1,2-*bis*(3´-Fluorophenyl)ethane-1,2-dione (158)

$$C_{14}H_8F_2O_2$$
$$M = 246.21 \text{ g/mol}$$
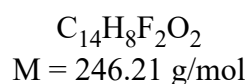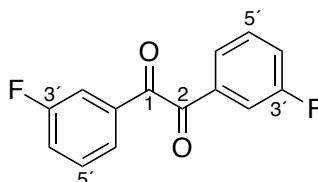
Benzoin **155** (3.60 g, 14.6 mmol, 1.0 eq.), NH₄NO₃ (1.26 g, 18.1 mmol, 1.3 eq.) and Cu(OAc)₂·H₂O (25.1 mg, 146 µg, 1.0 mol%) were dissolved in a mixture of H₂O (2.5 mL) and AcOH (10.5 mL) and the reaction mixture was heated to reflux for 4 h. The resulting precipitate was filtered and washed with H₂O (100 mL). Benzil **158** (3.06 g, 12.4 mmol, 85%) was obtained as yellow crystals.

TLC: R_f (pentane/EtOAc, 10:1) = 0.72 [UV, KMnO₄].

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.73 (*virt.* dt, ^3J = 7.6 Hz, ^4J = ^4J ≈ 1.4 Hz, 2H, 2 × C6´–H), 7.70 (ddd, $^3J_{H,F}$ = 8.9 Hz, ^4J = 2.6, Hz, 1.3 Hz, 2H, 2 × C2´–H), 7.51 (*virt.* td, ^3J = ^3J ≈ 7.9 Hz, $^4J_{H,F}$ = 5.3 Hz, 2H, 2 × C5´–H), 7.38 (*virt.* tdd, $^3J_{H,F}$ = ^3J ≈ 8.2 Hz, ^4J = 2.6 Hz, 1.0 Hz, 2H, 2 × C4´–H).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 192.3 (sd, $^4J_{C,F}$ = 2.3 Hz, 2 × C=O), 163.04 (d, $^1J_{C,F}$ = 249.8 Hz, 2 × C3´), 134.8 (sd, $^3J_{C,F}$ = 6.5 Hz, 2 × C1´), 131.0 (dd, $^3J_{C,F}$ = 7.6 Hz, 2 × C5´), 126.2 (dd, $^4J_{C,F}$ = 3.1 Hz, 2 × C6´), 122.4 (dd, $^2J_{C,F}$ = 21.4 Hz, 2 × C4´), 116.4 (dd, $^2J_{C,F}$ = 22.7 Hz, 2 × C2´).

¹⁹F-NMR (476 MHz, CDCl₃): δ [ppm] = –110.36 (s, 2F).

The analytical data are consistent with those in the literature.[132]

5,5-*bis*(3′-Fluorophenyl)-3-methylimidazolidine-2,4-dione (161)

$$C_{16}H_{12}F_2N_2O_2$$
$$M = 302.28 \text{ g/mol}$$
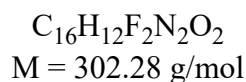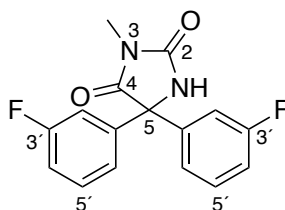
Benzil **158** (647 mg, 2.63 mmol, 1.0 eq.) and *N*-methylurea (352 mg, 4.76 mmol, 1.8 eq.) were dissolved in a mixture of H_2O (1.5 mL) and DMSO (9 mL). KOH (266 mg, 4.76 mmol, 1.8 eq.) was added portionwise and the reaction mixture was heated to reflux for 1 h. The reaction mixture was then allowed to cool to r.t., H_2O (20 mL) was added and it was acidified to pH 3 with conc. HCl. The resulting precipitate was filtered, washed with H_2O (50 mL) and recrystallized from EtOH (10 mL). Compound **161** (548 mg, 1.18 mmol, 45%) was obtained as colorless crystals.

TLC: R_f (pentane/acetone, 2:1) = 0.71 [UV, KMnO₄].

Mp: >230 °C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3176 (w, NH), 1768 (w, C=O), 1670 (s, C=O), 1484 (m, C=C), 1470 (m, C=C), 1445 (w, C=C), 1090 (m), 1077 (m), 788 (s, sp²-CH).

¹H-NMR (300 MHz, CDCl₃): δ [ppm] = 7.36 (*virt.* td, $^3J = {}^3J \approx 8.1$ Hz, $^4J_{H,F} = 5.8$ Hz, 2H, 2 × C5′–H), 7.16 (*virt.* dt, $^3J = {}^3J \approx 8.0$ Hz, $^4J = 1.2$ Hz, 2H, 2 × C6′–H), 7.13 – 7.02 (m, 4H, 2 × C2′–H, 2 × C4′–H), 6.63 (br s 1H, NH), 3.11 (s, 3H, N3-CH₃).

¹³C-NMR (75 MHz, CDCl₃): δ [ppm] = 172.5 (s, C4=O), 163.0 (d, $^1J_{C,F} = 248.0$ Hz, 2 × C3′), 156.5 (s, C2=O), 141.0 (sd, $^3J_{C,F} = 7.1$ Hz, 2 × C1′), 130.8 (dd, $^3J_{C,F} = 8.2$ Hz, 2 × C5′), 122.6 (dd, $^4J_{C,F} = 3.1$ Hz, 2 × C6′), 116.12 (dd, $^2J_{C,F} = 21.1$ Hz, 2 × C4′/C2′), 114.3 (dd, $^2J_{C,F} = 23.6$ Hz, 2 × C4′/C2′), 69.6 (s, C5), 25.4 (q, N3-CH₃).

HRMS (ESI): $C_{16}H_{12}F_2N_2O_2$ [(M+H)⁺] = calcd.: 303.0945, found: 303.0946.

5,5-*bis*(3´-Fluorophenyl)imidazolidine-2,4-dione (264)

$$C_{15}H_{10}F_2N_2O_2$$
$$M = 288.25 \text{ g/mol}$$
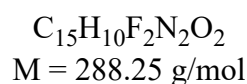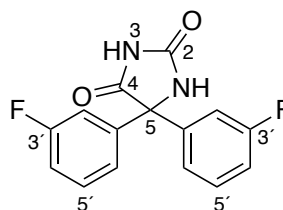
Benzil **158** (1.80 g, 6.44 mmol, 1.0 eq.), KOH (650 mg, 11.6 mmol, 1.8 eq.) and urea (504 mg, 8.34 mmol, 1.3 eq.) were dissolved dry EtOH (25 mL) and the reaction mixture was heated to 55°C for 24 h. The reaction mixture was then allowed to cool to r.t. and subsequently poured on ice (50 g). The resulting precipitate was filtered off and the filtrate was acidified to pH 3 with conc. HCl. The resulting precipitate was filtered and washed with H_2O (80 mL). Compound **264** (1.76 g, 6.10 mmol, 95%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone 2:1) = 0.48 [UV, KMnO$_4$].

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3215 (w, NH), 3065 (w, NH), 1781 (m, C=O), 1710 (s, C=O), 1690 (s, C=O), 1589 (m, Ar), 1442 (m), 1259 (m), 757 (s, sp^2-CH).

^{1}H-NMR (400 MHz, DMSO-d$_6$): δ [ppm] = 11.31 (s, 1H, N3–H), 9.46 (s, 1H, N1–H), 7.48 (*virt.* td, $^3J = {}^3J \approx 8.1$ Hz, $^4J_{H,F} = 6.2$ Hz, 2H, 2 × C5´–H), 7.28 – 7.20 (m, 4H, 2 × C4´–H, 2 × C6´–H), 7.13 (*virt.* dt, $^3J_{H,F} = 10.4$ Hz, $^4J = {}^4J \approx 2.2$ Hz, 2H, 2 × C2´–H).

^{13}C-NMR (126 MHz, DMSO-d$_6$): δ [ppm] = 173.9 (s, C4=O), 162.0 (d, $^1J_{C,F} = 244.9$ Hz, 2 × C3´), 155.8 (s, C2=O), 142.0 (sd, $^3J_{C,F} = 7.0$ Hz, 2 × C1´), 131.0 (dd, $^3J_{C,F} = 8.2$ Hz, 2 × C5´), 122.6 (dd, $^4J_{C,F} = 2.9$ Hz, 2 × C6´), 115.4 (d, $^2J_{C,F} = 20.8$ Hz, 2 × C4´), 113.4 (d, $^2J_{C,F} = 23.4$ Hz, 2 × C2´), 69.3 (s, C5).

HRMS (ESI): $C_{15}H_{10}F_2N_2O_2$ [(M+H)$^+$] = calcd.: 289.0788, found: 289.0788.

5,5-*bis*(3′Fluorophenyl)-3-(4-methoxyphenyl)imidazolidine-2,4-dione (265)

$$C_{22}H_{16}F_2N_2O_3$$
$$M = 394.38 \text{ g/mol}$$
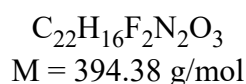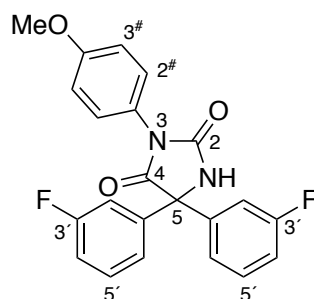
Compound **264** (500 mg, 1.74 mmol, 1.5 eq.), Cu_2O (166 mg, 1.15 mmol, 1.0 eq.) and 4-Iodoanisole (279 mg, 1.15 mmol, 1.0 eq.) were dissolved in dry DMF (5 mL) and heated to 150 °C for 24 h. The reaction mixture was allowed to cool to r.t. and filtered over Celite® and washed with EtOAc. The filtrate was concentrated to 500 μL, poured on ice H_2O (30 mL) and stirred for at r.t. for 30 mins. Aq. NH_4OH-solution (28%, 8 mL) was added and the solution was stirred at r.t. for additional 30 mins. The resulting precipitate was filtered and purified by column chromatography (silica, 15 × 2 cm, petane/EtOAc, 10:1 → 7:1) to yield Compound **265** (352 mg, 0.89 mmol, 78%) as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.67 [UV, $KMnO_4$].

Mp: 178 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3286 (w, NH), 2937 (w, sp^3-CH), 2842 (w, sp^3-CH), 1719 (s, C=O), 1609 (m, C=C), 1580 (m, C=C), 1512 (s, C=C), 1418 (s, C=C), 760 (s, sp^2-CH).

^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.75 (s, 1H, NH), 7.36 (*virt.* td, $^3J = {}^3J \approx 8.1$ Hz, $^4J_{H,F} = 5.8$ Hz, 2H, 2 × C5′–H), 7.29 (m, 2H, C2#–H, C6#–H), 7.24 (ddd, $^3J = 7.8$ Hz, $^4J = 1.8$ Hz, 1.0 Hz, 2H, 2 × C6′–H), 7.18 (*virt.* dt, $^3J_{H,F} = 9.9$ Hz, $^3J = {}^3J \approx 2.2$ Hz, 2H, 2 × C2′–H), 7.07 (*virt.* tdd, $^3J = {}^3J \approx 8.3$ Hz, $^3J_{H,F} = 8.3$ Hz, $^4J = 2.5$ Hz, 1.0 Hz, 2H, 2 × C4′–H), 6.96 (m, 2H, C3#–H, C5#–H), 3.80 (s, 3H, OCH_3).

^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 171.6 (s, C4=O), 163.0 (sd, $^1J_{C,F} = 248.0$ Hz, 2 × C3′), 159.7 (s, C2=O), 156.2 (s, C4#), 141.0 (sd, $^3J_{C,F} = 7.0$ Hz, 2 × C1′), 130.8 (dd, $^3J_{C,F} = 8.2$ Hz, 2 × C5′), 127.8 (d, C2#, C6#), 123.8 (s, C1#), 122.6 (dd, $^4J_{C,F} = 3.1$ Hz, 2 × C6′), 116.1 (d, $^2J_{C,F} = 21.1$ Hz, 2 × C4′/C2′), 114.6 (d, C3#, C5#), 114.4 (d, $^2J_{C,F} = 23.6$ Hz, 2 × C2′/C4′), 69.2 (s, C5), 55.7 (O-CH_3).

HRMS (ESI): $C_{22}H_{16}F_2N_2O_3$ $[(M+H)^+]$ = calcd.: 395.1207, found: 395.1209.

1,2-(2′-Fluorophenyl)-(2′′-fluorophenyl)-2-hydroxyethan-1-one (154)

$$C_{14}H_{10}F_2O_2$$
$$M = 248.23 \text{ g/mol}$$
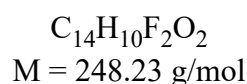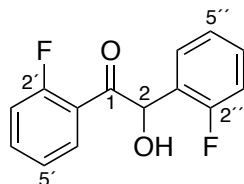
Finely grounded NaOH (1.18 g, 2.34 mmol, 0.1 eq) and EtOH (7.5 mL) were added to a heat-gun-dried *Schlenk*-flask purged with argon and heated to 55 °C until dissolution. Subsequently, thiamine dichloride (398 mg, 1.17 mmol, 5 mol%) and 3-fluoro-benzyldehyde (2.48 mL, 2.91 g, 23.4 mmol, 1.0 eq.) were added and the reaction mixture was stirred at 55 °C for 16 h. After the reaction mixture was allowed to cool to r.t., satd. aq. NaCl-solution (15 mL) was added, the phases were separated and the aqueous phase was extracted with DCM (3 × 40 mL). The combined organic phases were washed with H_2O (2 × 50 mL) and dried over $MgSO_4$. After the solvent was removed under reduced pressure, the crude product was purified by column chromatography (silica, 15 × 2.5 cm, hexane/EtOAc, 10:1 → 1:10) to yield benzoin **154** (2.21 g, 8.90 mmol, 38%) as a yellow solid. Benzil **157** (*vide infra*, 871 mg, 3.51 mmol, 15%) was obtained as a side product.

TLC: R_f (pentane/EtOAc, 10:1) = 0.44 [UV, KMnO$_4$].

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.88 (ddd, ^3J = 8.9 Hz, $^4J_{H,F}$ = 7.2 Hz, ^4J =1.8 Hz, 1H, C6′–H), 7.49 (dddd, ^3J = 8.3 Hz, ^3J = 7.1 Hz, $^4J_{H,F}$ = 5.1 Hz, ^4J = 1.8 Hz, 1H, C4′–H), 7.28 – 7.23 (m, 2H, C4′′–H, C6′′–H), 7.21 (*virt.* td, ^3J = ^3J ≈ 7.7 Hz, ^4J = 1.2 Hz, 1H, C5′–H), 7.07 (*virt.* td, ^3J = ^3J ≈ 7.6 Hz, ^4J =1.2 Hz, 1H, C5′′–H), 7.05 (ddd, $^3J_{H,F}$ = 11.0 Hz, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1H, C3′–H), 7.02 (ddd, $^3J_{H,F}$ = 9.4 Hz, ^3J = 8.1 Hz, ^4J = 1.0 Hz, 1H, C3′′–H), 6.08 (dd, ^3J = 5.7 Hz, $^4J_{H,F}$ = 2.3 Hz, 1H, C2–H), 4.47 (d, J = 5.8 Hz, 1H, OH).

13C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 197.5 (sd, $^3J_{F,C}$ = 4.3 Hz, C=O), 162.8 (d, $^1J_{F,C}$ = 33.8 Hz, C2′), 159.4 (d, $^1J_{F,C}$ = 26.7 Hz, C2′′), 135.6 (sd, $^2J_{F,C}$ = 9.1 Hz, C1′), 130.9 (dd, $^4J_{F,C}$ = 2.5 Hz, C5′′), 130.7 (sd, $^3J_{F,C}$ = 8.4 Hz, C1′′), 130.57 (dd, $^4J_{F,C}$ = 3.8 Hz, C5′), 125.6 (dd, $^3J_{F,C}$ = 14.3 Hz, C6′′), 125.4 (d, $^3J_{F,C}$ = 14.3 Hz, C6′), 124.7 (dd, $^3J_{F,C}$ = 16.0 Hz, C4′′), 122.7 (dd, $^3J_{F,C}$ = 3.0 Hz, C4′), 116.0 (d, $^2J_{F,C}$ = 22.2 Hz, C3′), 115.4 (d, $^2J_{F,C}$ = 22.1 Hz, C3′′), 74.0 (dd, $^3J_{F,C}$ = 8.0 Hz, C2).

19F-NMR (476 MHz, CDCl$_3$): δ [ppm] = −107.9 (s, 1F), −117.6 (s, 1F).

The analytical data are consistent with those in the literature. [132]

1,2-*bis*(2′-Fluorophenyl)ethane-1,2-dione (157)

$C_{14}H_8F_2O_2$
M = 246.21 g/mol
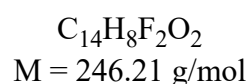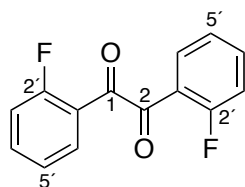
Benzoin **154** (2.21 g, 8.90 mmol, 1.0 eq.), NH$_4$NO$_3$ (0.89 g, 11.1 mmol, 1.3 eq.) and Cu(OAc)$_2$·H$_2$O (17.7 mg, 89.0 µg, 1.0 mol%) were dissolved in a mixture of H$_2$O (2.5 mL) and AcOH (10.5 mL) and the reaction mixture was heated to reflux for 90 mins. The resulting precipitate was filtered and washed with H$_2$O (100 mL). Benzil **157** (1.63 g, 6.60 mmol, 74%) was obtained as yellow crystals.

TLC: R_f (pentane/EtOAc, 10:1) = 0.71 [UV, KMnO$_4$].

1H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 8.08 (ddd, ^3J = 7.8 Hz, $^4J_{H,F}$ = 6.8 Hz, ^4J = 1.9 Hz, 2H, 2 × C6′–H), 7.66 (dddd, ^3J = 8.4 Hz, ^3J = 7.2 Hz, $^3J_{H,F}$ = 5.2 Hz, ^4J =1.9 Hz, 2H, 2 × C4′–H), 7.35 (*virt.* td, ^3J = ^3J ≈ 7.6 Hz, ^4J = 1.0 Hz, 2H, 2 × C5′–H), 7.15 (ddd, $^3J_{H,F}$ = 10.5 Hz, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 2H, 2 × C3′–H).

13C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 190.4 (s, 2 × C=O), 163.2 (d, $^1J_{C,F}$ = 257.3 Hz, 2 × C2′), 136.9 (dd, $^3J_{H,F}$ = 9.5 Hz, 2 × C4′), 131.0 (dd, $^3J_{C,F}$ = 1.5 Hz, 2 × C6′), 125.14 (dd, $^4J_{C,F}$ = 1.7 Hz, 2 × C5′), 121.5 (sdd, $^2J_{C,F}$ = 10.6 Hz, $^5J_{C,F}$ = 2.7 Hz, 2 × C1′), 116.6 (dd, $^2J_{C,F}$ = 21.5 Hz, 2 × C3′).

The analytical data are consistent with those in the literature.[132]

5,5-*bis*(3′-Fluorophenyl)-3-methylimidazolidine-2,4-dione (160)

$C_{16}H_{12}F_2N_2O_2$
M = 302.28 g/mol
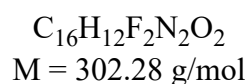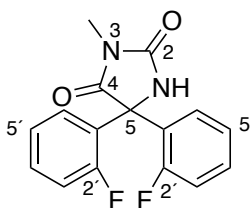
Benzil **157** (1.30 g, 5.28 mmol, 1.0 eq.) and *N*-methylurea (700 mg, 9.50 mmol, 1.8 eq.) were dissolved in a mixture of H_2O (3 mL) and DMSO (18 mL). KOH (530 mg, 9.46 mmol, 1.8 eq.) was added portionwise and the reaction mixture was heated to reflux for 1 h. The reaction mixture was then allowed to cool to r.t., H_2O (30 mL) was added and it was acidified to pH = 3 with conc. HCl. The resulting precipitate was filtered, washed with H_2O (100 mL) and recrystallized from EtOH (20 mL). Compound **160** (930 mg, 3.09 mmol, 58%) was obtained as colorless crystals.

TLC: R_f (pentane/acetone, 2:1) = 0.74 [UV, KMnO$_4$].

