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Synthesis of enantioenriched atropisomeric indolylquinolines following a central-to-axial chirality conversion approach

Tesi di laurea sperimentale

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Abstract

In this work, the enantioselective synthesis of atropisomeric indolylquinoline systems using a central-to-axial chirality conversion approach is presented. This methodology consists, first of all, in the synthesis of enantioenriched tetrahydroquinolines displaying central chirality. Then, conversion of central chirality to axial chirality by means of an oxidation reaction in order to obtain the corresponding atropisomeric quinolines has been carried out. Axial chirality is a type of unconventional chirality in which the molecules do not possess a stereogenic center but a chiral axis. Thanks to the spatial arrangement of the substituents around the axis, these molecules can exist in two non-superimposable mirror images, that is in two enantiomeric forms. The tetrahydroquinoline scaffolds are synthetized exploiting an acid catalyzed inverse-electron-demand [4 + 2] cycloaddition: the Povarov reaction. This cycloaddition consists in the reaction between an electron poor diene, an *N*-arylimine, and an electron rich dienophile, a 3-alkenylindole bearing a bulky substituent at the 4-position of the indole. The Povarov cycloaddition is promoted by the presence of (*R*)-TRIP, a bifunctional chiral phosphoric acid, that is able to deliver enantioenriched tetrahydroquinolines in excellent yields, stereo- and enantioselectivities. The tetrahydroquinoline scaffolds obtained in this way are subsequently oxidized to atropisomeric indolylquinolines with retention of the chiral information imparted in the Povarov reaction. Different oxidation reaction conditions were tested in order to achieve configurationally stable atropisomeric indolylquinolines with good yields and retention of enantiomeric excess. With the best reaction conditions in hand, the reaction scope has been thoroughly evaluated by modifying both the *N*-arylimine and 3-alkenylindole reaction partners.

Summary

1. Introduction

1.1. Axial chirality

Axial chirality is a particular type of chirality, in which the molecules do not possess a stereogenic center but a chiral axis; thanks to the spatial arrangement of the substituents around the axis, these molecules can exist in two non-superimposable mirror images, that is two enantiomers.

Atropisomers, allenes and alkylidenecycloalkanes are examples of this type of chirality *(Figure 1)*. Indeed, allenes present an axis along the cumulate dienes, and due to the different substituents on the terminal carbons they can exist in two enantiomeric forms. In alkylidenecycloalkanes instead, although presenting a tetrasubstitued sp^3 carbon, the element of chirality is the axis passing through the double bond, and, also in this case, the presence of different substituents on the terminal carbon of the alkene permits the existence of two enantiomers. Moreover, atropisomers can exist in two enantiomeric forms thanks to the hindered groups in proximity of the axis and the consequent rotational restriction around the σ-bond. This will be discussed in greater detail in the next paragraph.

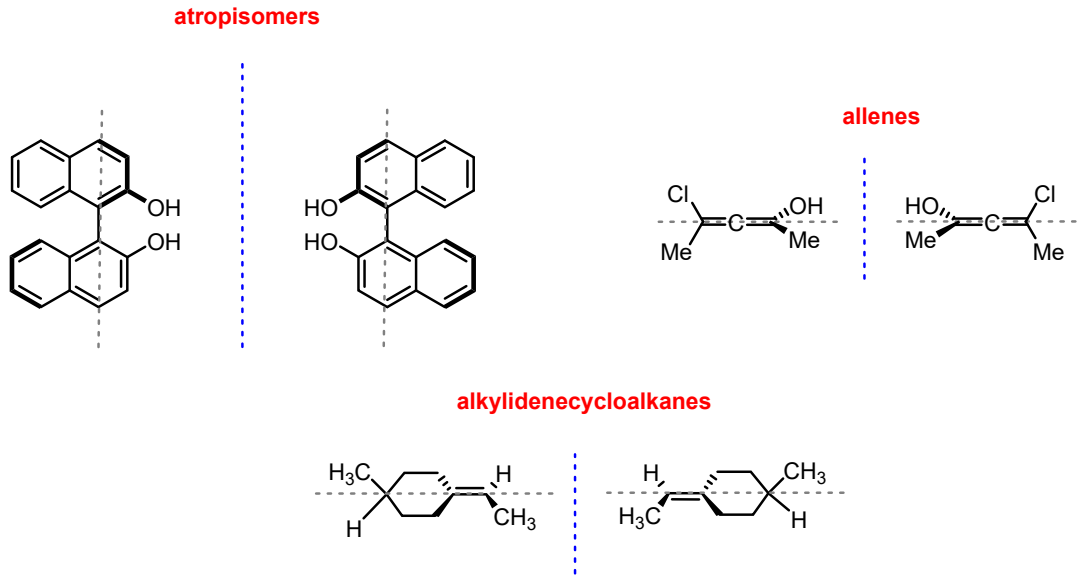


Figure 1. Examples of axial chirality

1.2. Atropisomers

Atropisomers are conformational isomers characterized by a restricted rotation around a single bond (red in *Figure 2*) due to the presence of hindered groups (blue in *Figure 2*) at

carbons 1, 1', 2 and 2'. The restricted rotation allows the existence of two separate enantiomers, whose chirality is provided by an axis. Interconversion of the two enantiomers requires overcoming an energy gap. The most representative example of atropisomeric compounds is represented by biarylic systems. However, particular types of hindered amides and styrenes might also generate configurationally stable atropisomers.[1,2]

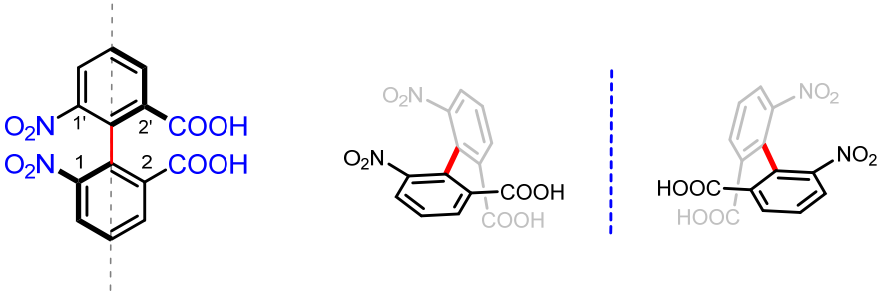


Figure 2. Example of atropisomers

A crucial requirement of atropisomerism is the rotational stability of the chiral axis. Temperature has a great influence on the stability because an increase in temperature causes a decrease of the half-life of the two enantiomers and the subsequent racemization, according to the Eyring equation. Hindered substituents in proximity to the axis increase the energy band gap and allows the isolation of the two separate enantiomers at ambient temperature.

The minimum requirement to obtain stable atropisomeric scaffold is the presence of at least three substituents in proximity of the axis. In addition, a crucial requirement for the existence of chiral atropisomers is the presence of different substituents on the same aryl ring, opposite to the chiral axis, in order to avoid the presence of a symmetry plane, responsible of non-chiral "*meso* forms" (*Figure 3*).

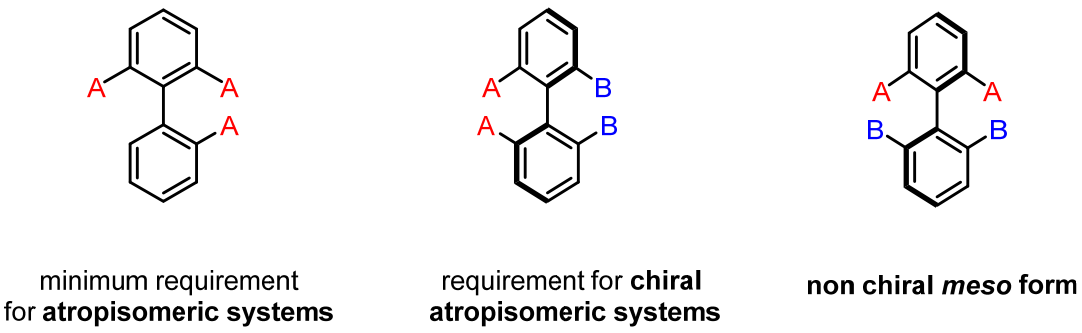


Figure 3. Requirements for chiral and achiral atropisomeric systems

The absolute configuration of these molecules can be denoted by analysis of Newman projections along the chiral axis. After assignment of priority to ortho substituents according to CIP rules, if the shortest 90° path from the substituent of highest priority on the carbon in front to the substituent of highest priority on the carbon in back turns counterclockwise, the descriptor is *aS* or *M* (minus); if it turns clockwise the descriptor is *aR* or *P* (plus)[3] (*Figure 4*).

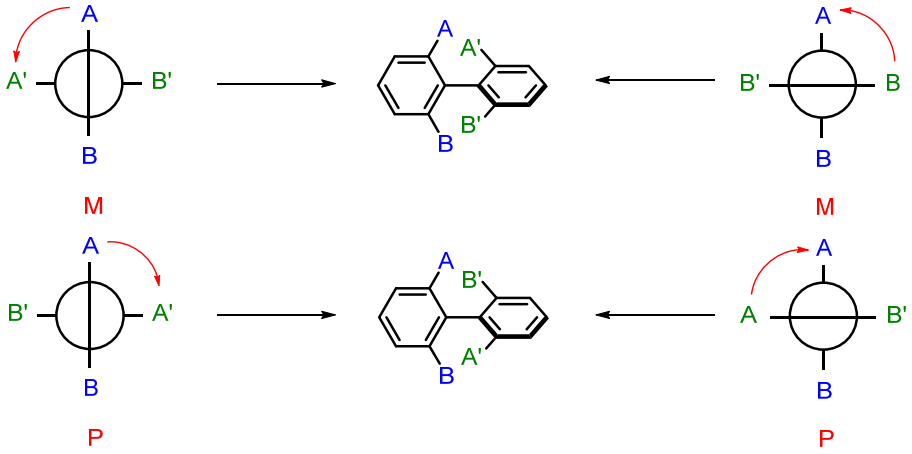


Figure 4. Absolute configuration of atropisomers: descriptors

1.3. Stereoselective synthesis of atropisomers

Numerous elegant strategies for the stereoselective synthesis of atropisomers have been developed in the last years. Most of them are typically based on direct atroposelective cross-couplings, atroposelective biaryl formations by construction of an aromatic ring and resolutions or desymmetrizations of stereochemically not defined biaryls. Another important approach for the stereoselective synthesis of atropisomers is the chirality conversion approach, which will be explained in detail in chapter 1.3.5.

1.3.1. Cross-coupling reactions

A classical approach for the synthesis of axially chiral biaryl compounds is represented by cross-coupling reactions, which lead to the formation of a new C-C bond between the two aromatic rings. This type of reactions generally involves the presence of a metal which can act as catalyst. One notable example is the employment of a catalytic amount of palladium in Suzuki couplings. Alternatively, the metal can be employed in a stoichiometric fashion in order to create an organometallic species, such as arylmagnesium halides in the Grignard reaction.

Meyers et al.[4] reported the synthesis of biaryl structures using aryl bromides and *o*-methoxyaryl oxazolines. In the presence of magnesium, the aryl bromide undergoes oxidative addition, i.e. insertion of the metal atom into a single bond, to create the Grignard reagent, which displaces the *o*-methoxy group from the aryl oxazoline, creating the new C-C bond and consequently the biarylic system *(Figure 5).*

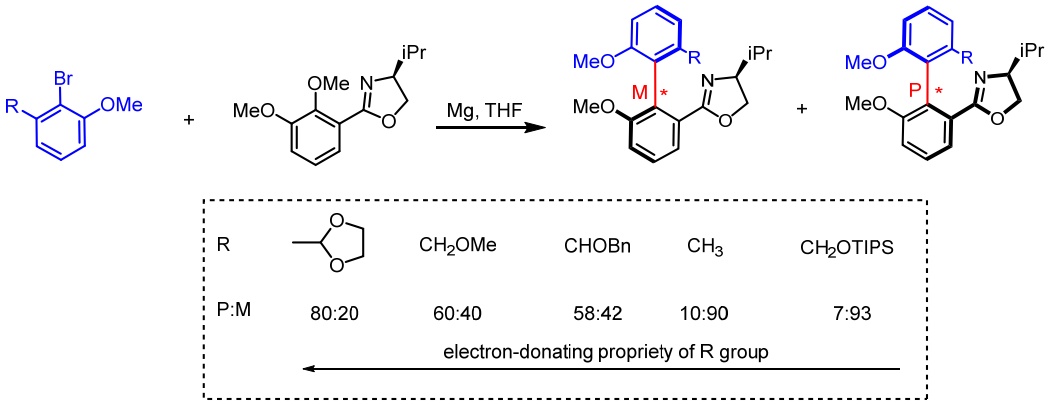


Figure 5. Grignard reaction for atropisomers synthesis

In this report, the diastereoselection is controlled by the complexation of the magnesium atom by the substituents of the aryl group. If the R group is hindered and not able to coordinate magnesium, the *M* stereoisomer is selectively obtained. If the ortho substituent of the aryl bromide (R) is not hindered, it is able to complex the magnesium atom as well and, owing to the competition in the complexation step, the reaction leads also the other stereoisomer (*P*) *(Figure 6).* However, both diastereoisomers were produced as single enantiomers thanks to the enantiopure starting material.

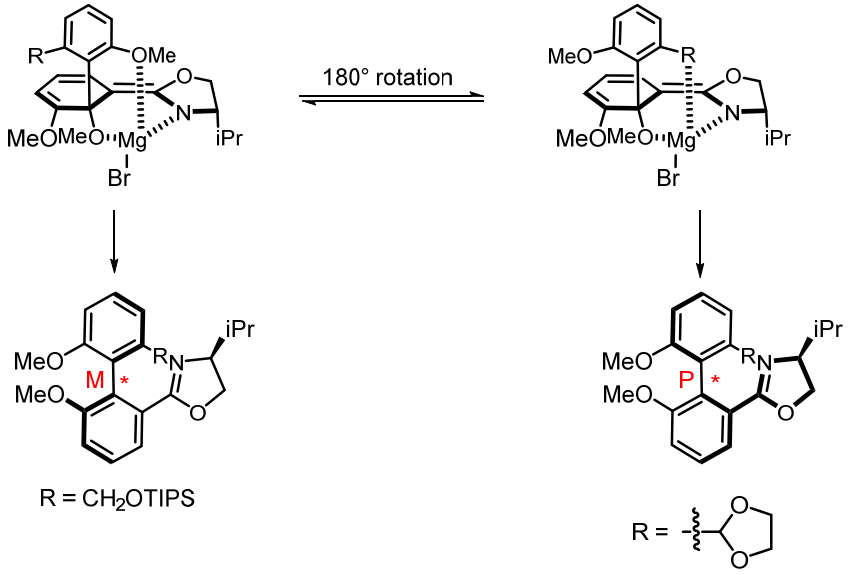


Figure 6. Diastereoselection control

Cammidge et al.[5] reported another important example of cross-coupling reactions, namely, the first asymmetric Suzuki coupling for the construction of binaphthalenes. Typically, the reaction partners in Suzuki cross-couplings are a boronic acid and a halide or triflate that, in the presence of a catalytic amount of palladium(0), lead to the formation of a new C-C bond.

This reaction can be exploited also for the formation of atropisomeric biarylic systems, and the use of chiral and enantiopure ligands for palladium allows the control of the enantioselection of the reaction. Cammidge et al. obtained good enantioselectivities using, as ligand, a ferrocene derivative which displays a diphenyl phosphine substituent and a tertiary amine on one of the two cyclopentadienyl rings (*Figure 7*).

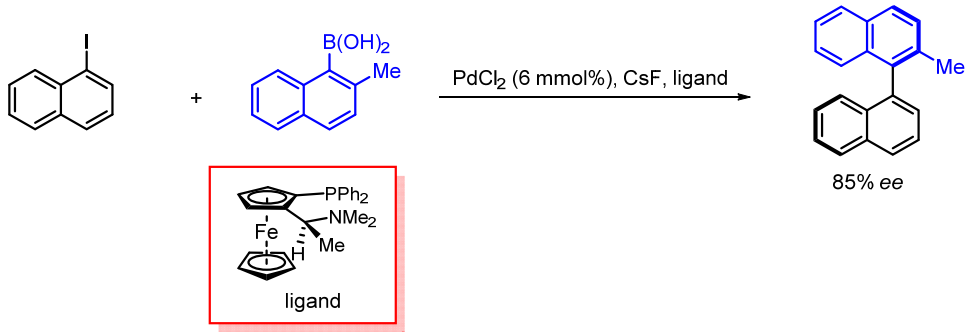


Figure 7. Example of Suzuki enantioselective cross-coupling

1.3.2. **Asymmetric biaryl synthesis by construction of an aromatic ring**

Another important approach for the synthesis of atropisomers is the construction of an aromatic ring. Among others, the use of alkynes and nitriles scaffolds in [2+2+2] cycloaddition reactions are a very elegant procedure to give a broad variety of benzene and pyridine derivatives in one synthetic step. This type of reactions is generally catalyzed by transition metals, and the use of a chiral ligand allows the synthesis of asymmetric atropisomers in an enantioenriched fashion.

In this field, Gutnov and Heller[6] reported the use of cobalt to catalyze [2+2+2] cycloadditions of alkynes and nitriles to give 5,6,7,8-tetrahydroquinoline scaffolds. The peculiarity of this reaction is the irradiation of the reaction mixture with visible light (λ= 350-500 nm) or alternatively with sun light for catalyst activation, permitting to carry out the reaction under mild conditions. Furthermore, the use of chiral ligands for cobalt allowed to obtain the desired product in high enantiomeric excess (*Figure* 8).

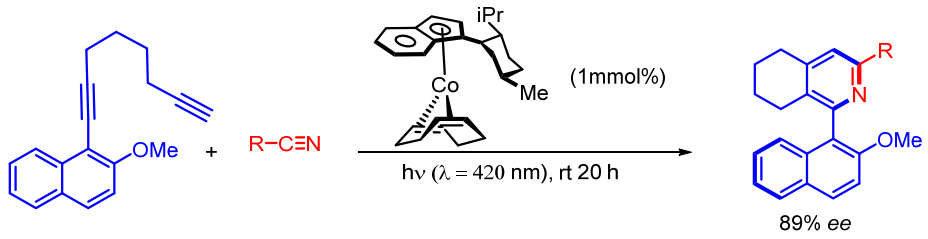


Figure 8. [2+2+2] Cycloadditions for stereoselective atropisomers synthesis

Another example for the synthesis of atropisomers using a [2+2+2] cycloaddition has been reported by Takagi et al.[7] In this work, the authors exploited the cycloaddition reactions of α,ω-diynes and monoalkynes using an iridium catalyst in combination with a chiral phosphine, such as (*S*,*S*)-Me-Duphos, to obtain particular atropisomers characterized by three aryl rings and two chiral axes (*Figure 9*) with excellent control of both enantio- and diastereoselectivities.

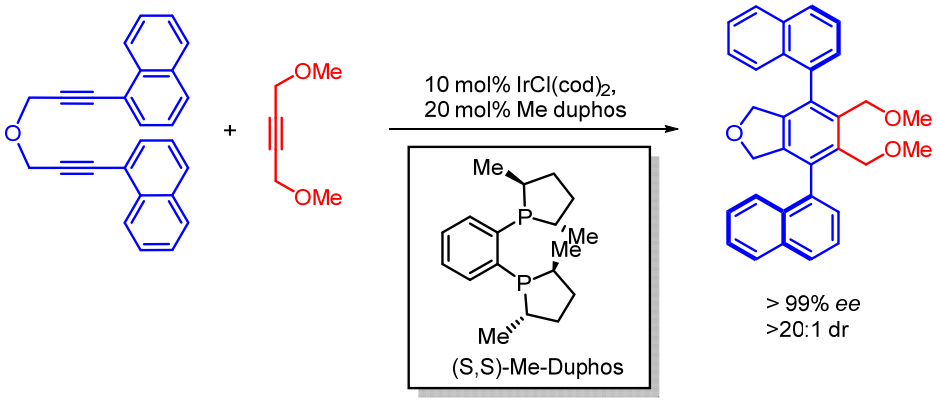


Figure 9. [2+2+2] cycloaddition to obtain three aryl rings atropisomeric compounds

The presence of two naphthalenic groups linked to the arylic core allow the formation of two different diastereoisomers, the *dl* and the *meso* form of the same product. However, owing to the presence of a symmetry plane, the *meso* isomer does not satisfy chirality requirements and only one of the two diastereoisomers, the *dl* form, can exist as two separate enantiomers.

1.3.3. **Desymmetrization of *meso* axes**

Moving away from the construction of chiral axes either by cross-couplings or aryl formation processes, another powerful tool to achieve axially chiral compounds is the desymmetrization of *meso* biaryls. More in detail, this approach takes into account achiral substrates, characterized by hindered rotation along a *meso* axis. In order to create

a chiral axis for this type of products it is possible to follow a desymmetrization approach.

Harada et al.[8] take advantage of two simple Mitsunobu reactions to create a bridge across the two aromatic rings of 2,2′,6,6′-tetrahydroxybiphenyl. In this work, the authors start from an achiral substrate, thanks to a double symmetry plane, which characterizes the tetraol. They are then able to create the first ethereal moiety with inversion of configuration of the chiral center involved in this reaction. After cleavage of the silyl protecting group, a second Mitsunobu reaction is employed to create the bridge across the two aromatic rings in a very stereoselective fashion (*Figure 10*).

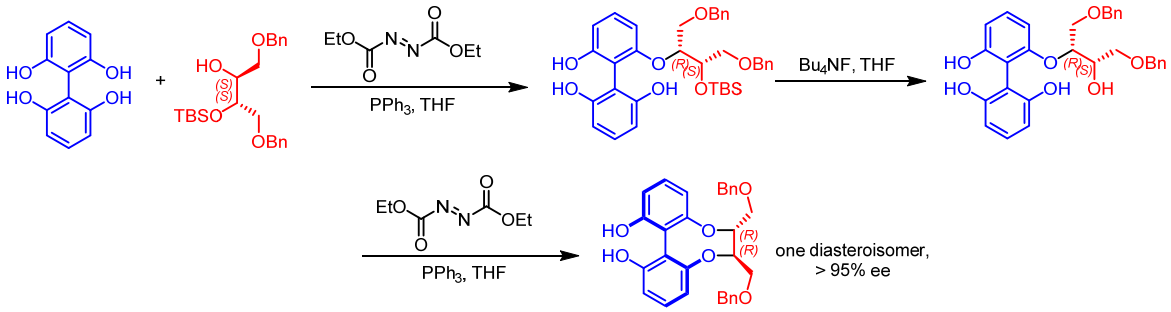


Figure 10. Desymmetrization of meso biaryls

Owing to the use of the enantiopure reagent, i.e. the aliphatic protected diol, and to the streospecificity of the Mitsunobu reaction, it is possible to obtain two different diastereoisomers from the desymmetrization of the achiral tetraol, but only one diastereoisomer was obtained. The authors tried to explain this experimental evidence through computational calculations and taking into account the steric hindrance, characterizing the non-observed diastereoisomer. Computational calculations showed that the observed diastereoisomer (showed in *Figure 11*) is 2.57 kcal/mol more stable than the disfavored one.

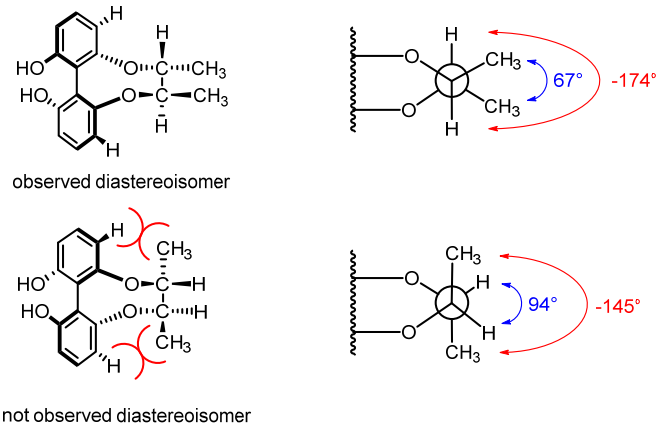


Figure 11. Analysis of steric hindrance in the two possible diastereomeric products

1.3.4. **Dynamic kinetic resolution of atropisomers**

One of the last strategies for the stereoselective synthesis of atropisomers mentioned in the introduction of this chapter is the dynamic kinetic resolution of chiral but stereochemically not defined biaryls. Besides common kinetic resolutions of racemic atropisomers displaying perfect rotational stability, which conceptually do not differ from kinetic resolutions of centrally chiral molecules, this approach relies on chiral substrates characterized by an unstable configuration. Rotation of the σ-bond, fast in the reactants, will be impaired in the products by the stereoselective process.

An example of this approach for the enantioselective synthesis of atropisomers was reported by Gu.[9] The process involved a racemic indole scaffold which, in the presence of a palladium catalyst and an enantiopure TADDOL-derived ligand, undergoes C-H cyclization in an enantioselective pathway. The free rotation of the σ-bond of the reactant, red in figure, allows the dynamic kinetic resolution process with very good yield and enantiomeric excess (*Figure 12*).

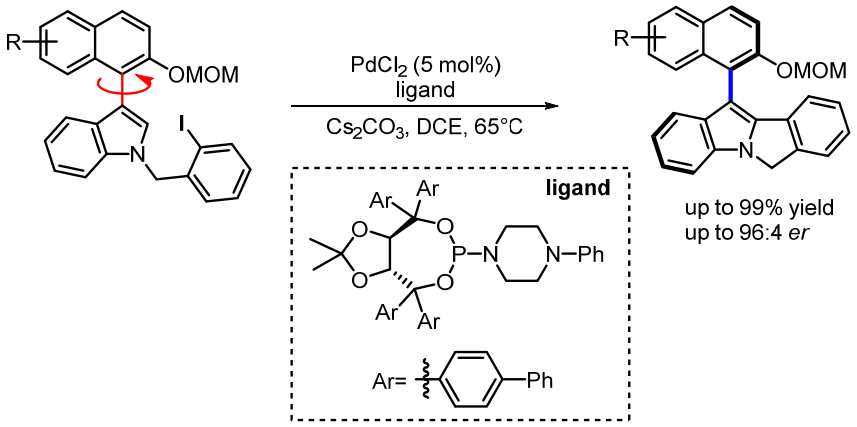


Figure 12. Example of dynamic kinetic resolution of a biaryl scaffold

1.3.5. **Central-to-axial chirality conversion approach**

The central-to-axial chirality conversion approach was theorized for the first time in 1955 by Berson,[10] who proposed an experiment to transform a chiral 4-aryl-1,4-dihydropyridine to a 4-arylpyridine with simultaneous destruction of the chiral center present at C-4 and the subsequent formation of the chiral axis (*Figure 13*).

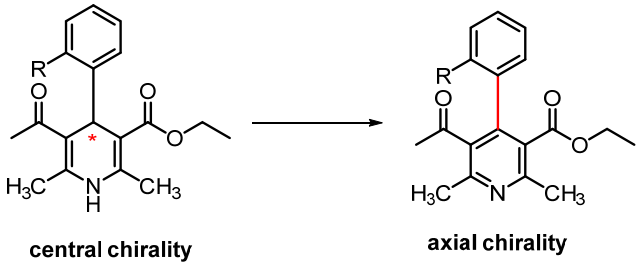


Figure 13. First proposal of a central-to-axial chirality conversion approach

In order to simplify the problem and allow an assessment of the efficiency of the asymmetric transfer, several criteria must be respected. In particular, the starting material must be resolvable, i.e. there should be free rotation around the sp^3-sp^2 σ-bond of the centrally chiral reagent (the dihydropyridine in the example below); this should be readily convertible to a product containing (possibly) only biphenyl asymmetry; the product should have complete optical stability under the conditions of the reaction, or at least the optical half-life should be conveniently measurable.