Mp: 160 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3246 (w, NH), 1778 (w, C=O), 1720 (s, C=O), 1486 (m, C=C), 1450 (m, C=C), 1392 (w, C=C), 1189 (m), 1087 (m), 758 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.40 (ddd, ^3J = 9.2, Hz, $^4J_{H,F}$ = 6.8 Hz, ^4J = 1.7 Hz, 2H, 2 × C4′–H), 7.33 (*virt.* td, ^3J = ^3J ≈ 8.4 Hz, ^4J = 2.2 Hz, 2H, 2 × C5′–H), 7.18 – 7.09 (m, 4H, 2 × C2′–H, 2 × C6′–H), 6.34 (s, 1H, NH), 3.14 (s, 3H, N3-CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 172.1 (s, C4=O), 160.98 (d, $^1J_{C,F}$ = 248.5 Hz, 2 × C2′), 156.0 (sd, C2=O), 131.3 (dd, $^3J_{C,F}$ = 9.0 Hz, 2 × C4′), 128.7 (dd, $^4J_{C,F}$ = 2.5 Hz, 2 × C5′), 124.6 (d, $^3J_{C,F}$ = 3.7 Hz, 2 × C6′), 124.5 (sd, $^2J_{C,F}$ = 10.2 Hz, 2 × C1′), 116.9 (dd, $^2J_{C,F}$ = 22.4 Hz, 2 × C3′), 65.9 (s, C5), 25.3 (q, N3-CH$_3$).

HRMS (ESI): $C_{16}H_{12}F_2N_2O_2$ [(M+H)$^+$] = calcd.: 303.0945, found: 303.0937.

Spiro[fluorene-9,4´-imidazolidine]-2´,5´-dione (164)

$$C_{15}H_{10}N_2O_2$$
$$M = 250.26 \text{ g/mol}$$
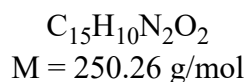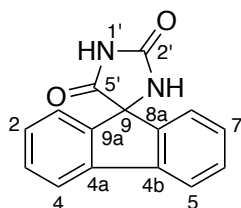
9*H*-fluoren-9-one (681 mg, 3.78 mmol, 1.0 eq.), KCN (400 mg, 5.67 mmol, 1.5 eq), $(NH_4)_2CO_3$ (1.60 g, 15.1 mmol, 4.0 eq.) and acetamide (16 g) were placed in a pressure tube and heated to 140 °C for 96 h. After the reaction mixture was allowed to cool to r.t., it was suspended in H_2O (100 mL), carefully neutralized with HCl (6 M) until pH = 6. The resulting precipitate was washed with DCM (200 mL) and dried *in vacuo.* Compound **164** (745 mg, 2.98 mmol, 78%) was obtained as a pale brown solid.

Mp: >230 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3270 (m, NH), 3200 (m, NH), 1770 (m, C=O), 1730 (s, C=O), 1400 (s, C=C), 1590 (m), 1442 (m), 1261 (m), 740 (s, sp^2-CH).

^{1}H-NMR (500 MHz, acetone-$_6$): δ [ppm] = 10.01 (s, 1H, NH), 7.85 (dt, ^3J = 7.6 Hz, ^4J = 1.0 Hz, 2H, C4–H, C5–H), 7.55 (*virt.* dt, ^3J = 7.5 Hz, ^4J = ^4J ≈ 0.9 Hz, 2H, C1–H, C8–H), 7.49 (*virt.* td, ^3J = ^3J ≈ 7.5 Hz, ^4J = 1.2 Hz, 2H, C2–H, C7–H), 7.39 (*virt.* td, ^3J = ^3J ≈ 7.5 Hz, ^4J = 1.2 Hz, 2H, C3–H, C6–H).

^{13}C-NMR (126 MHz, acetone-$_6$): δ [ppm] = 164.5 (s, C4=O), 147.9 (s, C2=O), 133.3 (s, C8a, C9a), 131.0 (s, C4a, C4b), 120.2 (d, C2, C7), 118.7 (d, C3, C6), 113.9 (d, C1, C8), 111.1 (d, C4, C5), 62.7 (s, C9).

HRMS (ESI): $C_{15}H_{10}N_2O_2$ [(M)$^+$] = calcd.: 250.0742, found: 250.0791.

1´-Methylspiro[fluorene-9,4´-imidazolidine]-2´,5´-dione (165)

$C_{16}H_{12}N_2O_2$

M = 264.28 g/mol
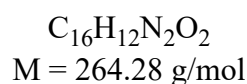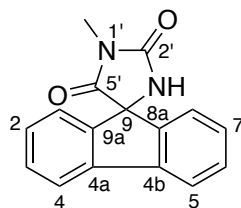
Compound **164** (300 mg, 1.20 mmol, 1.0 eq.) and K_2CO_3 (166 mg, 1.20 mmol, 1.0 eq.) were suspended in DMF (8 mL) and stirred at r.t. for 30 mins. Subsequently, methyl iodide (187 mg, 81.8 µL, 1.32 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 10 mins. H_2O (24 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 2 cm, pentane/acetone, 5:1 → 1:1) yielded **165** (176 g, 66.5 µmol, 55%) as colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.50 [UV].

Mp: 225 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3461 (m), 3232 (m, NH), 2946 (m, sp^3-CH_2), 2814 (m, sp^3-CH_2), 1775 (m, C=O), 1717 (s, C=O), 1606 (s, C=C), 1585 (m), 1452 (m), 1390 (m), 745 (s, sp^2-CH).

^{1}H-NMR (400 MHz, acetone-$_6$): δ [ppm] = 10.08 (s, 1H, NH), 7.91 (*virt.* dt, ^3J = 7.6 Hz, ^4J = ^4J ≈ 0.9 Hz, 2H, C4–H, C5–H), 7.53 (*virt.* td, ^3J = ^3J ≈ 7.4 Hz, ^4J = 1.2 Hz, 2H, C3–H, C6–H), 7.51 (*virt.* dt, ^3J = 7.3 Hz, ^4J = ^4J ≈ 1.1 Hz, 2H, C1–H, C8–H), 7.41 (*virt.* td, ^3J = ^3J ≈ 7.5 Hz, ^4J = 1.1 Hz, 2H, C2–H, C7–H), 2.46 (s, 3H, N3–CH_3).

^{13}C-NMR (101 MHz, acetone-$_6$): δ [ppm] = 174.6 (s, C4=O), 156.9 (s, C2=O), 142.7 (s, C8a, C9a), 141.6 (s, C4a, C4b), 13.1 (d, C1, C8), 129.2 (d, C2, C7), 124.6 (d, C3, C6), 121.7 (d, C4, C5), 77.2 (s, C9), 25.4 (q, N3–CH_3).

HRMS (ESI): $C_{16}H_{12}N_2O_2$ [(M+H)$^+$] = calcd.: 265.2918, found: 265.0970.

5,5-Dibenzylimidazolidine-2,4-dione (266)

$$C_{17}H_{16}N_2O_2$$
$$M = 280.33 \text{ g/mol}$$
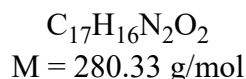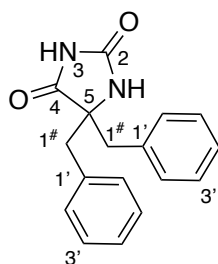
1,3-Diphenylpropan-2-one (2.19 g, 10.4 mmol, 1.0 eq.), KCN (1.50 g, 15.6 mmol, 1.5 eq), $(NH_4)_2CO_3$ (8.50 g, 41.6 mmol, 4.0 eq.) and a mixture of $EtOH/H_2O$ (1:2, 25 mL) were placed in a pressure tube and heated to 120 °C for 72 h. After the reaction mixture was allowed to cool to r.t., it was suspended in H_2O (100 mL), carefully neutralized with HCl (6 M) until pH = 6. The resulting precipitate was washed with DCM (200 mL) and dried *in vacuo*. Compound **266** (2.90 g, 10.3 mmol, 99%) was obtained as colorless crystals.

Mp: >230 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3211 (w, NH), 2930 (m, sp^3-CH$_2$), 1725 (s, C=O), 1705 (s, C=O), 1494 (w, C=C), 1456 (w, C=C), 1280 (m), 697 (s, sp^2-CH).

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ [ppm] = 9.45 (s, 1H, N3–H), 8.03 (s, 1H, N1–H), 7.27 (*virt.* t, $^3J = {}^3J \approx 7.2$ Hz, 4H, 2 × C3′–H, 2 × C5′–H), 7.22 (*virt.* t, $^3J = {}^3J \approx 7.3$ Hz, 2H, 2 × C4′–H), 7.18 (d, $^3J = 6.6$ Hz, 4H, 2 × C2′–H, 2 × C6′–H), 3.11 (d, $^2J = 13.4$ Hz, 2H, 2 × C1$^\#$–H$_A$), 2.86 (d, $^2J = 13.4$ Hz, 2H, 2 × C1$^\#$–H$_B$).

^{13}C-NMR (126 MHz, DMSO-d$_6$): δ [ppm] = 176.2 (s, C4=O), 155.9 (s, C2=O), 135.2 (s, 2 × C1′), 130.2 (d, 2 × C3′, 2 × C5′), 128.0 (d, 2 × C2′, 2 × C6′), 126.8 (d, 2 × C4′), 67.9 (s, C5), 42.4 (t, 2 × C1$^\#$).

HRMS (ESI): $C_{17}H_{16}N_2O_2$ [(M+H)$^+$] = calcd.: 281.1290, found: 281.1288.

5,5-Dibenzyl-3-methylimidazolidine-2,4-dione (187)


$C_{18}H_{18}N_2O_2$
M = 294.35 g/mol
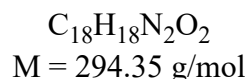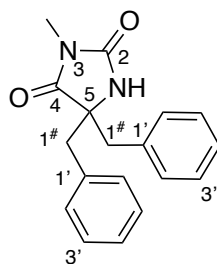
Compound **266** (280 mg, 1.00 mmol, 1.0 eq.) and K_2CO_3 (133 mg, 1.00 mmol, 1.0 eq.) were suspended in DMF (8 mL) and stirred at r.t. for 30 mins. Subsequently, methyl iodide (156 mg, 68.5 µL, 1.10 mmol, 1.3 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 1 h. Water (25 mL) was added and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (15 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 2 cm, pentane/acetone, 10:1 → 3:1) yielded compound **187** (121.6 mg, 410 µmol, 41%) as colorless crystals.

TLC: R_f (pentane/acetone, 4:1) = 0.44 [UV].

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3252 (w, NH), 2924 (m, sp^3-CH$_2$), 1723 (m, C=O), 1705 (s, C=O), 1494 (w, C=C), 1456 (m, C=C), 1350 (w), 1016 (m), 698 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.36 – 7.23 (m, 6H, 2 × C3′–H, 2 × C4′–H, 2 × C5′–H), 7.23 – 7.11 (m, 4H, 2 × C2′–H, 2 × C6′–H), 5.81 (s, 1H, NH), 3.23 (d, ^2J = 13.6 Hz, 2H, 2 × C1$^\#$–H$_A$), 2.95 (d, ^2J = 13.7 Hz, 2H, 2 × C1$^\#$–H$_B$), 2.61 (s, 3H, N3–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 175.4 (s, C4=O), 156.6 (s, C2=O), 134.2 (s, 2 × C1′), 130.2 (d, 2 × C2′, 2 × C6′), 128.6 (d, 2 × C3′, 2 × C5′), 127.6 (d, 2 × C4′), 67.1 (s, C5), 42.7 (t, 2 × C1$^\#$), 24.2 (N3–CH$_3$).

HRMS (ESI): $C_{18}H_{18}N_2O_2$ [(M+H)$^+$] = calcd.: 295.1446, found: 295.1445.

3-Methyl-5,5-diphenylimidazolidine-2,4-dione (136)

$$C_{16}H_{14}N_2O_2$$
$$M = 266.30 \text{ g/mol}$$
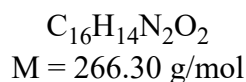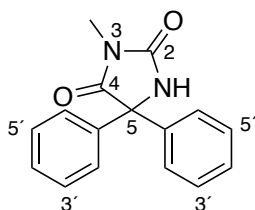
Phenytoin (2.52 g, 10.0 mmol, 1.0 eq.) and K_2CO_3 (1.33 g, 10.0 mmol, 1.0 eq.) were suspended in DMF (80 mL) and stirred at r.t. for 30 mins. Subsequently, methyl iodide (1.56 g, 0.66 mL, 11.0 mmol, 1.3 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 5 mins. H_2O (100 mL) was added and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 4 cm, pentane/acetone, 5:1 → 2:1) yielded compound **136** (2.16 g, 8.10 mmol, 81%) as colorless crystals.

TLC: R_f (pentane/acetone, 2:1) = 0.67 [UV].

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.42 – 7.31 (m, 10H, 10 × Ar′–H), 7.23 (s, 1H, NH), 3.08 (s, 3H, N3–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.6 (s, C4=O), 157.1 (s, C2=O), 139.3 (s, 2 × C1′), 128.9 (d, 4 × Ar′–C), 128.7 (d, 4 × Ar′–C), 127.6 (d, 2 × Ar–C′), 70.4 (s, C5), 25.2 (q, N3–*C*H$_3$).

The analytical data are consistent with those in the literature.[84]

3-Cyclohexyl-5,5-diphenylimidazolidine-2,4-dione (183)
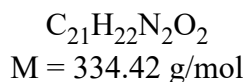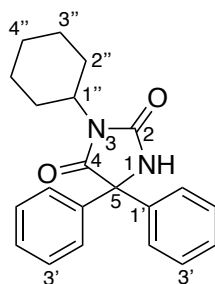
$$C_{21}H_{22}N_2O_2$$
$$M = 334.42 \text{ g/mol}$$

Phenytoin (500 mg, 1.98 mmol, 1.0 eq.) and K_2CO_3 (276 mg, 1.98 mmol, 1.0 eq.) were suspended in DMF (15 mL) and stirred at r.t. for 30 mins. Subsequently, bromocyclohexane (356 mg, 270 µL, 2.20 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 6 days. Water (45 mL) was added and the aqueous phase was extracted with EtOAc (3 × 45 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 2.5 cm, pentane/acetone, 10:1 → 2:1) yielded compound **183** (34.5 mg, 103 µmol, 5%) as colorless crystals.

**TLC:** R_f (pentane/acetone, 4:1) = 0.48 [UV].

Mp: 174 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3229 (w, NH), 3097 (w, sp^3-CH$_2$), 2924 (m, sp^3-CH$_2$), 2852 (m, sp^3-CH$_2$), 1770 (w, C=O), 1706 (s, C=O), 1411 (s, C=C), 1375 (s, C=C), 692 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.42 – 7.29 (m, 10H, 10 × Ar′–H), 5.76 (s, 1H, NH), 3.97 (*virt.* tt, $^3J = {}^3J \approx 12.4$ Hz, $^3J = {}^3J \approx 3.9$ Hz, 1H, C1′′–H), 2.18 (*virt.* qd, $^2J = {}^3J \approx 12.5$, $^3J = 3.6$ Hz, 2H, C2′′–H$_A$, C6′′–H$_A$), 1.86 – 1.80 (m, 2H, C3′′–H$_A$, C5′′–H$_A$), 1.71 (dd, $^3J = 12.8$ Hz, $^3J = 3.1$ Hz, 2H, C4′′–H$_2$), 1.66 (m, 2H, C2′′–H$_B$, C6′′–H$_B$), 1.38 – 1.15 (m, 2H, C3′′–H$_B$, C5′′′–H$_B$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.2 (s, C4=O), 156.6 (s, C2=O), 139.3 (s, 2 × C1′), 129.3 (d, 2 × Ar′–C), 129.0 (d, 2 × Ar′–C), 1280 (d, 2 × Ar′–C), 127.7 (d, 2 × Ar′–C), 127.4 (d, 2 × Ar′–C), 126.1 (d, 2 × Ar′–C), 69.1 (s, C5), 52.3 (d, C1′′), 29.2 (t, C2′′′/C6′′′), 25.7 (t, C3′′′, C5′′′), 24.7 (t, C4′′′).

HRMS (ESI): $C_{21}H_{22}N_2O_2$ [(M+H)$^+$] = calcd.: 335.1759, found: 335.1752.

3-(Cyclohexylmethyl)-5,5-diphenylimidazolidine-2,4-dione (184)
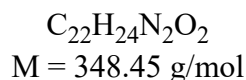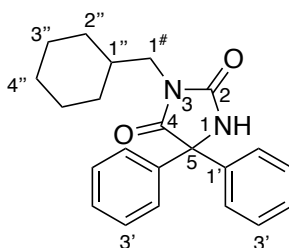
$$C_{22}H_{24}N_2O_2$$
$$M = 348.45 \text{ g/mol}$$

Phenytoin (500 mg, 1.98 mmol, 1.0 eq.) and K_2CO_3 (276 mg, 1.98 mmol, 1.0 eq.) were suspended in DMF (15 mL) and stirred at r.t. for 30 mins. Subsequently, (bromomethyl)cyclohexane (390 mg, 307 µL, 2.20 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 24 h. Water (45 mL) was added and the aqueous phase was extracted with EtOAc (3 × 45 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 2.5 cm, pentane/acetone, 8:1 → 4:1) yielded compound **184** (566 mg, 1.62 mmol, 82%) as colorless crystals.

TLC: R_f (pentane/acetone, 4:1) = 0.67 [UV].

Mp: 192 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3302 (m, NH), 2928 (m, sp^3-CH$_2$), 2851 (m, sp^3-CH$_2$), 1768 (s, C=O), 1670 (s, C=O), 1447 (s, C=C), 1429 (s, C=C), 1105 (m), 690 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.41 – 7.30 (m, 10H, 10 × Ar′–H), 6.75 (s, 1H, NH), 3.40 (d, ^3J = 7.4 Hz, 2H, C1$^\#$-H$_2$), 1.78 (ttt, ^3J 11.1 Hz, ^3J = 7.4 Hz, ^3J = 3.5 Hz, 1H, C1′′–H), 1.72 – 1.56 (m, 6H, C2′′–H$_A$, C3′′–H$_A$, C4′′–H$_2$, C5′′–H$_A$, C6′′–H$_A$), 1.27 – 1.08 (m, 2H, C2′′–H$_B$, C6′′–H$_B$), 1.03 – 0.88 (m, 2H, C3′′–H$_B$, C5′′–H$_B$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.6 (s, C4=O), 157.2 (s, C2=O), 139.5 (s, 2 × C1′), 128.9 (d, 4 × Ar′–C), 128.7 (d, 2 × Ar′–C), 127.0 (d, 4 × Ar′–C), 70.2 (s, C5), 45.2 (t, C1$^\#$), 36.5 (d, C1′′), 30.7 (t, 2 × C2′′, C6′′), 26.7 (t, C4′′), 25.7 (t, 2 × C3′′, C5′′).

HRMS (ESI): $C_{22}H_{24}N_2O_2$ [(M+H)$^+$] = calcd.: 349.4538, found: 349.1914.

3-Isopropyl-5,5-diphenylimidazolidine-2,4-dione (185)
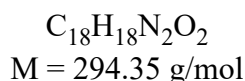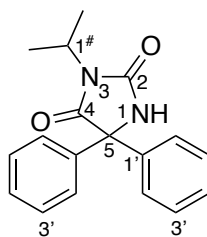
$$C_{18}H_{18}N_2O_2$$
$$M = 294.35 \text{ g/mol}$$

Phenytoin (500 mg, 1.98 mmol, 1.0 eq.) and K_2CO_3 (276 mg, 1.98 mmol, 1.0 eq.) were suspended in DMF (15 mL) and stirred at r.t. for 30 mins. Subsequently, 2-bromopropane (268 mg, 207 µL, 2.20 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 19 h. Water (45 mL) was added and the aqueous phase was extracted with EtOAc (3 × 45 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 2.5 cm, pentane/acetone, 8:1 → 7:1) yielded compound **185** (465 mg, 1.58 mmol, 80%) as colorless crystals.

TLC: R_f (pentane/acetone, 4:1) = 0.64 [UV].

Mp: 192 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3096 (m, NH), 1769 (m, C=O), 1701 (s, C=O), 1448 (m, C=C), 1421 (m, C=C), 1370 (s, C=C), 1190 (m), 1034 (m), 696 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.43 – 7.30 (m, 10H, 10 × Ar′–H), 6.49 (s, 1H, NH), 4.38 (p, ^3J = 6.9 Hz, 1H, C1$^\#$–H), 1.44 (d, ^3J = 6.9 Hz, 6H, 2 × C1$^\#$–CH_3).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.3 (s, C4=O), 156.7 (s, C2=O), 139.6 (s, 2 × C1′), 128.9 (d, 4 × Ar′–C), 128.6 (d, 2 × Ar′–C), 127.0 (d, 4 × Ar′–C), 69.4 (s, C5), 44.3 (d, C1$^\#$), 19.9 (q, 2 × C1$^\#$–CH_3).

HRMS (ESI): $C_{18}H_{18}N_2O_2$ [(M+H)$^+$] = calcd.: 295.1446, found: 295.1445.

5,5-Diphenyl-3-propylimidazolidine-2,4-dione (186)
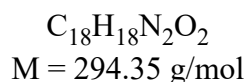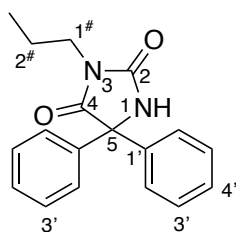
$C_{18}H_{18}N_2O_2$
M = 294.35 g/mol

Phenytoin (500 mg, 1.98 mmol, 1.0 eq.) and K_2CO_3 (276 mg, 1.98 mmol, 1.0 eq.) were suspended in DMF (15 mL) and stirred at r.t. for 30 mins. Subsequently, 2-bromopropane (268 mg, 207 μL, 2.20 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 30 mins. Water (45 mL) was added and the aqueous phase was extracted with EtOAc (3 × 45 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 2.5 cm, pentane/acetone, 8:1 → 7:1) yielded compound **186** (542 mg, 1.84 mmol, 93%) as colorless crystals.

TLC: R_f (pentane/acetone, 4:1) = 0.54 [UV].

Mp: 162 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3096 (m, NH), 2962 (m, sp^3-CH$_2$), 1773 (m, C=O), 1705 (s, C=O), 1494 (w, C=C), 1449 (s, C=C), 1420 (s, C=C), 1201 (m), 757 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.42 – 7.30 (m, 10H, 10 × Ar′–H), 6.77 (s, 1H, NH), 3.54 (t, ^3J = 7.3 Hz, 2H, C1$^\#$–H$_2$), 1.68 (*virt.* sx, ^3J = ^3J ≈ 7.3 Hz, 2H, C2$^\#$–H$_2$), 0.90 (t, ^3J = 7.3 Hz, 3H, C3$^\#$–H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.5 (s, C4=O), 156.9 (s, C2=O), 139.4 (s, 2 × C1′), 128.9 (d, 4 × Ar′–C), 128.7 (d, 2 × Ar′–C), 127.0 (d, 4 × Ar′–C), 70.2 (s, C5), 40.8 (t, C1$^\#$), 21.5 (t, C2$^\#$), 11.2 (q, C3$^\#$).

HRMS (ESI): $C_{18}H_{18}N_2O_2$ [(M+H)$^+$] = calcd.: 295.1446, found: 295.1444.

3-(4-Methoxyphenyl)-5,5-diphenylimidazolidine-2,4-dione (196)

$$C_{22}H_{18}N_2O_3$$
$$M = 358.40 \text{ g/mol}$$
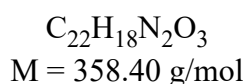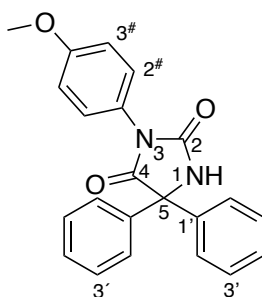
Phenytoin (2.00 g, 8.00 mmol, 1.5 eq.), Cu_2O (760 mg, 5.30 mmol, 1.0 eq.) and 4-Iodoanisole (1.25 g, 5.30 mmol, 1.0 eq.) were dissolved in dry DMF (13 mL) and heated to 150 °C for 24 h. The reaction mixture was allowed to cool to r.t. and filtered over Celite® and washed with EtOAc. The filtrate was concentrated to 100 μL, poured on ice water (30 mL) and stirred for at r.t. for 30 mins. Aq. NH_4OH-solution (28%, 8 mL) was added and the solution was stirred at r.t. for additional 30 mins. The resulting precipitate was filtered and purified by column chromatography (silica, 15 × 4 cm, petane/EtOAc, 4:1 → 2:1) to yield Compound **196** (352 mg, 0.89 mmol, 78%) as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.56 [UV].

Mp: 188 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3175 (w, NH), 3102 (w, sp^3-CH$_2$), 1774 (m, C=O), 1713 (s, C=O), 1513 (s, C=C), 1409 (s, C=C), 1250 (m), 1172 (m), 694 (s, sp^2-CH).

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.47 – 7.35 (m, 10H, 10 × Ar′–H), 7.31 (d, ^3J = 9.0 Hz, 2H, C2$^\#$–H, C6$^\#$–H), 6.96 (d, ^3J = 9.0 Hz, 2H, C3$^\#$–H, C5$^\#$–H), 6.93 (s, 1H, NH), 3.82 (s, 3H OCH$_3$).

^{13}C-NMR (126 MHz, CDCl$_3$): δ [ppm] = 171.5 (s, C4=O), 159.6 (s, C2=O), 156.0 (s, C4$^\#$), 139.3 (s, 2 × C1′), 129.0 (d, 4 × Ar′–H), 128.8 (d, 2 × Ar′–H), 127.8 (d, C2$^\#$, C6$^\#$), 127.0 (d, 4 × Ar′–H), 124.2 (s, C1$^\#$), 114.6 (d, C3$^\#$, C5$^\#$), 70.0 (s, C5), 55.7 (q, O-CH$_3$).

HRMS (ESI): $C_{22}H_{18}N_2O_3$ [(M+H)$^+$] = calcd.: 359.4048, found: 359.1398.

3-(4#-Methoxybenzyl)-5,5-diphenylimidazolidine-2,4-dione (197)

$$C_{23}H_{20}N_2O_3$$
$$M = 372.42 \text{ g/mol}$$
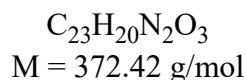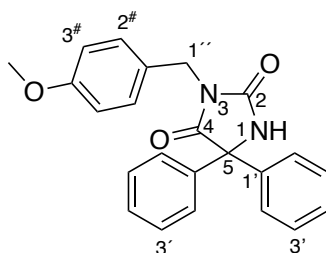
Phenytoin (3.38 g, 13.3 mmol, 1.0 eq.) and K_2CO_3 (1.80 g, 13.3 mmol, 1.0 eq.) were suspended in acetone (80 mL) and stirred at r.t. for 30 mins. Subsequently, 4-methoxybenzyl chloride (2.31 g, 2.00 mL, 15.0 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred at r.t. for 48 h. After the solvent was removed *in vacuo*, the crude product was purified by column chromatography (silica, 15 × 4 cm, pentane/acetone, 5:1 → 2:1), yielding compound **197** (1.41 g, 3.77 mmol, 28%) as a colorless solid.

TLC: R_f (pentane/acetone, 5:1) = 0.35 [UV].

Mp: 134 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3302 (m, NH), 1763 (s, C=O), 1702 (s, C=O), 1512 (m, C=C), 1440 (s, C=C), 1343 (m, C=C), 1248 (m), 1183 (m), 1024 (m), 694 (s, sp^2-CH).

^{1}H-NMR (300 MHz, CDCl$_3$): δ [ppm] = 7.36 – 7.31 (m, 10H, 10 × Ar′–H), 7.30 (d, ^3J = 8.9 Hz, 2H, C2#–H, C6#–H), 7.08 (s, 1H, NH), 6.81 (d, ^3J = 8.9 Hz, 2H, C3#–H, C5#–H), 4.65 (s, 2H, C1″–H$_2$), 3.78 (s, 3H, OCH$_3$).

^{13}C-NMR (75 MHz, CDCl$_3$): δ [ppm] = 173.3 (s, C4=O), 159.4 (s, C2=O), 156.7 (s, C4#), 139.3 (s, 2 × C1′), 130.0 (d, C2#, C6#), 128.9 (d, 4 × Ar′–H), 128.6 (d, 2 × Ar′–H), 128.3 (s, C1#), 127.0 (d, 4 × Ar′–H), 114.1 (d, C3#, C5#), 70.3 (s, C5), 55.4 (q, O-CH$_3$), 42.3 (t, C1″).

HRMS (ESI): $C_{23}H_{20}N_2O_3$ [(M+H)$^+$] = calcd.: 373.1552, found: 373.1554.

N-benzhydrylacetamide (148)


$$C_{15}H_{15}NO$$
$$M = 225.29 \text{ g/mol}$$
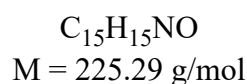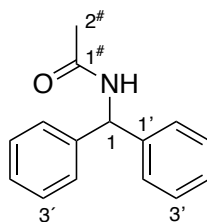
Benzydrylamine (1.72 mL, 1.83 g, 10.0 mmol, 1.0 eq.) and NEt$_3$ (2.77 mL, 20.2 g, 20.0 mmol, 2.0 eq.) were dissolved in dry DCM (30 mL) and cooled to 0 °C. Acyl chloride (1.07 mL, 1.18 g, 15.0 mmol, 1.5 eq.) was added dropwise at 0 °C, the reaction mixture was allowed to warm to r.t. and stirred for 3 h at r.t. Then, the reaction mixture was extracted with DCM (3 × 20 mL), the combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo*. Purification by column chromatography (silica, 15 × 4 cm, pentane/acetone, 20:1 → 10:1) yielded compound **148** (1.55 g, 6.90 mmol, 69%) as a colorless solid.

TLC: R_f (pentane/acetone, 4:1) = 0.65 [UV].

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = δ 7.37 – 7.19 (m, 10H, 10 × Ar′–H), 6.25 (d, ^3J = 7.9 Hz, 1H, C1–H), 6.18 (br s, 1H, NH), 2.06 (s, 3H, C2$^\#$-H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 169.3 (s, C=O), 141.6 (s, 2 × C1′), 128.8 (d, 4 × Ar′–C), 127.7 (d, 2 × Ar–C′), 127.6 (d, 4 × Ar′–C), 57.2 (d, C1), 23.4 (q, C2$^\#$).

The analytical data are consistent with those in the literature.[85]

(*E*)-2#-(2,2-Diphenylethylidene)-1#,1#dimethylhydrazine (267)

$$C_{16}H_{18}N_2$$
$$M = 283.33 \text{ g/mol}$$
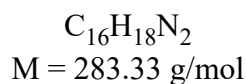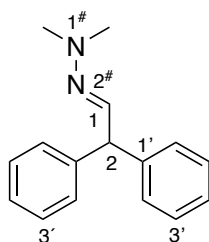
N,N-dimethylhydrazine (1.55 µL, 1.58 g, 26.3 mmol, 1.2 eq.) and 2,2-diphenylacetyldehyde (3.00 mL, 3.32 g, 16.9 mmol, 1.0 eq.) were dissolved in toluene (30 mL) and heated to reflux under *Dean-Stark*-conditions for 2 h. The reaction mixture was allowed to cool to r.t. and the solvent was removed *in vacuo*. Hydrazone **267** (3.77 g, 18.8 mmol, 94%) was obtained as a colorless wax.

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.34 – 7.29 (m, 4H, 2 × C2′–H, 2 × C6′–H), 7.25 – 7.20 (m, 6H, 2 × C3′–H, 2 × C4′–H, 2 × C5′–H), 6.97 (d, ^3J = 7.5 Hz, 1H, C1–H), 4.93 (d, ^3J = 7.4 Hz, 1H, C2–H), 2.81 (s, 6H, 2 × N1#–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 142.8 (s, 2 × C1′), 128.7 (d, 10 × Ar′–C), 126.6 (d, C1), 54.3 (d, C2), 43.3 (q, 2 × N1#–CH$_3$).

The analytical data are consistent with those in the literature.[82]

(*E*)-2[#]-(5-Chloro-2,2diphenylpentylidene)-1[#],1[#]dimethylhydrazine (268)

$C_{19}H_{23}ClN_2$
M = 314.86 g/mol
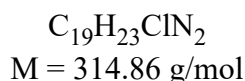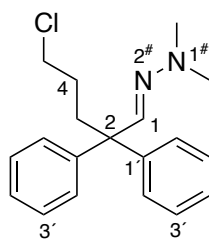
Di*iso*propylamine (2.88 mL, 2.08 g, 20.6 mmol, 1.3 eq.) was dissolved in THF (40 mL) and the solution was cooled to 0 °C. *i*-Butyllithium (2.5 M in hexane, 7.59 mL, 18.97 mmol, 1.2 eq.) was added and the solution was stirred for 5 mins. at 0 °C. Hydrazone **267** (3.77 g, 18.8 mmol, 1.0 eq.) dissolved in THF (20 mL) was added dropwise and the reaction mixture was stirred for 10 mins. at 0 °C. Subsequently, 1-Chloro-3-iodopropane (2.21 mL, 4.20 g, 20.4 mmol, 1.3 eq.) was added and the reaction mixture was stirred for 1 h at r.t. Et$_2$O (180 mL) was added and the solution was washed with aq. citric acid (10%, 60 mL), H$_2$O (30 mL), aq. Na$_2$S$_2$O$_3$-solution (20%, 30 mL) and brine (30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica, 15 × 5 cm, hexane/EtOAc, 40:1 → 10:1) to give compound **268** (3.69 g, 11.7 mmol, 74%) as a yellow solid.

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.33 – 7.27 (m, 4H, 2 × C2′–H, 2 × C6′–H), 7.25 – 7.18 (m, 6H, 2 × C3′–H, 2 × C4′–H, 2 × C5′–H), 6.97 (s, 1H, C1–H), 3.48 (t, ^3J = 6.7 Hz, 2H, C5–H$_2$), 2.78 (s, 6H, 2 × N1[#]–CH$_3$), 2.49 (t, ^3J = 7.0 Hz, 2H, C3–H$_2$), 1.67 – 1.51 (m, 2H, C4-H$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 128.5 (d, 10 × Ar′–C), 128.3 (s, 2 × C1′), 126.4 (d, C1), 54.1 (t, C5), 46.1 (s, C2), 43.4 (q, 2 × N1[#]–CH$_3$), 34.6 (t, C3), 28.8 (t, C4).

The analytical data are consistent with those in the literature.[82]

5-Chloro-2,2-diphenylpentanal (269)



$$C_{17}H_{17}ClO$$
$$M = 272.77 \text{ g/mol}$$
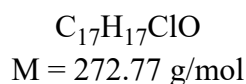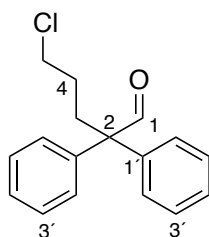
Compound **268** (2.52 g, 8.01 mmol, 1.0 eq.) was suspended in conc. HCl (41 mL) and the reaction mixture was heated to reflux for 20 mins. The reaction mixture was then allowed to cool to r.t. and extracted with Et$_2$O (200 mL). The combined organic phases were washed with H$_2$O (50 mL), and brine (30 mL) and were dried over Na$_2$SO$_4$. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (silica, 15 × 5 cm, hexane/EtOAc, 40:1 → 10:1) to give compound **269** (1.66 g, 6.10 mmol, 76%) as a colorless oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 9.81 (s, 1H, C1–H), 7.38 (*virt.* t, $^3J = {}^3J \approx 7.3$ Hz, 4H, 2 × C3′–H, 2 × C5′–H), 7.32 (*virt.*t, $^3J = {}^3J \approx 7.3$ Hz, 2H, 2 × C4′–H), 7.22 – 7.16 (m, 4H, 2 × C2′–H, 2 × C6′–H), 3.49 (t, $^3J = 6.5$ Hz, 2H, C5–H$_2$), 2.49 – 2.31 (m, 2H, C3–H$_2$), 1.60 – 1.48 (m, 2H, C4–H$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 198.3 (C1), 139.8 (s, 2 × C1′), 129.1 (d, 2 × C3′, 2 × C5′), 129.0 (d, 2 × C2′, 2 × C6′), 127.7 (d, 2 × C4′), 63.5(s, C2), 45.5 (t, C5), 31.5 (t, C3), 28.2 (t, C4).

The analytical data are consistent with those in the literature.[82]

5-Azido-2,2-diphenylpentanal (270)

$$C_{17}H_{17}N_3O$$
$$M = 279.34 \text{ g/mol}$$
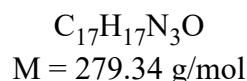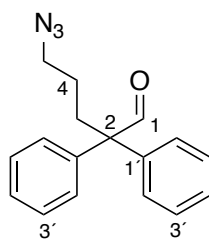
Compound **269** (1.66 g, 6.10 mmol, 1.0 eq.) and NaN$_3$ (1.59 g, 24.4 mmol, 4.0 eq) were dissolved in DMF (7.3 mL) and heated to 85 °C for 3 h. Et$_2$O (230 mL) was then added and the mixture was washed with H$_2$O (2 × 50 mL) and brine (50 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo*. Compound **270** (1.57 g, 5.62 mmol, 94%) was obtained as a colorless oil.

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 9.81 (s, 1H, C1–H), 7.38 (*virt.* t, $^3J = {}^3J \approx 7.3$ Hz, 4H, 2 × C3′–H, 2 × C5′–H), 7.32 (*virt.*t, $^3J = {}^3J \approx 7.3$ Hz, 2H, 2 × C4′–H), 7.21 – 7.15 (m, 4H, 2 × C2′–H, 2 × C6′–H), 3.24 (t, $^3J = 6.8$ Hz, 2H, C5–H$_2$), 2.40 – 2.29 (m, 2H, C3–H$_2$), 1.40 – 1.29 (m, 2H, C4–H$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 198.2 (C1), 139.8 (s, 2 × C1′), 129.1 (d, 2 × C3′, 2 × C5′), 129.0 (d, 2 × C2′, 2 × C6′), 127.7 (d, 2 × C4′), 63.6 (s, C2), 51.9 (t, C5), 31.2 (t, C3), 24.7 (t, C4).

The analytical data are consistent with those in the literature.[82]

3,3-Diphenylpiperidin-2-one (134)

$C_{17}H_{17}NO$
M = 251.33 g/mol
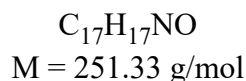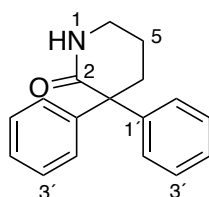
Compound **270** (1.47 g, 5.26 mmol, 1.0 eq.) was dissolved in DCM (14.6 mL) and the solution was cooled to –78 °C. TMSOTf (1.90 mL, 2.34 g, 10.5 mmol, 2.0 eq.) was then added and the reaxtion mixture was allowed to warm to r.t. over the period of 3.5 h. EtOAc (500 mL) was added and the solution was washed with aq. NaHCO$_3$-solution (300 mL) and brine (300 mL). The combined organic layers were dried over Na$_2$SO$_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (silica, 15 × 3 cm, hexane/EtOAc, 2:1 → 1:2) to give compound **134** (426 mg, 1.79 mmol, 34%) as colorless crystals.

TLC: R_f (hexane/EtOAc, 1:1) = 0.35 [UV, KMnO$_4$].

^{1}H-NMR (400 MHz, CDCl$_3$): δ [ppm] = 7.35 – 7.21 (m, 10H, 10 × Ar′–H), 6.24 (s, 1H, NH), 3.39 (*virt.* td, $^3J = {}^3J \approx 6.4$ Hz, $^3J = 2.2$ Hz, 2H, C6–H$_2$), 2.63 – 2.54 (m, 2H, C4-H$_2$), 1.80 (*virt.* p, $^3J = {}^3J \approx 6.3$ Hz, 2H, C5-H$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 174.2 (s, C=O), 144.0 (s, 2 × C1′), 128.7 (d, 4 × Ar′–C), 128.2 (d, 4 × Ar′–C), 126.8 (d, 2 × Ar–C′), 57.0 (s, C3), 42.8 (t, C6), 34.9 (t, C4), 19.1 (t, C5).

The analytical data are consistent with those in the literature.[82]

5. Catalytic borylations

(6-(4´,4´,5´,5´-Tetramethyl-1´,3´,2´-dioxaborolan-2´-yl)-3,3-di-*p*-tolylindolin-2-one (147c)

C$_{28}$H$_{30}$BNO$_3$
M = 439.36 g/mol
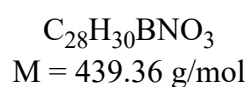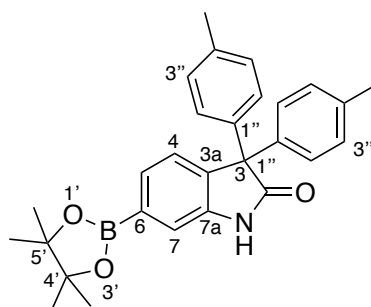
Compound **147c** was synthesized according to general procedure **GP3** using starting material **135c** (9.40 mg, 30.0 µmol, 1.0 eq.). Purification by column chromatography (silica, dry load, 10 × 1 cm, DCM/EtOAc, 40:1 → 10:1) provided compound **147c** (2.64 mg, 6.00 µmol, 20%) as a colorless solid.