Unfortunately, due to experimental difficulties, this postulate was not verified until 1984 when Meyers and Wettlaufer[11] developed the first example of the central-to-axial chirality conversion approach using a chiral and enantiopure 1,2,3,4-tetrahydroquinoline substrate. They thus obtained, after oxidation, a quinoline, characterized by a chiral axis.

In this work, the authors started from a chiral and enantiopure quinoline (**I**, *Figure 14*) and, thanks to the reaction with two different organometallic compounds, 1-naphthyl lithium and 1-naphthyl magnesium bromide, along with different reaction conditions, they obtained the desired tetrahydroquinolines **(II)** and **(IIa)** in two opposite diastereomeric forms. Subsequently, following an oxidation reaction with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), it was possible to achieve the aromatic P-quinoline **(III)** and M-quinoline **(IIIa)**, with respect to the chiral axis, with complete retention of the starting enantiomeric excess of the chiral center.

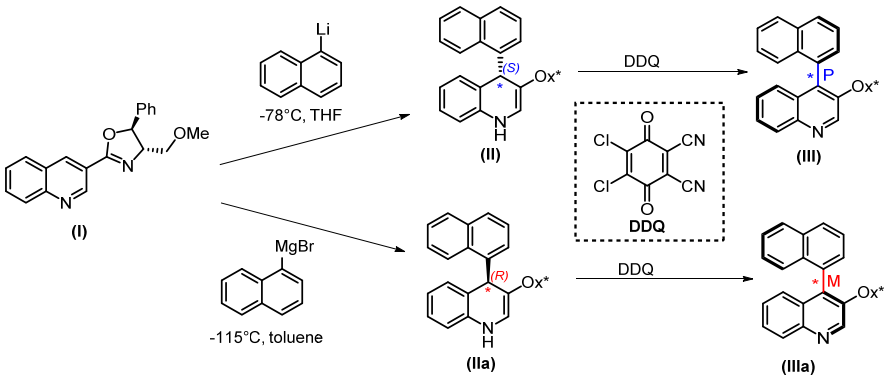


Figure 14. First example of central-to-axial chirality conversion approach

This work is important not only because it demonstrates the feasibility of the process theorized by Berson, but also because confirms the proposed mechanism for the oxidation step. Indeed, starting from a stereochemically defined centrally chiral parent molecule, both the enantiomers of the derived axially chiral compound can be obtained, in a central-to-axial chirality conversion approach. In other words, starting from an "*R*" chiral center, both the "*M*" and the "*P*" axes can be obtained. This implies that retention of chirality is not granted. Indeed, considering the example by Meyers, rotation of the sigma bond (sp^3-sp^2) is free in the dihydroquinoline, and becomes impaired only in the oxidized quinoline (sp^2-sp^2). Thus, oxidation of conformer A (*Figure 15*) will lead to stereoisomer X, while oxidation of conformer B will lead to Y. This means that, if these two oxidations occur at an equivalent ratio, a racemic mixture of the quinoline product will be obtained, starting from the enantiopure starting material. It is also worth of note that conformer A is supposed to be more stable, as the bulky naphthalene group points towards the small hydrogen atom. However, at the same time this hydrogen atom is well shielded from the action of an external reagent.

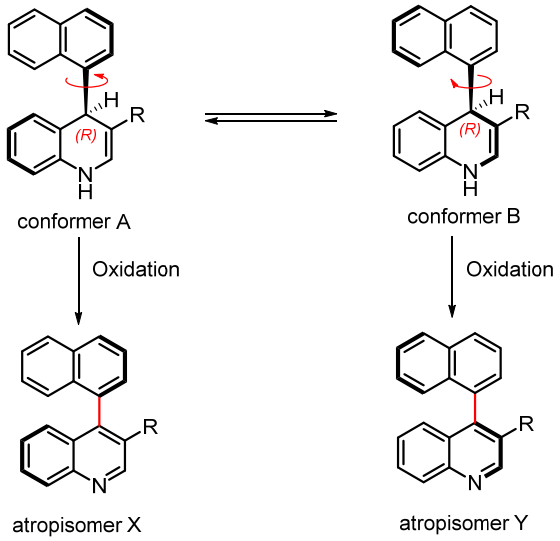


Figure 15. Racemizing central-to-axial chirality conversion starting from enantiopure reagent

To explain that racemization was not observed, the process leading instead to the complete retention of the enantiomeric excess in the central-to-axial chirality conversion, the authors proposed that oxidation occurred on only one of the two possible conformations present in the reaction mixture. In particular, they hypothesized a hydride transfer mechanism from the substrate to DDQ, and subsequent oxidation. This was proposed to occur selectively on the minor, but more reactive due to the more accessible hydride, conformer (B in *Figure 15*). This means that DDQ manages to oxidize only the minor conformation that the reagent takes in solution, after the rotation of the σ-bond between the dihydroquinoline and the naphthalene (*Figure 16*).

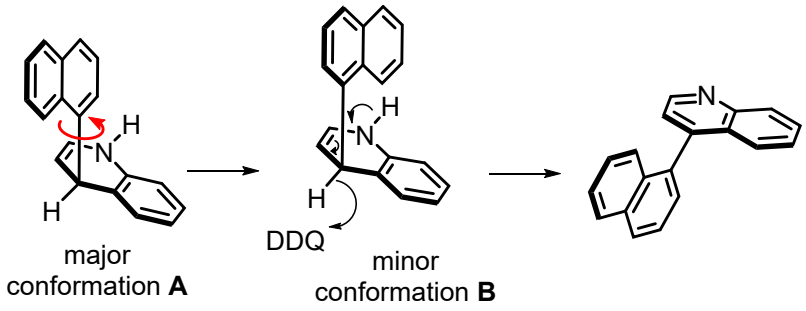


Figure 16. Exemplification of mechanism proposed

Rodriguez et al. have studied two important examples for the central-to-axial chirality conversion approach. In the first work,[12] they take advantage of an enantioselective Michael addition reaction to synthetize 4-aryl-1,4-dihydropyridines, followed by a central-to-axial chirality conversion through an oxidative aromatization. In particular, they exploited the reaction between dimedone (**I**) and β-aryl-2-enoylpyridines such as

(**II**) as suitable electron-poor Michael acceptors which, in the presence of (*R*,*R*)-Takemoto thiourea catalyst, undergo Michael addition to create 1,4-dihydropyridines (**III**) with good enantiomeric excesses. The dihydropyridines were later oxidized with manganese dioxide to create enantioenriched 4-arylpiridines (**IV**) with good retention of the starting enantiomeric excess, indicated as *cp*, conversion percentage (*Figure 17*).

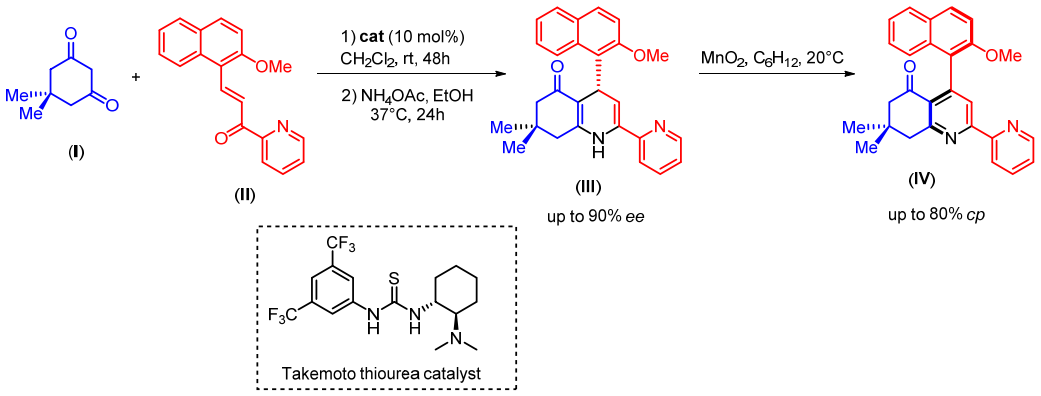


Figure 17. Enantioselective Michael addition followed by oxidative aromatization

The proposed model for the chirality conversion from 1,4-dihydropyridines to 4-arylpiridines is showed in *Figure 18* and follows the lines proposed by Myers depicted in *Figure 16*. In particular, these 1,4-dihydropyridines can exist as two different conformers (**I** and **II**), with different steric hindrance neighboring the hydrogen atom (green in conformer **I** and red in conformer **II**) which will be removed during the oxidation step, in fast equilibrium. The steric hindrance created by the substituents of the aromatic ring permits the oxidation of only one of the two different conformers (minor conformer **I**) which leads to the formation of *P* atropisomers as major enantiomers.

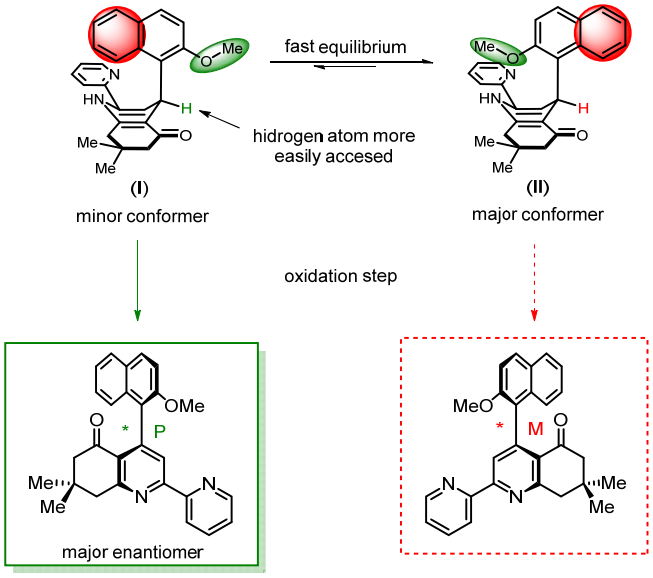


Figure 18. Proposed model for the chirality conversion

In the second work,[13] Rodriguez et al. exploited again an enantioselective Michael addition between dimedone (**I**) and in this case a particularly designed nitroolefin such as (**II**) as electron-poor Michael acceptor to create dihydrofuran (**III**), possessing central chirality. The synthetized dihydrofurans were later oxidized with (bisacetoxyiodo)-benzene (BAIB) under basic conditions, to give atropisomeric furan derivatives (**IV**) (*Figure 19*).

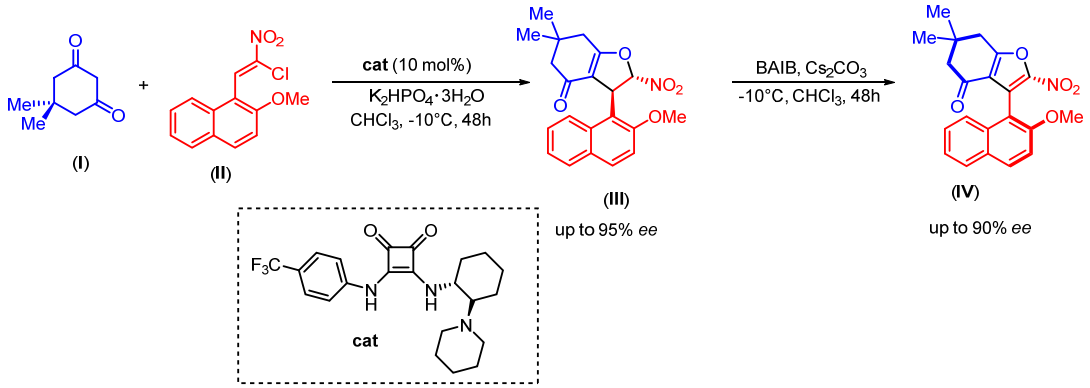


Figure 19. Chirality conversion approach for atropisomeric synthesis of furan derivatives

In this case, the proposed model for the chirality conversion approach is different to the previous one, as the oxidation reaction occurs on the major conformer. In particular, the dihydrofuran derivative, under basic conditions, loses its acidic proton to create a nitronate intermediate with free rotation around the C-C bond (green in figure). The nitronate intermediate acts as a nucleophile towards the oxidant agent to create two different conformers in equilibrium, thanks to the slow but accessible rotation around the

C-C bond (red in figure). The oxidation reaction occurs only on the major conformer thanks to the minor steric hindrance between the methoxy and nitro groups, compared to the steric hindrance between the naphthalene and the nitro groups that characterizes the minor conformer (*Figure 20*). In other words, in this case the hydride abstraction occurs intramolecularly and is less affected by steric factors. Therefore, stability of the intermediates dictates the major product obtained.

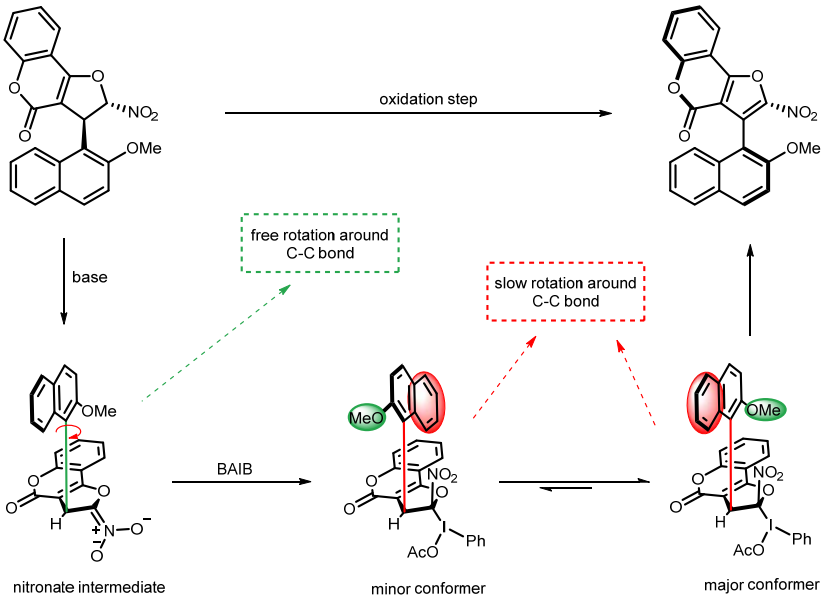


Figure 20. Proposed model for the chirality conversion

These two examples are important not only because they demonstrate further the potential of the chirality conversion approach for the synthesis of atropisomeric systems, but also because in the last contribution the authors incorporate a more demanding five-membered ring into the chiral biarylic compounds, since rotation of the σ-bond between bi(het)aryl rings wherein one of the two rings is five-membered is generally easier than rotation of the σ-bond between two aromatic systems, even with *ortho*-substituents featuring similar steric hindrance. Therefore, synthesis and isolation of atropisomers is more demanding in the former than in the latter case.

1.3.6. **Povarov Reaction**

Numerous enantioselective organocatalytic transformations deliver partially saturated carbo- or heterocycles bearing stereogenic centers, optimal candidates for the preparation of axially chiral compounds following a central-to-axial chirality conversion approach. A powerful tool for the synthesis of 1,2,3,4-tetrahydroquinolines (indeed a partially saturated heterocycle), is the organocatalytic enantioselective Povarov reaction. The Povarov reaction can be described as an acid catalyzed inverse-electron-demand [4 + 2] cycloaddition, between an *N*-arylimine and an electron rich olefin (*Figure 21*).[14]

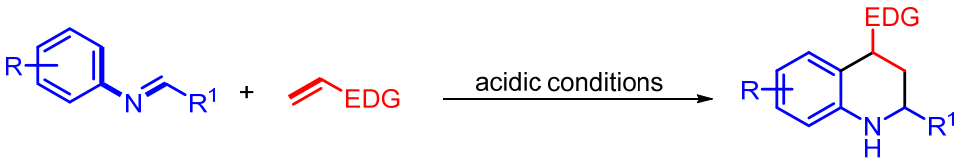


Figure 21. General scheme for Povarov reaction

In contrast with the famous Diels-Alder cycloaddition which involves the reaction between an electron rich diene and an electron poor dienophile, the Povarov reaction involves the reaction between an electron poor dienophile and an electron rich diene, and is thus described as an inverse-electron-demand cycloaddition (*Figure 22*).

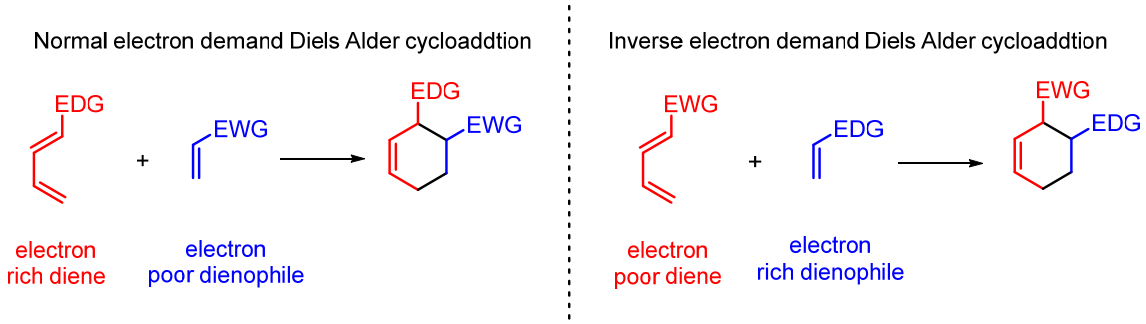


Figure 22. Differences between normal and inverse electron demand Diels-Alder cycloadditions

Two reaction pathways are possible, depending on the features of the reaction partners and promoters: a concerted asynchronous transition state, resembling the Diels-Alder cycloaddition, and a stepwise mechanism which involves a nucleophilic addition to the imine, which leads to the formation of a zwitterionic intermediate, followed by a Friedel-Crafts reaction for the ring closure (*Figure 23*).

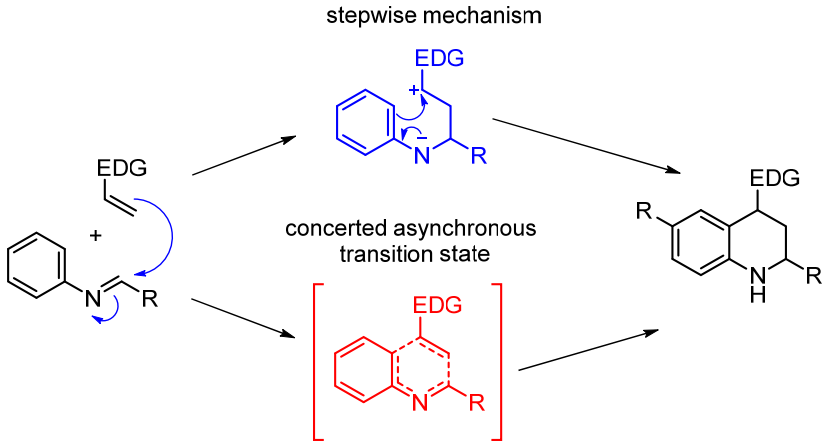


Figure 23. Proposed mechanisms for Povarov reaction

The stepwise mechanism is more common, and explains the byproduct of interrupted Povarov reactions, observed in many examples of this cycloaddition.[15] The interrupted Povarov reaction product is formed due to the nucleophilic attack of a an external nucleophile (or a second molecule of the electron rich dienophile) to the intermediate **I**, instead of the ring closing event (*Figure 24*).

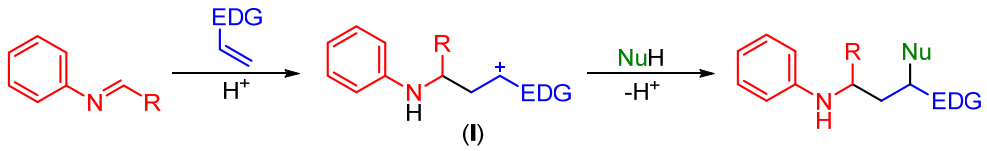


Figure 24. Interrupted Povarov reaction

1.3.7. **Enantioselective Povarov reaction**

Since the Povarov reaction proceeds via acid catalysis, the enantioselective version of this reaction has been extensively developed with chiral acids. The best catalysts for this reaction are BINOL derived, bifunctional phosphoric acids, which contain both a Brønsted acid site and a Lewis basic site that can coordinate the electron poor diene and the electron rich dienophile, respectively (*Figure 25*).

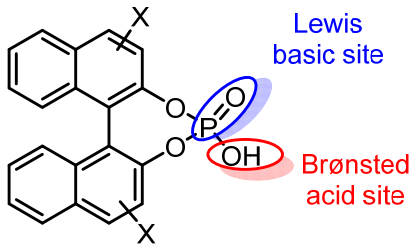


Figure 25. Generic bifunctional phosphoric acid catalysts

The enantioselective Povarov reaction was developed with different electron rich dienophiles and in two different approaches, a two-component and a three-component version. In the first case a pre-formed imine is employed, while in the second this is generated *in situ* by reaction of an aniline and an aldehyde.

An example of the three-component Povarov reaction employing *N*-vinylcarbamates as dienophiles was reported by Masson and coworkers.[16] In this work, the authors take advantage of the reaction between different anilines and both aromatic and aliphatic aldehydes for the synthesis of the imine. Addition of the *N*-vinylcarbamate and the chiral acid catalyst to this imine allows the formation of tetrahydroquinoline scaffolds in very good yields and enantioselectivities, as single *cis* diastereoisomers (*Figure 26*).

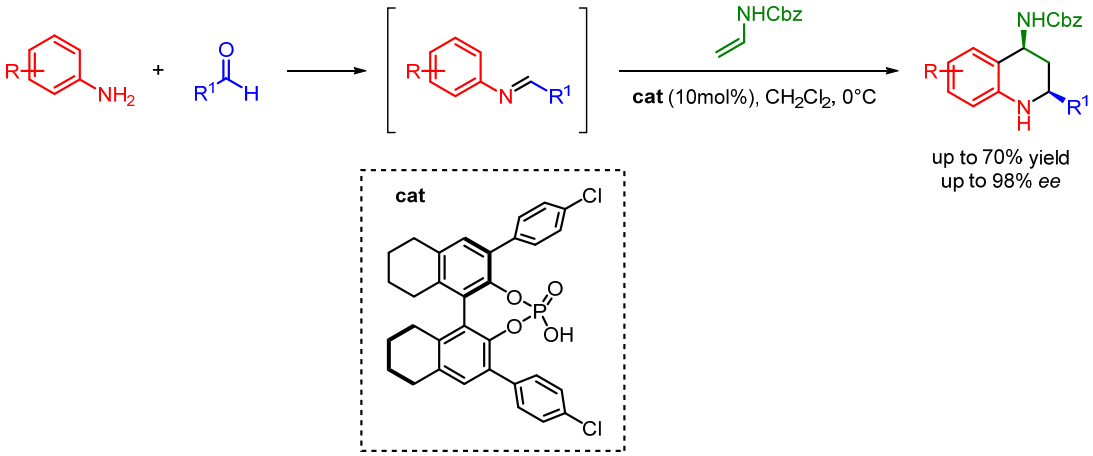


Figure 26. Example of three-component Povarov reaction and enecarbamate as dienophile

As previously mentioned, chiral phosphoric acids are the best catalysts for this type of reactions, owing to the presence of both Brønsted acid sites and Lewis basic sites, prone to coordinate, in the chiral pocket, the two partners of the reaction. In particular, thanks to hydrogen bonding interactions, the Brønsted acid moiety coordinates the electron poor diene (arylimine) while the Lewis basic moiety coordinates the electron rich dienophile, in this case the *N*-vinylcarbamate. Regarding the stereochemistry of the product, the authors assume that the bifunctional phosphoric acid create the transition state shown below in which the *Si*-face of the *N*-vinylcarbamate reacts in a *pseudo*-intramolecular fashion with the *Si*-face of the imine (*Figure 27*).

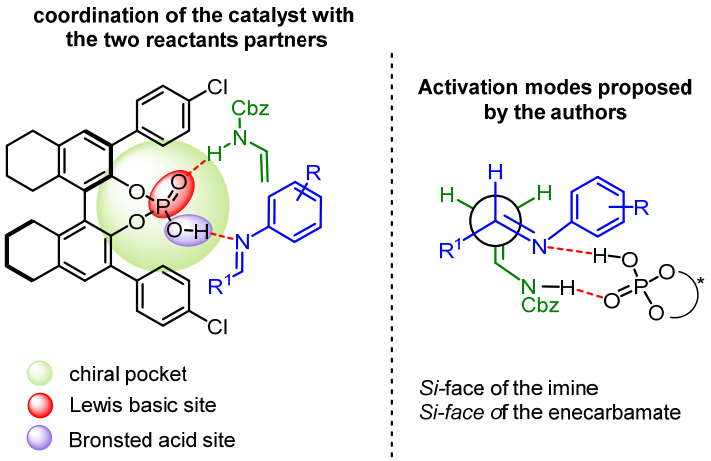


Figure 27. Coordination of the catalyst and transition state proposed by the authors

An example of two-component Povarov reaction approach and vinylindoles as dienophiles was reported by Bernardi et. al.[17] In this work, the authors change the nature of the dienophile system using vinyl(hetero)arenes, in particular 2- and 3-vinylindoles, as electron rich partners for this reaction. These two electron rich dienophiles, sharing a very similar structure, have actually a very different reactivity and stability. In particular, 3-vinylindoles, less stable species, react with an electrophile through the terminal double bond, activated by the NH moiety without involving the electrons of the fused benzene ring. On the other hand, activation of 2-vinylindoles requires breaking of the aromaticity, rendering these species less activated and thus more stable (*Figure 28*).

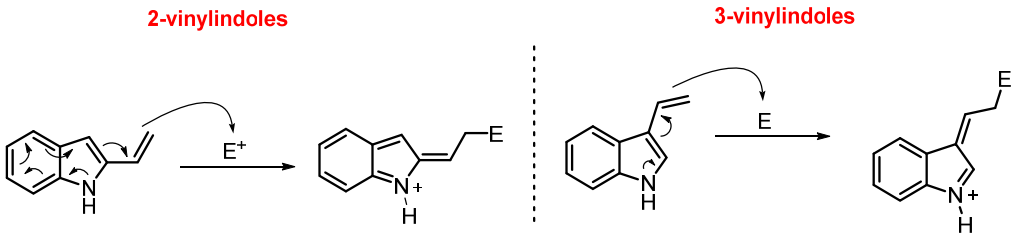


Figure 28. Different reactivity of 2- and 3-vinylindoles

The different stability and reactivity of these species is observed also when they are employed as dienophiles in the Povarov reaction. In particular, the reaction conditions with 3-vinylindoles are milder, indeed the authors employed THF as the solvent (which thanks to the ether moiety decreases the acidity of the catalyst) and a slow addition of the dienophile, to prevent its degradation. On the other hand, the reaction conditions with 2-vinylindoles are harsher, due to the use of a non-coordinating solvent and molecular sieves, employed to increase further the acidity of the catalyst. In both cases the authors obtained tetrahydroquinoline scaffolds in very good yields and enantioselectivities (*Figure 29*).