TLC: R_f (DCM/EtOAc, 10:1) = 0.33 [UV, KMnO$_4$].

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3220 (w, NH), 2943 (w, sp^3-CH), 1710 (m, C=O), 1713 (s, C=O), 1513 (s, C=C), 1471 (s, C=C), 1440 (m), 1263 (m), 1172 (m), 698 (s, sp^2-CH).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.27 (s, 1H, NH), 7.71 (dd, ^3J = 7.8, 1.2 Hz, 1H, C4–H), 7.62 (s, 1H, C7–H), 7.17 (d, ^3J = 8.3 Hz, 4H, 2 × C2´´–H, 2 × 6´´–H), 7.10 (d, ^3J = 8.4 Hz, 4H, 2 × 3´´-H, 2 × 5´´–H), 6.94 (d, ^3J = 7.8 Hz, 1H, C5–H), 2.31 (s, 6H, 2 × C4´´–C*H*$_3$), 1.31 (s, 12H, C4´(CH$_3$)$_2$, C5´(CH$_3$)$_2$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 180.2 (s, C=O), 143.0 (s, C7a), 138.8 (s, 2 × C1´´), 137.1 (s, 2 × C4´´), 135.7 (s, C6), 135.4 (d, C4), 132.4 (C7), 129.3 (d, 2 × C3´´, 2 × C5´´), 128.6 (d, 2 × C2´´, 2 × C6´´), 123.2 (s, C3a), 109.6 (d, C5), 83.9 (C4´, C5´), 62.32 (s, C3), 25.03 (C4´(CH$_3$)$_2$, C5´(CH$_3$)$_2$), 21.2 (2 × C4´´–CH$_3$).

HRMS (ESI): C$_{28}$H$_{30}$BNO$_3$ [(M+H)$^+$] = calcd.: 440.2397, found: 440.2392.

5-(3′-Chloro-5′-hydroxyphenyl)-5-(3′′-chlorophenyl)-3-methylimidazolidine-2,4-dione (169)

$$C_{16}H_{12}Cl_2N_2O_3$$
$$M = 351.18 \text{ g/mol}$$
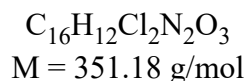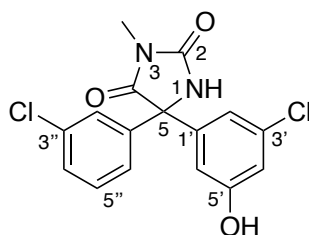
Starting material **162** (10.1 mg, 30.0 μmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound **169** (7.16 mg, 20.4 μmol, 68%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.57 [UV, KMnO$_4$].

Mp: 192 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3299 (m, NH), 2956 (w, sp^3-CH$_3$), 2926 (w, sp^3-CH$_3$), 2855 (w, sp^3-CH$_3$), 1773 (m, C=O), 1705 (s, C=O), 1593 (m, C=C), 1462 (m, C=C), 1396 (w, C=C), 1170 (w).

¹H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.37 – 7.33 (m, 2H, C2′′–H, C4′′–H), 7.30 (dd, ^3J = 8.5 Hz, 7.5 Hz, 1H, C5′′–H), 7.22 (*virt.* dt, ^3J = 7.6, Hz, $^4J = {}^4J \approx$ 1.7 Hz, 1H, C6′′–H), 6.90 (*virt.* t, $^4J = {}^4J \approx$ 1.7 Hz, 1H, C4′–H), 6.86 (*virt.* t, $^4J = {}^4J \approx$ 2.0 Hz, 1H, C2′–H), 6.76 (dd, ^4J = 2.3 Hz, 1.6 Hz, 1H, C6′–H), 6.69 (s, 1H, NH), 6.11 (br s, 1H, OH), 3.08 (s, 3H, N3–CH$_3$).

¹³C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 172.5 (s, C4=O), 157.1 (s, C5′), 156.5 (s, C2=O), 141.3 (s, C1′), 140.3 (s, C3′′), 135.9 (s, C3′), 135.2 (s, C1′′), 130.4 (d, C5′′), 129.4 (d, C4′′/C2′′), 127.0 (d, C4′′/C2′′), 125.2 (d, C6′′), 119.2 (d, C4′), 116.8 (d, C2′), 112.8 (d, C6′), 69.5 (s, C5), 25.4 (q, N3–CH$_3$).

HRMS (ESI): C$_{16}$H$_{12}$Cl$_2$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 351.0303, found: 351.0305.

5-(3′-Fluoro-5′-hydroxyphenyl)-5-(3′′-fluorophenyl)-3-methylimidazolidine-2,4-dione (*meta*-168)

5-(3′-Fluoro-4′-hydroxyphenyl)-5-(3′′-fluorophenyl)-3-methylimidazolidine-2,4-dione (*para*-168)

$$C_{16}H_{12}F_2N_2O_3$$
$$M = 318.28 \text{ g/mol}$$
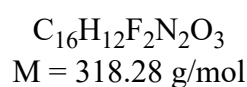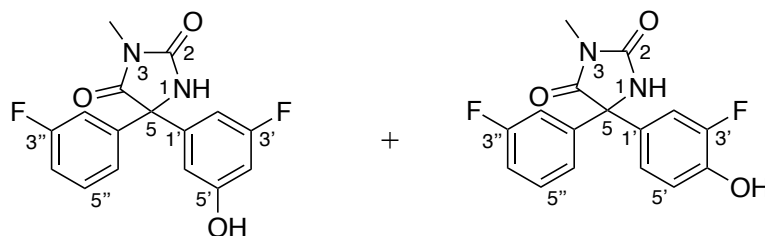
Starting material **161** (9.07 mg, 30.0 μmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Alcohol **168a** (4.25 mg, 13.2 μmol, 44%) was obtained as a colorless solid. Compound **168b** (3.39 mg, 10.6 μmol, 36%) was obtained as an inseparable mixture of the two regioisomers.[10] Analysis was conducted on the products obtained from small, pure fractions eluted prior to the elution of the inseparable mixed fractions.

TLC: **meta-168**: R_f (pentane/acetone, 2:1) = 0.38 [UV, KMnO$_4$].

ortho-168: R_f (pentane/acetone, 2:1) = 0.35 [UV, KMnO$_4$].

Alcohol **meta-168**:

Mp: 208 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3252 (w, NH), 2948 (w, sp^3-CH$_3$), 2853 (w, sp^3-CH$_3$), 1779 (w, C=O), 1715 (s, C=O), 1586 (m, C=C), 1451 (m, C=C), 1392 (w, C=C), 1187(m).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 9.00 (s, 1H, NH), 8.42 (s, 1H, OH), 7.47 (*virt*. td, $^3J = {}^3J \approx 8.1$ Hz, $^4J_{H,F} = 6.0$ Hz, 1H, 5′′–H), 7.31 (ddd, $^3J = 7.9$, $^4J = 1.8$ Hz, 1.0 Hz, 1H, C6′′–H), 7.23 (*virt*. dt, $^3J_{H,F} = 10.4$ Hz, $^4J = {}^4J \approx 2.3$ Hz, 1H, C2′′–H), 7.16 (*virt*. tdd, $^3J_{H,F} = {}^3J \approx 8.4$ Hz, $^4J = 2.6$ Hz, 1.0 Hz, 1H, C4′′–H), 6.78 (*virt*. t, $^4J = {}^4J \approx 2.2$ Hz, 1H, C6′–H), 6.68 (ddd, $^3J_{H,F} = 10.0$ Hz, $^4J = 2.4$ Hz, 1.6 Hz, 1H, C4′–H), 6.59 (*virt*. dt, $^3J_{H,F} = 10.4$ Hz, $^4J = {}^4J \approx 2.2$ Hz, 1H, C2′–H), 3.01 (s, 3H, N3–CH$_3$).

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[10] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction in addition to the isolated yield of the clean fractions.

13C-NMR (101 MHz, acetone-d_6): δ [ppm] = 173.2 (s, C4=O), 164.3 (d, $^1J_{C,F}$ = 242.9 Hz, C3′), 163.5 (d, $^1J_{C,F}$ = 244.9 Hz, C3′′), 160.1 (sd, $^3J_{C,F}$ = 12.1 Hz, C5′), 156.3 (s, C2=O), 143.6 (sd, $^3J_{C,F}$ = 9.5 Hz, C1′), 143.0 (sd, $^3J_{C,F}$ = 7.0 Hz, C1′′), 131.4 (dd, $^3J_{C,F}$ =8.5 Hz, C5′′), 123.7 (dd, $^4J_{C,F}$ = 4.8 Hz, C6′′), 116.0 (dd, $^2J_{C,F}$ = 18.7 Hz, C4′′), 114.8 (dd, $^2J_{C,F}$ = 21.9 Hz, C2′′), 111.2 (d, C6′), 105.6 (d, $^2J_{C,F}$ = 24.1 Hz, C4′), 103.43 (d, $^2J_{C,F}$ = 24.1 Hz, C2′), 69.7 (s, C5), 25.1 (q, N3–CH_3).

19F-NMR (476 MHz, acetone-d_6): δ [ppm] = –112.71 (dd, $^3J_{F,H}$ = 10.1 Hz, 8.8 Hz), –113.59 - – 113.69 (m).

HRMS (ESI): $C_{16}H_{12}F_2N_2O_3$ [(M+H)$^+$] = calcd.: 319.0894, found: 319.0893.

5-(2′-Fluoro-5′-hydroxyphenyl)-5-(2′′-fluorophenyl)-3-methylimidazolidine-2,4-dione (*meta*-166)

5-(2′-Fluoro-4′-hydroxyphenyl)-5-(2′′-fluorophenyl)-3-methylimidazolidine-2,4-dione (*para*-166)

**5-(2′-Fluoro-3′-hydroxyphenyl)-5-(2′′-fluorophenyl)-3-methylimidazolidine-2,4-dione (*ortho*-166)**

$C_{16}H_{12}F_2N_2O_3$
M = 318.28 g/mol
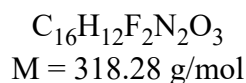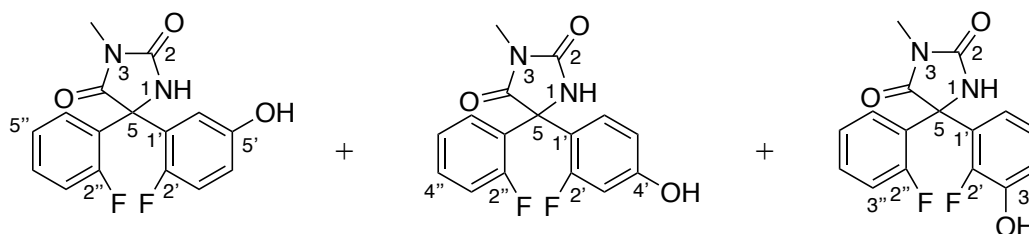
Starting material **160** (9.07 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. The products ***meta*-166, *para*-166** and ***ortho*-166** (7.35 mg, 23.1 µmol, 77%) were obtained as an inseparable mixture of the three regioisomers.

TLC: R_f (pentane/acetone, 2:1) = 0.42 [UV, KMnO$_4$].

1H-NMR, 13C-NMR: Due to the overlap of the signals of all three regioisomers and additional C,F-/H,F-coupling, unequivocal assignment of the signals is impossible.

HRMS (ESI): $C_{16}H_{12}F_2N_2O_3$ [(M+H)$^+$] = calcd.: 319.0894, found: 319.0894.

5-(3´-Fluoro-5´-hydroxyphenyl)-5-(3´´-fluorophenyl)-3-(4-methoxyphenyl)imidazolidine-2,4-dione (265b)

$$C_{22}H_{16}F_2N_2O_4$$
$$M = 410.38 \text{ g/mol}$$
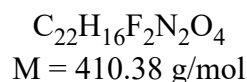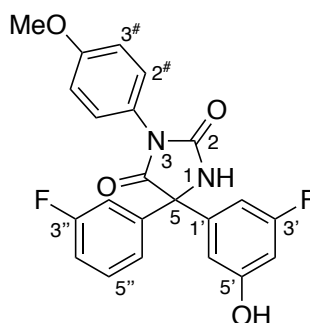
Starting material **265** (10.9 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Alcohol **265b** (3.20 mg, 7.8 µmol, 26%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.65 [UV, KMnO$_4$].

Alcohol **265b**:

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3173 (w, NH), 3106 (w, sp^3-CH$_2$), 1769 (m, C=O), 1711 (s, C=O), 1515 (s, C=C), 1409 (s, C=C), 1251 (m), 1170 (m), 691 (s, sp^2-CH).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 9.00 (s, 1H, NH), 8.42 (s, 1H, OH), 7.42 – 7.31 (m, 1H, 5´´–H), 7.30 – 7.22 (m, 1H, C6´´–H), 7.29 (d, ^3J = 9.2 Hz, 2H, C2$^\#$–H, C6$^\#$–H), 7.16 (*virt.* dt, $^3J_{H,F}$ = 8.0 Hz, $^4J = {}^4J \approx 2.1$ Hz, 1H, C2´´–H), 7.10 – 6.97 (m, 2H, C4´´–H, C6´–H), 6.89 (d, ^3J = 9.2 Hz, 2H, C3$^\#$–H, C5$^\#$–H), 6.75 (dt, ^3J = 7.8 Hz, $^4J = {}^4J \approx 2.1$ Hz, 1H, C4´–H), 6.64 – 6.54 (m, 1H, C2´–H), 3.70 (d, ^4J = 0.9 Hz, 3H, OCH$_3$).

^{13}C-NMR (101 MHz, acetone-d$_6$): δ [ppm] = 172.4 (s, C4=O), 164.4 (d, $^1J_{C,F}$ = 248.4 Hz, C3´), 163.4 (d, $^1J_{C,F}$ = 248.6 Hz, C3´´), 160.4 (s, C2=O), 156.2 (s, C4$^\#$), 156.2 (sd, $^3J_{C,F}$ = 12.1 Hz, C5´), 145.8 (sd, $^3J_{C,F}$ = 9.5 Hz, C1´), 143.4 (sd, $^3J_{C,F}$ = 7.0 Hz, C1´´), 131.7 (dd, $^3J_{C,F}$ = 8.5 Hz, C5´´), 128.9 (d, C2$^\#$, C6$^\#$), 123.9 (dd, $^3J_{C,F}$ = 7.8 Hz, C6´´), 123.8 (s, C1$^\#$), 116.2 (dd, $^2J_{C,F}$ = 18.7 Hz, C4´´), 115.0 (dd, $^2J_{C,F}$ = 21.9 Hz, C2´´), 114.9 (d, C3$^\#$, C5$^\#$), 111.4 (d, C6´), 103.7 (d, $^2J_{C,F}$ = 23.8 Hz, C4´), 103.6 (d, $^2J_{C,F}$ = 24.2 Hz, C2´), 74.7 (s, C5), 55.8 (q, O–CH$_3$).

^{19}F-NMR (476 MHz, acetone-d$_6$): δ [ppm] = –112.71 (dd, $^3J_{F,H}$ = 10.1 Hz, 8.8 Hz), –113.59- –113.69 (m).

HRMS (ESI): $C_{16}H_{12}F_2N_2O_3$ [(M+H)$^+$] = calcd.: 411.1156, found: 411.1157.

5-(3´-Hydroxyphenyl)- 3-methyl-5-phenylimidazolidine-2,4-dione (*meta*-150)

5-(4´-Hydroxyphenyl)- 3-methyl-5-phenylimidazolidine-2,4-dione (*para*-150)

$$C_{16}H_{14}N_2O_3$$
$$M = 282.30 \text{ g/mol}$$
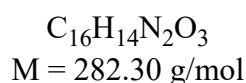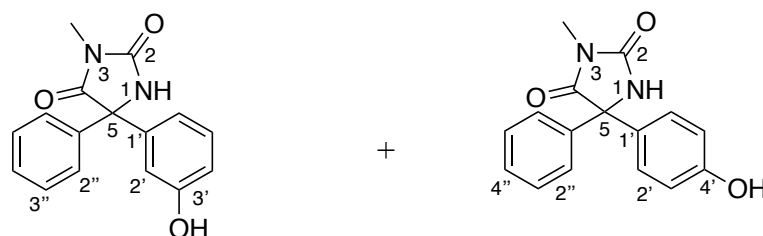
Starting material **136** (7.90 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound ***meta*-150** (2.50 mg, 8.91 µmol, 30%) was obtained as a colorless solid. ***Meta*-150** (2.90 mg, 10.3 µmol, 34%)[11] was obtained as a mixture of regioisomers. Analysis was conducted on the products obtained from small, pure fractions eluted prior to the elution of the inseparable mixed fractions.

Alcohol ***meta*-150:**

TLC: R_f (pentane/acetone, 2:1) = 0.57 [UV, KMnO$_4$].

Mp: 163 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3230 (m, NH), 2955 (w, sp^3-CH$_3$), 2923 (w, sp^3-CH$_3$), 2851 (w, sp^3-CH$_3$), 1777 (m, C=O), 1706 (s, C=O), 1590 (m, C=C), 1458 (m, C=C), 1393 (w, C=C), 1165 (w).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 8.29 (s, 1H, NH), 8.13 (s, 1H, OH), 7.47 – 7.42 (m, 2H, C3´´–H, C5´´–H), 7.41 – 7.32 (m, 3H, C2´´–H, C4´´–H, C6´´–H), 7.20 (*virt.* t, $^3J = {}^3J \approx 8$. Hz, 1H, C5´–H), 6.91 – 6.89 (m, 1H, C4´–H), 6.89 (t, $^4J = 1.7$ Hz, 1H, C2´–H), 6.81 (ddd, $^3J = 8.0$ Hz, $^4J = 2.4$ Hz, 1.0 Hz, 1H, C6´–H), 3.00 (s, 3H, N3–CH$_3$).

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[11] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 174.0 (s, C4=O), 158.2 (s, C3′), 156.4 (s, C2=O), 142.5 (s, C1′), 140.9 (s, C1′′), 130.4 (s, C5′), 129.2 (s, C3′′, C5′′), 128.9 (d, C2′′, C6′′), 127.8 (d, C4′′), 118.8 (d, C6′), 115.8 (d, C2′), 115.0 (d, C4′), 70.5 (s, C5), 29.2 (q, N3–CH_3).

HRMS (ESI): $C_{16}H_{14}N_2O_3$ [(M+H)$^+$] = calcd.: 283.3068, found: 283.3070.

2-Hydroxy-1´-methylspiro[fluorene-9,4´-imidazolidine]-2´,5´-dione (*meta*-167)

3-Hydroxy-1´-methylspiro[fluorene-9,4´-imidazolidine]-2´,5´-dione (*para*-167)

$$C_{16}H_{12}N_2O_3$$
$$M = 280.28 \text{ g/mol}$$
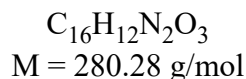
Starting material **165** (7.90 mg, 30.0 μmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound ***meta*-167** (4.09 mg, 14.4 μmol, 48%) was obtained as a colorless solid. Alcohol ***para*-167** (2.96 mg, 10.5 μmol, 35%) was obtained as an inseparable mixture of the two regioisomers. Analysis was conducted on the products obtained from small, pure fractions eluted prior to the elution of the inseparable mixed fractions.

TLC: ***meta*-167**: R_f (pentane/acetone, 2:1) = 0.36 [UV, KMnO$_4$].

   ***para*-167**: R_f (pentane/acetone, 2:1) = 0.34 [UV, KMnO$_4$].

Alcohol ***meta*-167**:

Mp: 154 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3178 (m, NH), 2954 (w, sp^3-CH$_3$), 2925 (w, sp^3-CH$_3$), 2849 (w, sp^3-CH$_3$), 1776 (m, C=O), 1706 (s, C=O), 1594 (m, C=C), 1461 (m, C=C), 1185 (w, C=C), 1163 (w).

^{1}H-NMR (500 MHz, acetone-$_6$): δ [ppm] = 10.01 (br s, 1H, NH), 8.73 (br s, 1H, OH), 7.75 (d, ^3J = 7.6 Hz, 1H, C5–H), 7.71 (d, ^3J = 8.2 Hz, 1H, C4–H), 7.46 (dd, ^3J = 8.7 Hz, 7.6 Hz, 1H, C6–H), 7.42 (d, J = 7.6 Hz, 1H, C8–H), 7.31 – 7.26 (m, 1H, C7–H), 6.99 (dd, ^3J = 8.2 Hz, ^4J = 2.2 Hz, 1H, C3–H), 6.93 (d, ^4J = 2.2 Hz, 1H, C1–H), 2.47 (s, 3H, N1´–CH$_3$).

^{13}C-NMR (101 MHz, acetone-$_6$): δ [ppm] = 164.9 (s, C4´=O), 158.8 (s, C2), 156.6 (s, C2´=O), 143.5 (s, C4b), 143.1 (s, C9a), 140.8 (s, C8a), 134.2 (s, C4a),130.9 (d, C6), 127.6 (d, C7), 127.5 (d, C8), 122.7 (d, C4), 120.7 (d, C5), 118.1 (d, C3), 111.6 (d, C1), 76.8 (s, C9), 25.4 (q, N3–*C*H$_3$).

HRMS (ESI): C$_{16}$H$_{12}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 281.0926, found: 281.0923.

3-Cyclohexyl-5-(3´-hydroxyphenyl)- 5-phenylimidazolidine-2,4-dione (*meta*-183b)

3-Cyclohexyl-5-(4´-hydroxyphenyl)- 5-phenylimidazolidine-2,4-dione (*para*-183b)

$$C_{21}H_{22}N_2O_3$$
$$M = 359.42 \text{ g/mol}$$
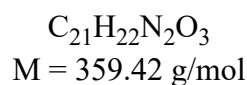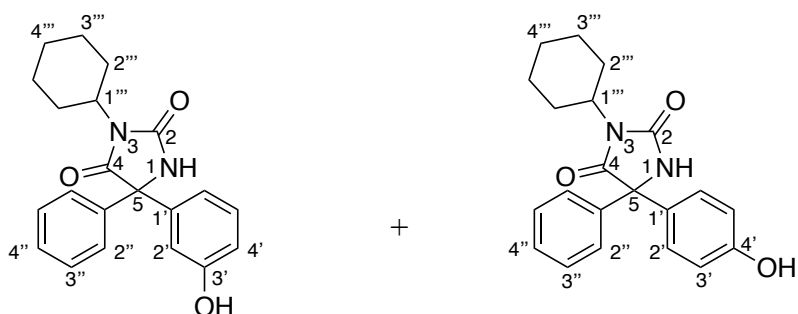
Starting material **183** (10.0 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-183b** (4.63 mg, 12.9 µmol, 43%) and ***para*-183b** (3.55 mg, 10.0 µmol, 33%)[12] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-183b:**

TLC: R_f (pentane/acetone, 2:1) = 0.59 [UV, KMnO₄].

Mp: 193 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3291 (m, NH), 2926 (w, sp^3-CH₃), 2856 (w, sp^3-CH₃), 1756 (m, C=O), 1695 (s, C=O), 1589 (w, C=C), 1449 (m, C=C), 1419 (m, C=C), 736 (m).

^{1}H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.37 – 7.29 (m, 5H, C2´´–H, C3´´–H, C4´´–H, C5´´–H, C6´´–H), 7.23 (*virt*. t, $^3J = {}^3J \approx 7.8$ Hz, 1H, C5´–H), 6.89 (d, $^3J = 8.4$ Hz, 1H, C4´–H), 6.85 – 6.80 (m, 2H, C2´–H, C6´–H), 6.10 (s, 1H, NH), 5.47 (br s, 1H, OH), 3.95 (tt, $^3J = 12.4$ Hz, $^3J = 3.9$ Hz, 1H, C1´´´–H), 2.17 – 2.10 (m, 2H, C2´´´–H$_a$, C6´´´–H$_a$), 1.85 – 1.78 (m, 2H, C3´´´–H$_a$, C5´´´–H$_a$), 1.72 – 1.67 (m, 2H, C4´´´–H₂), 1.67 – 1.60 (m, 2H, C2´´´–H$_b$, C6´´´–H$_b$), 1.33 – 1.27 (m, 2H, C3´´´–H$_b$, C5´´´–H$_b$).

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[12] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.3 (s, C4=O), 157.0 (s, C2=O), 156.0 (s, C3′), 141.0 (s, C1′), 139.4 (s, C1′′), 130.9 (d, C5′), 129.6 (d, C–Ar′′), 129.4 (d, C–Ar′′), 128.4 (d, C–Ar′′), 127.7 (d, C–Ar′′), 127.5 (d, C–Ar′′), 126.3 (C4′′), 119.8 (C4′), 116.4 (d, C2′/C6′), 114.9 (d, C2′/C6′), 76.5 (s, C5), 52.8 (d, C1′′′), 29.9 (t, C2′′′/C6′′′), 25.7 (t, C3′′′, C5′′′), 25.2 (t, C4′′′).

HRMS (ESI): C$_{21}$H$_{22}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 351.1708, found: 351.1710.

Alcohol *para*-**183b**:

TLC: R_f (pentane/acetone, 2:1) = 0.50 [UV, KMnO$_4$].

Mp: 198 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3292 (m, NH), 2926 (w, sp^3-CH$_3$), 2856 (w, sp^3-CH$_3$), 1757 (m, C=O), 1695 (s, C=O), 1590 (w, C=C), 1448 (m, C=C), 1419 (m, C=C), 736 (m).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 8.39 (s, 1H, NH), 8.02 (s, 1H, OH), 7.32 – 7.18 (m, 5H, 2′′–H, 3′′–H, 4′′H, 5′′–H, 6′′–H), 7.10-1.06 (m, 2H, C2′–H, C6′–H), 6.72 – 6.68 (m, 2H, C3′–H, C5′–H), 3.77 (tt, ^3J = 12.2 Hz, ^3J = 3.9 Hz, 1H, C1′′′–H), 2.06 – 2.03 (m, 2H, C2′′′–H$_a$, C6′′′–H$_a$), 1.73 – 1.65 (m, 2H, 3′′′–H$_a$, C5′′′–H$_a$), 1.57 – 1.49 (m, 2H, C2′′′–H$_b$, C6′′′–H$_b$), 1.49 – 1.40 (m, 1H, C4′′′–H$_a$), 1.26 – 1.11 (m, 2H, C3′′′–H$_b$, C5′′′–H$_b$), 1.13 – 0.99 (m, 1H, C4′′′H$_b$).

^{13}C-NMR (101 MHz, acetone-d$_6$): δ [ppm] = 173.8 (s, C4=O), 156.8 (s, C2=O), 156.2 (s, C4′), 139.1 (s, C1′′), 131.3 (C1′), 129.9 (d, C-Ar′′), 129.8 (d, C2′, C6′), 129.7 (d, C-Ar′′) 129.0 (d, C-Ar′′), 128.6 (d, C-Ar′′), 128.8 (d, C-Ar′′), 128.5 (d, C2′′/C6′′), 116.6 (d, C3′, C5′), 76.0 (s, C5), 48.9 (d, C1′′′), 29.9 (t, C2′′′, C6′′′), 26.5 (t, C3′′′, C5′′′), 26.6 (t, C4′′′).

HRMS (ESI): C$_{21}$H$_{22}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 351.1708, found: 351.1709.

3-(Cyclohexylmethyl)-5-(3′-hydroxyphenyl)-5-phenylimidazolidine-2,4-dione
(***meta*-184b**)

3-(Cyclohexylmethyl)-5-(4′-hydroxyphenyl)-5-phenylimidazolidine-2,4-dione
(***para*-184b**)

$$C_{22}H_{24}N_2O_3$$
$$M = 364.45 \text{ g/mol}$$
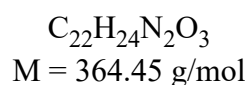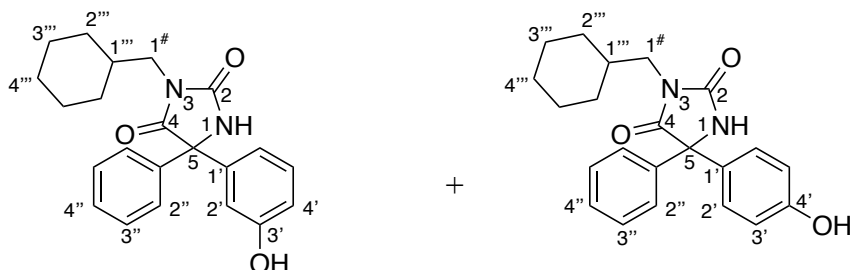
Starting material **184** (10.5 mg, 30.0 µmol, 1.0 eq.) was borylated according to general proce-
dure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**.
Hexane/EtOAc, 5:1 → 4:1 was used for purification by column chromatography. Compounds
***meta*-184b** (4.8 mg, 13.2 µmol, 44%) and ***para*-184b** (2.83 mg, 7.76 µmol, 31%)[13] were ob-
tained as colorless solids. Analysis was conducted on the products obtained from small, pure
fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-184b:**

TLC: R_f (Hex:EtOAc, 2:1) = 0.72 [UV, KMnO$_4$].

Mp: 175 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3318 (m, NH), 2926 (m, sp^3-CH), 2853 (m, sp^3-CH), 1764 (m,
C=O), 1697 (s, C=O), 1603 (m, C=O), 1448 (s, C=C), 1421 (m, C=C), 1264 (m), 1132 (w),
1034 (w), 734 (s, sp^2-CH).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.40 – 7.31 (m, 5H, C2″–H, C3″–H, C4″–H,
C5″–H, C6″–H), 7.24 (*virt*. t, $^3J = {}^3J \approx 7.9$ Hz, 1H, C5′–H), 6.92 (d, $^3J = 7.9$ Hz, 1H, C4′–H),
6.85 – 6.80 (m, 2H, C2′–H, C6′–H), 5.93 (s, 1H, NH), 5.05 (br s, 1H, OH), 3.35
(d, $^3J = 7.4$ Hz, 2H, C1$^\#$–H$_2$), 1.74 (dtd, $^3J = 11.2$ Hz, 7.5 Hz, 3.6 Hz, 1H, C1‴–H),
1.69 – 1.50 (m, 6H, C2‴–H$_a$, C6‴–H$_a$, 3‴–H$_a$, C5‴–H$_a$, C4‴–H$_2$), 1.19 – 1.05 (m, 2H,
3‴–H$_b$, C5‴–H$_b$), 0.99 – 0.81 (m, 2H, C2‴–H$_b$, C6‴–H$_b$).

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[13] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed
fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

13C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.8 (s, C4=O), 157.2 (s, C2=O), 156.5 (s, C3′), 140.7 (s, C1′), 139.2 (s, C1′′), 129.4 (d, C5′), 128.1 (d, C–Ar′′), 128.0 (d, C–Ar′′), 127.7 (d, C–Ar′′), 127.5 (d, C–Ar′′), 126.1 (d, C–Ar′′), 118.1 (d, C2′/C6′), 115.1 (d, C4′), 113.4 (d, C2′/C6′), 76.3 (s, C5), 45.3 (t, C1$^{\#}$), 35.8 (d, C1′′′), 30.7 (t, C2′′′, C6′′′), 29.4 (t, C4′′′), 25.6 (t, C3′′′, C5′′′).

HRMS (ESI): C$_{22}$H$_{24}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 365.1865, found: 365.1866.

Alcohol *para*-**184b** :

TLC: R_f (Hex:EtOAc, 2:1) = 0.67 [UV, KMnO$_4$].

Mp: 186 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3288 (m, NH), 2925 (m, sp^3-CH), 2853 (m, sp^3-CH), 1768 (m, C=O), 1698 (s, C=O), 1514 (m, C=C), 1447 (s, C=C), 1155 (w), 1035 (w), 698 (s, sp^2-CH).

1H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 8.39 (s, 1H, NH), 8.02 (s, 1H, OH), 7.32 – 7.18 (m, 5H, 2′′–H, 3′′–H, 4′′H, 5′′–H, 6′′–H), 7.10 – 7.07 (m, 2H, C2′–H, C6′–H), 6.73 – 7.68 (m, 2H, C3′–H, C5′–H), 3.77 (tt, ^3J = 12.2 Hz, 3.9 Hz, 1H, C1′′′–H), 3.34 (d, ^3J = 7.4 Hz, 2H, C1$^{\#}$–H$_2$), 2.06 – 2.03 (m, 2H, C2′′′–H$_a$, C6′′′–H$_a$), 1.73 – 1.65 (m, 2H, 3′′′–H$_a$, C5′′′–H$_a$), 1.57 – 1.49 (m, 2H, C2′′′–H$_b$, C6′′′–H$_b$), 1.49 – 1.40 (m, 1H, C4′′′–H$_a$), 1.26 – 1.11 (m, 2H, C3′′′–H$_b$, C5′′′–H$_b$), 1.13 – 0.99 (m, 1H, C4′′′H$_b$).

13C-NMR (101 MHz, acetone-d$_6$): δ [ppm] = 174.6 (s, C4=O), 158.2 (s, C2=O), 156.7 (s, C4′), 141.5 (s, C1′′), 141.3 (C1′), 128.9 (d, C-Ar′′), 128.8 (d, C2′), 128.7 (d, C-Ar′′) 128.0 (d, C-Ar′′), 127.7 (d, C-Ar′′), 127.0 (d, C-Ar′′), 128.5 (d, C6′), 115.4 (d, C3′, C5′), 70.1 (s, C5), 44.3 (t, C1$^{\#}$), 36.8 (d, C1′′′), 30.7 (t, C2′′′, C6′′′), 26.2 (t, C4′′′), 25.6 (t, C3′′′, C5′′′).

HRMS (ESI): C$_{22}$H$_{24}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 365.1865, found: 365.1865.

5-(3′-Hydroxyphenyl)-3-isopropyl-5-phenylimidazolidine-2,4-dione (*meta*-185b)

5-(4′-Hydroxyphenyl)-3-isopropyl-5-phenylimidazolidine-2,4-dione (*para*-185b)

$C_{18}H_{18}N_2O_3$

M = 310.35 g/mol
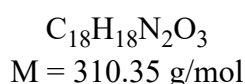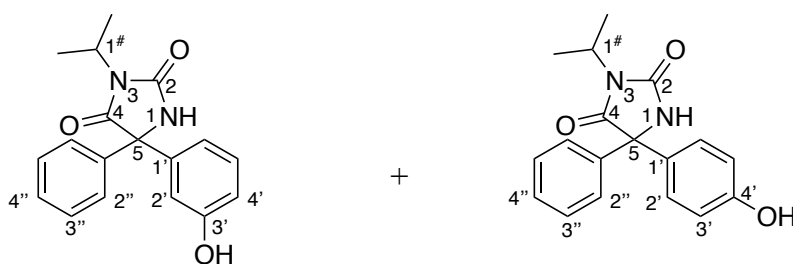
Starting material **185** (10.0 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-185b** (2.30 mg, 7.41 µmol, 25%) and ***para*-185b** (4.50 mg, 14.5 µmol, 32%)[14] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-185b:**

TLC: R_f (pentace/acetone, 2:1) = 0.53 [UV, KMnO4].

Mp: 189 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3299 (m, NH), 2977 (w, sp^3-CH), 2855 (w, sp^3-CH), 1767 (m, C=O), 1693 (s, C=O), 1600 (m, C=C), 1448 (m, C=C), 1228 (m), 1034 (w), 693 (s, sp^2-CH).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.35 – 7.28 (m, 5H, C2′′–H, C3′′–H, C4′′–H, C5′′–H, C6′′–H), 7.18 (*virt.* t, $^3J = {}^3J \approx 8.2$ Hz, 1H, C5′–H), 6.92 (s, 1H, NH), 6.82 (s, 1H, OH), 6.89 – 6.83 (m, 2H, C2′–H, C6′–H), 6.83 – 6.78 (m, 1H, C4′–H), 4.32 (hept, $^3J = 6.9$ Hz, 1H, C1$^\#$–H), 1.38 (d, $^3J = 7.0$ Hz, 6H, 2 × C1$^\#$–CH_3).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.5 (s, C4=O), 156.9 (s, C2=O), 156.4 (s, C3′), 140.8 (s, C1′), 139.2 (s, C1′′), 129.4 (d, C5′–H), 128.1 (d, C–Ar′′), 128.0 (d, C–Ar′′), 127.8 (d, C–Ar′′), 127.5 (d, C–Ar′′), 126.2 (d, C–Ar′′), 118.2 (d, C2′/C6′), 115.0 (C4′–H), 113.4 (d, C2′/C6′), 69.3 (s, C5), 43.7 (d, C1$^\#$), 19.7 (q, 2 × C1$^\#$-CH_3).

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[14] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

HRMS (ESI): $C_{18}H_{18}N_2O_3$ [(M+H)$^+$] = calcd.: 310.1395, found: 310.1394.

Alcohol *para*-**185b**

**TLC:** R_f (pentace/acetone, 2:1) = 0.48 [UV, KMnO$_4$].

Mp: 208 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3303 (m, NH), 2980 (w, sp^3-CH), 2924 (w, sp^3-CH), 2854 (w, sp^3-CH), 1764 (m, C=O), 1701 (s, C=O), 1613 (m, C=C), 1448 (m, C=C), 1422 (m, C=C), 697 (s, sp^2-CH).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.39 – 7.30 (m, 5H, C2′′–H, C3′′–H, C4′′H, C5′′–H, C6′′–H), 7.12 – 7.08 (m, 2H, C2′–H, C6′–H), 6.77 (s, 1H, NH), 5.01 (s, 1H, OH), 6.75 – 6.73 (dm, 2H, C3′–H, C5′–H), 4.35 (hept, ^3J = 6.9 Hz, 1H, C1$^\#$–H), 1.41 (d, ^3J = 7.0 Hz, 6H, 2 × C1$^\#$–CH_3).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.9 (s, C4=O), 157.0 (s, C2=O), 156.3 (s, C4′), 139.9 (s, C1′′), 131.3 (C1′), 129.4 (d, C-Ar′′), 128.6 (d, C2′, C6′), 128.0 (d, C-Ar′′), 127.7 (d, C-Ar′′), 127.5 (d, C-Ar′′), 126.2 (d, C-Ar′′), 115.8 (d, C3′, C5′), 69.2 (s, C5), 38.3 (d, C1$^\#$), 19.8 (q, 2 × C1$^\#$-CH$_3$).

HRMS (ESI): $C_{18}H_{18}N_2O_3$ [(M+H)$^+$] = calcd.: 310.1395, found: 310.1395.

5-(3´-Hydroxyphenyl)-5-phenyl-3propylimidazolidine-2,4-dione (*meta*-186b)

5-(4´-Hydroxyphenyl)-5-phenyl-3propylimidazolidine-2,4-dione (*para*-186b)

$$C_{18}H_{18}N_2O_3$$
$$M = 310.35 \text{ g/mol}$$
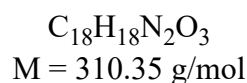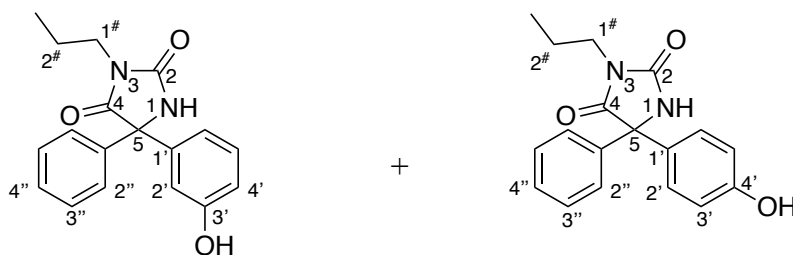
Starting material **186** (10.0 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-186b** (2.60 mg, 8.38 µmol, 27%) and ***para*-186b** (4.80 mg, 15.4 µmol, 52%)[15] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-186b :**

TLC: R_f (pentace/acetone, 2:1) = 0.43 [UV, KMnO$_4$].

Mp: 198 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3307 (w, NH), 2963 (w, sp^3-CH), 2928 (m, sp^3-CH), 2855 (m, sp^3-CH), 1769 (w, C=O), 1698 (s, C=O), 1603 (w, C=O), 1448 (s, C=C), 1422 (m, C=C), 1383 (m).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.39 – 7.30 (m, 5H, C2´´–H, C3´´–H, C4´´–H, C5´´–H, C6´´–H), 7.23 (*virt.* t, $^3J = {}^3J \approx$ 8.0 Hz, 1H, C5´–H), 6.91 (ddd, ^3J = 7.8 Hz, ^4J =1.8 Hz, 0.9 Hz, 1H, C6´–H), 6.86 (*virt.* t, $^4J = {}^4J \approx$ 2.1 Hz, 1H, C2´–H), 6.82 (ddd, ^3J = 8.1 Hz, ^4J =2.5 Hz, 0.9 Hz, 1H, C4´–H), 6.20 (s, 1H, NH), 5.36 (s, 1H, OH), 3.52 (t, ^3J = 7.4 Hz, 2H, C1$^\#$–H$_2$), 1.67 (h, ^3J = 7.3 Hz, 2H, C2$^\#$–H$_2$), 0.89 (t, ^3J = 7.5 Hz, 3H, C3$^\#$–H$_3$).