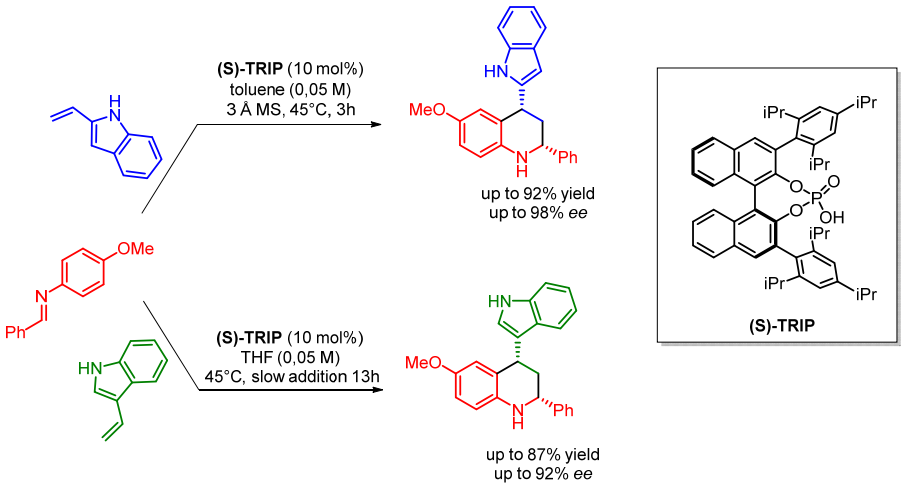


Figure 29. 2- and 3-vinylindoles as dienophile

The hypothesized coordination of the phosphoric acid to the two reaction partners is similar to the previous one (see *Figure 27*). The arylimine is coordinated to the Brønsted acid moiety and the vinylindole is coordinated to the Lewis basic moiety (*Figure 30*).

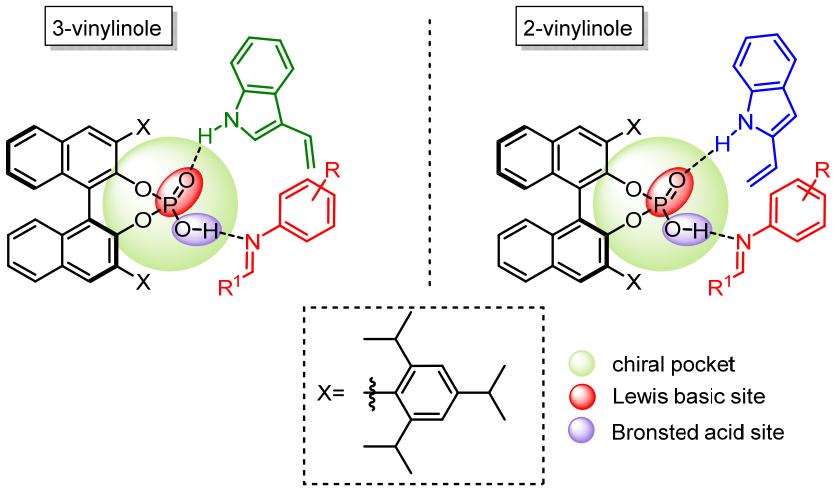


Figure 30. Coordination of the phosphoric acid to the two reaction partners

2. Aim of the Thesis

Aim of this thesis is the enantioselective synthesis of atropisomeric indolyl-quinoline systems, using a central-to-axial chirality conversion approach. This approach consists first in the construction of enantioenriched tetrahydroquinolines **3** exploiting an organocatalytic asymmetric Povarov cycloaddition between *N*-arylimines **1** and 3-alkenylindoles **2**. Then, the central chirality of products **3** will be converted into the axial chirality of products **4**, through an oxidation reaction (*Figure 31*).

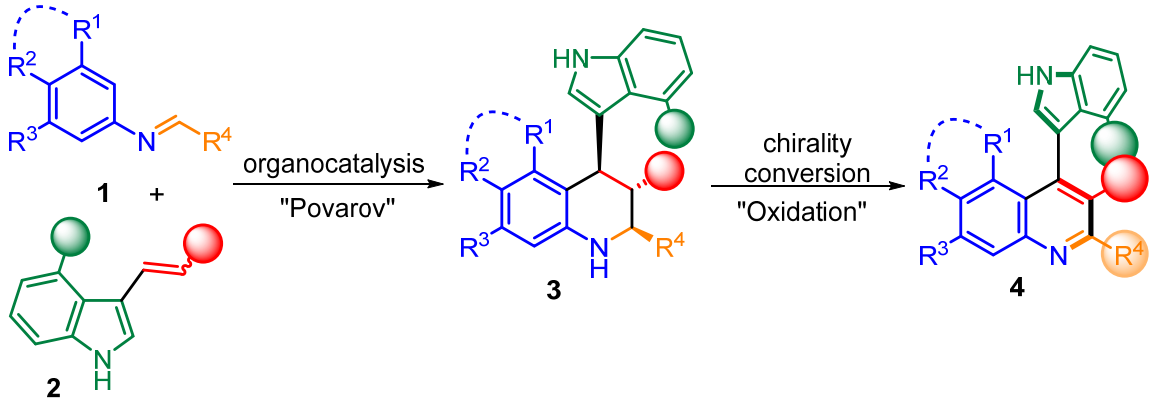


Figure 31. Merging organocatalytic enantioselective Povarov cycloadditions with the central-to-axial chirality conversion concept

In order to realize this approach, optimization of all process and auxiliary synthetic steps is required. First of all, the synthesis of the starting materials (*N*-arylimines **1** and 3-alkenylindoles **2**) displaying the correct substitution pattern will be carried out, facing the challenges of optimizing practical and fast procedures, able to produce easily the required amount of material.

Optimization of the Povarov cycloaddition will be studied by modifying a known procedure,[17] in order to adapt the protocol to differently substituted substrates. With the best conditions for the Povarov reaction in hand, we will start our investigation in order to identify the substrate requirements for the obtainment of configurationally stable axially chiral quinolines **4**. Subsequently, we will move to the optimization of the reaction parameters for the oxidation process, to obtain the highest retention of the enantiomeric excess possible, along with useful synthetic yields (*Figure 32*).

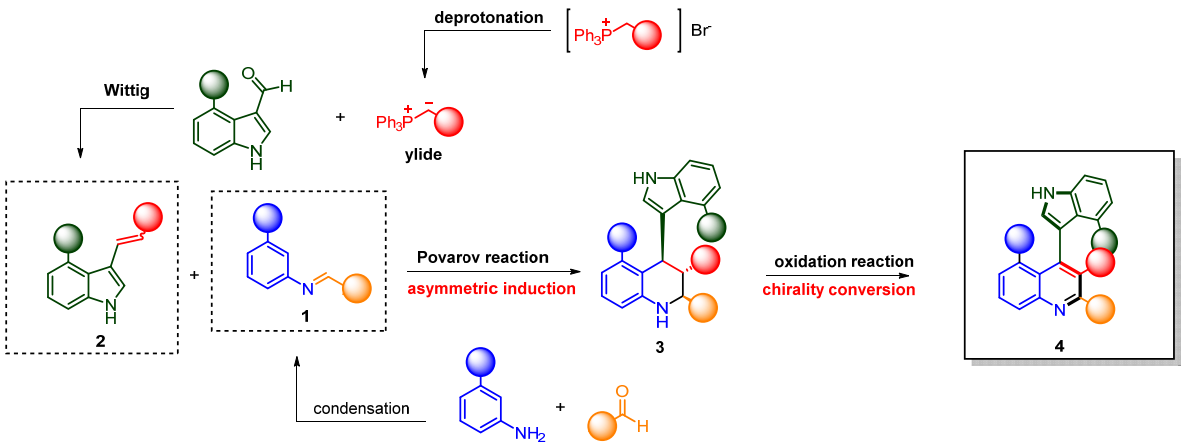


Figure 32. Project overview

We will finally move to the evaluation of the reaction scope, synthesizing different products, modifying imines **1** (on two different positions), as well as the substituent at the 4-position of the indole ring and on the vinyl group of **2** (*Figure 33*).

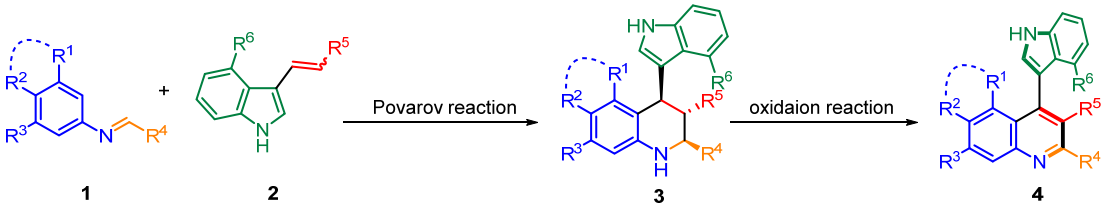


Figure 33. Scope of the Povarov cycloaddition-oxidative chirality conversion process

3. Results and Discussion

Our first efforts were devoted to the identification of the requirements necessary to obtain tetrahydroquinoline scaffolds **3** as starting materials for the application of the central-to-axial chirality conversion approach. We thus desired to achieve good yields and enantioselectivities in the Povarov reaction for the preparation of suitable substrates **4**, able to retain the chiral information after the oxidation step (*Figure 34*).

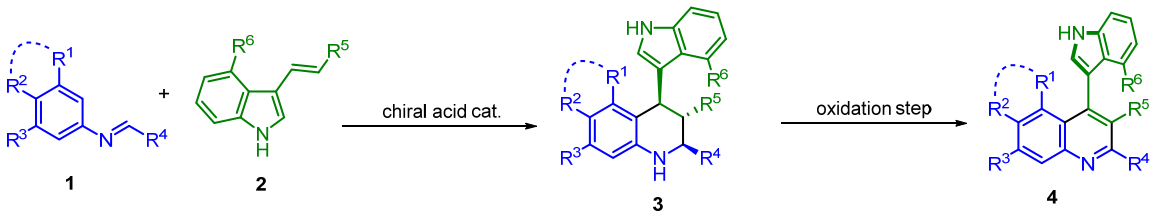


Figure 34. General scheme for the central-to-axial chirality conversion approach

As it will be explained later, 3-alkenylindoles **2**, substituted at the terminal carbon of the vinyl group (and at the 4-position of the indole skeleton) and suitably encumbered *N*-aryl imines **1** are the starting materials for the Povarov reaction, in order to obtain the desired tetrahydroquinolines **3** and, after oxidation, axially chiral quinolines **4**.

3.1. Synthesis of *N*-arylimines 1

The synthesis of *N*-arylimine substrates **1** requires a condensation reaction between an aniline and an arylaldehyde, in order to provide stable *N*-arylimines **1** (*Figure 35*).

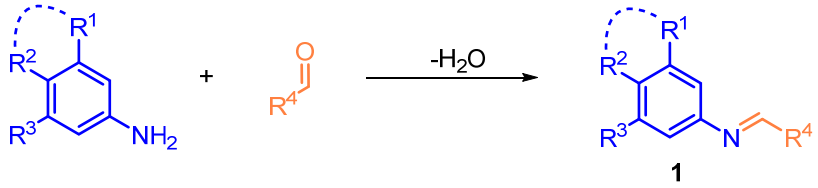


Figure 35. General scheme for the synthesis of N-arylimines

The reaction is run in refluxing toluene or ethanol as solvent and using a Dean-Stark apparatus, in order to facilitate the condensation reaction (when the reaction is run in toluene), due to the removal of water. As a result of the instability of the imines towards acidic sources, their purification cannot involve chromatography on silica gel. In particular, imines **1a** and **1c-f** (*Figure 36*) synthetized using ethanol as solvent, were purified by direct crystallization from the reaction mixture, while imines **1g-i**,

synthetized using toluene as solvent, were purified by precipitation induced by slow addition of diethyl ether to the reaction mixture. Imine **1b** is commercially available.

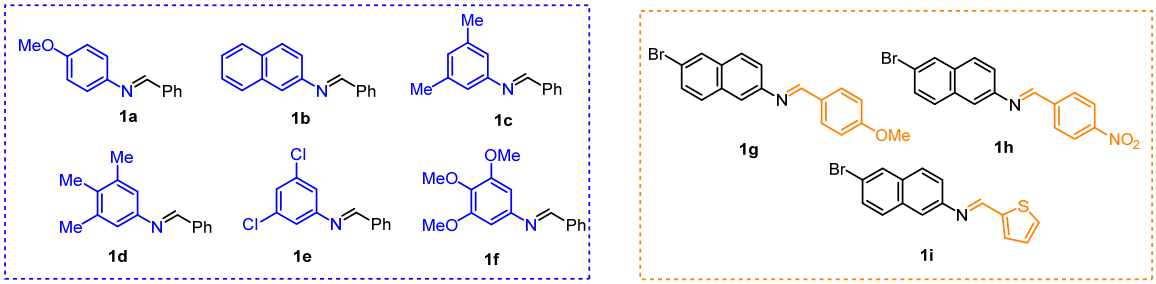


Figure 36. N-arylimines used in the Povarov reaction

3.2.Synthesis of 3-alkenylindoles 2

The synthesis of 3-alkenylindole substrates **2** was one of the first issues encountered in this methodology, because, at least theoretically, a dienophile with *trans* configuration of the double bond is required in the Povarov reaction, for stereoelectronic reasons.[16] In the literature, only one procedure for the synthesis of exclusively *trans* 3-alkenylindoles is present.[18] This methodology is a two-step process and involves the reaction between indoles **I**, aldehydes **II** and benzenesulfinic acid, which, in the presence of substoichiometric amounts of *p*TSA (*p*-toluenesulfonic acid), leads to the formation of intermediates **III**. Subsequently, intermediates **III** undergo E2 elimination under basic conditions (2.5 equiv of NaH and 5 mol% of DBU), with the consequent formation of 3-alkenylindoles **IV** displaying exclusively *trans* configuration at the double bond (*Figure 37*).

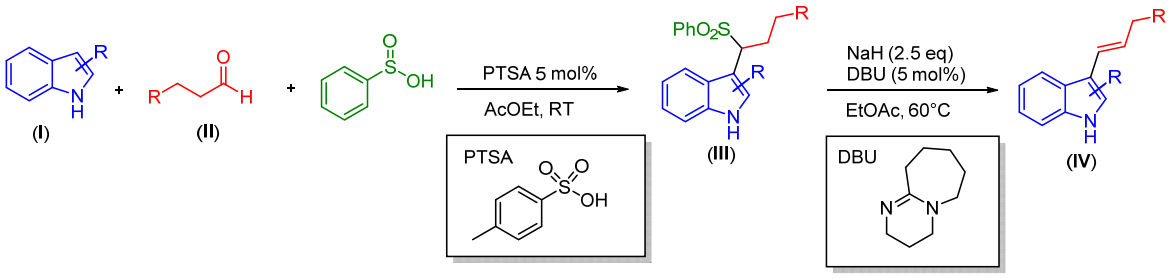
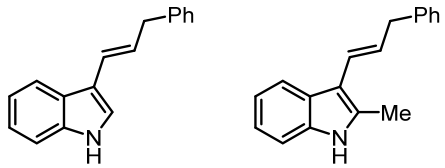


Figure 37. Synthesis of trans 3-alkenylindoles

According to this procedure, two different 3-alkenylindoles, **2a** and **2b**, were synthetized in good yields (*Figure 38*).



2a, yield 80% **2b,** yield 75%

Figure 38. 3-Alkenylindoles synthetized with literature methodology

Unfortunately, this procedure was not found to be suitable for the synthesis of 3-alkenylindoles having a substituent at the 4-position of the aromatic ring. The first step of the reaction led to the formation of the desired sulfone intermediate **III**, but the subsequent step caused an unexpected decomposition of the reaction mixture (*Figure 39*).

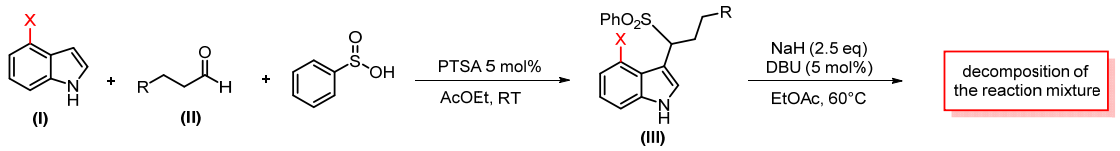


Figure 39. Not suitable two step reaction for the synthesis of 3-alkenyl-4-substituted-indoles

Since main substrate **2c** (*vide infra*) for the Povarov reaction is characterized by a halide substituent at the C-4 position of the aromatic ring, a more versatile process, such as the Wittig reaction, was taken into account.

Wittig olefination employs the reaction of an aldehyde or a ketone with a phosphonium ylide. Generally, the geometry of the resulting alkene depends on the stability of the ylide. If R (*Figure 40*) is an electron withdrawing group (EWG), then the ylide is stabilized and the reaction gives predominantly *(E)*-alkenes, whereas non-stabilized ylides lead to (*Z*)-alkenes. However, many exceptions are encountered in the literature. In particular, olefination of indole-3-carbaldehyde is reported to give nearly equimolar mixtures of *E*/*Z* isomers when reacted with non-stabilized ylides.[19]

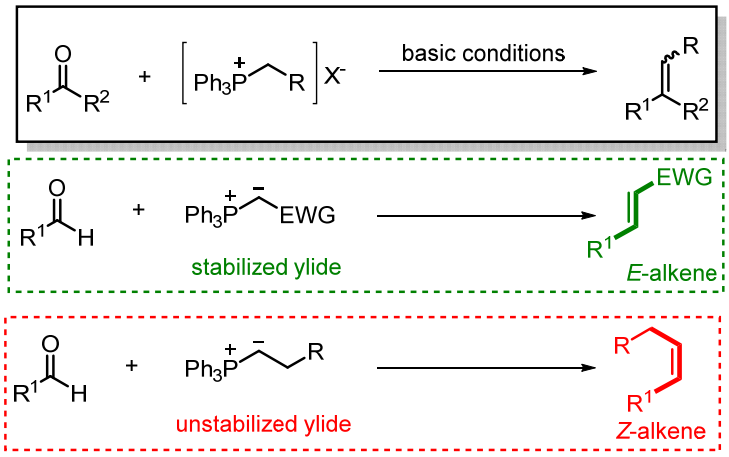


Figure 40. Description of Wittig reaction

The synthesis of 3-alkenylindole **2c** derives from the reaction of 4-bromoindole-3-carbaldehyde **I** and the ylide derived from phosphonium salt **II** (*Figure 41*). In particular, phosphonium salt **II** was treated with *n*-BuLi at -50°C in order to create the ylide, while the aldehyde was treated with a freshly prepared solution of LiHMDS at 0°C, in order to avoid quenching of the highly basic ylide with the NH moiety. Subsequently, the resulting solution of lithiated aldehyde was added to the previously prepared solution of phosphonium ylide.

A mixture of *trans*/*cis* alkenes (*trans*/*cis* = 40: 60) was obtained in excellent yield after purification by very short and fast filtration on silica.

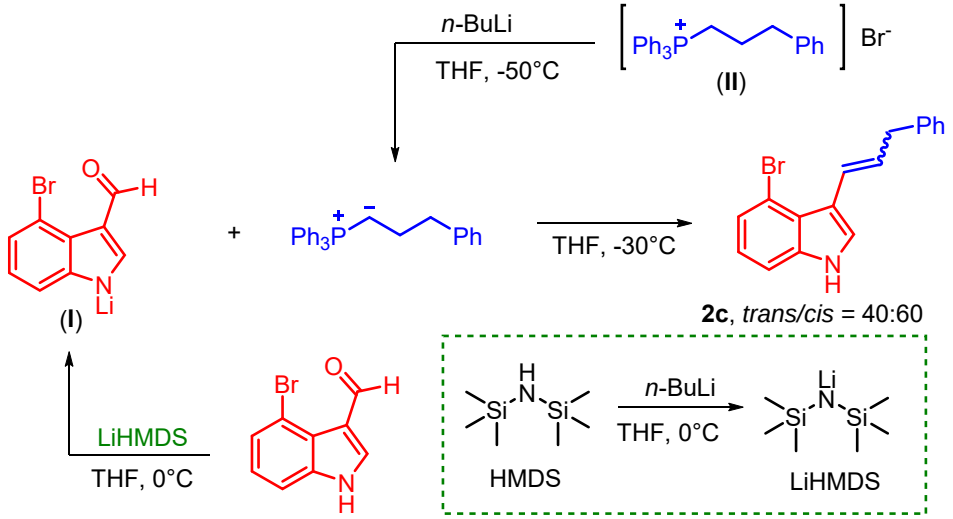


*Figure 41. Synthesis of 3-alkenylindole **2c** characterized by a halide substituent in C4 position of the aromatic ring*

Unfortunately, due to the instability of 3-alkenylindole **2c** in the presence of acidic species and high temperature, it was impossible to separate the two isomers either by proper column chromatography on silica gel or crystallization. The mixture of *trans/cis*

3-alkenylindoles **2c** was subsequently used in slight excess in the Povarov reaction. The presence of a *trans/cis* mixture of 3-alkenylindoles **2** should not represent a problem in the Povarov reaction, because, as reported in the literature,[16] electron rich dienophiles having *cis*-configuration of the double bond do not participate as such in the cycloaddition but undergo, in the presence of acidic species, isomerization of the double bond in order to form the corresponding *trans*-dienophile, which is the reactive species.

According to the previously described Wittig procedure, eight different 3-vinylindoles **2c-j** with different substituents both on the C-4 of the indole ring (**2c-e**) and on the alkenyl group (**2f-j**) were synthetized (*Figure 42*), starting from different indole-3-carbaldehydes and phosphonium salts (precursors of the ylides).

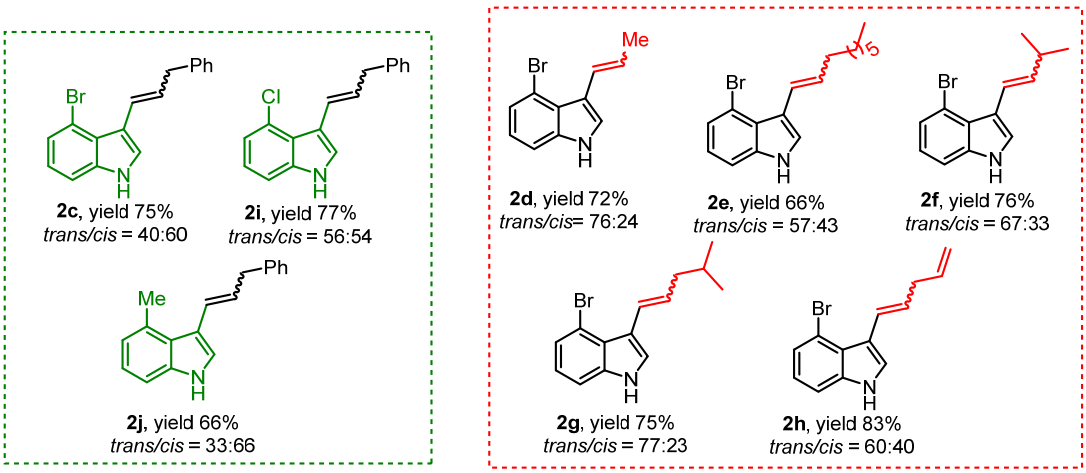


*Figure 42. Eight different 3-alkenylindoles **2c-j** were synthetized*

3.3. Feasibility of the Povarov cycloaddition - central-to-axial chirality conversion approach

Before studying the central-to-axial chirality conversion approach, we investigated the feasibility of the Povarov reaction employing β-substituted 3-alkenylindoles **2**. Indeed, in the literature only the reactivity of simple unsubstituted 3-vinylindole as diene in Povarov cycloaddition is reported.[17]

Regarding the feasibility of the Povarov reaction, we started focusing our attention on a 3-alkenylindole **2** bearing a substituent on the terminal carbon of the vinyl group. Indeed, the main requirement for the obtainment of configurationally stable atropisomers is the presence of at least three substituents around the chiral axis. Thus, after oxidation of tetrahydroquinolines **3**, a substituent at the carbon next to the one bearing the indolyl substituent of quinoline **4** is required. This derives from the residue on the terminal position of the alkenyl group in substrates **2** (*Figure 43*).

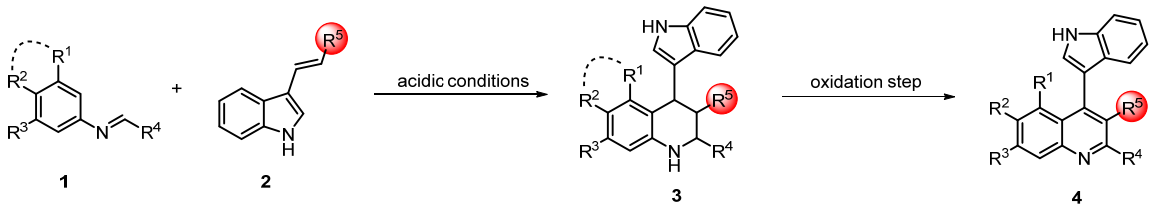


Figure 43. Initially hypothesized requirements for the synthesis of stable atropisomers

The first substrate was synthesized by Povarov reaction of imine **1a** and alkenylindole **2a**, in order to obtain tetrahydroquinoline **3aa** (*Figure 44*). For the reaction conditions of this step see paragraph 3.4. This substrate was obtained as a single diastereoisomer in good yield and enantioselectivity.

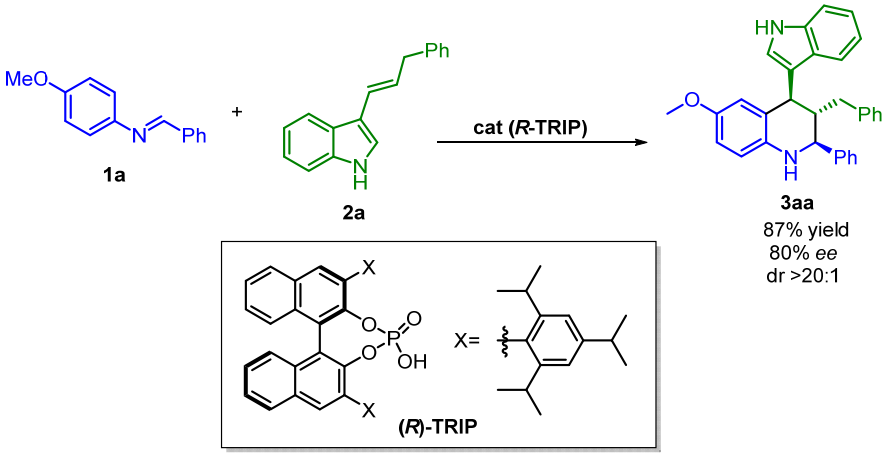


*Figure 44. Feasibility of Povarov reaction with more hindered 3-alkenylindole **2a***

The synthesis of substrate **3aa** demonstrates the feasibility of the Povarov reaction, but unfortunately, after the oxidation step, quinoline **4aa** was found to be configurationally unstable at room temperature and no retention of the chiral information could be observed (*Figure 45*). Indeed, fast rotation of the indole-quinoline σ-bond was observed.

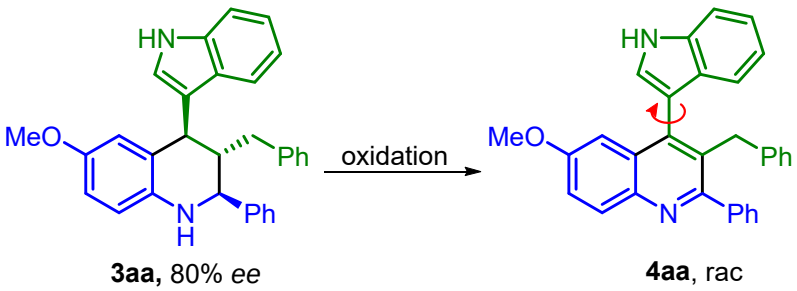


*Figure 45. No retention of chiral information in **4aa***

In order to lock the free rotation, we undertook two different approaches: an increase of the steric hindrance on the 3-vinylindole, employing compound **2b**, keeping imine **1a** as

the reaction partner, or an increase of the steric hindrance on the imine, using *N*-2-naphthylbenzaldimine **1b** and indole **2a** (*Figure 46*).

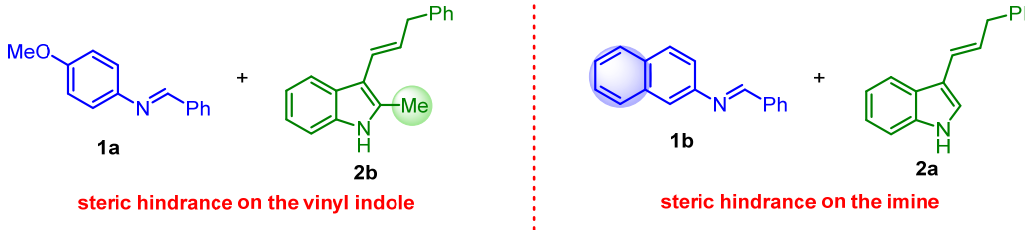


Figure 46. Two different approaches for the choice of the substrate

Regarding the approach providing an increase of the steric hindrance on the 3-vinylindole, tetrahydroquinoline **3ab**, with a methyl substituent on the C-2 position of the indole ring, was obtained in very low yield and enantioselectivity. After the oxidation step, product **4ab** was found to be configurationally stable, but no retention of the chiral information was observed. Product **3ba**, deriving from the reaction of imine **1b** with 3-vinylindole **2a**, was obtained in good yield and enantioselectivity but also in this case, after the oxidation step, product **4ba** was configurationally unstable at room temperature (*Figure 47*).

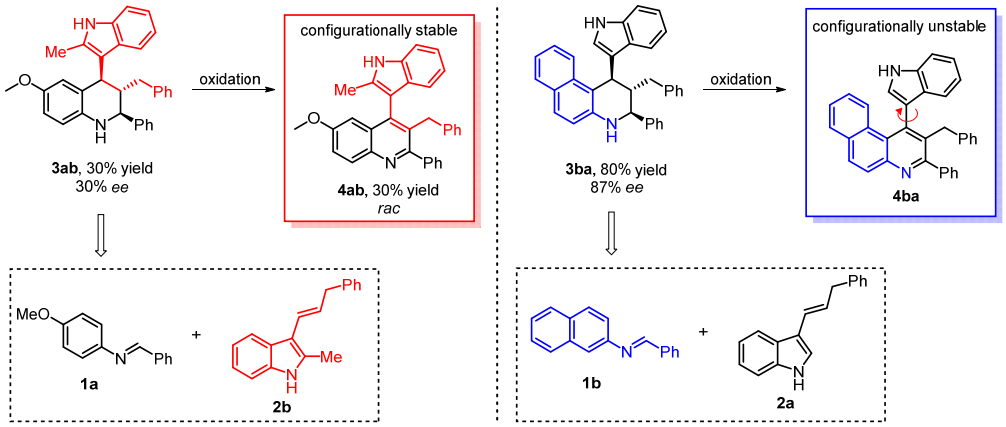


Figure 47. Example of substrates

Since product **3ba** was obtained in high yield and enantiomeric excess while product **3ab** rendered a configurationally stable quinoline **4ab** but obtained in low yield and enantiomeric excess, we decided to merge the two approaches in the synthesis of a new substrate, characterized by a remote steric hindrance on the indole ring. In particular, a substituent on the C-4 position was taken into account. The combination of 2-naphthyl imine **1b** and 3-alkenylindole **2c** in the Povarov reaction showed a very good reactivity with excellent yield and enantiomeric excess for tetrahydroquinoline **3bc**. After the

oxidation step, it was found that product **4bc** was configurationally stable and presented partial retention of the enantiomeric excess imparted in the previous step. However, the value was substantially lower than the one exhibited by parent tetrahydroquinoline **3bc** (*Figure 48*).

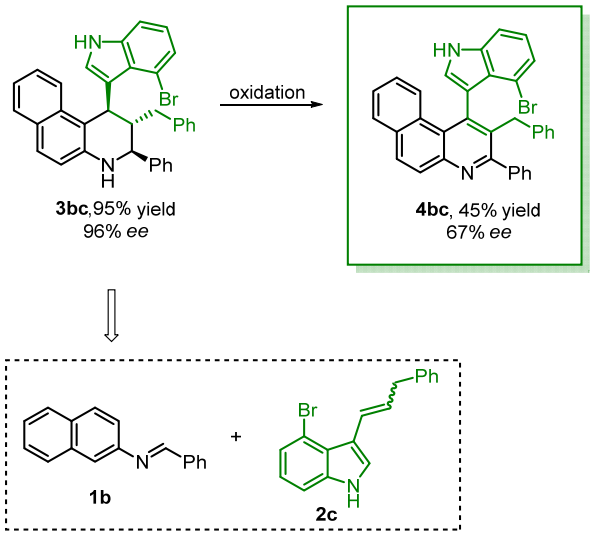


Figure 48. Suitable substrate combination for the central-to-axial chirality conversion approach

This was an exciting result because it demonstrated the feasibility of the central-to-axial chirality conversion approach in the synthesis of a new type of biarylic system. Indeed, the indole ring does not present a steric hindrance in proximity to the axis but in a remote position.

To summarize, we synthesized four different substrates (showed in *Figure 49*), but only one of them presented the correct combination between reactivity in the Povarov reaction and stability of the axial configuration after the oxidation step.

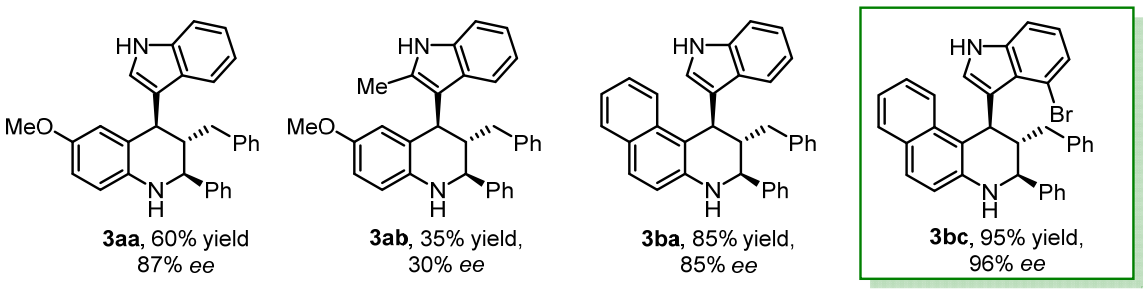


Figure 49. Different substrates synthetized

3.4. Optimization of Povarov reaction

The Povarov reaction using imines as dienes and vinylindoles as dienophiles is a known reaction,[17] and fortunately only minor changes had to be made to the reported procedure in order to adapt it to our differently substituted substrates. As explained in the introduction, both 2-vinylindole and 3-vinylindole can be productively engaged as dienophiles in the Povarov reaction. These two requiring different reaction conditions, however, a commonly employed chiral phosphoric acid such as (*S*)-TRIP was able to efficiently promote their cycloaddition with different imines, achieving high yield and enantiomeric excesses. In particular, 2-vinylindole, a less reactive species, required harsher conditions characterized by a non-coordinating solvent (toluene) and molecular sieves, in order to increase the acidity of the catalyst ((*S*)-TRIP). On the contrary, 3-vinylindole, a more reactive and unstable species, required milder reaction conditions characterized by a coordinating solvent (THF) able to decrease the acidity of the catalyst and a slow controlled addition of the dienophile. Moreover, both methodologies foresaw to run the reaction at 45°C (*Figure 50*).

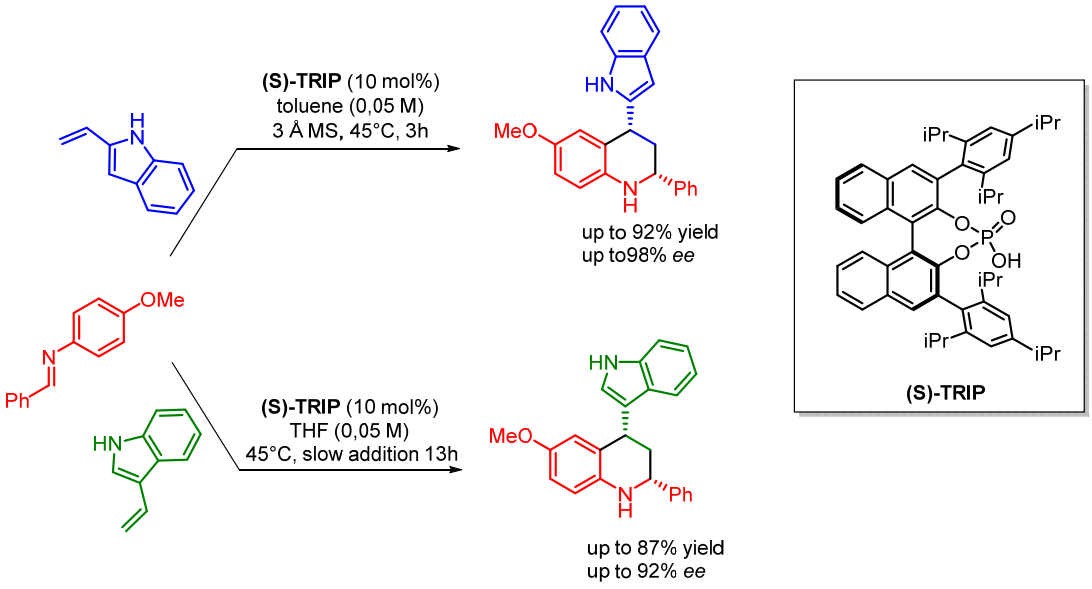
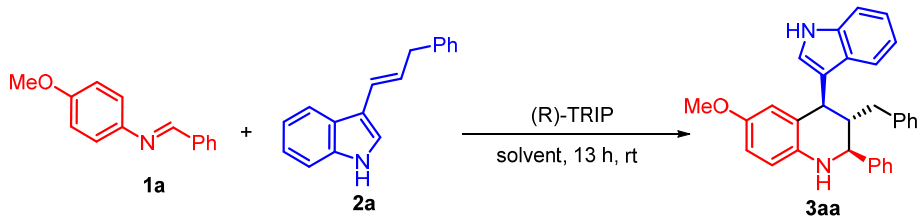


Figure 50. Original conditions of Povarov reactions with 2- and 3-vinylindoles

Taking into consideration the standard methodology for the Povarov reaction using 3-vinylindole as dienophile, we started our investigation with the reaction between *N*-aryl imine **1a** and 3-alkenylindole **2a**. Running the reaction under conditions similar to the ones reported in the literature and described above (entry 1, *Table 1*), the reaction mixture presented a large amount of unreacted 3-alkenylindole **2a**, with about 40% conversion into the desired product **3aa**, showing high enantiomeric excess. This means

that 3-alkenylindoles **2** (having a substituent on the vinyl group) are more similar to simple 2-vinylindole in terms of reactivity. Thus, we decided to carry out the reaction in toluene as solvent (entry 2), in order to avoid solvent coordination to the acidic catalyst, but at the same time we kept fairly mild conditions, avoiding the addition of drying agents and high temperatures. Under these new conditions, the reaction proceeded smoothly and product **3aa** was obtained in good yield and enantiomeric excess. Finally, once we found the best reaction conditions, we successfully lowered the catalytic loading from 10 mol% to 5 mol%, without affecting the yield and the stereoselectivity (entry 3). These conditions were then applied to all the Povarov reactions between imines **1** and 3-alkenylindoles **2**, rendering the results presented in the previous chapter and thereafter.

Table 1. Optimization of Povarov reaction



entry[a]	solvent	conversion [%][b]	yield %	*ee* [%][c]	mol% (*R*)-TRIP
1	THF	40	30	87	10
2	toluene	>99	80	87	10
3	toluene	>99	80	87	5

[a] General method: **1a** (0.1 mmol), **2a** (0.1 mmol), (*R*)-TRIP (x mol%), toluene (1 mL), rt. [b] Determined on the crude reaction mixture by ^{1}H NMR.[c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography.

In the employment of 3-alkenylindole **2c** in the Povarov reaction we had to face the problem of an inseparable *cis*/*trans* mixture (see chapter 3.2). However, by reacting an amount of *cis*/*trans*-**2c** equal to 1 equivalent of *trans*-**2c** with imine **1b**, product **3bc** was obtained as a single diastereoisomer. This represents a strong suggestion that *cis*-3-alkenylindoles are not reactive species. Indeed, if *cis*-**2c** reacted with imine **1b**, another diastereoisomer of **3bc** would have formed (*Figure 51*).

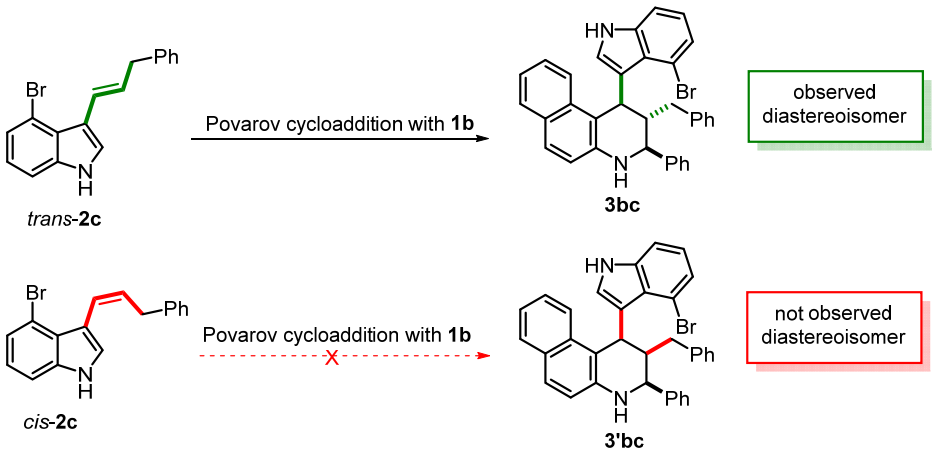


Figure 51. Possible products arising from E/Z-3-alkenylindole ***2c***

Moreover, in order to investigate the possibility of an isomerization of the double bond, as reported in the literature[16], we later set up an experiment by reacting 1 equivalent of *trans/cis* 3-alkenylindole **2c** (equal to 0.35 equivalents of *trans*-dienophile) with imine **1b**, in the presence of $SiEt_4$ as internal standard. Since product **3bc** was formed in 67% ^{1}H NMR yield as a single diastereoisomer, we verified that *cis*/*trans* isomerization occurs, turning the unreactive *cis* isomer into the productive *trans* one (*Figure 52*).

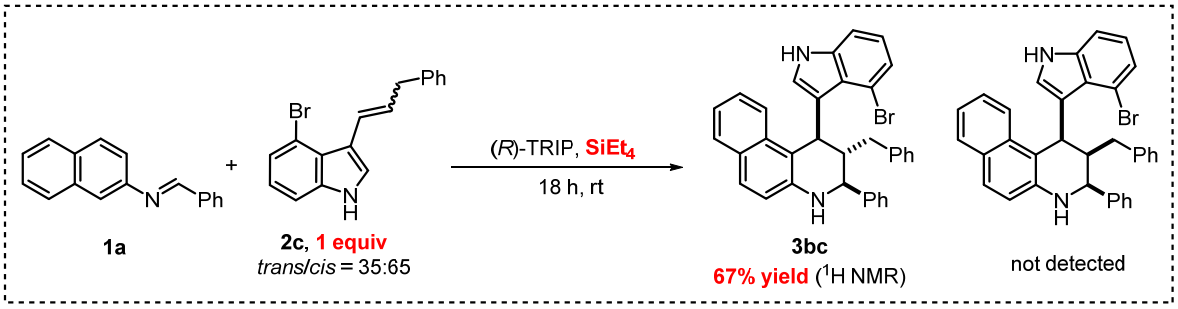


Figure 52. Cis-trans isomerization of alkenylindole ***2c*** *in the Povarov reaction*

3.5. Optimization of the oxidation step

After having demonstrated and optimized the organocatalytic step, we moved to study the central-to-axial chirality conversion step with the oxidation of model **3bc** into **4bc** (*Figure 53*).

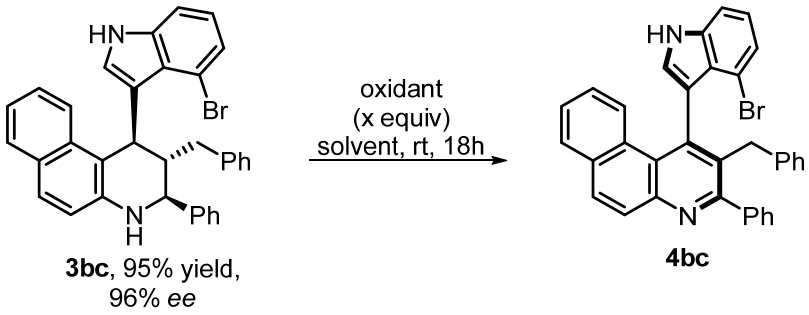


Figure 53. Oxidation step

Preliminarily, oxidations of **3bc** into **4bc** were carried out using DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) as oxidant in CH_2Cl_2 at room temperature. The oxidation reaction requires two stoichiometric equivalents of the oxidizing species. Indeed, one molecule of DDQ is able to remove only two hydrogen atoms, with the subsequent formation of the corresponding hydroquinone. The oxidation of **3bc** into the aromatized product **4bc** requires the loss of four hydrogen atoms, so two equivalents of the oxidizing agent are necessary. The driving force of this reaction is not only the aromatization of product **3bc**, but also the aromatization of the oxidizing species (*Figure 54*).

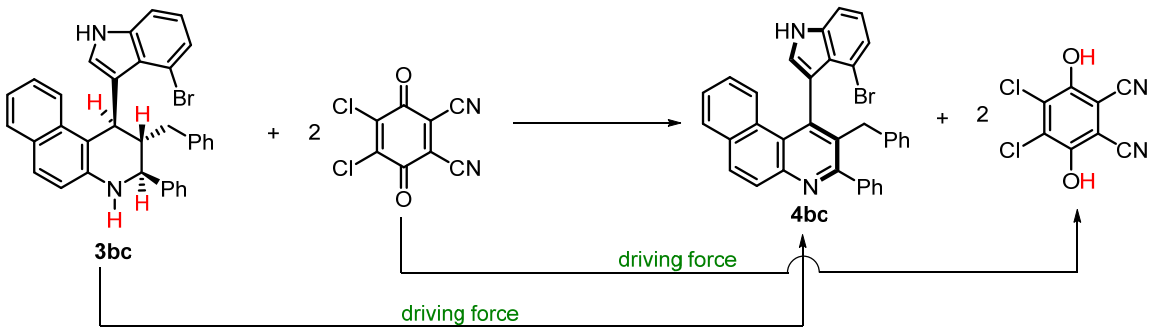


Figure 54. Stoichiometric equivalents for the oxidation reaction and driving force of the reaction

First experiments showed a low conversion into the desired product **4bc** along with the presence of an unknown product. Moreover, the reaction was found to be scarcely reproducible in terms of both reactivity and enantioselectivity.

One of the main problems encountered during the optimization regarded the reactivity. Indeed, in some cases (*vide infra*) the main product isolated from the reaction mixture

was compound **5bc**, a ketimine derived from the partial oxidation of compound **3bc**. Compound **5bc** has been shown to be an intermediate of the reaction. Indeed, once isolated and subsequently treated with DDQ, compound **5bc** led to the formation of product **4bc**, unfortunately with modest retention of the chiral information (*Figure 55*).

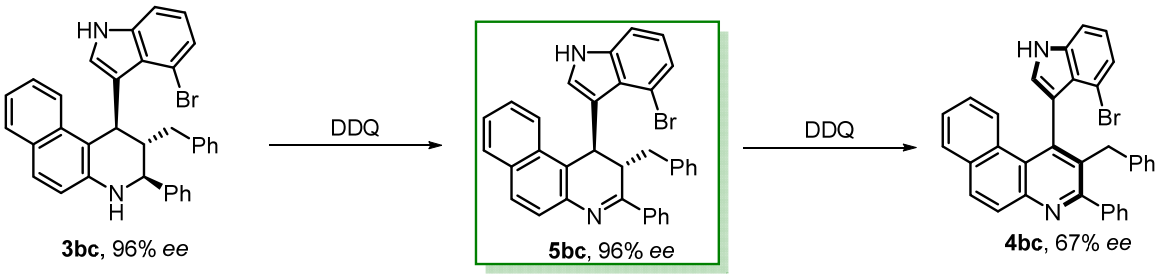


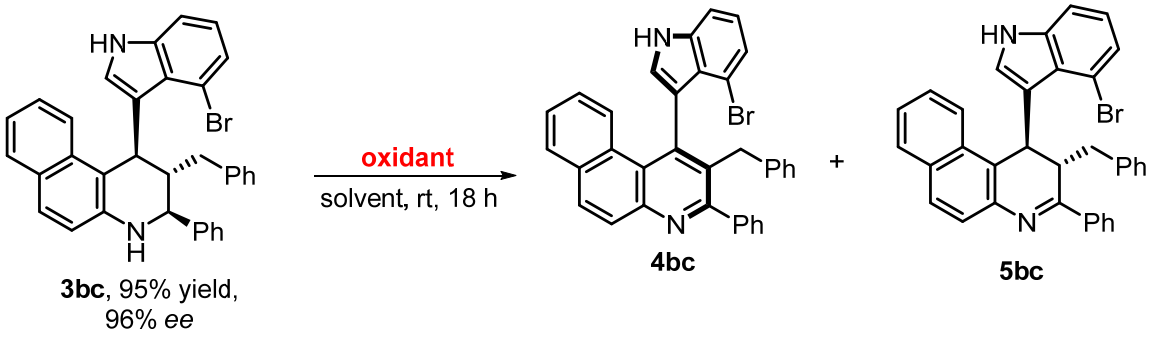
*Figure 55. Ketimine **5bc**: an intermediate of the reaction*

In order to improve the reactivity and the stereoselectivity of the overall process, numerous experiments have been carried out.

3.5.1. **Oxidizing agents screening**

First of all, we began our investigation in the attempt to find the best oxidizing agent, able to correlate a good reactivity to a good retention of the chiral information imparted in the organocatalytic step. Different oxidants have been tried and the results are shown in *Table 2*. Different solvents were employed case by case for optimal compatibility with the different oxidizing systems. Oxidants such as CAN (cerium ammonium nitrate, entry 5), TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, entry 6), *m*-CPBA (*m*-chloroperoxybenzoic acid, entry 8) *p*-chloranil (2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione, entry 10) and *p*-fluoranil (2,3,5,6-tetrafluorocyclohexa-2,5-diene-1,4-dione, entry 11) did not show any reactivity and, after appropriate quenching, only product **3bc** was present in the reaction mixture. Oxidizing agents such as manganese dioxide (entry 2) and the system TEMPO-BAIB (bis(acetoxy)iodobenzene, entry 7) gave selectively product **5bc**, while Dess-Martin periodinane provided a complex mixture (entry 3). Only PCC (pyridinium chlorochromate, entry 4), *o*-chloranil (3,4,5,6-tetrachlorocyclohexa-3,5-diene-1,2-dione, entry 9) and DDQ led to the formation of the desired product **4bc**, unfortunately in mixture with **5bc**. In particular, the best result in terms of both reactivity and stereoselectivity was obtained with the initially employed DDQ as oxidizing agent (entry 1), that was chosen as optimal for further screening.

Table 2. Oxidants screening



entry[a]	oxidant	solvent	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	DDQ	CH_2Cl_2	85	73:27
2	MnO_2	Toluene	-	>2:98
3	Dess Martin	CH_2Cl_2	-	nd [d]
4	PCC	CH_2Cl_2	63	30:70
5	CAN	THF/H_2O = 4:3	-	-
6	TEMPO	CH_2Cl_2	-	-
7	TEMPO-BAIB	CH_2Cl_2	-	>2:98
8	*m*-CPBA	CH_2Cl_2	-	-
9	*o*-chloranil	CH_2Cl_2	37	33:51[e]
10	*p*-chloranil	CH_2Cl_2	-	-
11	*p*-fluoranil	CH_2Cl_2	-	-

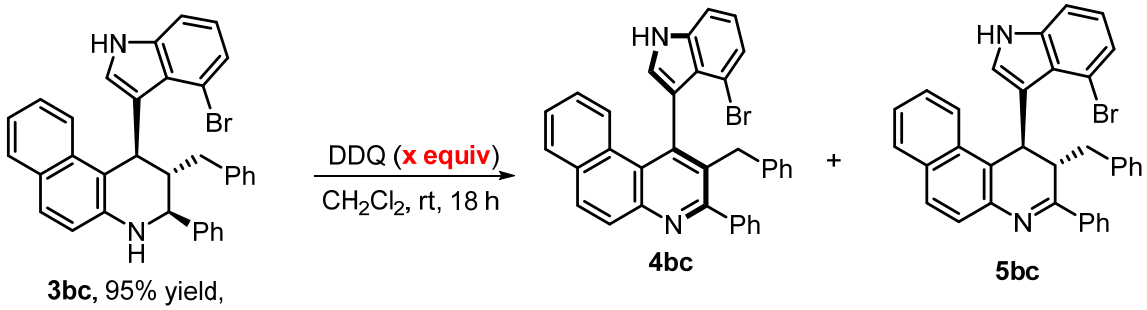
[a] General method: **3bc** (0.03 mmol), oxidant (0.06 mmol), solvent (300 µL), rt. Unless otherwise stated, complete consumption of **3bc** was observed. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^{1}H NMR. [d] Complex mixture**.** [e] 16% of product **3bc** recovered**.**

3.5.2. **Methods for the addition of the oxidant**

Another parameter investigated consisted in the methodology and the amount of oxidizing agent to be added to the reaction mixture (*Table 3*). We began our investigation by adding 2 or 3 equivalents of DDQ respectively (entry 1-2). Already in the first test (entry 1) we encountered several problems, such as the incomplete formation of the desired product **4bc** and the poor reproducibility of the reaction. Indeed, performing the same reaction under the same conditions, different values of **4bc**/**5bc** ratios and enantiomeric excesses were obtained. Running the reaction with 3 equivalents of DDQ (entry 2) both the **4bc**/**5bc** ratio and the enantiomeric excess of product **4bc** dropped. Taking into account the poor solubility of DDQ in the reaction solvent and the results

provided in terms of reactivity and stereoselectivity, two further tests adding a total of two equivalents of DDQ were carried out (entry 3-4). In order to improve the solubility of DDQ avoiding the formation of aggregates, two tests were carried out using portion-wise additions of DDQ in CH_2Cl_2 at room temperature. Running the reaction with additions of 0.2 equivalents per time of DDQ both the **4bc**/**5bc** ratio and the enantioselection dropped (entry 4), while performing the reaction with addition of 1 equivalent per time of DDQ (entry 3) was found to be a good compromise in terms of reactivity and stereoselectivity. However, the reaction presented still problems of poor reproducibility and gave hard to rationalize results. Thus, as we kept the 1+1 addition of DDQ as optimal for further screenings, we were aware that some unidentified parameter might have influenced the present outcomes and these screenings might have to be repeated once this parameter will be found.

Table 3. Amount of oxidizing agent added and addition ratio.