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[15] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 173.6 (s, C4=O), 156.8 (s, C2=O), 156.2 (s, C3′), 141.0 (s, C1′), 139.0 (s, C1′′), 130.9 (d, C5′), 129.6 (d, C–Ar′′), 129.3 (d, C–Ar′′), 128.0 (d, C–Ar′′), 127.5 (d, C–Ar′′), 126.7 (d, C–Ar′′), 119.1 (d, C6′), 115.7 (d, C4′), 113.4 (d, C2′), 69.3 (s, C5), 40.6 (t, C1#), 21.6 (t, C2#), 11.3 (q, C3#).

HRMS (ESI): C₁₈H₁₈N₂O₃ [(M+H)⁺] = calcd.: 311.1395, found: 311.1394.

Alcohol *para***-186b:**

TLC: R_f (pentace/acetone, 2:1) = 0.39 [UV, KMnO₄].

Mp: 210 °C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3288 (w, NH), 2965 (w, sp³-CH), 2936 (w, sp³-CH), 2877 (w, sp³-CH), 17697 (m, C=O), 1694 (s, C=O), 1612 (w, C=O), 1447 (s, C=C), 1420 (m, C=C), 1249 (m).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.39 – 7.30 (m, 5H, C2′′–H, C3′′–H, C4′′H, C5′′–H, C6′′–H), 7.12 – 7.08 (m, 2H, C2′–H, C6′–H), 6.77 (s, 1H, NH), 6.76 – 6.70 (m, 2H, C3′–H, C5′–H), 5.67 (s, 1H, OH), 4.35 (hept, ³*J* = 6.9 Hz, 1H, C1#–H), 1.41 (d, ³*J* = 7.0 Hz, 6H, 2 × C1#–C*H*₃).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 174.1 (s, C4=O), 157.0 (s, C2=O), 156.3 (s, C4′), 139.1 (s, C1′′), 131.1 (C1′), 129.3 (d, C-Ar′′), 129.2 (d, C-Ar′′), 128.7 (d, C2′, C6′), 127.7 (d, C-Ar′′), 127.6 (d, C-Ar′′), 126.1 (d, C-Ar′′), 115.7 (d, C3′, C5′), 69.9 (s, C5), 40.8 (d, C1#), 21.4 (d, C2#), 11.3 (q, C3#).

HRMS (ESI): C₁₈H₁₈N₂O₃ [(M+H)⁺] = calcd.: 311.1395, found: 311.1393.

5-(3′-Hydroxyphenyl)-3-(4[#]-methoxyphenyl)-5-phenylimidazolidine-2,4-dione (*meta*-196b)

5-(4′-Hydroxyphenyl)-3-(4[#]-methoxyphenyl)-5-phenylimidazolidine-2,4-dione (*para*-196b)

$$C_{22}H_{18}N_2O_4$$
$$M = 374.40 \text{ g/mol}$$
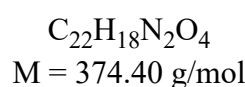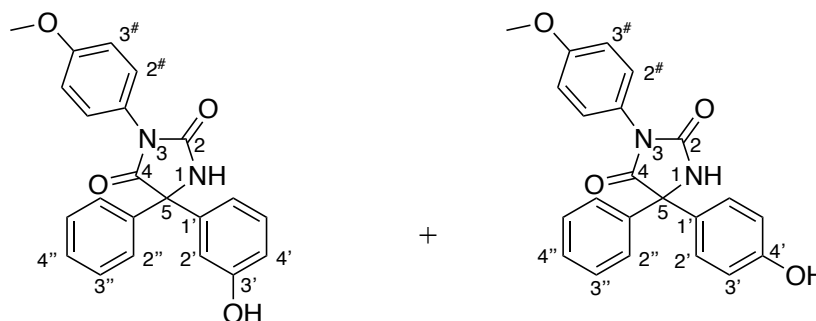
Starting material **196** (10.0 mg, 30.0 µmol, 1.0 eq.) was borylated according to general proce-dure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-196b** (4.90 mg, 13.1 µmol, 44%) and ***para*-196b** (3.60 mg, 9.62 µmol, 32%)[16] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-196b:**

TLC: R_f (pentace/acetone, 2:1) = 0.31 [UV, KMnO$_4$].

Mp: 185 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3120 (w, NH), 3066 (w, OH), 2966 (w, sp^3-CH), 2918 (m, sp^3-CH), 2762 (w, sp^3-CH), 1682 (s, C=O), 1613 (w, C=O), 1486 (m, C=C), 1370 (s, C=C), 744 (s).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.42 – 7.32 (m, 5H, C2′′–H, C3′′–H, C4′′–H, C5′′–H, C6′′–H), 7.26 (d, ^3J = 9.2 Hz, 2H, C2$^#$–H, C6$^#$–H), 7.22 (*virt.* t, ^3J = ^3J ≈ 8.0 Hz, 1H, C5′–H), 6.95 (d, ^3J = 8.7 Hz, 1H, C6′–H), 6.93 (d, ^3J = 9.0 Hz, 2H, C3$^#$–H, C5$^#$–H), 6.91 (*virt.* t, ^4J = ^4J ≈ 2.1 Hz, 1H, C2′–H), 6.85 (s, 1H, NH), 6.81 (ddd, ^3J = 8.2 Hz, ^4J = 2.5 Hz, 0.9 Hz, 1H, C4′–H), 5.43 (s, 1H, OH), 3.81 (s, 3H, C4$^#$–CH_3).

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[16] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 172.5 (s, C4=O), 159.6 (s, C4$^{\#}$), 156.3 (s, C3′), 156.1 (s, C2=O), 140.5 (s, C1′), 139.0 (s, C1′′), 130.3 (d, C5′), 129.0 (d, 2 × C–Ar′′), 128.9 (d, C–Ar′′),127.9 (d, C2$^{\#}$, C6$^{\#}$), 127.0 (d, 2 × C–Ar′′), 123.9 (s, C1$^{\#}$), 119.1 (d, C6′), 116.1 (C4′), 114.6 (d, C3$^{\#}$, C5$^{\#}$), 114.1 (d, C2′), 69.9 (s, C5), 55.7 (t, C4$^{\#}$-OCH$_3$).

HRMS (ESI): C$_{22}$H$_{18}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 375.1345, found: 375.1350.

Alcohol *para*-**196b:**

TLC: R_f (pentace/acetone, 2:1) = 0.23 [UV, KMnO$_4$].

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3426 (w, NH), 3336 (w, OH), 2930 (w, sp^3-CH), 2930 (w, sp^3-CH), 2853(m, sp^3-CH), 1775 (w, C=O), 1706 (s, C=O), 1586 (w, C=O), 1513 (s, C=C), 1206 (s, C=C), 787 (s).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 8.57 (s, 1H, NH), 8.48 (s, 1H, OH), 7.56 – 7.51 (m, 2H, C3′′–H, C5′′–H), 7.45 – 7.36 (m, 3H, C4′′–H, C2$^{\#}$–H, C6$^{\#}$–H), 7.34 (d, ^3J = 9.0 Hz, 2H, C2′–H, C6′–H), 7.32 (d, ^3J = 8.7 Hz, 2H, C2′–H, C6′–H), 7.01 (d, ^3J = 9.2 Hz, 2H, C3′–H, C5′–H), 6.88 (d, ^3J = 8.9 Hz, 2H, C3$^{\#}$–H, C5$^{\#}$–H), 3.83 (s, 3H, C4$^{\#}$–CH$_3$).

^{13}C-NMR (101 MHz, acetone-d$_6$): δ [ppm] = 173.7 (s, C4=O), 160.2 (s, C4′), 158.3 (s, C4$^{\#}$), 155.5 (s, C2=O), 141.4 (s, C1′′), 131.7 (s, C1$^{\#}$), 129.0 (d, C2$^{\#}$, C6$^{\#}$), 128.9 (d, C2′′, C6′′), 128.8 (d, C3$^{\#}$, C5$^{\#}$), 128.7 (d, C2′, C6′), 127.0 (C4′′), 126.1 (s, C1′), 115.9 (d, C3′′, C5′′), 114.6 (d, C3′, C5′), 70.1 (s, C5), 56.1 (t, C4$^{\#}$-OCH$_3$).

HRMS (ESI): C$_{22}$H$_{18}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 375.1345, found: 375.1348.

5-(3´-Hydroxyphenyl)-3-(4# -methoxybenzyl)-5-phenylimidazolidine-2,4-dione (*meta*-197b)

5-(4´-Hydroxyphenyl)-3-(4# -methoxybenzyl)-5-phenylimidazolidine-2,4-dione (*para*-197b)

$$C_{23}H_{20}N_2O_4$$
$$M = 388.42 \text{ g/mol}$$
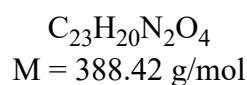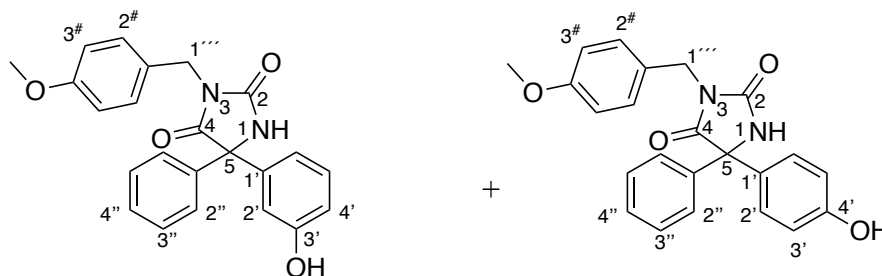
Starting material **197** (10.0 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound ***meta*-197b** (2.7 mg, 7.00 µmol, 23%) was obtained as a colorless solid, and ***para*-197b** (3.55 mg, 9.14 µmol, 30%)[17] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-197b:**

TLC: R_f (pentace/acetone, 2:1) = 0.33 [UV, KMnO₄].

Mp: 201°C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3313 (w, NH), 2960 (w, sp³-CH), 2923 (m, sp³-CH), 2851 (m, sp³-CH), 1771 (w, C=O), 1699 (s, C=O), 1606 (w, C=O), 1448 (s, C=C), 1421 (m, C=C), 1381 (m).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.36 – 7.26 (m, 7H, 5 × Ar´´–H, C2#–H, C6#–H), 7.21 (*virt.* t, ³*J* = ³*J* ≈ 8.0 Hz, 1H, C5´–H), 6.85 (d, *J* = 8.0 Hz, 1H, C6´–H), 6.83 (d, ³*J* = 8.7 Hz, 2H, C3#–H, C5#–H), 6.80 (ddd, ³*J* = 8.1 Hz, ⁴*J* = 2.5 Hz, 0.8 Hz, 1H, C4´–H), 6.75 (*virt.* t, ⁴*J* = ⁴*J* ≈ 2.1 Hz, 1H, C2´–H), 5.94 (s, 1H, NH), 5.43 (s, 1H, OH), 4.65 (s, 2H, C1´´´–H₂), 3.78 (s, 3H, C4#–C*H*₃).

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[17] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ¹H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 172.5 (s, C4=O), 159.6 (s, C4$^#$), 156.3 (s, C3′), 156.1 (s, C2=O), 140.5 (s, C1′), 139.0 (s, C1′′), 130.1 (d, C5′), 129.0 (d, 2 × C–Ar′′), 128.9 (d, C–Ar′′), 128.1 (d, C2$^#$, C6$^#$), 126.9 (d, 2 × C–Ar′′), 123.9 (s, C1$^#$), 119.2 (d, C6′), 116.6 (C4′), 114.4 (d, C3$^#$, C5$^#$), 114.2 (d, C2′), 70.3 (s, C5), 55.7 (q, C4$^#$-OCH$_3$), 42.3 (t, C1′′′).

HRMS (ESI): C$_{23}$H$_{20}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 389.1501, found: 389.1503.

Alcohol *para*-**197b**:

**TLC:** R_f (pentace/acetone, 2:1) = 0.34 [UV, KMnO$_4$].

Mp: 211 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3308 (w, NH), 2961 (w, sp^3-CH), 2925 (m, sp^3-CH), 2853 (m, sp^3-CH), 1763 (w, C=O), 1697 (s, C=O), 1601 (w, C=O), 1433 (s, C=C), 1421 (m, C=C), 1380 (m).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.36 – 7.27 (m, 7H, 5 × Ar′′–H, C2′–H, C6′–H), 7.15 – 7.10 (m, 2H, C2$^#$–H, C6$^#$–H), 6.85 – 6.80 (m, 2H, C3′–H, C5′–H), 6.77 (d, ^3J = 8.7 Hz, 2H, C3$^#$–H, C5$^#$–H), 6.76 (s, 1H, NH), 5.34 (s, 1H, OH), 4.66 (s, 2H, C1′′′–H$_2$), 3.79 (s, 3H, C4$^#$–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.5 (s, C4=O), 159.4 (s, C4′), 156.2 (s, C4$^#$), 155.9 (s, C2=O), 139.3 (s, C1′′), 131.5 (s, C1$^#$), 130.5 (d, C2$^#$, C6$^#$), 128.9 (d, C2′′, C6′′), 128.8 (d, C4′′), 128.6 (d, C3$^#$, C5$^#$), 128.2 (s, C1′), 127.0 (d, C2′, C6′), 115.7 (d, C3′′, C5′′), 114.1 (d, C3′, C5′), 69.9 (s, C5), 55.4 (t, C4$^#$-OCH$_3$), 42.3 (t, C1′′′).

HRMS (ESI): C$_{23}$H$_{20}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 389.1501, found: 389.1503.

5,5-*bis*(3-Chlorophenyl)-3-(4#-hydroxyphenyl)imidazolidine-2,4-dione (271)

5-(3′-Chloro-5′-hydroxyphenyl)-5-(3′′-chlorophenyl)-3-phenylimidazolidine-2,4-dione (198b)

$$C_{21}H_{14}Cl_2N_2O_3$$
$$M = 413.25 \text{ g/mol}$$
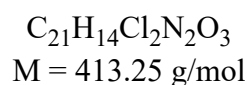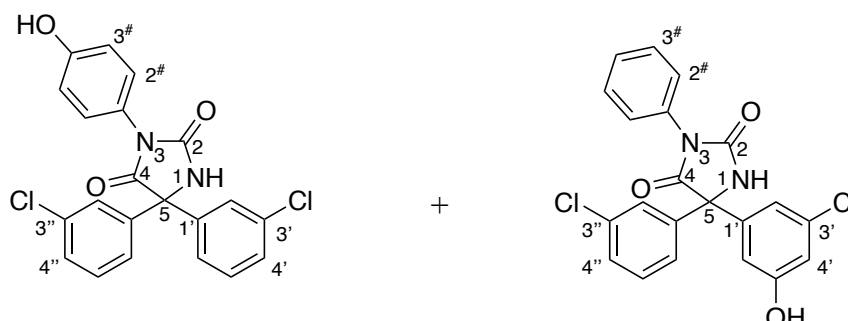
Starting material **198** (10.1 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds **271** (4.50 mg, 10.9 µmol, 36%) and **198b** (2.9 mg, 7.02 µmol, 23%) were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol **271**:

TLC: R_f (pentane/acetone, 2:1) = 0.62 [UV, KMnO$_4$].

Mp: >204°C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3356 (w, NH), 2962 (w, sp^3-CH), 2925 (w, sp^3-CH), 2855 (m, sp^3-CH), 1782 (s, C=O), 1708 (s, C=O), 1505 (m, C=C), 1185 (m), 696 (s).

¹H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.52 – 7.29 (m, 8H, 4 × Ar′-H, 4 × Ar′′–H), 7.13 (d, ^3J = 8.8 Hz, 2H, C2#–H, C6#–H), 6.81 (d, ^3J = 8.8 Hz, 2H, C3#–H, C5#–H), 6.40 (s, 1H, NH), 5.34 (br s, 1H, OH).

¹³C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 171.2 (s, C4=O), 156.4 (s, C4#), 154.9 (s, C2=O), 140.5 (s, C1′, C1′′), 135.3 (s, C3′, C3′′), 130.6 (d, C5′, C5′′), 129.4 (d, C4′, C4′′), 127.9 (s, C1#), 127.2 (d, C2#, C6#), 126.3 (d, C2′, C2′′), 125.3 (d, C6′, C6′′), 114.1 (d, C3#, C5#), 69.1 (s, C5).

HRMS (ESI): $C_{21}H_{14}Cl_2N_2O_3$ [(M+H)$^+$] = calcd.: 413.0459, found: 413.0458.

Alcohol **298b:**

TLC: R_f (pentane/acetone, 2:1) = 0.55 [UV, KMnO$_4$].

Mp: 172 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3289 (m, NH), 2961 (m, sp^3-CH), 2926 (w, sp^3-CH), 1779 (w, C=O), 1717 (s, C=O), 1594 (w, C=O), 1476 (w, C=C), 1416 (m, C=C), 1195 (m), 1095 (w).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.49 – 7.31 (m, 9H, 5 × Ar$^{\#}$–H, 4 × Ar$''$–H), 7.00 (*virt.* t, $^4J = {}^4J \approx$ 1.7 Hz, 1H, C4$'$–H), 6.89 (*virt.*t, $^4J = {}^4J \approx$ 2.0 Hz, 2H, C2$'$–H, NH), 6.84 (*virt.*t, $^4J = {}^4J \approx$ 2.0 Hz, 1H, C6$'$–H), 5.34 (br s, 1H, OH).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 171.2 (s, C4=O), 157.4 (s, C5$'$), 155.2 (s, C2=O), 141.3 (s, C1$'$), 140.4 (s, C3$''$), 135.9 (s, C3$'$), 135.2 (s, C1$''$), 131.1 (d, C5$''$), 130.5 (d, C4$''$/C2$''$), 129.3 (d, 2 × Ar$^{\#}$-C), 129.1 (s, C1$^{\#}$), 128.8 (d, Ar$^{\#}$-C), 127.1 (d, C4$''$/C2$''$), 126.4 (d, 2 × Ar$^{\#}$-C), 125.3 (d, C6$''$), 119.0 (d, C4$'$), 116.9 (d, C2$'$), 112.9 (d, C6$'$), 69.0 (s, C5).

HRMS (ESI): C$_{21}$H$_{14}$Cl$_2$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 413.0459, found: 413.0459.

3-(3#,5#-*bis*(Trifluoromethyl)phenyl-5-(3′-chloro-5′-hydroxyphenyl)-5-(3′′-chloro-phenyl)-imidazolidine-2,4-dione (199b)

$C_{23}H_{12}Cl_2F_6N_2O_3$
M = 549.25 g/mol
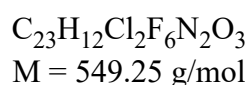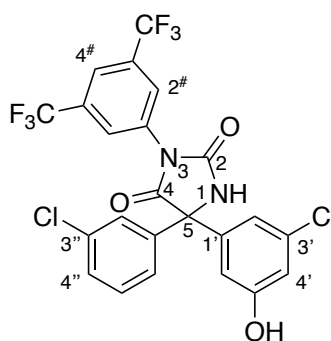
Starting material **199** (16.0 mg, 30.0 μmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound **199b** (9.06 mg, 16.5 μmol, 55%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.56 [UV, KMnO₄].

Mp: >230°C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3233 (w, NH), 3118 (w, OH), 2924 (w, sp³-CH), 2853 (w, sp³-CH), 1782 (w, C=O), 1721 (s, C=O), 1594 (w, C=O), 1472 (s, C=C), 1408 (m, C=C), 1276 (s).

¹H-NMR (500 MHz, acetone-d₆): δ [ppm] = 9.01 (s, 1H, NH), 8.45 (s, 1H, OH), 8.36 (s, 2H, C2#–H, C6#–H), 8.09 (s, 1H, C4#–H), 7.60 (*virt.* td, $^4J = {}^4J ≈ 1.9$ Hz, $^5J = 0.7$ Hz, 1H, C2′′–H), 7.55 (*virt.* dt, $^3J = 7.3$ Hz, $^4J = {}^4J ≈ 1.8$ Hz, 1H, C4′′–H), 7.49 (*virt.* t, $^3J = 7.8$ Hz, 1H, C5′′–H), 7.46 (*virt.* td, $^3J = {}^3J ≈ 7.9$ Hz, $^4J = 1.8$ Hz, 1H, C6′′–H), 7.06 (*virt.* t, $^4J = {}^4J ≈ 1.7$ Hz, 1H, C6′–H), 6.99 (*virt.* t, $^4J = {}^4J ≈ 1.9$ Hz, 1H, C2′–H), 6.92 (*virt.* t, $^4J = {}^4J ≈ 2.0$ Hz, 1H, C4′–H).

¹³C-NMR (101 MHz, acetone-d₆): δ [ppm] = 171.7 (s, C4=O), 159.5 (s, C5′), 154.0 (s, C2=O), 143.0 (s, C1′), 142.2 (s, C1′′), 135.7 (s, C3′), 135.2 (s, C1#), 135.1 (s, C3′′), 131.5 (q, $^1J = 33.7$ Hz, C3#-CF₃, C5#-CF₃), 131.4 (d, C5′′), 129.7 (d, C6′′), 127.9 (d, C2′′), 127.7 (d, C2#, C6#), 126.6 (d, C4′′), 125.5 (s, C3#/ C5#), 122.8 (s, C3#/ C5#), 122.1 (d, C4#), 118.9 (d, C6′), 116.7 (d, C4′), 114.1 (d, C2′), 69.6 (s, C5).

¹⁹F-NMR (476 MHz, CDCl₃): δ [ppm] = – 63.34 (s, 2 × CF₃).

HRMS (ESI): $C_{23}H_{12}Cl_2F_6N_2O_3$ [(M+H)⁺] = calcd.: 549.0207, found: 549.0210.

5-(3′-Chloro-5′-hydroxyphenyl)-5-(3′′-chlorophenyl)-3-((2##-(trimethylsilyl)ethoxy)methyl) -imidazolidine-2,4-dione (193b)

$C_{21}H_{24}Cl_2N_2O_4Si$
M = 467.42 g/mol
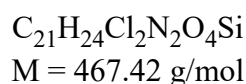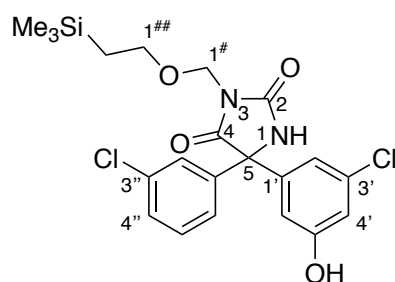
Starting material **193** (13.5 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound **193b** (7.60 mg, 15.6 µmol, 52%) was obtained as a colorless solid.

TLC: R_f (pentane/acetone, 2:1) = 0.81 [UV, KMnO$_4$].

Mp: 181 °C

**IR** (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3318 (m, NH), 2927 (w, sp^3-CH), 1771 (m, C=O), 1707 (s, C=O), 1594 (w, C=O), 1453 (s, C=C), 1396 (w, C=C), 1071 (s), 1087 (s).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 9.04 (s, 1H, NH), 8.56 (s, 1H, OH), 7.50 (*virt.* t, $^4J = ^4J \approx 2.2$ Hz, 1H, C2′′–H), 7.48 – 7.40 (m, 3H, C4′′–H, C5′′–H, C6′′–H), 6.96 (*virt.* t, $^4J = ^4J \approx 1.7$ Hz, 1H, C4′–H), 6.89 (*virt.* t, $^4J = ^4J \approx 2.0$ Hz, 1H, C2′–H), 6.87 (*virt.* t, $^4J = ^4J \approx 1.9$ Hz, 1H, C6′–H), 4.97 (s, 2H, C1#–H$_2$), 3.60 (dd, $^3J = 8.4$ Hz, 7.5 Hz, 2H, C1##–H$_2$), 0.86 (dd, $^3J = 8.4$ Hz, 7.5 Hz, 2H, C2##–H$_2$), -0.06 (s, 9H, Si(CH$_3$)$_3$).

^{13}C-NMR (101 MHz, acetone-d$_6$): δ [ppm] = 173.3 (s, C4=O), 157.0 (s, C5′), 155.6 (s, C2=O), 142.4 (s, C1′), 135.6 (s, C3′′), 135.0 (s, C3′), 131.4 (d, C4′′/C5′′/C6′′), 130.4 (s, C1′′), 129.5 (d, C4′′/C5′′/C6′′), 127.7 (d, C2′′), 126.4 (d, C4′′/C5′′/C6′′), 118.8 (d, C6′), 116.5 (d, C4′), 114.0 (d, C2′), 69.9 (s, C5), 68.9 (t, C1#), 67.6 (t, C1##), 18.5 (t, C2##), –1.34 (q, Si(*C*H$_3$)$_3$).

HRMS (ESI): $C_{21}H_{24}Cl_2N_2O_4Si$ [(M–2(CH$_3$)+H)$^+$] = calcd.: 439.0647, found: 439.0652.

5-(3′-Chloro-5′-hydroxyphenyl)-3-(4#-chlorobutyl)-5-(3′′-chlorophenyl)imidazolidine-2,4-dione (194b)

$$C_{19}H_{17}Cl_3N_2O_3$$
$$M = 427.71 \text{ g/mol}$$
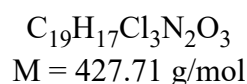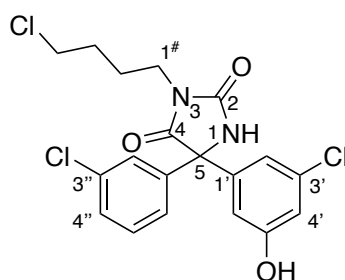
Starting material **194** (13.5 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compound **194b** (5.10 mg, 11.9 µmol, 40%) was obtained as a colorless solid.

**TLC:** R_f (pentane/acetone, 2:1) = 0.56 [UV, KMnO₄].

Mp: 122 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3274 (w, NH, OH), 2924 (m, sp³-CH), 2853 (m, sp³-CH), 1773 (w, C=O), 1704 (m, C=O), 1593 (m, C=C), 1448 (m, C=C), 1030 (s), 1189 (m), 730 (s, sp²-CH).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.39 – 7.29 (m, 5H, 5 × Ar′′–H), 6.90 (*virt.* t, $^4J = {}^4J \approx 1.6$ Hz, 1H, C4′–H), 6.87 (*virt.* t, $^4J = {}^4J \approx 2.0$ Hz, 1H, C2′–H), 6.73 (s, 1H, C6′–H), 6.78 (s, 1H, NH), 5.32 (s, 1H, OH), 3.62 (t, $^3J = 6.9$ Hz, 3H, C4#–H₂), 3.55 (t, $^3J = 6.3$ Hz, 2H, C1#–H₂), 1.83 – 1.78 (m, 2H, C2#–H₂, C3#–H₂).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 172.3 (s, C4=O), 157.3 (s, C5′), 156.5 (s, C2=O), 141.2 (s, C1′), 140.3 (s, C3′′), 135.9 (s, C3′), 130.5 (d, C-Ar′′), 129.6 (s, C1′′), 129.3 (d, C-Ar′′), 127.0 (d, C-Ar′′), 125.1 (d, C-Ar′′), 119.1 (d, C6′), 116.8 (d, C4′), 112.6 (d, C2′), 69.2 (s, C5), 44.3 (t, C4#), 38.6 (t, C1#), 29.6 (t, C2#/C3#), 25.5 (t, C2#/C3#).

HRMS (ESI): $C_{19}H_{17}Cl_3N_2O_3$ [(M+H)⁺] = calcd.: 427.0383, found: 427.0391.

5-Benzyl-5-(3′-hydroxyphenyl)- 3-methylimidazolidine-2,4-dione (*meta*-187b)

5-Benzyl-5-(4′-hydroxyphenyl)- 3-methylimidazolidine-2,4-dione (*para*-187b)

$$C_{18}H_{18}N_2O_3$$
$$M = 310.35 \text{ g/mol}$$
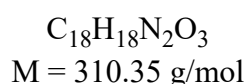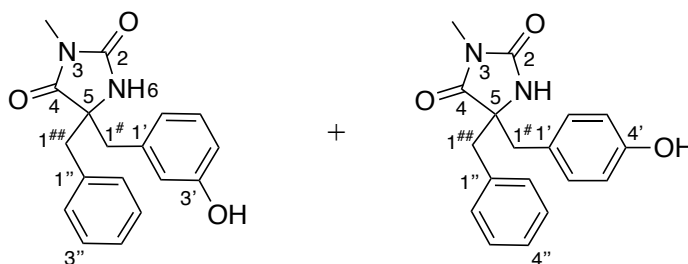
Starting material **187** (8.83 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-187b** (2.23 mg, 7.20 µmol, 24%) and ***para*-187b** (2.32 mg, 7.50 µmol, 25%)[18] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-187b:**

TLC: R_f (pentane/acetone, 2:1) = 0.26 [UV, KMnO$_4$].

Mp: 176 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3298 (w, NH), 2925 (w, sp^3-CH), 2854 (w, sp^3-CH), 1770 (w, C=O), 1706 (s, C=O), 1589 (w, C=O), 1456 (m, C=C), 1347 (w), 1278 (w), 1019 (w).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 8.10 (s, 1H, NH), 7.34-7.24 (m, 3H, C2′′–H, C4′′–H C6′′–H), 7.14 (*virt.* t, $^3J = {}^3J \approx 7.9$ Hz, 1H, C5′–H), 7.13 – 7.10 (m, 2H, C3′′–H, C5′′–H), 6.73 (d, $^3J = 8.2$ Hz, 1H, C6′–H), 6.69 (d, $J = 7.6$ Hz, 1H, C4′–H), 6.63 (s, 1H, C2′–H), 5.35 (s, 1H, OH), 3.19 (d, $^2J = 13.9$ Hz, 1H, C1$^{\#\#}$-H$_A$), 3.18 (d, $^2J = 13.9$ Hz, 1H, C1$^{\#}$-H$_A$), 2.92 (d, $^2J = 13.9$ Hz, 1H, C1$^{\#\#}$-H$_B$), 2.89 (d, $^2J = 13.9$ Hz, 1H, C1$^{\#}$-H$_B$), 2.62 (s, 3H, N3-CH$_3$).

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[18] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 175.0 (s, C4=O), 156.6 (s, C2=O), 155.7 (s, C3′), 135.9 (s, C1′), 134.2 (s, C1′′), 130.6 (d, C3′′/ C5′′), 130.5 (d, C2′′/C4′′/ C6′′), 129.6 (d, C3′′/ C5′′), 129.3 (d, C2′′/C4′′/ C6′′), 128.3 (d, C5′), 128.0 (d, C2′′/C4′′/ C6′′), 121.8 (d, C4′), 116.5 (d, C2′), 114.2 (d, C6′), 67.1 (s, C5), 42.5 (t, C1$^{\#\#}$), 41.4 (t, C1$^{\#}$), 24.3 (q, N3–CH_3).

HRMS (ESI): C$_{18}$H$_{18}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 311.1395, found: 311.1394.

Alcohol *para*-**187b:**

**TLC:** R_f (pentane/acetone, 2:1) = 0.22 [UV, KMnO$_4$].

Mp: 193 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3295 (w, NH), 3065 (w, OH), 2925 (w, sp^3-CH), 2854 (w, sp^3-CH), 1763 (w, C=O), 1698 (s, C=O), 1590 (w, C=O), 1455 (m, C=C), 1350 (w), 1266 (w), 670 (w).

^{1}H-NMR (500 MHz, acetone-d$_6$): δ [ppm] = 8.18 (s, 1H, NH), 7.27 – 7.16 (m, 5H, 5 × Ar′′–H), 7.14 (s, 1H, OH), 7.04 – 6.98 (m, 2H, C2′–H, C6′–H), 6.72 – 6.68 (m, 2H, C3′–H, C5′–H), 3.21 (d, ^2J = 13.5 Hz, 1H, C1$^{\#\#}$-H$_A$), 3.14 (d, ^2J = 13.7 Hz, 1H, C1$^{\#}$-H$_A$), 2.98 (d, ^2J = 13.5 Hz, 1H, C1$^{\#\#}$-H$_B$), 2.91 (d, ^2J = 13.7 Hz, 1H, C1$^{\#}$-H$_B$), 2.38 (s, 3H, N3-CH$_3$).

^{13}C-NMR (101 MHz, acetone-d$_6$): δ [ppm] = 175.8 (s, C4=O), 157.3 (s, C2=O), 156.3 (s, C4′), 136.2 (s, C1′′), 132.1 (s, C1′), 132.0 (d, Ar′′–H), 131.0 (d, Ar′′–H), 128.8 (d, Ar′′–H), 128.6 (d, C2′, C6′), 127.7 (d, Ar′′–H), 126.6 (d, Ar′′–H), 115.7 (d, C3′, C5′), 68.5 (s, C5), 43.3 (C1$^{\#\#}$), 42.7 (C1$^{\#}$), 23.9 (N3–CH_3).

HRMS (ESI): C$_{18}$H$_{18}$N$_2$O$_3$ [(M+H)$^+$] = calcd.: 311.1395, found: 311.1393.

3 -(3´-Hydroxyphenyl)- 3-phenylpiperidin-2-one (*meta*-180)

3 -(4´-Hydroxyphenyl)- 3-phenylpiperidin-2-one (*para*-180)

$$C_{17}H_{17}NO_2$$
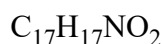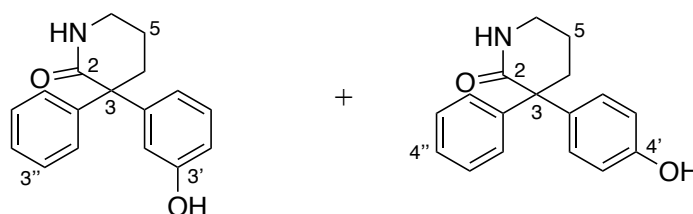
Starting material **134** (7.50 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-180** (4.55 mg, 12.4 µmol, 41%) and ***para*-180** (2.28 mg, 6.20 µmol, 21%)[19] were obtained as colorless solids. ***para*-180** was obtained as a mixture of the two regioisomers. Analysis was conducted on the products obtained from small, pure fractions eluted prior to the elution of the inseparable mixed fractions.

Alcohol ***meta*-180**

TLC: R_f (pentane/acetone, 1:1) = 0.43 [UV, KMnO$_4$].

Mp: 210 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3192 (m, NH), 3033 (w, sp^3-CH), 2953 (m, sp^3-CH), 2926 (m, sp^3-CH), 1646 (s, C=O), 1583 (s, C=O), 1488 (s, C=C), 1447 (m, C=C), 1327 (m, C=C), 1240 (m).

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ [ppm] = 9.23 (s, 1H, NH), 7.69 (1H, OH), 7.33 – 7.24 (m, 2H, C3´´–H, C5´´–H), 7.27 – 7.17 (m, 3H, C2´´–H, C4´´–H, C6´´–H), 7.09 (*virt.* td, $^3J = {}^3J \approx 7.6$ Hz, ^4J =1.2 Hz, 1H, C5´–H), 6.71 – 6.58 (m, 3H, C2´–H, C4´–H, C6´–H), 3.21 (td, ^3J = 6.2 Hz, ^4J =2.5 Hz, 2H, C6-H$_2$), 2.52 – 2.36 (m, 2H, C4-H$_2$), 1.60 (*virt.* p, $^3J = {}^3J \approx 6.3$ Hz, 2H, C5-H$_2$).

^{13}C-NMR (101 MHz, DMSO-d$_6$): δ [ppm] = 172.1 (s, C=O), 156.8 (s, C3´), 145.9 (s, C1´), 144.7 (s, C1´´), 128.6 (d, C5´–H), 128.5 (d, C2´´, C6´´), 127.6 (d, C3´´, C5´´), 126.1 (d, C4´), 118.8 (d, C2´/C4´/C6´), 115.9 (d, C2´/C4´/C6´), 113.2 (d, C2´/C4´/C6´), 56.0 (s, C3), 41.5 (t, C6), 34.2 (t, C4), 18.7 (t, C5).

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[19] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

HRMS (ESI): $C_{17}H_{17}NO_2$ [(M+H)$^+$] = calcd.: 268.1337, found: 268.1336.

2-(3′-Hydroxyphenyl)-*N*-methyl-2-phenylacetamide (*meta*-137b)

2-(4′-Hydroxyphenyl)-*N*-methyl-2-phenylacetamide (*para*-137b)

$$C_{15}H_{15}NO_2$$
$$M = 241.29 \text{g/mol}$$
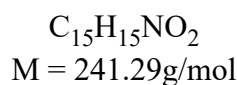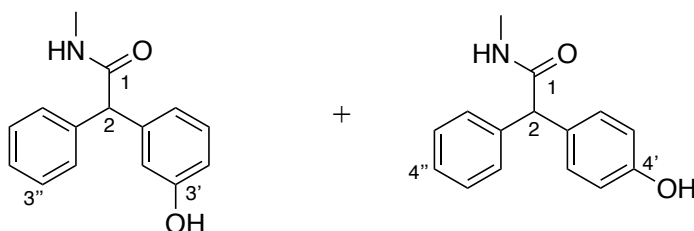
2,2-diphenyacetamide (7.90 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-137b** (2.50 mg, 8.91 µmol, 30%) and ***para*-137b** (2.90 mg, 10.3 µmol, 34%)[20] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-137b:**

TLC: R_f (pentane/acetone, 2:1) = 0.57 [UV, KMnO$_4$].

Mp: 163 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3277 (m, NH), 3046 (w, sp^3-CH), 2923 (m, sp^3-CH), 2853 (m, sp^3-CH), 1746 (s, C=O), 1612 (s, C=O), 1512 (s, C=O), 1371 (m, C=C), 1250 (m).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.39 – 7.20 (m, 5H, 5 × Ar′′–H), 7.14 (*virt.* t, $^3J = {}^3J \approx 7.8$ Hz, 1H, C5′–H), 6.75 (*virt.* t, $^4J = {}^4J \approx 2.0$ Hz, 1H, C2′–H), 6.72 (d, $^3J = 7.9$ Hz, 2H, C4′–H, C6′–H), 6.01 (d, $^3J = 4.9$ Hz, 1H, NH), 5.76 (s, 1H, OH), 4.88 (s, 1H, C2–H), 2.79 (d, $^3J = 4.7$ Hz, 3H, N–CH$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 173.8 (s, C=O), 157.0 (s, C3′), 140.5 (s, C1′), 130.0 (s, C1′′), 130.1 (d, C5′), 129.0 (d, 2 × C–Ar′′), 128.9 (d, 2 × C–Ar′′), 127.4 (d, C–Ar′′), 120.6 (d, C4′/C6′), 116.3 (d, C2′), 114.9 (d, C4′/C6′), 58.9 (s, C2), 26.9 (q, N–CH$_3$).

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[20] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

HRMS (ESI): $C_{15}H_{15}NO_2$ [(M+H)$^+$] = calcd.: 242.1181, found: 242.1178.

Alcohol *para*-**137b:**

TLC: R_f (pentane/acetone, 2:1) = 0.50 [UV, KMnO$_4$].

Mp: 176 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3276 (m, NH), 3046 (w, sp^3-CH), 2921 (m, sp^3-CH), 2850 (m, sp^3-CH), 1745 (s, C=O), 1612 (s, C=O), 1510 (s, C=O), 1372 (m, C=C), 1249 (m).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.39 – 7.20 (m, 5H, 5 × Ar′′–H), 7.04 – 7.00 (m, 2H, C2′–H, C6′–H), 6.75 – 6.73 (m, 2H, C3′–H, C5′–H), 5.94 (d, 1H, ^3J = 5.0 Hz, NH), 5.35 (s, 1H, OH), 4.90 (s, 1H, C2–H), 2.83 (d, ^3J = 4.7 Hz, 3H, N–CH$_3$).
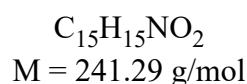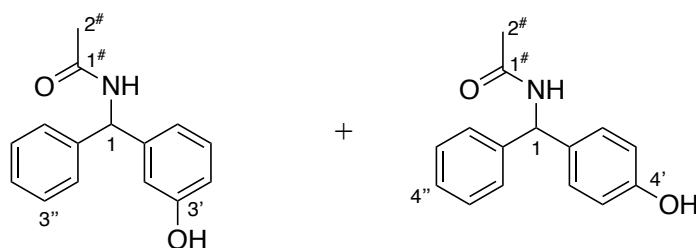
^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 174.2 (s, C=O), 155.8 (s, C4′), 139.6 (s, C1′′), 130.5 (C1′), 129.0 (d, 2 × Ar′′–H), 128.9 (d, 2 × Ar′′–H), 130.5 (d, C2′, C6′), 127.4 (d, Ar′′–H), 116.0 (d, C3′, C5′), 58.4 (s, C2), 26.9 (q, N–CH$_3$).