3bc, 95% yield, 96% *ee*

4bc

5bc

entry[a]	equiv DDQ	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	2	70-85	73:27
2	3	76	35:65
3	1+1[d]	67-90	65:35
4	0.2 equiv [e]	79	50:50

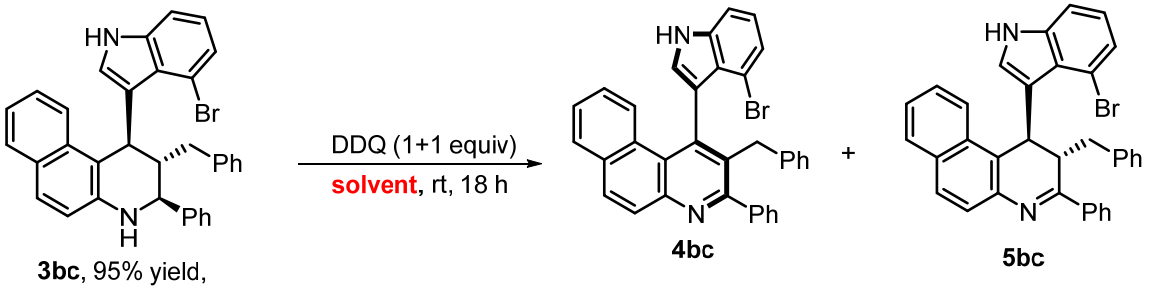
[a] General method: **3bc** (0.03 mmol), DDQ (x equiv), CH_2Cl_2 (300 µL), rt. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^{1}H NMR. [d] Second equivalent added after 2 hours**.** [e] 0.2 equiv added every 30 minutes for 8 hours**.**

3.5.3. **Solvents screening**

At this point, we moved to the study of the solvent effect. Many polar and apolar solvents were tested and the results are shown in *Table 4*. In particular, apolar solvents such as benzene and toluene (entry 2 and 5) gave unfavorable **4bc**/**5bc** ratios and moderate enantiomeric excesses. On the contrary, polar solvents such as acetonitrile, propionitrile and THF (entry 3,4 and 6) gave excellent reactivity but low enantiomeric excesses.

However, the best results were found running the reaction in halogenated solvents (entry 1 and 7). So, we decided to continue our investigation in dichloromethane as solvent in order to increase the amount of desired product **4bc** and to obtain reproducible results, keeping in mind the possible alternative to work with a solvent in which the reactivity is optimal (acetonitrile) aiming at improving the stereoselectivity.

Table 4. Solvents screening



3bc, 95% yield, 96% *ee*

4bc

5bc

entry[a]	solvent	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	CH_2Cl_2	67-90	65:35
2	toluene	75	40:60
3	CH_3CN	65	>98:2
4	THF	50	>98:2
5	Benzene	75	47:53
6	CH_3CH_2CN	63	86:14
7	$ClCH_2CH_2Cl$	90	75:25

[a] General method: **3bc** (0.03 mmol), DDQ (0.03 + 0.03 mmol), solvent (300 µL), rt. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^{1}H NMR.

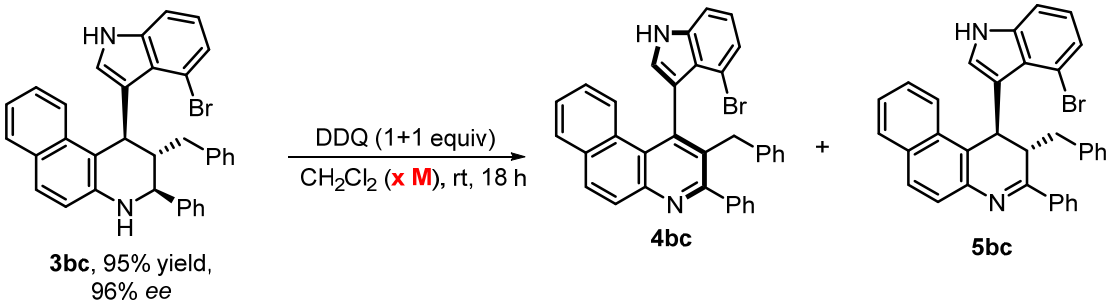
Taking in consideration the poor reproducibility of the reaction, a great effort was dedicated to the investigation of various parameters such as: the addition of acids or bases, the concentration of the reaction mixture and the presence of either atmospheric oxygen, water or free radical species.

3.5.4. **Other parameters**

In order to understand which parameter was responsible for the poor reproducibility of the reaction, we started to investigate the influence of the concentration of the medium. Taking in consideration the best results obtained in the previous screenings, CH_2Cl_2 as solvent and a portion-wise addition of DDQ, three different tests were set up (*Table 5*). From these results we understood that the retention of the enantiomeric excess was not

correlated to the concentration of **3bc** in the reaction mixture. However, despite these tests provided contrasting results, some improvement in terms of reactivity was found under diluted conditions (entry 3). This is probably due to a smaller degree of precipitation of some activated species or intermediate.

Table 5. Influence of dilution



3bc, 95% yield, 96% *ee*

4bc

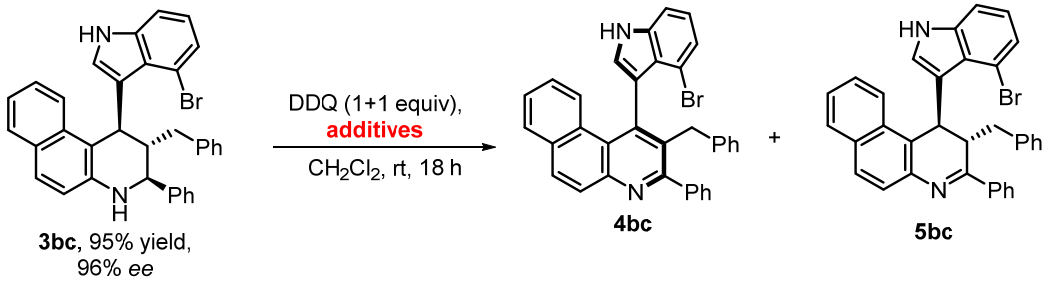
5bc

entry[a]	M (mol/L)	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	0.1	90	66:34
2	0.3	87	71:29
3	0.03	86	84:16

[a] General method: **3bc** (0.03 mmol), DDQ (0.03 + 0.03 mmol), CH_2Cl_2 (100, 300 or 900 μL), rt. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^1H NMR.

Other parameters studied were the presence of acids, bases, atmospheric oxygen and water (*Table 6*). Regarding acid and base additives, no changes were observed in terms of both stereoselectivity and reactivity (entry 1 and 2). However, it was found that atmospheric oxygen might take a role in the oxidation of **3bc** into **4bc** (or of **5bc** to **4bc**), but with irrelevant consequences for the enantioselection of the reaction. Indeed, a low reactivity was observed running the reaction under inert atmosphere (entry 3 and 4). A crucial role was represented by the presence of water (entry 5 and 6). Regarding the reactivity, the **4bc**/**5bc** ratio was similar, but an important lowering of the enantiomeric excess was observed when the solvent was saturated with water (entry 5) in comparison with the anhydrous solvent (entry 6). Therefore, the strict absence of water was hypothesized to be crucial in order to obtain reproducible results, at least in halogenated solvents.

Table 6. Screening of additives and reaction atmosphere



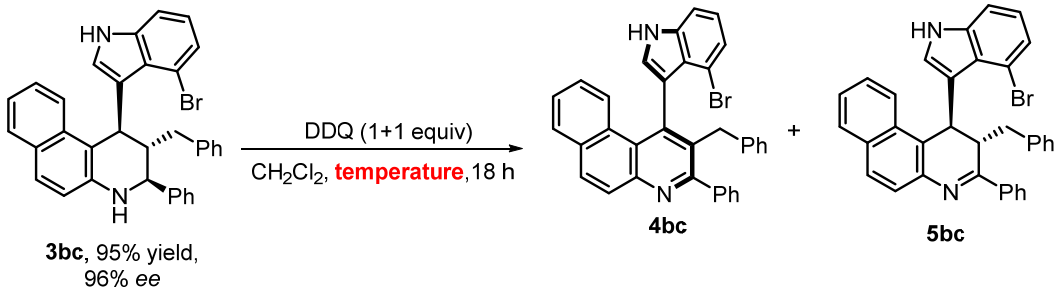
3bc, 95% yield, 96% *ee*

entry[a]	additives	atmosphere	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	Na_2CO_3	air	87	83:17
2	PhCOOH	air	87	78:22
3	-	nitrogen	84	32:78
4	-	air	67-90	65:35
5	H_2O	air	55	60:40
6	Molecular sieves	nitrogen	90	75:25

[a] General method: **3bc** (0.03 mmol), DDQ (0.03 + 0.03 mmol), additives (0.03 mmol), CH_2Cl_2 (900 µL), rt. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^{1}H NMR.

Another parameter important to investigate was the behavior of the oxidation reaction at different temperatures (*Table 7*). In particular, no reaction was observed at -20 °C (entry 2), while an intermediate temperature (entry 3) gave better results in terms of stereoselection, but low reactivity.

Table 7. Temperature screening



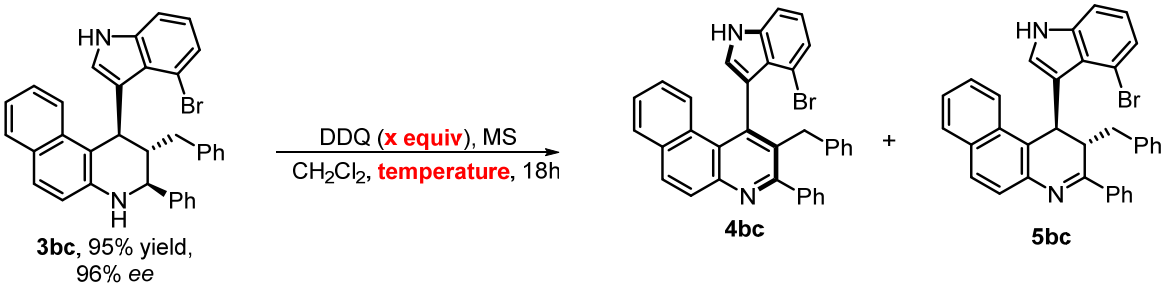
3bc, 95% yield, 96% *ee*

entry[a]	temperature °C	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	25	67-90	65:35
2	-20	-	-
3	0	92	35:75

[a] General method: **3bc** (0.03 mmol), DDQ (0.03 + 0.03 mmol), additives (0.03 mmol), CH_2Cl_2 (900 µL), rt. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^{1}H NMR.

Finally, taking into account the importance of the dilution, the use of anhydrous dichloromethane and low temperature, we decided to reinvestigate the number of equivalents and the mode of addition of the oxidant, in order to obtain product **4bc** in good yield and enantiomeric excess. We decided to conduce the experiments for 48 hours in anhydrous dichloromethane (in the presence of molecular sieves) adding respectively two, three and a portion-wise addition of DDQ first at room temperature and then at 0°C (*Table 9*). Regarding the experiments run at room temperature, a good reactivity was observed adding an excess of oxidant (entry 3). This reveals that the removal of water is an essential parameter and the results of the experiments reported in chapter 3.5.2 may be affected by considerable errors, although providing useful indications. Regarding the enantioselection of the reactions, no important improvements were observed (entry 1-3). Unfortunately, running the same experiments at 0°C, no improvements in both stereoselection and reactivity were observed.

Table 8. Screening of equivalents of oxidant and temperature in dry CH_2Cl_2



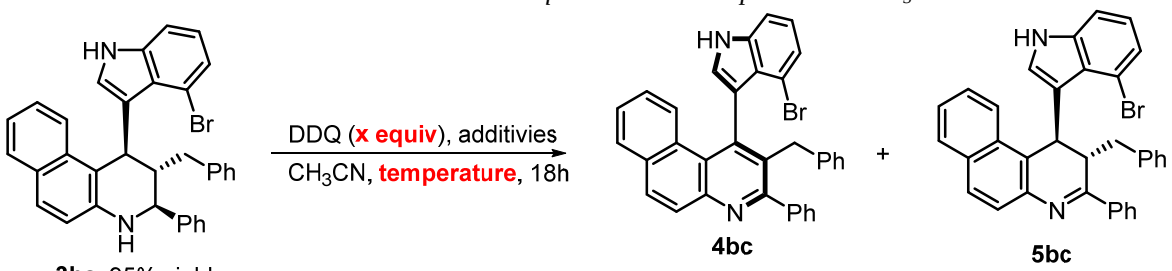
entry[a]	equiv.	temperature °C	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	1+1	25	67-90	65:35
2	2	25	86	40:60
3	3	25	90	85:15
4	1+1	0	92	35:75
5	2	0	86	40:60
6	3	0	90	50:50

[a] General method: **3bc** (0.03 mmol), CH_2Cl_2 (900 µL), DDQ (0.03 + 0.03 mmol or 0.06 mmol or 0.09 mmol), 4Å MS (30 mg), thermally activated *in vacuo*. Reaction run under nitrogen atmosphere. [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [d] Determined on the crude reaction mixture by ^{1}H NMR.

Since we were not successful in achieving a good reactivity in chlorinated solvents and owing to the good reactivity and moderate enantiomeric excess observed in acetonitrile, we decided to move back to evaluate the behavior of the oxidation reaction in this latter

solvent. This was carried out taking into account the presence of water, and again the temperature, the number of equivalents and the ratio of the addition of the oxidant (*Table 9*). All the experiments are characterized by a very good reactivity, indeed no trace of product **5bc** was present in the crude mixtures. Moreover, a very different stereoselection was verified with the increase of the number of equivalents of the oxidant both at room temperature and at 0°C. Another important result obtained with these experiments was the reproducibility of the reaction outcomes, as, repeating the same experiment multiple times, the same results were recorded. Moreover, the presence of water was found to be irrelevant in acetonitrile. Finally, performing the reaction at 0 °C, in acetonitrile and with excess oxidant (entry 6) we are able to obtain very good reactivity and enantioretention, with fully reproducible results. These conditions were taken as optimal for the central-to-axial chirality conversion from tetrahydroquinolines **3** to quinolines **4**.

Table 9. Correlation between equivalents and temperature in CH_3CN



3bc, 95% yield, 96% *ee*

4bc

5bc

entry[a]	equiv.	temperature °C	additives	*ee*[b] [%] **4bc**	**4bc**/**5bc**[c] ratio
1	1+1	25	-	65	>98:2
2	2	25	-	40	>98:2
3	3	25	-	93	>98:2
4	1+1	0	-	79	>98:2
5	2	0	-	90	>98:2
6	**3**	**0**	**-**	**94**	**>98:2**
7	2	0	molecular sieves[d]	90	>98:2

[a] General method: **3bc** (0.03 mmol), CH_3CN (900 µL), DDQ (0.03 + 0.03 mmol or 0.06 mmol or 0.09 mmol). [b] Determined by CSP (chiral stationary phase) chiral HPLC analysis after column chromatography. [c] Determined on the crude reaction mixture by ^1H NMR. [d] 4Å MS (30 mg), thermally activated *in vacuo*. Reaction run under nitrogen atmosphere.

3.6. Scope of the reaction

After the optimization of both Povarov cycloaddition and oxidation steps, we moved to evaluate the scope of the reaction. In each example, Povarov adduct **3** was isolated and fully characterized prior to the oxidation step in order to evaluate the corresponding *cp* factor of atropisomeric quinoline **4**, i.e the ability of products **4** to retain the enantiomeric excess imparted in the organocatalytic step.

Variations of the amine portion of *N*-arylimines **1** (*Figure **56.** Variations of the amine portionFigure 56*) showed that methyl and methoxy substituents were very well tolerated in the Povarov reaction as well as in the oxidation step, albeit with slight decrease in the isolated yields of the final products (**3cc-ec**, **4cc-ec**). Electron-poor imine **1f** showed sloppy reactivity in the cycloaddition, however oxidation of corresponding **3fc** proceeded with total retention of the enantiomeric excess. Pleasingly, a substituent at the position-5 (R^1) of quinolines **4** was not strictly necessary to provide configurational stability. Indeed, compound **4ac** was obtained in good yield and enantioselectivity.

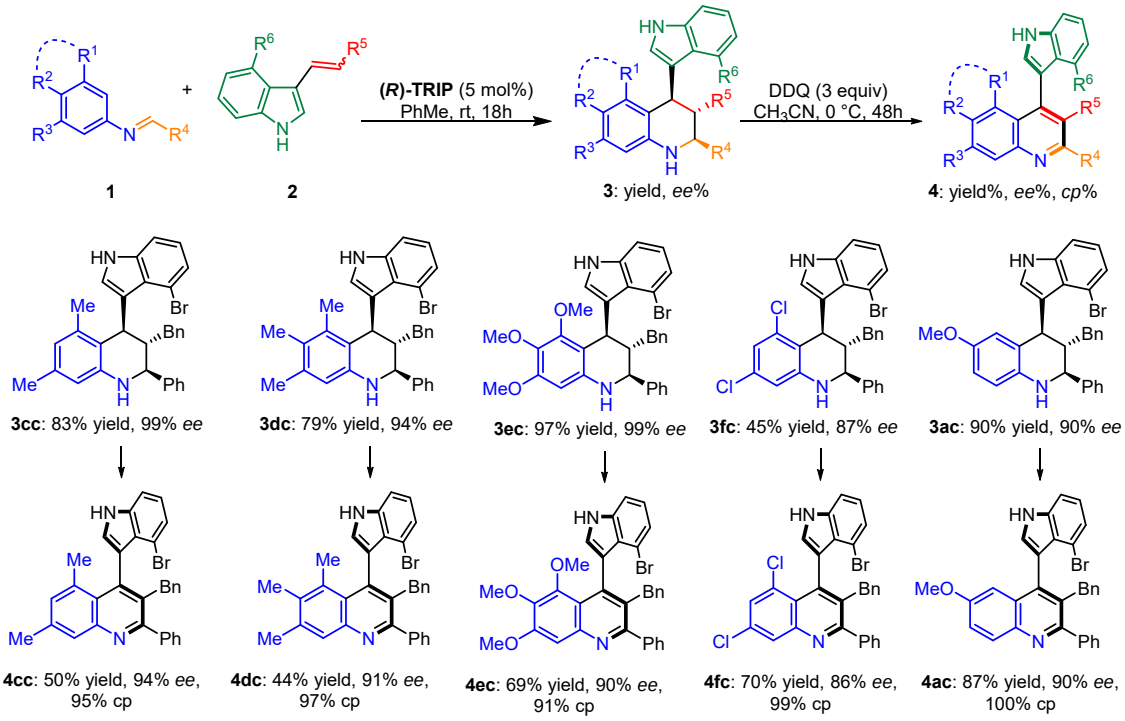


Figure 56. Variations of the amine portion

By modification at the aldehyde portion (*Figure 57*) we observed that an electron-rich substituent (imine **1g**) afforded good results in both synthetic steps,[20] while an electron-poor or an heteroaromatic one delivered adducts **3hc** and **3ic**[21] in high yields and selectivities but caused less satisfactory retention of the chiral information in the following oxidation step. On the contrary, product **3jc**, derived by a three-component protocol, was obtained with modest results but behaved efficiently in the subsequent aromatization reaction.

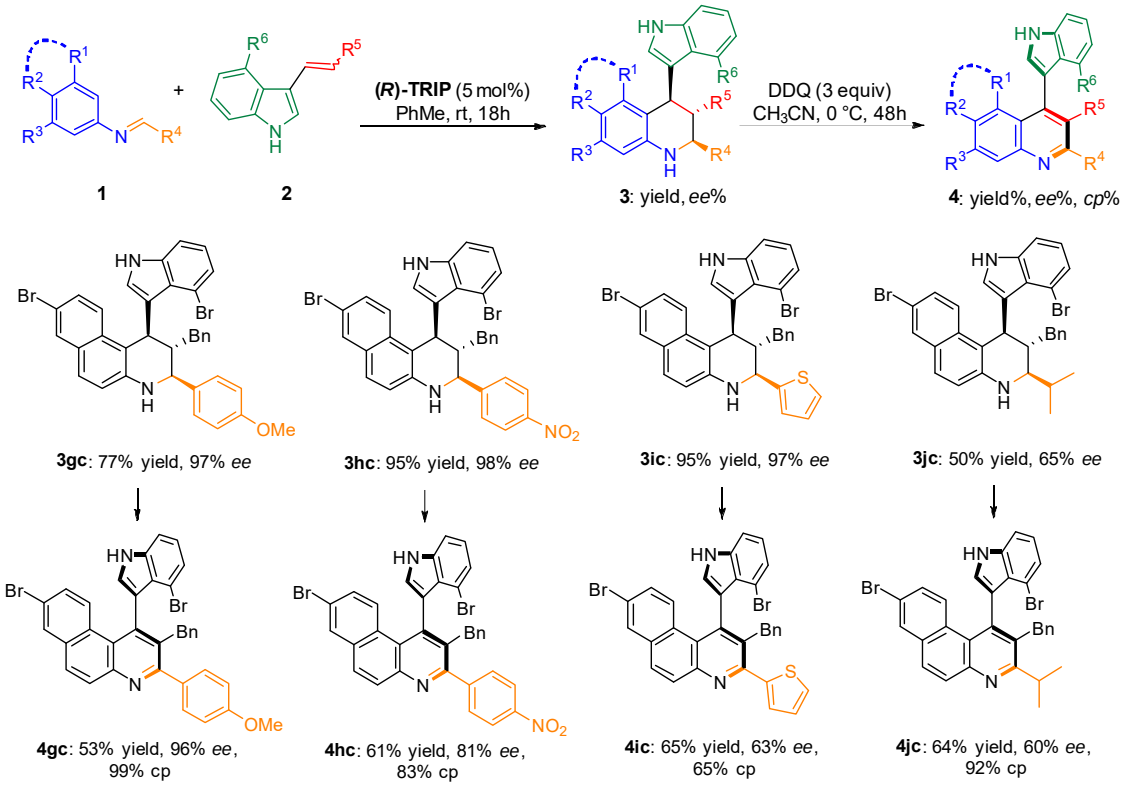


Figure 57. Variation at the aldehyde portion

Variation of the terminal substituent of the vinyl group (*Figure 58*) was smoothly carried out achieving excellent results in both Povarov and oxidation reactions; notably, only encumbered product **3bf** could not reach full conversion into the desired quinoline **4bf**.

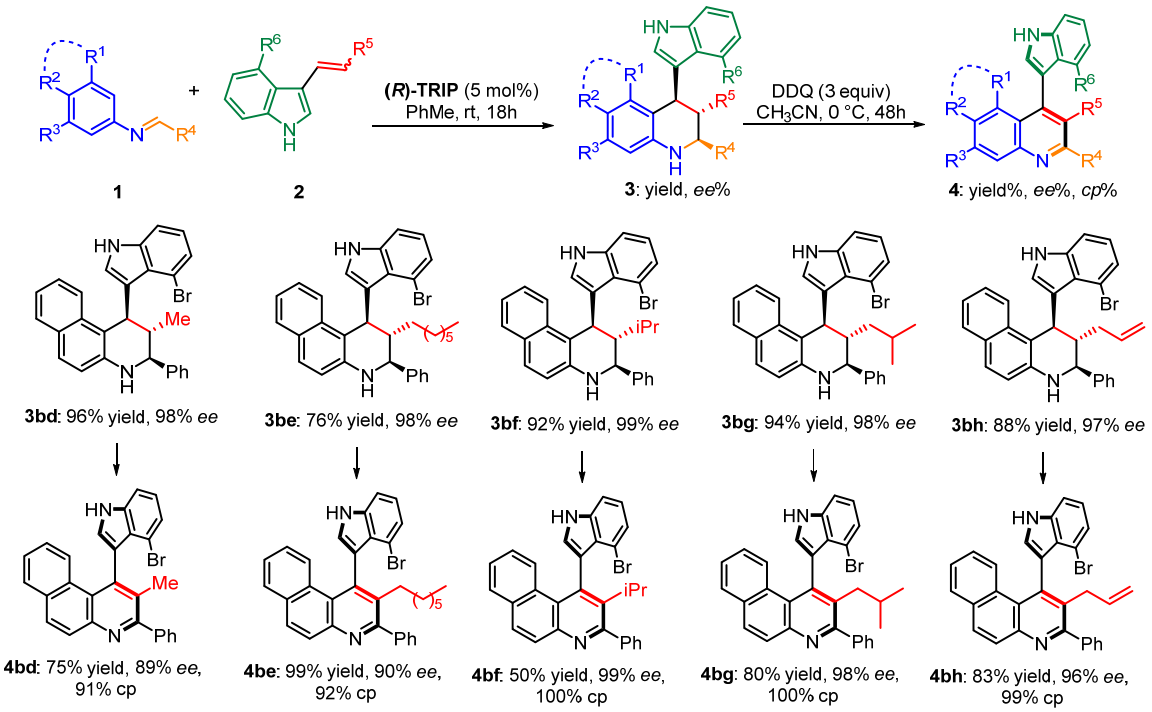


Figure 58. Variation of the terminal substituent of the vinyl group

Gratifyingly, modification at the C-4 position of the indole moiety (***Figure 59***), crucial for the configurational stability of atropisomeric products **4**, was also possible with no substantial detriment of the final enantiomeric excess.

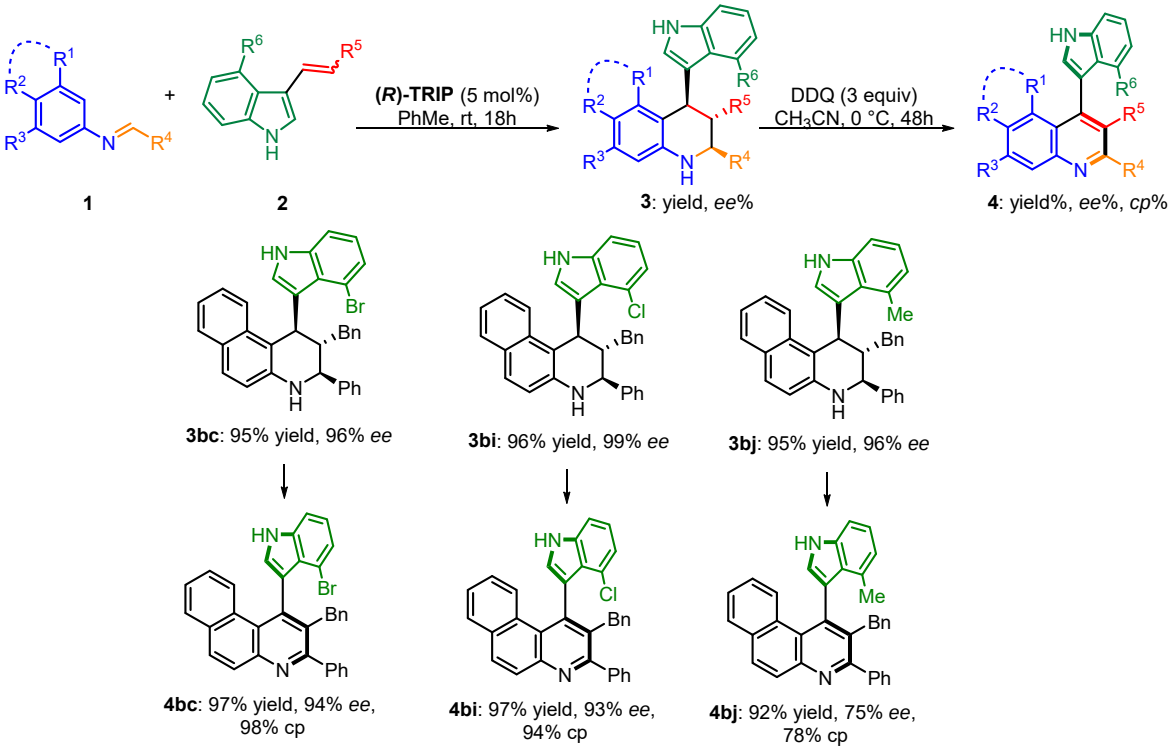


Figure 59. Modification at the C-4 position of the indole moiety

4. Conclusions

In conclusion, the feasibility of the preparation of novel enantioenriched atropisomeric indolylquinoline systems following a central-to-axial chirality conversion approach was demonstrated. First of all, 7 different *N*-arylimines **1** and 8 different 3-alkenylindoles **2** were synthesized in useful preparative yields. Having first identified the substrate requirements of **4** in order to display a thermally stable chiral axis, both the Povarov cycloaddition and the oxidation reaction have been optimized. In particular, the catalytic loading of the Povarov cycloaddition was halved compared to literature protocols, the problem of 3-alkenylindoles **2** being produced as *cis*/*trans* mixture was circumvented and 17 different tetrahydroquinolines **3** were prepared in generally very high yields and excellent stereoselectivity, and fully characterized. The oxidation step was then investigated thoroughly, varying, for example, the oxidant species, the temperature and the solvent. The irreproducibility of this step, in terms of yield and retention of the enantiomeric excess, was solved. In particular, the effect of the equivalents of the oxidant (DDQ) and the presence of water were thoroughly investigated in two different solvents (CH_3CN and CH_2Cl_2). After this optimization, an initially unreliable and poorly performing protocol was turned into a very versatile and efficient procedure, tolerating a wide variety of different substituents. Thus, 17 different enantioenriched atropisomeric indolyl-quinolines **4** were synthetized, in very good yields and generally almost complete enantioretention. These products were also fully characterized. (*Figure 60*).