HRMS (ESI): $C_{15}H_{15}NO_2$ [(M+H)$^+$] = calcd.: 242.1181, found: 242.1180.

N-((3´-hydroxyphenyl)-(phenyl)methyl)phenylacetamide (*meta*-148b)

N-((4´-hydroxyphenyl)-(phenyl)methyl)phenylacetamide (*para*-148b)

$$C_{15}H_{15}NO_2$$
$$M = 241.29 \text{ g/mol}$$

Starting material **148** (7.90 mg, 30.0 µmol, 1.0 eq.) was borylated according to general procedure **GP3**, followed by oxidation of the crude borylated products using general procedure **GP4**. Compounds ***meta*-148b** (1.88 mg, 7.8 µmol, 26%) and ***para*-148b** (1.23 mg, 5.10 µmol, 17%)[21] were obtained as colorless solids. Analysis was conducted on the products obtained from small, pure fractions eluted prior and subsequently to the elution of the inseparable mixed fractions.

Alcohol ***meta*-148b:**

TLC: R_f (pentane/acetone, 2:1) = 0.57 [UV, KMnO$_4$].

Mp: 135 °C

IR (ATR, neat): $\tilde{\nu}$ [cm^{-1}] = 3280 (m, NH), 3052 (w, sp^3-CH), 2926 (m, sp^3-CH), 2855 (m, sp^3-CH), 1748 (s, C=O), 1615 (s, C=O), 1514 (s, C=O), 1373 (m, C=C), 1250 (m).

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.39 – 7.21 (m, 5H, 5 × Ar´´–H), 7.13 (*virt.* t, ^3J = ^3J ≈ 8.1 Hz, 1H, C5´–H), 6.75 – 6.71 (m, 3H, C2´–H, C4´–H, C6´–H), 6.35 (d, ^3J = 8.1 Hz, 1H, NH), 6.13 (d, ^3J = 8.1 Hz, 1H, C1–H), 3.64 (br s, 1H, OH), 2.03 (s, 3H, C2$^\#$–H$_3$).

^{13}C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 170.2 (s, C=O), 156.7 (s, C3´), 140.5 (s, C1´), 141.1 (s, C1´´), 130.0 (d, C5´), 128.8 (d, 2 × C–Ar´´), 128.7 (d, C–Ar´´), 127.6 (d, 2 × C–Ar´´), 115.8 (d, C4´/C6´/C2´), 115.0 (d, C4´/C6´/C2´), 114.7 (d, C4´/C6´/C2´), 57.4 (s, C1), 23.3 (q, C2$^\#$).

HRMS (ESI): C$_{15}$H$_{15}$NO$_2$ [(M+H)$^+$] = calcd.: 242.1181, found: 242.1179.

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[21] Yields of the regioisomers were calculated based on the *meta:para* ratio of signals in the ^{1}H-NMR of the mixed fraction obtained by column chromatography, in addition to the isolated yield of the clean fractions.

Alcohol *para*-**148b:**

TLC: R_f (pentane/acetone, 2:1) = 0.50 [UV, KMnO₄].

Mp: 140 °C

IR (ATR, neat): $\tilde{\nu}$ [cm⁻¹] = 3277 (m, NH), 3050 (w, sp³-CH), 295 (m, sp³-CH), 2857 (m, sp³-CH), 1752 (s, C=O), 1617 (s, C=O), 1513 (s, C=O), 1373 (m, C=C), 1251 (m).

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.39 – 7.21 (m, 5H, 5 × Ar′′–H), 7.02 – 6.98 (m, 2H, C2′–H, C6′–H), 6.78 – 6.75 (m, 2H, C3′–H, C5′–H), 6.28 (d, ³J = 7.9 Hz, 1H, NH), 6.13 (d, ³J = 7.9 Hz, 1H, C1–H), 3.65 (s, 1H, OH), 2.04 (s, 3H, C2#–H₃).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 169.9 (s, C=O), 155.7 (s, C4′), 142.9 (s, C1′′), 141.2 (C1′), 133.0 (d, 2 × C–Ar′′), 127.8 (d, C2′, C6′) 127.7 (d, 2 × C–Ar′′), 127.5 (d, C–Ar′′), 119.1 (d, C3′, C5′), 57.0 (s, C2), 23.4 (q, C2#).

HRMS (ESI): C₁₅H₁₅NO₂ [(M+H)⁺] = calcd.: 242.1181, found: 242.1177.

6. Catalytic chlorinations

[*Bis*(1,10-phenanthroline)]silvertrifluoromethanesulfonate (251)

$$C_{25}H_{16}AgN_4F_3O_3S$$
$$M = 617.36 \text{ g/mol}$$
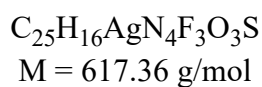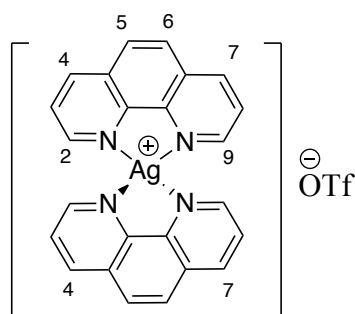
AgOTf (257 mg, 1.00 mmol, 1.0 eq.) was dissolved in MeOH (5 mL) and 1,10-phenanthroline anhydrate (360 mg, 2.00 mmol, 2.0 eq.) in MeOH (10 mL) was added. The reaction mixture was stirred for 3 h at r.t. and the resulting precipitate was filtered and washed with MeOH (20 mL). After removing the remaining solvent *in vacuo*, Ag(phen)$_2$OTf **251** (545 mg, 883 µmol, 88%) was obtained as a yellow-green solid.

^{1}H-NMR (500 MHz, DMSO-d$_6$): δ [ppm] = 9.17 (dd, ^3J = 4.5 Hz, ^4J = 1.8 Hz, 4H, 2 × C2–H, 2 × C9–H), 8.81 (dd, ^3J = 8.1 Hz, ^4J = 1.8 Hz, 4H, 2 × C4–H, 2 × C7–H), 8.24 (s, 4H, 2 × C5–H, 2 × C6–H), 8.02 (dd, ^3J = 48.1 Hz, ^4J = 4.5 Hz, 4H, 2 × C3–H, 2 × C8–H).

The analytical data are consistent with those in the literature.[118]

4-Chloro-1-tetralone (241)
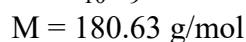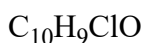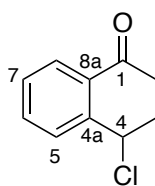
$C_{10}H_9ClO$
M = 180.63 g/mol

1-Tetralone (3.99 μL, 4.39 mg, 30.0 μmol, 1.0 eq.) was chlorinated according to general procedure **GP5**. Purification by column chromatography (silica, dry load, 15 × 1.5 cm, hexane/EtOAc, 10:1 → 5:1) yielded compound **241** (2.17 mg, 12.0 μmol, 40%) as a yellow liquid.

TLC: R_f (hexane/EtOAC, 5:1) = 0.40 [UV, KMnO₄].

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 8.06 (d, ^3J = 8.6 Hz, 1H, C8–H), 7.58 (*virt.* t, ^3J = ^3J ≈ 8.3 Hz, 1H, C6–H), 7.51–7.42 (m, 2H, C5–H, C7–H), 5.40 (t, ^3J = 3.9 Hz, 1H, C4–H), 3.18 (ddd, ^2J = 17.2 Hz, ^3J = 12.0 Hz, ^3J = 5.0 Hz, 1H, C2–H$_A$), 2.73 (dtd, ^2J = 17.4 Hz, ^3J = 8.6 Hz, ^4J = 0.8 Hz, 1H, C2–H$_B$), 2.63 (dt, ^2J = 12.0 Hz, ^3J = 3.8 Hz, 1H, C3–H$_A$), 2.59 – 2.52 (m, 1H, C3–H$_B$).

¹³C-NMR (101 MHz, CDCl₃): δ [ppm] = 196.3 (s, C=O), 142.2 (s, C4a), 134.1 (s, C8a), 131.0 (d, C6), 129.3 (d, C5), 129.0 (d, C8), 127.3 (d, C7), 56.6 (d, C4), 33.9 (t, C2), 31.8 (t, C3).

The analytical data are consistent with those in the literature.[118]

(3-Bromo-1-chloropropyl)benzene (240b)

$C_9H_{10}BrCl$
M = 233.53 g/mol
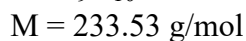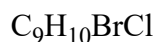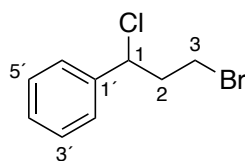
(3-Bromopropyl)benzene (4.56 µL, 5.98 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP5**. Purification by column chromatography (silica, dry load, 15 × 1.5 cm, hexane) yielded compound **240b** (4.97 mg, 21.3 µmol, 71%) as a yellow liquid.

TLC: R_f (hexane) = 0.44 [UV, KMnO$_4$].

¹H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.43 – 7.32 (m, 5H, Ar–H), 5.12 (dd, ^3J = 8.8 Hz, ^3J = 5.4 Hz, 1H, C1–H), 3.58 (ddd, ^2J = 10.2 Hz, ^3J =8.0 Hz, ^3J = 5.5 Hz, 1H, C3–H$_A$), 3.44 – 3.37 (m, 1H, C3–H$_B$), 2.63 (ddt, ^2J = 14.6 Hz, ^3J = 8.9 Hz, ^3J = 5.7 Hz, 1H, C2–H$_A$), 2.48 (ddt, ^2J = 14.9 Hz, ^3J = 8.1 Hz, ^3J = 5.6 Hz, 1H, C2–H$_B$).

¹³C-NMR (101 MHz, CDCl$_3$): δ [ppm] = 140.4 (s, C1′), 128.8 (d, C3′, C5′), 128.6 (d, C2′, C5′), 127.0 (d, C4′), 61.1 (d, C1), 42.3 (t, C2), 30.1 (t, C3).

The analytical data are consistent with those in the literature.[118]

1,4,6-Trichloro-3,4-dihydroquinolin-2(1*H*)-one (255a)
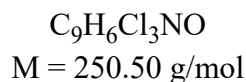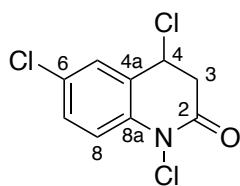
C₉H₆Cl₃NO

M = 250.50 g/mol

3,4-Dihydroquionoline-2(1*H*)-one (4.42 mg, 30.0 μmol, 1.0 eq.) was chlorinated according to general procedure **GP6**. Due to the instability of the product, **255a** was only observed in the crude ^{1}H-NMR.

^{1}**H-NMR** (500 MHz, CDCl₃): δ [ppm] = 7.50 (d, ^3J = 8.8 Hz, 1H, C8–H), 7.44 (dd, ^3J = 8.8 Hz, ^4J = 2.3 Hz, 1H, C7–H), 7.12 (d, ^4J = 2.0 Hz, 1H, C5–H), 5.19 (t, ^3J = 3.9 Hz, 1H, C4–H), 3.38 (dd, ^2J = 16.5 Hz, ^3J = 3.6 Hz, 1H, C3–H$_A$), 3.26 (dd, ^2J = 16.5 Hz, ^3J = 4.3 Hz, 1H, C3–H$_B$).

1,6-Dichloro-3,4-dihydroquinolin-2(1*H*)-one (254a)
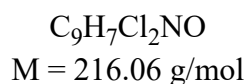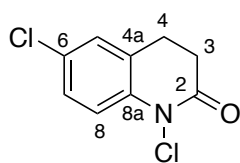
C₉H₇Cl₂NO

M = 216.06 g/mol

3,4-Dihydroquionoline-2(1*H*)-one (4.42 mg, 30.0 μmol, 1.0 eq.) was chlorinated according to general procedure **GP6** using DCM as the solvent. Due to the instability of the product, **254a** was only observed in the crude ^{1}H-NMR.

^{1}**H-NMR** (500 MHz, CDCl₃): δ [ppm] = 7.40 (d, ^3J = 8.7 Hz, 1H, C8–H), 7.30 (dd, ^3J = 8.7 Hz, ^3J = 2.2 Hz, 1H, C7–H), 7.20 (d, ^4J = 2.3 Hz, 1H, C5–H), 2.99 (dd, ^2J = 8.8 Hz, ^3J = 5.9 Hz, 2H, C4–H$_A$, C4–H$_B$), 2.87 (dd, ^2J = 8.4 Hz, ^3J = 5.6 Hz, 2H, C3–H$_A$, C3–H$_B$).

6-Chloroquinolin-2(1*H*)-one (256b)
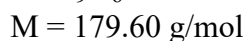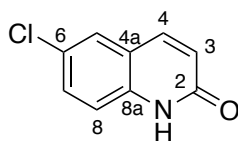
C$_9$H$_6$ClNO

M = 179.60 g/mol

3,4-Dihydroquinolin-2(1*H*)-one (4.42 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP6** using DCE as the solvent. Compound **256b** was obtained as a mixture with *N*-chlorinated compound **256a** due to slow elimination of chloride from the amide nitrogen atom as well as elimination of HCl.

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 8.06 (s, 1H, NH), 7.79 (d, ^3J = 9.5 Hz, 1H, C4–H), 7.59 (d, ^4J = 2.3 Hz, 1H, C5–H), 7.50 (dd, ^3J = 8.7 Hz, ^4J = 2.2 Hz, 1H, C7–H), 7.33 (d, ^3J = 8.9 Hz, 1H, C8–H), 6.77 (d, ^3J = 9.5 Hz, 1H, C3–H).

The analytical data are consistent with those in the literature.[133]

6-Chloro-3,4-dihydroquinolin-2(1*H*)-one (254b)
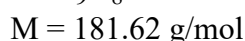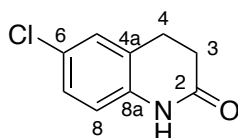
C$_9$H$_8$ClNO

M = 181.62 g/mol

3,4-Dihydroquinolin-2(1*H*)-one (4.42 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP6** using DCE as the solvent. Compound **254b** was obtained as a mixture with N-chlorinated compound **254a** due to slow elimination of chloride from the amide nitrogen.

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 8.06 (s, 1H, NH), 7.18 – 7.12 (m, 2H, C5–H, C7–H), 6.70 (d, ^3J = 8.1 Hz, 1H, C8–H), 2.95 (t, ^3J = 7.6 Hz, 2H, C4–H₂), 2.63 (t, ^3J = 6.8 Hz, 2H, C3–H₂).

The analytical data are consistent with those in the literature.[134]

1,4,6-Dichloro-3,3-dimethyl-3,4-dihydroquinolin-2(1*H*)-one (259a)


$$C_{11}H_{10}Cl_3NO$$
$$M = 278.56 \text{ g/mol}$$

3,3-Dimethyl-3,4-dihydroquionoline-2(1*H*)-one (5.26 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP6**. Due to the instability of the product, **259a** was only observed in the crude ^{1}H-NMR.

^{1}H-NMR (500 MHz, CDCl$_3$): δ [ppm] = 7.46 (d, ^3J = 8.7 Hz, 1H, C8–H), 7.42 (dd, ^3J = 8.6 Hz, ^4J = 2.2 Hz, 1H, C7–H), 7.09 (dd, ^4J = 2.0 Hz, 1.0 Hz, 1H, C5–H), 4.77 (s, 1H, C4–H), 1.58 (s, 3H, C3–CH$_3$), 1.54 (s, 3H, C3–CH$_3$).

1,6-Dichloro-3,3-dimethyl-3,4-dihydroquinolin-2(1*H*)-one (258a)

$$C_{11}H_{11}Cl_2NO$$
$$M = 244.12 \text{ g/mol}$$

3,3-Dimethyl-3,4-dihydroquionoline-2(1*H*)-one (5.26 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP6** using DCM as the solvent. Due to the instability of the product, **258a** was only observed in the crude ^{1}H-NMR.

**^{1}H-NMR** (400 MHz, CDCl$_3$): δ [ppm] = 7.37 (d, ^3J = 8.9 Hz, 1H, C8–H), 7.30 (dd, ^3J = 8.6 Hz, ^3J = 2.4 Hz, 1H, C7–H), 7.16 (dd, ^4J = 2.3 Hz, 1.3 Hz, 1H, C5–H), 2.83 (s, 2H, C4-H$_2$), 1.26 (s, 3H, C3–CH$_3$), 1.23 (s, 3H, C3–CH$_3$).

6-Chloro-3,3-dimethyl-3,4-dihydroquinolin-2(1*H*)-one (258b)

$C_{11}H_{12}ClNO$

M = 209.67 g/mol

3,3-Dimethyl-3,4-dihydroquionoline-2(1*H*)-one (5.26 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP6** using DCE as the solvent. Compound **258b** was obtained as a mixture with N-chlorinated compound **258a** due to slow elimination of chloride from the amide nitrogen.

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 7.66 (s, 1H, NH), 7.17 – 7.12 (m, 2H, C5–H, C7–H),), 6.65 (d, ^3J = 9.0 Hz, 1H, C8–H), 2.77 (s, 2H, C4–H₂), 1.21 (s, 6H, 2 × C3–CH₂), 1.20 (s, 5H).

The analytical data are consistent with those in the literature.[135]

6-Chloro-3,3-dimethyl-3,4-quinolin-2,4(1*H*,3*H*)-dione (262a)

$C_{11}H_{10}ClNO_2$

M = 223.66 g/mol
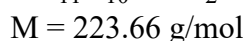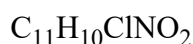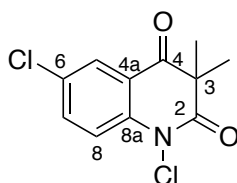
3,3-Dimethyl-3,4-dihydroquinoline-2(1*H*)-one (5.26 mg, 30.0 µmol, 1.0 eq.) was chlorinated according to general procedure **GP6** using DCE as the solvent. Due to the instability of the product, **262a** was only observed in the crude ¹H-NMR.

¹H-NMR (500 MHz, CDCl₃): δ [ppm] = 9.40 (d, ^4J = 4.3 Hz, 1H, C5–H), 8.63 (d, ^3J = 8.1 Hz, 1H, C8–H), 7.98 (dd, ^3J = 8.2 Hz, ^4J = 4.8 Hz, 1H, C7–H, 1.21 (s, 6H, 2 × C3–CH₂).

III. Abbreviations

Ac:	Acetyl
ATR:	Attenuated Total Reflection
Calc.:	Calculated
Bn:	Benzyl
Boc:	tert-Butyloxycarbonyl
bpy:	2,2′-Bipyridine
Bu:	Butyl
COSY:	Correlated Spectroscopy
CSA:	Camphorsulfonic Acid
TLC:	Thin-Layer Chromatography
DEPT:	Distortionless Enhancement by Polarization Transfer
DIPEA:	N,N-Diisopropylethylamine
DMAP:	4-Dimethylaminopyridine
DMF:	N,N-Dimethylformamide
DMSO:	Dimethyl sulfoxide
dppf:	1,1′-Bis(diphenylphosphino)ferrocene
d.r.:	Diastereomeric Ratio
dtbbpy:	4,4′-Di-tert-butyl-2,2′-bipyridine
ΔT:	Refluxing
EDA:	Electron Donor-Acceptor
ee:	Enantiomeric Excess
EI:	Electron Impact Ionization
ESI:	Electrospray Ionization
Et:	Ethyl
Eq.:	Equivalents
GC:	Gas Chromatography
GP:	General Procedure
Satd..:	Saturated
h:	Hour(s)
HMBC:	Heteronuclear Multiple-Bond Correlation
HPLC:	High-Performance Liquid Chromatography
HSQC:	Heteronuclear Single Quantum Coherence

IR:	Infrared
Me:	Methyl
MeCN:	Acetonitrile
min:	Minute(s)
MLCT:	Metal to Ligand Charge Transfer
MS:	Mass Spectrometry
NMR:	Nuclear Magnetic Resonance
NOE:	Nuclear Overhauser Effect
Ph:	Phenyl
PMP:	para-Methoxyphenyl
py:	Pyridine
Pr:	Propyl
R_f:	Relative Migration Velocity (TLC)
r.t.:	Room Temperature
SET:	Single Electron Transfer
Mp.:	Melting Point
TBS:	tert-Butyldimethylsilyl
Tf:	Trifluoromethylsulfonyl
TFA:	Trifluoroacetic Acid
THF:	Tetrahydrofuran
TMS:	Trimethylsilyl
t_R:	Retention Time (GC and HPLC)
Ts:	p-Toluenesulfonyl
UV:	Ultraviolet
Vis:	Visible
DMF	*N*,*N*-Dimetylformamid
DMSO	Dimethylsulfoxid

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