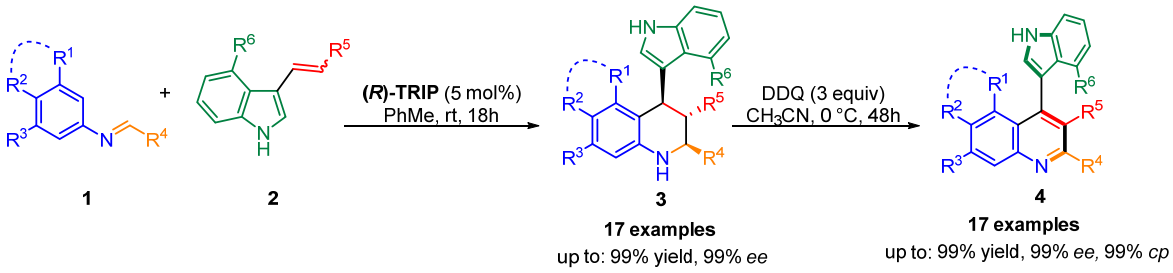


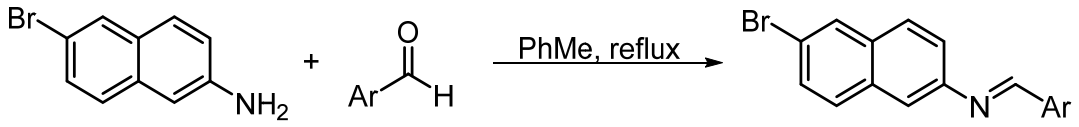
Figure 60. Reaction conditions of Povarov cycloaddition and oxidation reaction

5. Experimental section

General Methods. ^{1}H, ^{13}C NMR spectra were recorded on a Varian AS 300 or 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals[22] for ^{1}H and ^{13}C NMR. Multiplicity is explained in brackets as follow: "s", singlet; "d", doublet; "t", triplet; "q", quadruplet; "sept", septuplet; "m", multiplet; a "b" before the letter means "broad" ^{13}C NMR spectra were acquired with ^{1}H broad band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES) ionisation techniques or using electron impact (EI) ionisation techniques The enantiomeric excess of the products (*ee*) were determined by chiral stationary phase HPLC (Daicel Chiralpak AD-H or Chiralcel OD-H columns), using an UV detector operating at 254 nm..

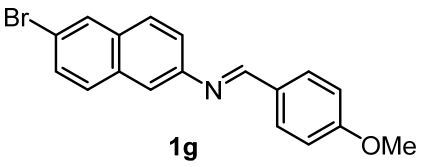
Materials. Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. Catalyst **(*R*)-TRIP** was synthesized following literature procedures.[23] Imine **1b** was purchased from TCI-chemicals. Imines **1a**, **1c**, **1d**, **1e** and **1f** are known compounds and were synthesized following the general procedure reported for imines **1g-l**. For imines **1g-l**, 6-bromo-2-naphthylamine was employed instead of simple 2-naphthylamine, which use is discouraged by the Italian law. 3-Alkenylindoles **2a** and **2b** were synthetized following an unmodified literature procedure.[18] Racemic products **3** were prepared using diphenyl phosphate (10 mol%) instead of **(*R*)-TRIP** as catalyst. Racemic **4** and **5** were prepared from racemic **3**.

Synthesis of *N*-arylimines 1g-i



To a stirred suspension of 6-bromonaphthalen-2-amine (1.11 g, 5 mmol) in toluene (5 mL), the corresponding aldehyde (5 mmol) was added. The resulting suspension was stirred at 110 °C in a Dean-Stark apparatus for 18 h, before it was cooled to room temperature and precipitated with 10 mL of Et_2O. The resulting solid was dried under reduced pressure and used without further purification.

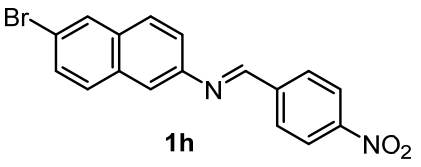
(*E*)-*N*-(6-bromonaphthalen-2-yl)-1-(4-methoxyphenyl)methanimine 1g



1g

Following the model procedure using 4-methoxybenzaldehyde compound **1g** was obtained as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.47 (s, 1H), 7.96 (d, *J* = 1.9 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 2H), 7.70 (dd, *J* = 16.3, 8.7 Hz, 2H), 7.59 – 7.47 (m, 2H), 7.43 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.98 (d, *J* = 8.6 Hz, 2H), 3.86 (s, 3H).

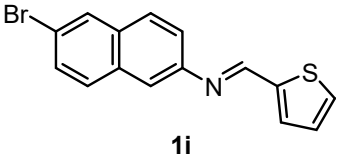
(*E*)-*N*-(6-bromonaphthalen-2-yl)-1-(4-nitrophenyl)methanimine 1h



1h

Following the model procedure using 4-nitrobenzaldehyde compound **1h** was obtained as a yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.63 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.97 (d, *J* = 1.9 Hz, 1H), 7.72 (dd, *J* = 19.8, 8.8 Hz, 2H), 7.58 (d, *J* = 2.1 Hz, 1H), 7.53 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.44 (dd, *J* = 8.7, 2.1 Hz, 1H).

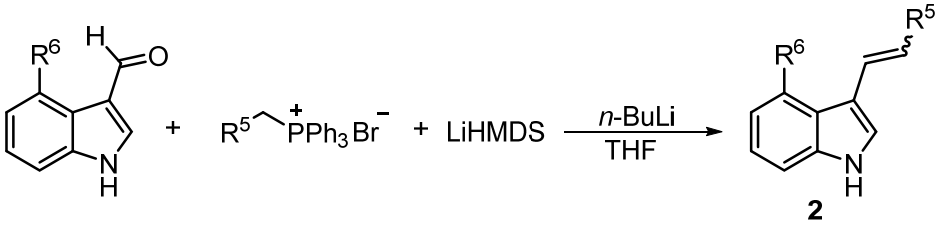
(*E*)-*N*-(6-bromonaphthalen-2-yl)-1-(thiophen-2-yl)methanimine 1i



1i

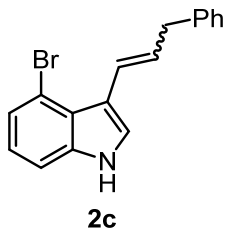
Following the model procedure using thiophene-2-carbaldehyde compound **1i** was obtained as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.70 (s, 1H), 7.98 (s, 1H), 7.83 – 7.42 (m, 7H), 7.17 (t, *J* = 4.4 Hz, 1H).

Synthesis of 3-Vinylindoles 2



The following procedure, serving for the synthesis of compound **2c** can be used as the model for the preparation of all the analogous substrates, obtained upon variation of indole-3-carbaldehydes or phosphonium salts, accordingly. To a stirred suspension of phenethtyltripenylphosphonium bromide (3.22 g, 7.2 mmol) in anhydrous THF (16 mL), n-BuLi (1.6 M solution in hexanes, 4.5 mL, 8.64 mmol) was added dropwise at -50 °C. The resulting red solution, containing the phosphonium ylide, was stirred and warmed to 0 °C for approximately 45 minutes. A solution of HMDS (1,1,1,3,3,3-hexamethyldisilazane, 1.25 mL, 5 mmol) in anhydrous THF (9 mL) was lithiated by slow addition of a solution of *n*-BuLi at 0 °C (1.6 M solution in hexanes, 3.9 mL, 6.19 mmol). This freshly prepared solution of LiHMDS was added to a pre-cooled solution of indole-3-carboxaldehyde (0.897 g, 5 mmol) in anhydrous THF (8 mL) at 0 °C. The resulting solution of lithiated aldehyde was added dropwise to the previously prepared solution of phosphonium ylide cooled back to -30 °C. The resulting mixture was stirred at room temperature for 1 h before it was poured into H_2O and extracted with EtOAc (2 x 100 mL). The combined organic phases were dried over Mg_2SO_4, filtered and evaporated under reduced pressure. The crude residue was then purified by a short and fast column chromatography on silica gel (*n*-hexane/EtOAc = 1:1).

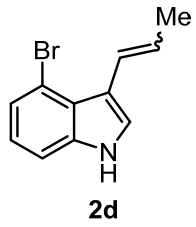
4-bromo-3-(3-phenylprop-1-en-1-yl)-1*H*-indole 2c



2c

Following the model procedure compound **2c** was obtained in 75% yield (35:65 trans/cis ratio), as an orange oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.54 (bs, 1H cis), 11.48 (bs, 1H trans), 7.62 (s, 1H trans), 7.44 (s, 1H cis), 7.41 (dd, *J* = 8.1, 0.9 Hz, 1H cis), 7.35 (dd, *J* = 8.1, 0.9 Hz, 1H trans), 7.33 – 7.14 (m, 7H cis + 7H trans), 7.00 (t, *J* = 7.80 Hz, 1H cis), 6.94 (t, *J* = 7.80 Hz, 1H trans), 6.06 (dt, *J* = 15.7, 6.9 Hz, 1H trans), 5.72 (dt, *J* = 11.4, 7.1 Hz, 1H cis), 3.62 (dd, *J* = 7.2, 1.9 Hz, 2H cis), 3.49 (dd, *J* = 7.0, 1.5 Hz, 2H trans).

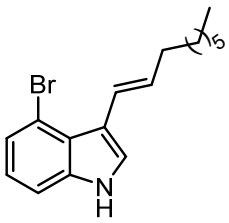
4-bromo-3-(prop-1-en-1-yl)-1*H*-indole 2d



2d

Following the model procedure, from 4-bromoindole-3-carboxaldehyde and ethyltripenylphosphonium bromide, compound **2d** was obtained in 72% yield (76:24 trans/cis ratio), as a pale yellow oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.54 (bs, 1H cis), 11.43 (bs, 1H trans), 7.57 (d, *J* = 2.5 Hz, 1H trans), 7.45 (d, *J* = 2.4 Hz, 1H cis), 7.41 (dd, *J* = 8.1, 0.9 Hz, 1H cis), 7.37 (dd, *J* = 8.1, 0.8 Hz, 1H trans), 7.27 – 7.07 (m, 2H cis + 2H trans), 6.99 (t, *J* =8.24 Hz, 1H cis), 6.95 (t, *J* =7.54 Hz, 1H trans), 5.92 (dq, *J* = 15.6, 6.6 Hz, 1H trans), 5.66 (dq, *J* = 11.4, 7.0 Hz, 1H cis), 1.86 – 1.78 (m, 3H cis + 3H trans).

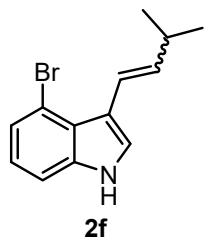
4-bromo-3-(oct-1-en-1-yl)-1*H*-indole 2e



2e

Following the model procedure, from 4-bromoindole-3-carboxaldehyde and octyltripenylphosphonium bromide, compound **2e** was obtained in 66% yield (57:43 trans/cis ratio), as a green oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.49 (bs, 1H cis), 11.43 (bs, 1H trans), 7.57 (d, *J* = 2.2 Hz, 1H trans), 7.39 (dd, *J* = 8.1, 0.9 Hz, 1H cis), 7.36 (dd, *J* = 2.7, 0.6 Hz, 1H trans), 7.36 (dd, *J* = 8.1, 0.9 Hz, 1H trans), 7.19 (dd, J = 4.7, 0.9 Hz, 1H cis), 7.18 – 7.09 (m, 1H cis + 1H trans), 7.06 (m, 1H cis), 7.01 – 6.91 (m, 1H cis + 1H trans), 5.91 (dt, *J* = 15.7, 6.9 Hz, 1H trans), 5.54 (dt, *J* = 11.5, 7.0 Hz, 1H cis), 2.34 – 2.07 (m, 2H cis + 2H trans), 1.49 – 1.10 (m, 10H cis + 10H trans), 0.94 – 0.73 (m, 3H cis + 3H trans).

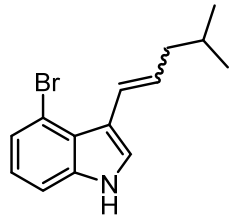
4-bromo-3-(3-methylbut-1-en-1-yl)-1*H*-indole 2f



2f

Following the model procedure, from 4-bromoindole-3-carboxaldehyde and isobutyltripenylphosphoniumbromide, compound **2f** was obtained in 76% yield (67:33 trans/cis ratio), as a green oil. **^{1}H NMR** (400 MHz, DMSO-d_6) δ = 11.46 (bs, 1H cis), 11.42 (bs, 1H trans), 7.57 (d, *J* = 2.6 Hz, 1H trans), 7.41 – 7.37 (m, 1H cis + 1H trans), 7.35 (dd, *J* = 8.1, 0.8 Hz, 1H cis), 7.32 (d, *J* = 2.6 Hz, 1H cis), 7.26 – 7.19 (m, 1H trans), 7.19 – 7.08 (m, 1H cis + 1H trans), 6.94 (m, 1H cis + 1H trans), 5.92 (dd, *J* = 15.9, 6.4 Hz, 1H trans), 5.38 (dd, *J* = 11.4, 9.8 Hz, 1H cis), 2.88 – 2.72 (m, 1H cis), 2.46 – 2.34 (m, 1H trans), 1.06 (d, *J* = 6.7 Hz, 3H trans), 1.00 (d, *J* = 6.6 Hz, 3H cis).

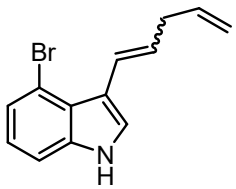
4-bromo-3-(4-methylpent-1-en-1-yl)-1*H*-indole 2g



2g

Following the model procedure, from 4-chloroindole-3-carboxaldehyde and isopentyltripenylphosphonium bromide, compound **2g** was obtained in 75% yield (77:23 trans/cis ratio), as a green oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.48 (bs, 1H cis), 11.44 (bs, 1H trans), 7.59 (d, *J* = 2.5 Hz, 1H trans), 7.40 (dd, *J* = 8.3, 0.9 Hz, 1H cis), 7.36 (dd, *J* = 7.9, 0.9 Hz, 1H trans), 7.36 (d, *J* = 2.84 Hz, 1H cis), 7.16 (m, 2H cis + 2H trans), 6.96 (m, 1H cis + 1H trans), 5.90 (dt, *J* = 15.6, 7.3 Hz, 1H trans), 5.58 (dt, *J* = 11.6, 7.0 Hz, 1H cis), 2.16 (td, *J* = 6.9, 1.9 Hz, 2H cis), 2.04 (td, *J* = 7.1, 1.3 Hz, 2H trans), 1.69 (m, 1H cis + 1H trans), 0.91 (m, 6H cis + 6H trans).

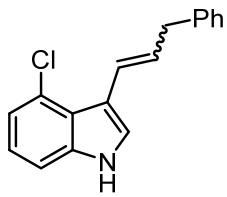
4-bromo-3-(penta-1,4-dien-1-yl)-1*H*-indole 2h



2h

Following the model procedure, from 4-bromoindole-3-carboxaldehyde and allyltripenylphosphonium bromide, compound **2h** was obtained in 83% yield (60:40 trans/cis ratio), as a green oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.50 (bs, 1H trans), 11.43 (bs, 1H cis), 7.59 (d, *J* = 2.5 Hz, 1H cis), 7.40 – 7.29 (m, 1H cis + 2H trans), 7.20 – 7.07 (m, 2H cis + 2H trans), 7.00 – 6.87 (m, 1H cis + 1H trans), 5.98 – 5.79 (m, 2H cis + 1H trans), 5.54 (ddd, *J* = 11.4, 8.3, 6.6 Hz, 1H trans), 5.07 (dd, *J* = 17.4, 1.8 Hz, 1H cis + 1H trans), 4.99 (dd, *J* = 10.2, 2.0 Hz, 1H cis + 1H trans), 2.98 (td, *J* = 7.4, 6.9, 2.0 Hz, 2H trans), 2.94 – 2.82 (m, 2H cis).

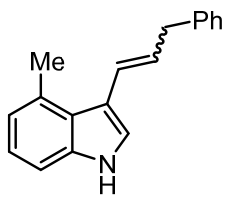
4-chloro-3-(3-phenylprop-1-en-1-yl)-1*H*-indole 2i



2i

Following the model procedure, from 4-chloroindole-3-carboxaldehyde and phenethtyltripenylphosphonium bromide, compound **2i** was obtained in 77% yield (46:54 trans/cis ratio), as a dark yellow oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.58 (bs, 1H cis), 11.49 (bs, 1H trans), 7.65 (s, 1H cis), 7.46 (s, 1H trans), 7.42 – 6.97 (m, 9H cis + 9H trans), 6.11 (dt, *J* = 15.6, 6.9 Hz, 1H trans), 5.72 (dt, *J* = 11.4, 7.1 Hz, 1H cis), 3.66 (dd, *J* = 7.0, 1.9 Hz, 2H cis), 3.51 (d, *J* = 7.0 Hz, 2H trans).

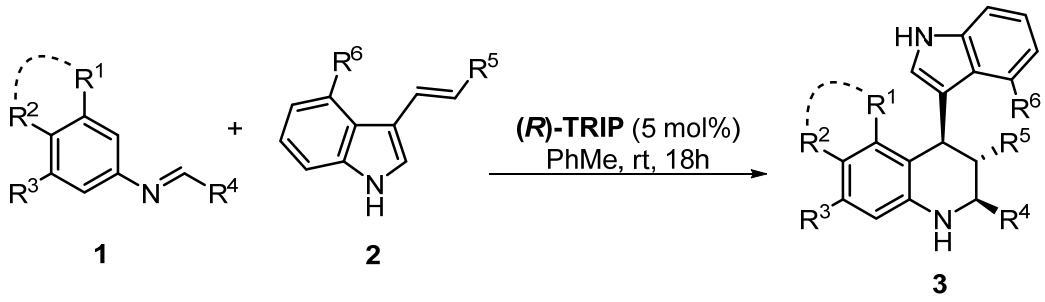
4-methyl-3-(3-phenylprop-1-en-1-yl)-1*H*-indole 2j



2h

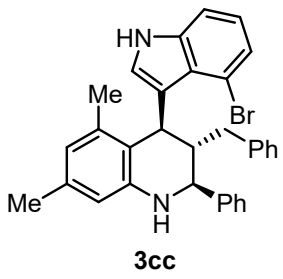
Following the model procedure, from 4-methylindole-3-carboxaldehyde and phenethtyltripenylphosphonium bromide, compound **2j** was obtained in 66% yield (33:66 trans/cis ratio), as an intense orange oil. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 11.16 (bs, 1H cis), 11.08 (bs, 1H trans), 7.44 (s, 1H trans), 7.37 – 7.09 (m, 7H cis + 6H trans), 7.02 – 6.85 (m, 2H cis + 2H trans), 6.80 – 6.69 (m, 1H cis + 1H trans), 6.02 (dt, *J* = 15.5, 6.9 Hz, 1H trans), 5.70 (dt, *J* = 11.2, 7.1 Hz, 1H cis), 3.64 (dd, *J* = 7.1, 1.8 Hz, 2H cis), 3.51 (dd, *J* = 6.9, 1.5 Hz, 2H trans), 2.63 (s, 3H cis), 2.59 (s, 3H trans).

General procedure for the synthesis of products 3.



In a small vial equipped with a magnetic stirring bar, 3-vinylindole **2** (1.5 equiv, 0.45 mmol, *E*/*Z* mixture), *N*-arylimine **1** (1.0 equiv, 0.3 mmol), toluene (2 mL) and catalyst **(*R*)-TRIP** (11 mg, 0.015 mmol, 5 mol%) were added in this order. The resulting solution was stirred for 18 h at room temperature and then directly purified by column chromatography on silica gel to afford the desired compounds **3** as solids. Products **3** were found to be sensitive to traces of DCl in $CDCl_3$ darkening immediately upon contact and showing slow decomposition upon prolonged standing. In order to conveniently record the spectra in $CDCl_3$ the solvent had to be filtered over basic alumina prior to use. Products **3** were all obtained as single all-*trans* isomers.

(2*S*,3*S*,4*R*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,7-dimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline 3cc

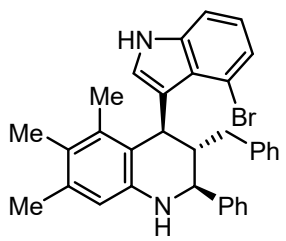


3cc

Following the general procedure from *N*-arylimine **1c** and 3-vinylindole **2c**, product **3cc** was obtained as a white solid in 83% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 2:1). $[\alpha]_D^{25}$ = +100 (c = 0.2 in $CHCl_3$) for 99% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 7.1 Hz, 2H), 7.35 – 7.29 (m, 2H), 7.27 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.23 – 7.16 (m, 2H), 6.99 (dd, *J* = 8.1, 0.9 Hz, 1H), 6.89 (t, *J* = 7.8 Hz, 1H), 6.86 – 6.80 (m, 2H), 6.78 – 6.68 (m, 3H), 6.55 (s, 1H), 6.44 (s, 1H), 5.80 (dd, *J* = 2.5, 0.8 Hz, 1H), 4.77 (s, 1H), 4.38 (s, 1H), 4.20 (s, 1H), 3.40 (ddt, *J* = 11.6, 3.9, 1.8 Hz, 1H), 3.22 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.78 (dd, *J* = 13.4, 11.7 Hz, 1H), 2.35 (s, 3H), 2.04 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.0, 143.0, 141.3, 138.7, 137.8, 136.7, 129.5 (2C), 128.4 (2C), 127.0 (2C), 126.7, 126.0, 125.1 (2C), 124.8, 124.6, 123.6, 121.9, 120.2, 118.7, 116.8, 113.6, 112.0, 110.0, 52.3, 45.0, 40.4, 35.6, 21.3, 19.0. **ESI-MS**: 543 [M(^{79}Br) + Na^+], 545

[M(^{81}Br) + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 7.0 min; t_{minor} = 7.9 min).

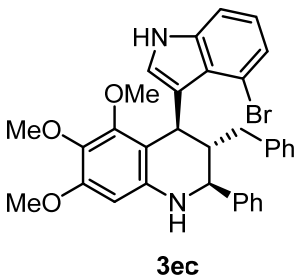
(2*S*,3*S*,4*R*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,6,7-trimethyl-2-phenyl-1,2,3,4-tetrahydroquinoline 3dc



3dc

Following the general procedure from *N*-arylimine **1d** and 3-vinylindole **2c**, product **3dc** was obtained as a white solid in 79% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 2:1). $[\alpha]_D^{25}$ = +39 (c = 0.2 in $CHCl_3$) for 94% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.45 (d, *J* = 7.3 Hz, 2H), 7.31 (dd, *J* = 15.1, 7.5 Hz, 3H), 7.19 (dd, *J* = 13.9, 6.4 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 15.0, 7.2 Hz, 1H), 6.83 (d, *J* = 6.7 Hz, 2H), 6.78 – 6.67 (m, 3H), 6.60 (s, 1H), 5.78 (d, *J* = 2.0 Hz, 1H), 4.84 (s, 1H), 4.28 (s, 1H), 4.17 (s, 1H), 3.45 – 3.34 (m, 1H), 3.24 (dd, *J* = 13.4, 3.8 Hz, 1H), 2.80 (dd, *J* = 13.4, 11.7 Hz, 1H), 2.36 (s, 3H), 2.14 (s, 3H), 2.00 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.3, 141.4, 140.6, 137.8, 136.9, 135.4, 129.5 (2C), 128.4 (2C), 127.2, 127.0 (2C), 126.0, 125.1 (2C), 124.7, 124.5, 123.8, 123.6, 121.9, 119.1, 117.5, 113.6, 113.0, 110.0, 51.9, 45.0, 40.5, 36.3, 21.1, 15.7, 15.3. **ESI-MS**: 559 [M(^{79}Br) + Na^+], 561 [M(^{81}Br) + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 5.9 min; t_{minor} = 8.1 min).

(2*S*,3*S*,4*R*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,6,7-trimethoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 3ec

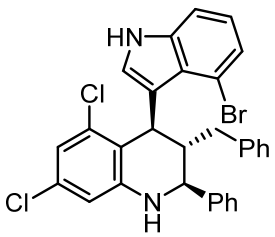


3ec

Following the general procedure from *N*-arylimine **1e** and 3-vinylindole **2c**, product **3ec** was obtained as a white solid in 97% yield after column chromatography on silica gel (CH_2Cl_2/Et_2O = 50:1). $[\alpha]_D^{25}$ = +82 (c = 0.2 in $CHCl_3$) for 99% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 7.3 Hz, 2H), 7.33 – 7.22 (m, 4H), 7.17 (t, *J* = 7.3 Hz, 1H), 6.97 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.86 (dd, *J* = 13.5, 5.7 Hz, 1H), 6.82 (d, *J* = 6.8 Hz, 2H), 6.78 – 6.70 (m, 3H), 6.17 (s, 1H), 5.90 (d, *J* = 2.0 Hz, 1H), 4.93 (s, 1H), 4.28 (s, 1H), 4.17 (bs, 1H), 3.93 (s, 3H), 3.79 (s, 3H), 3.60 (s, 3H), 3.34 (ddt, *J* = 11.7, 4.0, 2.1 Hz, 1H), 3.24 (dd, *J* =

13.5, 3.7 Hz, 1H), 2.71 (dd, *J* = 13.3, 11.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 153.1, 153.0, 144.8, 141.3, 139.5, 137.8, 133.8, 129.4 (2C), 128.3 (2C), 127.1 (2C), 126.1, 126.0, 125.1 (2C), 124.9, 124.6, 123.6, 121.9, 120.3, 113.7, 110.1, 107.4, 92.7, 61.0, 60.8, 55.8, 52.8, 44.9, 40.1, 33.1. **ESI-MS**: 605 [M(^{79}Br) + Na^+], 607 [M(^{81}Br) + Na^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 11.3 min; t_{minor} = 13.4 min).

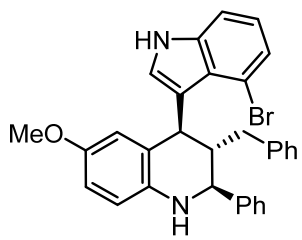
(2*S*,3*S*,4*R*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,7-dichloro-2-phenyl-1,2,3,4-tetrahydroquinoline 3fc



3fc

Following the general procedure from *N*-arylimine **1f** and 3-vinylindole **2c**, product **3fc** was obtained as a white solid in 45% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 2:1). $[\alpha]_D^{25}$ = +67 (c = 0.2 in $CHCl_3$) for 83% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.19 (m, 3H), 7.00 (dd, *J* = 8.0, 0.7 Hz, 1H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.85 – 6.71 (m, 7H), 5.81 (d, *J* = 1.8 Hz, 1H), 5.01 (s, 1H), 4.66 (s, 1H), 4.27 (s, 1H), 3.57 – 3.44 (m, 1H), 3.26 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.65 (dd, *J* = 13.4, 12.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.3, 143.6, 140.5, 137.8, 137.1, 133.0, 129.4 (2C), 128.5 (2C), 127.1 (2C), 126.3, 125.9, 125.1, 124.7 (2C), 124.4, 123.8, 122.2, 117.6, 117.5, 117.3, 113.5, 111.6, 110.1, 52.4, 44.4, 40.1, 36.2. **ESI-MS**: 583 [M(^{79}Br,^{35}Cl,^{35}Cl) + Na^+], 585 [M(^{79}Br,^{37}Cl,^{35}Cl) and M(^{81}Br,^{35}Cl,^{35}Cl) + Na^+], 587 [M(^{81}Br,^{37}Cl,^{35}Cl) and M(^{79}Br,^{37}Cl,^{37}Cl) + Na^+], 589 [M(^{81}Br,^{37}Cl,^{37}Cl) + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 7.9 min; t_{minor} = 10.6 min).

(2*S*,3*S*,4*R*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-6-methoxy-2-phenyl-1,2,3,4-tetrahydroquinoline 3ac

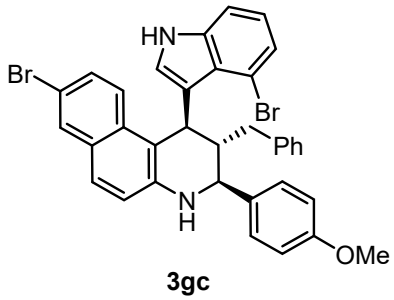


3ac

Following the general procedure from *N*-arylimine **1a** and 3-vinylindole **2c**, product **3ac** was obtained as a white solid in 90% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2/Et_2O = 10:1:1). $[\alpha]_D^{25}$ = +39 (c = 0.37 in $CHCl_3$) for 90% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.76 (bs,

1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.19 – 7.10 (m, 3H), 7.08 – 6.91 (m, 7H), 6.85 (d, *J* = 7.0 Hz, 2H), 6.70 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.66 – 6.56 (m, 2H), 6.38 (bs, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 4.27 (d, *J* = 6.6 Hz, 1H), 4.03 (bs, 1H), 3.63 (s, 3H), 3.07 (s, 1H), 2.95 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.71 (dd, *J* = 13.9, 8.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 151.8, 143.5, 141.0, 137.9, 137.2, 128.9 (2C), 127.85 (2C), 127.70 (2C), 127.0 (2C), 126.5, 125.9, 125.7, 125.5, 125.3, 124.4, 122.3, 120.2, 116.4, 114.5, 113.8, 113.5, 110.4, 58.5, 55.8, 47.2, 39.3, 38.7. **ESI-MS**: 545 [M(^{79}Br) + Na^+], 547 [M(^{81}Br) + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 11.2 min; t_{minor} = 12.3 min).

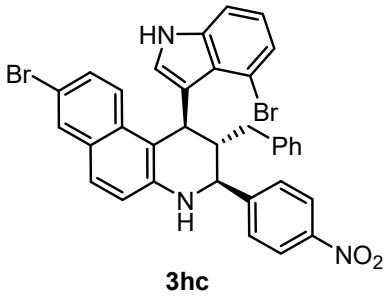
(1*R*,2*S*,3*S*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline 3gc



3gc

Following the general procedure from *N*-arylimine **1g** and 3-vinylindole **2c**, product **3gc** was obtained as a white solid in 77% yield after column chromatography on silica gel (from *n*-hexane/CH_2Cl_2/Et_2O = 10:1:1 to *n*-hexane/CH_2Cl_2/Et_2O = 8:1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +84 (c = 0.2 in $CHCl_3$) for 97% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 2.1 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.36 – 7.29 (m, 4H), 7.39 – 7.31 (m, 3H), 7.11 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.94 (t, *J* = 7.7 Hz, 1H), 6.78 – 6.72 (m, 2H), 6.32 – 6.27 (m, 2H), 5.58 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.18 (s, 1H), 4.69 (bs, 1H), 4.24 (bs, 1H), 3.57 (s, 3H), 3.52 – 3.43 (m, 1H), 3.27 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.73 (dd, *J* = 13.6, 11.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.0, 141.0, 140.5, 137.7, 136.4, 132.4, 130.1, 129.55 (2C), 129.43, 129.2, 128.4 (2C), 127.5, 127.4, 126.1, 125.9 (2C), 124.8, 124.4, 123.8, 122.1, 118.65, 118.61, 114.7, 113.6, 112.7 (2C), 110.9, 110.1, 55.2, 51.6, 44.4, 40.2, 34.8. **ESI-MS**: 651 [M(^{79}Br, ^{79}Br) + H^+], 653 [M(^{81}Br, ^{79}Br) + H^+], 655 [M(^{81}Br,^{81}Br) + H^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 11.9 min; t_{minor} = 23.5 min).

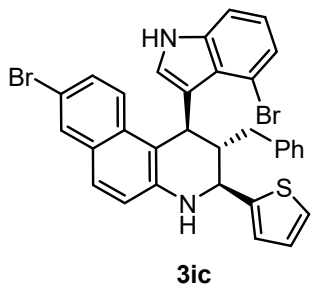
(1*R*,2*S*,3*S*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-(4-nitrophenyl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline 3hc



3hc

Following the general procedure from *N*-arylimine **1h** and 3-vinylindole **2c**, product **3hc** was obtained as a white solid in 95% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 1.5:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +237 (c = 0.2 in $CHCl_3$) for 97% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 2.1 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.57 – 7.50 (m, 2H), 7.49 – 7.41 (m, 4H), 7.39 – 7.31 (m, 3H), 7.31 – 7.23 (m, 2H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.01 – 6.95 (m, 2H), 6.95 – 6.89 (m, 2H), 5.59 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.22 – 5.15 (m, 1H), 4.70 (dd, *J* = 5.1, 1.4 Hz, 1H), 4.30 (d, *J* = 4.9 Hz, 1H), 3.63 (ddd, *J* = 11.8, 4.4, 1.9 Hz, 1H), 3.26 (dd, *J* = 13.6, 4.2 Hz, 1H), 2.70 (dd, *J* = 13.7, 11.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 153.0, 145.2, 140.4, 139.7, 137.9, 132.2, 130.2, 129.7, 129.4 (2C), 128.7 (2C), 127.9, 127.1, 126.5, 125.7 (2C), 124.5, 124.3, 124.1 (2C), 122.8, 122.1, 118.4 (2C), 118.0, 115.2, 113.4, 110.8, 110.4, 52.5, 44.9, 39.9, 34.7. **ESI-MS**: 666 [M(^{79}Br, ^{79}Br) + H^+], 668 [M(^{81}Br, ^{79}Br) + H^+], 670 [M(^{81}Br,^{81}Br) + H^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 16.8 min; t_{minor} = 33.2 min).

(1*R*,2*S*,3*S*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-(thiophen-2-yl)-1,2,3,4-tetrahydrobenzo[*f*]quinoline 3ic

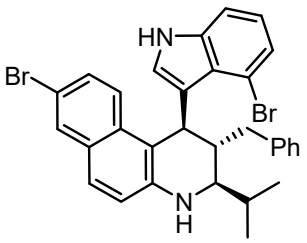


3ic

Following the general procedure from *N*-arylimine **1i** and 3-vinylindole **2c**, product **3ic** was obtained as a white solid in 95% yield after column chromatography on silica gel (*n*-hexane/ CH_2Cl_2 = 1.5:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +8 (c = 0.2 in $CHCl_3$) for 97% ee. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 2.1 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.48 – 7.37 (m, 4H), 7.36 – 7.27 (m, 3H), 7.24 – 7.16 (m, 2H), 7.13 – 7.04 (m, 2H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.69 (dt, *J* = 5.0, 0.9 Hz, 1H), 6.39 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.18 (dt, *J* = 3.6, 1.4 Hz, 1H), 5.72 (dd, *J* = 2.6, 0.9 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.83 (bs, 1H), 4.48 (s, 1H), 3.45 (ddd, *J* = 11.8, 4.2, 2.0 Hz, 1H), 3.29 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.70 (dd, *J* = 13.7, 11.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 151.5, 140.5, 139.7, 137.5, 132.3, 130.1, 129.58, 129.51,

129.3 (2C), 128.5 (2C), 127.6, 126.8, 126.6, 126.3, 124.9, 124.4, 123.9, 122.39, 122.34, 120.9, 119.1, 118.7, 115.0, 113.6, 110.9, 110.3, 49.9, 44.8, 39.9, 34.6. **ESI-MS**: 627 [M(^{79}Br, ^{79}Br) + H$^+$], 629 [M(^{81}Br, ^{79}Br) + H$^+$], 631 [M(^{81}Br,^{81}Br) + H$^+$]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 9.7 min; t_{minor} = 13.5 min).

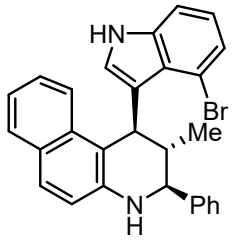
(1*R*,2*S*,3*R*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-isopropyl-1,2,3,4-tetrahydrobenzo[*f*]quinoline 3jc



3jc

Compound **3jc** was prepared following a three-component procedure. In a small vial equipped with a magnetic stirring bar, 6-bromo-2-naphthylamine (73 mg, 1 equiv, 0.3 mmol) and isobutyraldehyde (27.4 μL, 2 equiv, 0.6 mmol) were mixed in toluene (2 mL) until a clear solution was obtained (30 min). Then, 3-vinylindole **2c** (140 mg, 1.5 equiv, 0.45 mmol, *E*/*Z* mixture), and catalyst **(*R*)-TRIP** (11 mg, 0.015 mmol, 5 mol%) were added in this order, and the resulting mixture was stirred for 18 h at room temperature. Product **3jc** was obtained as a white solid in 95% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 2:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -29 (c = 0.2 in $CHCl_3$) for 65% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.86 (bs, 1H), 7.81 (bs, 1H), 7.52 (bd, *J* = 8.8 Hz, 1H), 7.41 (dd, *J* = 7.6, 0.9 Hz, 1H) overlapped with 7.60 – 7.35 (very broad s, 1H), 7.34 – 7.23 (m, 6H), 7.22 – 7.15 (m, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.89 (bs, 1H), 6.25 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.20 (bs, 1H), 4.51 (bs, 1H), 3.32 (bd, *J* = 10.7 Hz, 1H), 3.11 (dd, *J* = 13.6, 4.4 Hz, 1H), 2.55 (dd, *J* = 13.6, 11.3 Hz, 1H), 2.45 (bs, 1H), 1.45 – 1.36 (m, 1H), 0.70 (d, *J* = 6.5 Hz, 3H), 0.07 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 140.9, 140.7, 138.0, 132.3, 130.1, 129.5 (2C), 129.3, 128.2 (2C), 127.2, 125.9, 125.8, 125.4, 124.3 (2C), 122.7, 119.7, 118.7, 114.2, 113.7, 110.7, 109.7, 58.4, 41.1, 38.8, 34.7, 31.8, 21.2, 18.5. **ESI-MS**: 587 [M(^{79}Br, ^{79}Br) + H$^+$], 589 [M(^{81}Br, ^{79}Br) + H$^+$], 591 [M(^{81}Br,^{81}Br) + H$^+$]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{minor} = 6.4 min; t_{major} = 7.3 min).

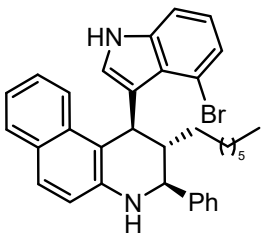
(1*R*,2*S*,3*S*)-1-(4-bromo-1*H*-indol-3-yl)-2-methyl-3-phenyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3bd



3bd

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2d**, product **3bd** was obtained as a white solid in 96% yield after column chromatography on silica gel (from *n*-hexane/CH_2Cl_2 = 3:2 to *n*-hexane/CH_2Cl_2 = 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -110 (c = 0.2 in $CHCl_3$) for 98% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.68 – 7.55 (m, 3H), 7.39 (bs, 1H), 7.34 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 7.16 – 6.98 (m, 7H), 6.95 (t, *J* = 7.8 Hz, 1H), 6.01 (d, *J* = 2.4 Hz, 1H), 5.28 (d, *J* = 4.5 Hz, 1H), 4.49 (bs, 1H), 4.30 (d, *J* = 5.1 Hz, 1H), 3.08 – 2.88 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 143.7, 141.4, 137.2, 133.7, 128.4, 128.2, 128.1, 127.8 (2C), 126.22 (2C), 126.20 (2C), 126.1, 124.9, 124.1, 123.5, 122.0, 121.4, 121.2, 117.8, 113.9, 113.7, 110.3, 60.0, 42.2, 36.3, 19.8. **ESI-MS**: 467 [M(^{79}Br) + H^+], 469 [M(^{81}Br) + H^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 14.9 min; t_{minor} = 20.8 min).

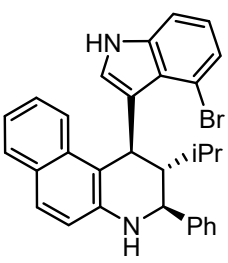
(1*R*,2*S*,3*S*)-1-(4-bromo-1*H*-indol-3-yl)-3-phenyl-2-heptyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3be



3be

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2e**, product **3be** was obtained as a white solid in 76% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 2:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -15 (c = 0.2 in $CHCl_3$) for 98% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.70 – 7.63 (m, 2H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.29 (dt, *J* = 7.1, 3.5 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.15 – 7.01 (m, 5H), 7.00 – 6.95 (m, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.89 – 6.76 (m, 3H), 5.67 (s, 1H), 5.12 (s, 1H), 4.59 (s, 2H), 3.15 (d, *J* = 6.7 Hz, 1H), 1.84 – 1.48 (m, 4H), 1.40 – 1.30 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.8, 140.3, 137.6, 133.8, 128.2, 128.0, 127.33, 127.25 (3C), 126.2, 125.4 (2C), 125.1, 124.6, 123.7, 122.9, 121.9, 121.2, 119.3, 117.6, 113.7, 111.8, 110.0, 53.8, 43.2, 35.8, 34.1, 31.9, 29.8, 29.4, 27.9, 22.7, 14.2. **ESI-MS**: 551 [M(^{79}Br) + H^+], 553 [M(^{81}Br) + H^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 7.6 min; t_{minor} = 9.3 min).

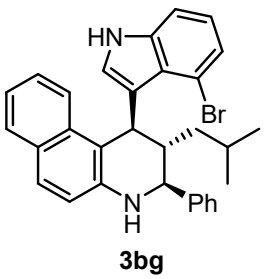
(1*R*,2*S*,3*S*)-1-(4-bromo-1*H*-indol-3-yl)-2-isopropyl-3-phenyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3bf



3bf

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2f**, product **3bf** was obtained as a white solid in 92% yield after column chromatography on silica gel (*n*-hexane/Et_2O/CH_2Cl_2 = 10:1:1). $[\alpha]_D^{25}$ = -88 (c = 0.2 in $CHCl_3$) for 99% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.75 – 7.68 (m, 2H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.25 (ddd, *J* = 8.5, 6.8, 1.3 Hz, 2H), 7.20 (bs, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.06 (d, *J* = 8.2, 1.1 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.92 – 6.79 (m, 4H), 6.77 – 6.71 (m, 1H), 5.86 (dd, *J* = 2.6, 1.0 Hz, 1H), 5.39 (s, 1H), 4.64 (s, 1H), 4.44 (bs, 1H), 3.12 (dt, *J* = 7.2, 2.3 Hz, 1H), 2.01 (sept, *J* = 6.9 Hz, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 145.5, 141.3, 138.0, 133.1, 128.3, 128.0, 127.8, 127.4, 126.9 (2C), 126.5, 125.2 (2C), 124.9, 124.7, 123.6, 122.0, 121.8, 121.2, 118.9, 117.2, 113.6, 112.2, 110.0, 54.3, 49.0, 32.3, 31.3, 21.4, 21.0. **ESI-MS**: 495 [M(^{79}Br) + H^+], 497 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 16.6 min; t_{minor} = 20.4 min).

(1*R*,2*S*,3*S*)-1-(4-bromo-1*H*-indol-3-yl)-2-isobutyl-3-phenyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3bg

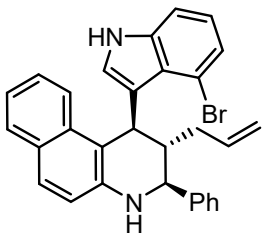


3bg

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2g**, product **3bg** was obtained as a white solid in 92% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 =2:1). $[\alpha]_D^{25}$ = -7 (c = 0.2 in $CHCl_3$) for 98% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 8.9 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.20 – 7.02 (m, 6H), 6.97 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.89 – 6.75 (m, 3H), 5.62 (d, *J* = 2.1 Hz, 1H), 5.04 (s, 1H), 4.61 (s, 2H), 3.28 (d, *J* = 11.3 Hz, 1H), 1.95 – 1.80 (m, 1H), 1.71 (ddd, *J* = 15.3, 11.5, 3.8 Hz, 1H), 1.52 (ddd, *J* = 13.9, 10.7, 3.3 Hz, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.9, 140.1, 137.6, 133.8, 128.25, 128.22, 128.0, 127.6, 127.3 (2C), 126.2, 125.2 (2C), 125.1, 124.6, 123.6, 122.9, 121.9, 121.2, 119.0, 117.6, 113.6, 111.7, 110.0, 53.1, 42.8, 40.0,

35.7, 25.5, 24.4, 21.6. **ESI-MS**: 509 [M(^{79}Br) + H$^+$], 511 [M(^{81}Br) + H$^+$]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 13.7 min; t_{minor} = 15.3 min).

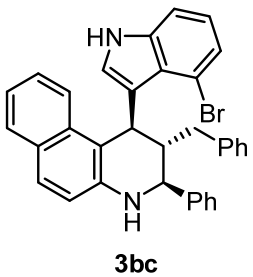
(1*R*,2*S*,3*S*)-2-allyl-1-(4-bromo-1*H*-indol-3-yl)-3-phenyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3bh



3bh

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2h**, product **3bh** was obtained as a white solid in 88% yield after column chromatography on silica gel (*n*-hexane/Et_2O/CH_2Cl_2 = 10:1:1). $[\alpha]_D^{25}$ = +40 (c = 0.2 in $CHCl_3$) for 98% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.70 – 7.64 (m, 2H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.30 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.22 – 6.97 (m, 7H), 6.90 (t, *J* = 7.63 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 1H), 6.88 – 6.76 (m, 3H), 6.09 (dddd, *J* = 17.0, 10.1, 8.7, 5.5 Hz, 1H), 5.69 (bs, 1H), 5.17 – 5.08 (m, 3H), 4.58 (d, *J* = 2.4 Hz, 1H), 3.32 – 3.21 (m, 1H), 2.58 (d, *J* = 13.9 Hz, 1H), 2.36 (ddd, *J* = 14.0, 10.3, 8.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.6, 140.2, 137.74, 137.68, 133.8, 128.3, 128.2, 128.0, 127.4, 127.3 (2C), 126.3, 125.3 (2C), 125.1, 124.5, 123.7, 122.9, 122.0, 121.3, 118.9, 117.6, 116.8, 113.6, 111.0, 110.0, 53.1, 42.6, 38.7, 35.1. **ESI-MS**: 493 [M(^{79}Br) + H$^+$], 495 [M(^{81}Br) + H$^+$]. **HPLC**: AD-H (*n*-hexane/i-PrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 9.0 min; t_{minor} = 9.6 min).

(1*R*,2*S*,3*S*)-2-benzyl-1-(4-bromo-1*H*-indol-3-yl)-3-phenyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3bc

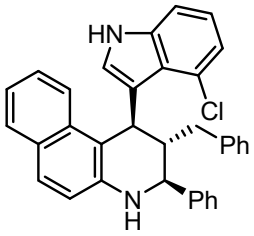


3bc

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2c**, product **3bc** was obtained as a white solid in 95% yield after column chromatography on silica gel (*n*-hexane/CH_2Cl_2 = 2:1). **$[\alpha]_D^{25}$** = +107 (c = 0.2 in $CHCl_3$) for 98% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.79 – 7.67 (m, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 8.3 Hz, 2H), 7.35 (dt, *J* = 13.3, 4.6 Hz, 3H), 7.25 – 7.11 (m, 4H), 7.09 (bs, 1H), 6.99 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.90 (t, *J* = 7.90 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.81 – 6.66 (m, 3H), 5.62 (d, *J* = 1.9 Hz, 1H), 5.27 (s, 1H), 4.67 (bs, 1H), 4.29 (s, 1H), 3.62 – 3.45 (m, 1H), 3.33 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.80 (dd, *J* = 13.5, 12.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.6, 141.2, 140.1, 137.7, 133.9, 129.5 (2C), 128.5, 128.4 (2C), 128.3, 128.0, 127.7, 127.2 (2C), 126.4, 126.1, 125.10 (2C), 125.05,

124.5, 123.7, 122.9, 122.0, 121.3, 118.6, 117.7, 113.6, 110.7, 110.1, 52.1, 44.4, 40.3, 34.9. **ESI-MS**: 565 [M(^{79}Br) + Na^+], 567 [M(^{81}Br) + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 20.9 min; t_{minor} = 42.8 min).

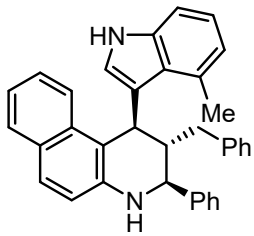
(1*R*,2*S*,3*S*)-2-benzyl-1-(4-chloro-1*H*-indol-3-yl)-3-phenyl-1,2,3,4-tetrahydrobenzo [*f*]quinoline 3bi



3bi

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2i**, product **3bi** was obtained as a white solid in 97% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +129 (c = 0.2 in $CHCl_3$) for 93% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.77 – 7.68 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 7.0 Hz, 2H), 7.38 – 7.30 (m, 2H), 7.25 – 7.07 (m, 6H), 7.00 (t, J = 8.03 Hz, 1H), 6.94 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.91 – 6.84 (m, 2H), 6.80 – 6.69 (m, 3H), 5.59 (dd, *J* = 2.5, 0.8 Hz, 1H), 5.18 (s, 1H), 4.67 (bs, 1H), 4.30 (s, 1H), 3.52 (ddd, *J* = 5.9, 4.3, 2.3 Hz, 1H), 3.24 (dd, *J* = 13.5, 4.1 Hz, 1H), 2.82 (dd, *J* = 13.4, 11.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.5, 141.2, 140.1, 137.8, 133.9, 129.5 (2C), 128.5, 128.4 (2C), 128.3, 128.0, 127.2 (2C), 127.1, 126.3, 126.1, 125.6, 125.1 (3C), 123.1, 122.9, 121.7, 121.3, 120.2, 118.4, 117.7, 110.8, 109.5, 52.3, 44.6, 40.7, 35.4. **ESI-MS**: 521 [M(^{35}Cl) + Na^+], 523 [M(^{37}Cl) + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 9.4min; t_{minor} = 16.7 min).

(1*R*,2*S*,3*S*)-2-benzyl-1-(4-methyl-1*H*-indol-3-yl)-3-phenyl-1,2,3,4-tetrahydrobenzo[*f*]qui- noline 3bj

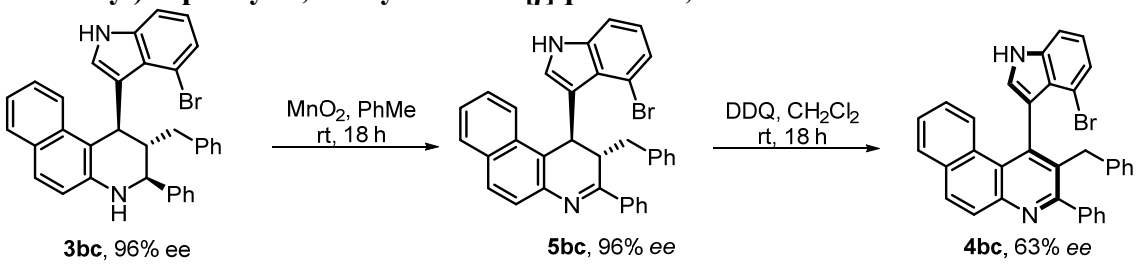


3bj

Following the general procedure from *N*-arylimine **1b** and 3-vinylindole **2j**, product **3bj** was obtained as a white solid in 92% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 4:1). $[\alpha]_D^{25}$ = +75 (c = 0.2 in $CHCl_3$) for 96% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.78 – 7.67 (m, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.30 (m, 4H), 7.24 – 7.08 (m, 4H), 7.00 (dd, *J* = 9.2, 5.9 Hz, 2H), 6.96 – 6.85 (m, 4H), 6.85 – 6.75 (m, 3H), 5.54 (s, 1H), 4.99 (s, 1H), 4.67 (bs, 1H), 4.34 (s, 1H), 3.37 – 3.23 (m, 1H), 3.14 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.00 (s, 3H), 2.91 (dd, *J* = 13.6, 11.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 144.1, 140.7, 139.9, 136.6,

133.8, 129.6, 129.3 (2C), 128.5 (2C), 128.4, 128.2, 128.1, 127.2 (2C), 126.34, 126.32, 126.2, 125.1, 125.0 (2C), 124.7, 123.0, 121.3, 121.0, 120.8, 118.8, 117.6, 111.4, 108.7, 52.6, 44.6, 40.9, 36.2, 20.9. **ESI-MS**: 501 [M + Na^+]. **HPLC**: AD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 9.0 min; t_{minor} = 11.6 min).

Preparation, characterization and reactivity of (1*R*,2*S*)-2-benzyl-1-(4-bromo-1*H*-indol-3-yl)-3-phenyl-1,2-dihydrobenzo[*f*]quinoline, intermediate 5bc.



3bc, 96% ee **5bc**, 96% *ee* **4bc**, 63% *ee*

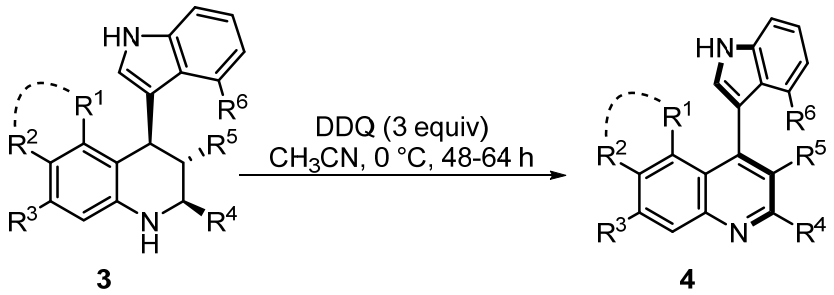
In a small vial equipped with a magnetic stirring bar, tetrahydroquinoline **3bc** (0.15 mmol, 78.8 mg, 96% *ee*), toluene (8 mL) and MnO_2 (378 mg, 4.5 mmol, 30 equiv) were added. MnO_2 was activated prior to use by standing in a 120 °C oven and then under *vacuum* for 30 min. The resulting solution was stirred for 18 h at room temperature and then filtered over a short plug of Celite®, eluted multiple times with CH_2Cl_2, obtaining an analytically pure product as a yellow powder in quantitative yield. This compound was found to be identical to **5bc**, isolated by column chromatography (*n*-hexane/Et_2O = 3:1) from mixtures containing **4bc**, obtained using DDQ as the oxidant. Similarly to products **3** and **4**, **5bc** was found to be extremely sensitive to traces of DCl in $CDCl_3$, darkening immediately upon contact and showing slow decomposition upon prolonged standing. In order to take the spectra in $CDCl_3$ the solvent had to be filtered over basic alumina immediately prior to use.

$[\alpha]_D^{25}$ = +131 (c = 0.2 in $CHCl_3$) for 96% ee.**^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 2.7 Hz, 1H), 7.91 (dd, *J* = 7.4, 2.1 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.73 – 7.63 (m, 4H), 7.41 – 7.32 (m, 2H), 7.22 – 7.10 (m, 4H), 7.10 – 7.00 (m, 3H), 6.98 – 6.91 (m, 3H), 6.82 (t, *J* = 7.9 Hz, 1H), 6.00 (d, *J* = 2.7 Hz, 1H), 5.67 (s, 1H), 4.00 (ddd, *J* = 9.3, 5.9, 1.3 Hz, 1H), 2.79 (dd, *J* = 13.3, 6.0 Hz, 1H), 2.64 (dd, *J* = 13.3, 9.3 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 167.4, 138.3, 135.7, 135.1, 130.9, 128.7, 127.9, 127.5 (2C), 126.0, 125.8 (2C), 125.7, 125.6 (2C), 125.4, 124.7 (2C), 124.2, 123.9, 123.4, 123.0, 122.9, 121.8, 121.6, 121.3, 121.1, 119.9, 112.2, 110.9, 108.0, 42.3, 34.0, 28.7. . **ESI-MS**: 540 [M(^{79}Br) + H^+], 542 [M(^{81}Br) + H^+] **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 10.6; t_{major} = 11.5 min).

Compound **5bc** was proved as a reactive intermediate as follows. In a small vial equipped with a magnetic stirring bar, **5bc** (0.05 mmol, 26.2 mg, 96% *ee*) was dissolved in CH_2Cl_2 (300 μL) and treated with DDQ (0.15 mmol, 3 equiv, 34.1 mg) for 18 h. The crude mixture was then poured into a solution of Na_2SO_3 (1 M) and extracted with DCM (3 x 30 mL). The combined organic phases were dried over Mg_2SO_4, filtered and

evaporated under reduced pressure. The crude residue was then purified by column chromatography on silica gel (*n*-hexane/Et_2O = 3:1) to obtain **4bc** in 90% yield (63% *ee*). On the other hand, chemical intuition points towards the effective intermediacy of **5bc** in the oxidation of **3bc** to **4bc**, as DDQ is in fact a two-electron oxidant and the loss of the two couples of protons should proceed stepwise. Moreover, NMR analysis performed at different times on the same reaction mixture revealed the **4bc**/**5bc** ratio to increase over time, indicating a transformation of **5bc** into **4bc** (**3bc** being already consumed).

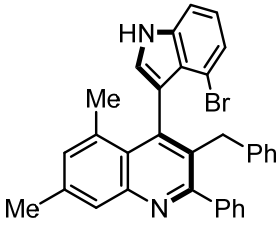
General procedure for the synthesis of products 4



3 **4**

In a test tube equipped with a magnetic stirring bar, tetrahydroquinoline **3** (0.1 mmol) and CH_3CN (3 mL) were added. In the case of poorly soluble substrates, a small amount of DCM (300 μL) could be added in order to ensure complete dissolution (*vide infra*). The resulting mixture was cooled to 0°C and DDQ (68.4 mg, 0.03 mmol, 3 equiv.) was added in one portion. The resulting solution was stirred for 48-64 h at 0°C and then poured into a solution of Na_2SO_3 (1 M, 10 mL) and extracted with DCM (3 x 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude residue was then purified by column chromatography on silica gel. Similarly to products **3**, products **4** were found to be sensitive to traces of DCl in $CDCl_3$ darkening immediately upon contact and showing slow decomposition upon prolonged standing. In order to record the spectra in $CDCl_3$ the solvent had to be filtered over basic alumina prior to use.

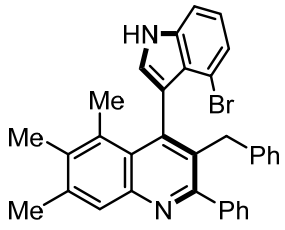
(*aS*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,7-dimethyl-2-phenylquinoline 4cc



4cc

Following the general procedure (64 h, CH_2Cl_2 added) from tetrahydroquinoline **3cc**, product **4cc** was obtained as a white solid in 50% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +162 (c = 0.2 in $CHCl_3$) for 92% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.37 (bs, 1H), 7.88 (s, 1H), 7.49 – 7.39 (m, 2H), 7.35 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.33 – 7.27 (m, 4H), 7.11 – 7.04 (m, 2H), 6.99 – 6.92 (m, 3H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.53 – 6.44 (m, 2H), 4.08 (d, *J* = 15.9 Hz, 1H), 3.75 (d, *J* = 16.0 Hz, 1H), 2.48 (d, *J* = 0.9 Hz, 3H), 1.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.1, 147.9, 141.8, 141.6, 138.3, 136.3, 135.8, 132.9, 132.2, 128.8 (2C), 128.3, 128.03 (2C), 127.95 (2C), 127.74, 127.68, 127.6 (2C), 126.8, 125.9, 125.1, 125.0, 124.4, 123.4, 115.8, 114.7, 110.7, 36.6, 23.4, 21.3. **ESI-MS**: 517 [M(^{79}Br) + H^+], 519 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 11.6; t_{major} = 28.5 min).

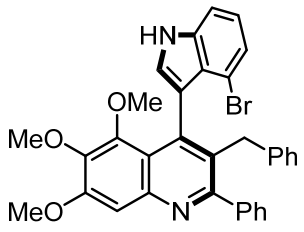
(*aS*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,6,7-trimethyl-2-phenylquinoline 4dc



4dc

Following the general procedure (48 h) from tetrahydroquinoline **3dc**, product **4dc** was obtained as a white solid in 44% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +102 (c = 0.1 in $CHCl_3$) for 96% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.25 (bs, 1H), 7.89 (s, 1H), 7.48 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.38 (dd, *J* = 3.0, 0.8 Hz, 1H), 7.36 (dd, *J* = 2.6, 0.8 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.95 – 6.82 (m, 3H), 6.45 (d, *J* = 2.5 Hz, 1H), 6.34 (dd, *J* = 7.8, 1.6 Hz, 2H), 4.13 (d, *J* = 15.9 Hz, 1H), 3.79 (d, *J* = 15.9 Hz, 1H), 2.49 (s, 3H), 2.27 (s, 3H), 1.90 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.3, 145.9, 141.6, 141.1, 138.5, 136.5, 135.6, 133.1, 133.0, 130.0, 128.9 (2C), 128.2, 128.1 (2C), 127.82, 127.76 (2C), 127.6, 127.5 (2C), 126.9, 125.4, 125.0, 124.5, 123.5, 117.0, 114.9, 110.7, 36.6, 21.6, 19.2, 16.7. **ESI-MS**: 531 [M(^{79}Br) + H^+], 533 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/i-PrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 11.3; t_{major} = 25.3 min).

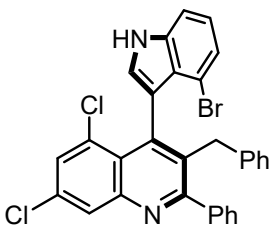
(*aS*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,6,7-trimethoxy-2-phenylquinoline 4ec



4ec

Following the general procedure (64 h, CH_2Cl_2 added) from tetrahydroquinoline **3ec**, product **4ec** was obtained as a white solid in 69% yield after column chromatography on silica gel (CH_2Cl_2/Et_2O = 50:1). $[\alpha]_D^{25}$ = +67 (c = 0.27 in $CHCl_3$) for 90% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.26 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.37 – 7.27 (m, 4H), 7.23 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 7.00 – 6.95 (m, 3H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.60 – 6.51 (m, 2H), 4.05 (d, *J* = 16.1 Hz, 1H), 3.99 (s, 3H), 3.85 (s, 3H), 3.79 (d, *J* = 16.1 Hz, 1H), 3.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.2, 155.1, 149.3, 144.7, 142.6, 141.8, 141.5, 140.2, 136.2, 131.8, 128.6 (2C), 128.1 (2C), 128.0 (2C), 127.7, 127.6 (2C), 125.9, 125.1, 124.0, 123.4, 122.8, 120.4, 115.7, 114.7, 110.5, 104.9, 61.0, 60.7, 56.0, 36.4. **ESI-MS**: 579 [M(^{79}Br) + H^+], 581 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 12.9; t_{major} = 22. 7 min).

(*aS*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-5,7-dichloro-2-phenylquinoline 4fc

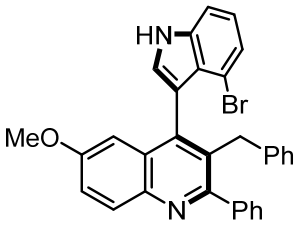


4fc

Following the general procedure but running the reaction at room temperature (64 h, CH_2Cl_2 added) from tetrahydroquinoline **3fc**, product **4fc** was obtained as a white solid in 70% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -157 (c = 0.2 in $CHCl_3$) for 86% ee. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.31 (bs, 1H), 8.15 (d, *J* = 2.2 Hz, 1H), 7.51 (d, *J* = 2.2 Hz, 1H), 7.46 – 7.40 (m, 2H), 7.38 – 7.32 (m, 4H), 7.28 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 7.02 – 6.96 (m, 3H), 6.64 (d, *J* = 2.5 Hz, 1H), 6.54 – 6.48 (m, 2H), 4.12 (d, *J* = 15.9 Hz, 1H), 3.87 (d, *J* = 15.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.3, 147.9, 141.8, 141.0, 140.6, 136.3, 135.4, 133.5, 132.3, 130.0, 128.6 (2C), 128.5, 128.3, 128.2 (2C), 128.0 (2C), 127.8 (2C), 126.4, 125.4, 125.3, 125.0, 124.4, 123.4, 114.6, 113.5, 110.7, 36.8. **ESI-MS**: 557 [M(^{79}Br,^{35}Cl,^{35}Cl) + H^+], 559 [M(^{79}Br,^{37}Cl,^{35}Cl) and M(^{81}Br,^{35}Cl,^{35}Cl) + H^+], 561 [M(^{81}Br,^{37}Cl,^{35}Cl) and M(^{79}Br,^{37}Cl,^{37}Cl) + H^+], 563 [M(^{81}Br,^{37}Cl,^{37}Cl) + H^+]. **HPLC**: ODH (*n*-hexane/i-PrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 11.23; t_{major} = 18.98 min).

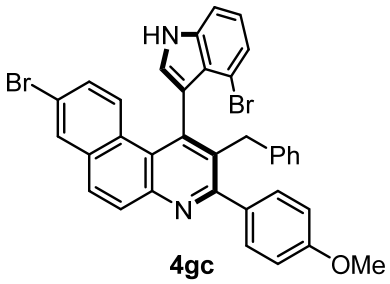
(*aS*)-3-benzyl-4-(4-bromo-1*H*-indol-3-yl)-6-methoxy-2-phenylquinoline 4ac



4ac

Following the general procedure (48 h) but running the reaction at room temperature from tetrahydroquinoline **3ac**, product **4ac** was obtained as a white solid in 87% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = -120 (c = 0.2 in $CHCl_3$) for 90% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.59 (bs, 1H), 8.11 (d, *J* = 9.1 Hz, 1H), 7.48 – 7.40 (m, 2H), 7.40 – 7.29 (m, 5H), 7.29 – 7.27 (m, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.01 – 6.95 (m, 3H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.60 – 6.52 (m, 2H), 4.15 (d, *J* = 15.8 Hz, 1H), 3.88 (d, *J* = 15.8 Hz, 1H), 3.67 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 154.0, 152.9, 137.6, 136.8, 136.6, 132.0, 128.5, 126.0, 125.2, 124.1 (2C), 123.5, 123.4 (2C), 123.3 (2C), 122.9 (2C), 122.1, 120.7, 120.5, 120.4, 119.9, 118.7, 116.1, 109.7, 107.6, 106.0, 100.3, 50.7, 32.3. **ESI-MS**: 519 [M(^{79}Br) + H^+], 521 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 12.73; t_{major} = 22.37 min).

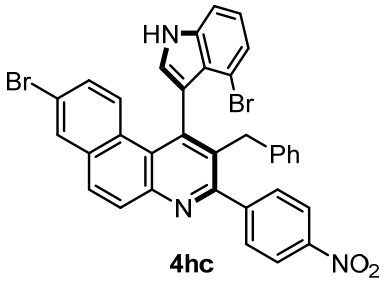
(*aS*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-(4-methoxyphenyl)benzo[*f*] quinoline 4gc



4gc

Following the general procedure (64 h, CH_2Cl_2 added) from tetrahydroquinoline **3gc**, product **4gc** was obtained as a white solid in 53% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +108 (c = 0.2 in $CHCl_3$) for 96% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.42 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 2.3 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.56 – 7.50 (m, 3H), 7.43 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.33 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.00 – 6.88 (m, 5H), 6.49 – 6.42 (m, 2H), 6.41 (d, *J* = 2.5 Hz, 1H), 4.28 (d, *J* = 15.9 Hz, 1H), 3.86 (d, *J* = 15.9 Hz, 1H), 3.81 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.6 (2C), 147.0, 142.1, 141.5, 136.9, 134.8, 134.7, 133.7, 130.6, 130.4 (2C), 130.1, 129.7, 129.4, 128.8, 128.7, 127.8 (2C), 127.7 (2C), 125.8, 125.3, 124.8, 124.6, 123.9, 123.8, 120.2, 116.1, 114.5, 113.8 (2C), 111.0, 55.4, 36.8. **ESI-MS**: 647 [M(^{79}Br, ^{79}Br) + H^+], 649 [M(^{81}Br, ^{79}Br) + H^+], 651 [M(^{81}Br,^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{major} = 17.3 min; t_{minor} = 23.0 min).

(*aS*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-(4-nitrophenyl)benzo[*f*]quinoline 4hc

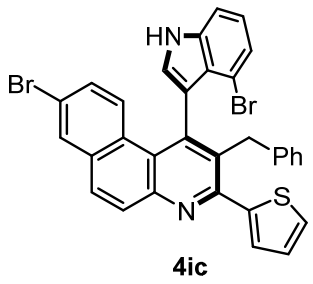


4hc

Following the general procedure (64 h) from tetrahydroquinoline **3hc**, product **4hc** was obtained as a white solid in 61% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +116 (c = 0.2 in $CHCl_3$) for 81% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.53 (d, *J* = 2.6 Hz, 1H), 8.26 – 8.18 (m, 2H), 8.07 (d, *J* = 9.0 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.88 (dt, *J* = 8.9, 0.7 Hz, 1H), 7.73 – 7.65 (m, 2H), 7.56 (dt, *J* = 9.3, 0.6 Hz, 1H), 7.46 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.35 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.21 – 7.15 (m, 1H), 7.12 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.02 – 6.93 (m, 3H), 6.61 (d, *J* = 2.5 Hz, 1H), 6.48 – 6.42 (m, 2H), 4.09 (d, *J* = 16.2 Hz, 1H), 3.94 (d, *J* = 16.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 157.4, 147.7, 147.5, 147.1, 142.7, 140.6,

136.9, 134.9, 134.4, 130.7 (2C), 130.4, 130.1, 129.8, 129.2, 129.0, 128.9, 128.0 (2C), 127.8 (2C), 126.5, 125.7, 125.0, 124.6, 124.2, 123.6, 123.4 (2C), 120.9, 115.7, 114.4, 111.2, 36.5. **ESI-MS**: 662 [M(^{79}Br, ^{79}Br) + H^+], 664 [M(^{81}Br, ^{79}Br) + H^+], 666 [M(^{81}Br,^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{major} = 25.7 min; t_{minor} = 54.2 min).

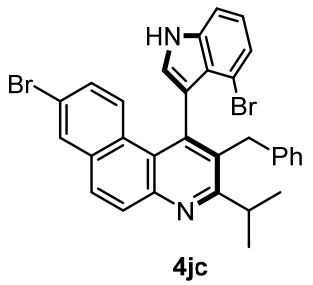
(*aS*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-(thiophen-2-yl)benzo[*f*]quinoline 4ic



4ic

Following the general procedure but running the reaction at room temperature (64 h) from tetrahydroquinoline **3ic**, product **4ic** was obtained as a white solid in 92% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +101 (c = 0.2 in $CHCl_3$) for 63% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.36 (bs, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 2.3 Hz, 1H), 7.84 (d, *J* = 9.1 Hz, 1H), 7.51 – 7.38 (m, 3H), 7.32 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.14 – 7.02 (m, 5H), 7.00 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.80 – 6.65 (m, 2H), 6.51 (d, *J* = 2.6 Hz, 1H), 4.53 (d, *J* = 16.5 Hz, 1H), 4.02 (d, *J* = 16.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 152.3, 147.2, 144.4, 143.1, 141.3, 136.8, 134.7, 133.0, 130.7, 130.1, 129.3 (2C), 128.9, 128.5, 128.13 (2C), 128.05, 128.0 (2C), 127.7, 127.6, 126.0, 125.6, 124.8, 124.4, 124.0, 123.7, 120.4, 115.7, 114.6, 110.9, 37.1. **ESI-MS**: 623 [M(^{79}Br, ^{79}Br) + H^+], 625 [M(^{81}Br, ^{79}Br) + H^+], 627 [M(^{81}Br,^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{major} = 14.5 min; t_{minor} = 18.2 min).

(*aS*)-2-benzyl-8-bromo-1-(4-bromo-1*H*-indol-3-yl)-3-isopropylbenzo[*f*]quinoline 4jc

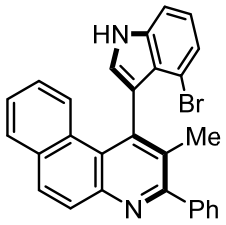


4jc

Following the general procedure (64 h) from tetrahydroquinoline **3jc**, product **4jc** was obtained as a white solid in 64% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +122 (c = 0.2 in $CHCl_3$) for 60% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.37 (s, 1H), 8.06 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 2.3 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.29 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.18 – 7.01 (m, 5H), 6.79 – 6.74 (m, 2H), 6.63 (d, *J* = 2.5 Hz, 1H), 4.20 (d, *J* = 16.5 Hz, 1H), 3.96 (d, *J* = 16.5 Hz,

1H), 3.39 (sept, *J* = 6.9 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.32 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 165.4, 147.4, 141.1, 141.0, 136.9, 134.5, 133.3, 130.5, 130.4, 129.6, 129.0, 128.5, 128.4, 128.1 (2C), 127.9 (2C), 125.6, 125.1, 124.9, 124.7, 124.0, 123.2, 119.8, 116.7, 114.7, 110.9, 35.3, 32.4, 23.2, 21.2. **ESI-MS**: 583 [M(^{79}Br, ^{79}Br) + H^+], 585 [M(^{81}Br, ^{79}Br) + H^+], 587 [M(^{81}Br,^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{major} = 9.0 min; t_{minor} = 12.1 min).

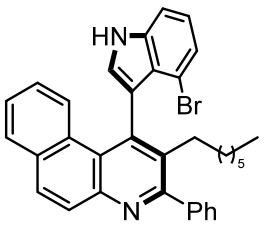
(*aS*)-1-(4-bromo-1*H*-indol-3-yl)-2-methyl-3-phenylbenzo[*f*]quinoline 4bd



4bd

Following the general procedure (48 h) from tetrahydroquinoline **3bd**, product **4bd** was obtained as a white solid in 75% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +10 (c = 0.2 in $CHCl_3$) for 89% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.07 (bs, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.75 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.74 – 7.68 (m, 2H), 7.51 – 7.43 (m, 3H), 7.43 – 7.36 (m, 2H), 7.35 (dd, *J* = 7.6, 0.9 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H), 7.04 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 6.86 (d, *J* = 2.5 Hz, 1H), 2.13 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 158.4, 146.6, 141.9, 141.4, 137.3, 133.2, 132.0, 130.7, 130.5, 129.3 (2C), 128.6, 128.5, 128.3 (2C), 128.0, 127.3, 126.1, 125.7, 125.6, 125.3, 124.5, 123.8, 122.6, 117.6, 114.7, 111.1, 19.1. **ESI-MS**: 463 [M(^{79}Br) + H^+], 465 [M(^{81}Br) + H^+]. **HPLC**: AD-H (*n*-hexane /iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 7.1 min; t_{major} = 9.2 min).

(*aS*)-1-(4-bromo-1*H*-indol-3-yl)-2-heptyl-3-phenylbenzo[*f*]quinoline 4be

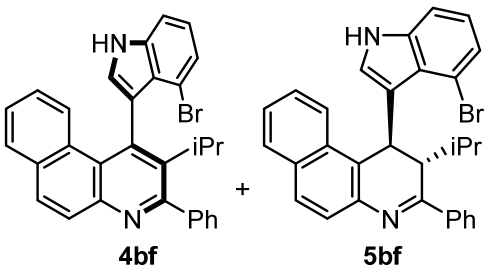


4be

Following the general procedure (48 h) from tetrahydroquinoline **3be**, product **4be** was obtained as a white solid in 99% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +37 (c = 0.2 in $CHCl_3$) for 90% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = δ 9.75 – 9.46 (m, 1H), 8.13 – 8.03 (m, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 – 7.62 (m, 3H), 7.48 – 7.34 (m, 5H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.12 (td, *J* = 7.9, 1.4 Hz, 1H), 7.05 (dddd, *J* = 8.5, 6.9, 2.7, 1.4 Hz, 1H), 6.85 (dd, *J* = 4.1, 2.4 Hz, 1H), 2.75 (ddd, *J* = 13.3, 11.1, 4.9 Hz, 1H), 2.58 – 2.43 (m, 1H), 1.19 – 0.95 (m, 4H), 0.95 – 0.63 (m, 9H). **^{13}C NMR** (101

MHz, $CDCl_3$) δ = 159.0, 146.3, 141.5, 137.2, 137.0, 136.9, 133.2, 130.8, 130.7, 129.0 (2C), 128.6, 128.3, 128.2 (2C), 127.9, 127.3, 126.2, 126.1, 125.7, 125.4, 124.5, 123.62, 123.57, 116.3, 114.8, 111.2, 31.3, 30.5, 29.7, 29.4, 28.1, 22.5, 14.0. **ESI-MS**: 547 [M(^{79}Br) + H^+], 549 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 10.5; t_{major} = 52.5 min).

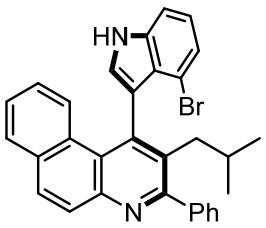
(*aS*)-1-(4-bromo-1*H*-indol-3-yl)-2-isopropyl-3-phenylbenzo[*f*]quinoline 4bf and (1*R*,2*S*)-1-(4-bromo-1*H*-indol-3-yl)-2-isopropyl-3-phenyl-1,2-dihydrobenzo[*f*]quinoline 5bf



4bf **5bf**

Following the general procedure but running the reaction at room temperature (64 h, CH_2Cl_2 added) from tetrahydroquinoline **3bf**, product **4bf** was obtained as a white solid in 50% yield (along with 32% of **5bf**, 0.64:1 **4bf**/**5bf**, inseparable mixture) after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.38 (bs, 1H **4bf**), 8.17 – 8.08 (m, 1H **5bf**), 8.02 (d, *J* = 8.9 Hz, 1H **4bf**), 7.93 (bd, *J* = 2.5 Hz, 1H **5bf**), 7.91 – 7.88 (m, 1H **4bf**), 7.88 – 7.81 (m, 2H **5bf** + 1H **4bf**), 7.78 (d, *J* = 8.6 Hz, 1H **5bf**), 7.70 – 7.65 (m, 2H **5bf**), 7.58 – 7.52 (m, 2H **4bf**), 7.49 (dd, *J* = 8.7, 1.0 Hz, 1H **4bf**), 7.47 – 7.33 (m, 4H **4bf** + 4H **5bf**), 7.33 – 7.23 (m, 2H **4bf** + 2H **5bf**), 7.11 (t, *J* = 7.9 Hz, 1H **4bf**), 7.06 (dd, *J* = 8.1, 1.1 Hz, 1H **5bf**), 7.02 – 6.93 (m, 1H **4bf** + 1H **5bf**), 6.86 (d, *J* = 2.4 Hz, 1H **4bf**), 6.14 (d, *J* = 2.6 Hz, 1H **5bf**), 5.92 (s, 1H **5bf**), 3.71 (dd, *J* = 8.3, 1.4 Hz, 1H **5bf**), 3.26 (sept, *J* = 7.2 Hz, 1H **4bf**), 1.90 (sept, *J* = 7.3 Hz, 1H **5bf**), 1.04 (d, *J* = 6.8 Hz, 3H **5bf**), 0.91 (d, *J* = 7.2 Hz, 3H **4bf**), 0.88 (d, *J* = 7.2 Hz, 3H **4bf**), 0.73 (d, *J* = 6.8 Hz, 3H **5bf**). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 171.6, 159.3, 145.8, 143.1, 141.9, 141.7, 141.0, 140.7, 137.8, 137.0, 133.3, 133.19, 131.14, 130.8 (2C), 130.1, 129.4 (2C), 128.7, 128.5 (2C), 128.4, 127.8, 127.78 (2C), 127.72, 127.2 (2C), 127.1, 126.6, 126.2, 126.1, 126.0, 125.7 (2C), 125.6, 125.3, 124.6, 124.5, 124.3, 124.1, 124.0, 123.7, 123.5, 122.4, 116.7, 115.1, 115.0, 113.4, 111.0, 110.7, 48.9, 31.5, 30.7, 30.7, 30.6, 23.1, 22.9, 22.8, 22.5 (all peaks are given without assignment). **ESI-MS**: 491 [M(**4bf**, ^{79}Br) + H^+], 493 [M(**4bf**, ^{81}Br) or M(**5bf**, ^{81}Br) + H^+], 495 [M(**5bf**, ^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 14.6; t_{major} = 55.3 min), 99% *ee*.

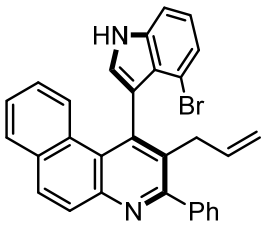
(*aS*)-1-(4-bromo-1*H*-indol-3-yl)-2-isobutyl-3-phenylbenzo[*f*]quinoline 4bg



4bg

Following the general procedure (48 h) from tetrahydroquinoline **3bg**, product **4bg** was obtained as a white solid in 80% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +42 (c = 0.2 in $CHCl_3$) for 98% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.32 (bs, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.84 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.73 (dd, *J* = 5.1, 3.2 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.49 – 7.31 (m, 6H), 7.14 (t, *J* = 7.9 Hz, 1H), 7.01 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 2.93 (dd, *J* = 13.9, 6.5 Hz, 1H), 2.51 (dd, *J* = 13.9, 7.6 Hz, 1H), 1.40 – 1.25 (m, 1H), 0.39 (d, *J* = 6.7 Hz, 3H), 0.34 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.1, 146.4, 141.8, 141.7, 137.1, 135.3, 133.3, 130.8, 130.6, 129.4 (2C), 128.5, 128.4, 128.3 (2C), 127.9, 127.5, 126.0, 125.8, 125.4, 125.3, 124.7, 124.2, 123.6, 116.7, 114.8, 111.1, 38.9, 28.9, 22.7, 22.3. **ESI-MS**: 505 [M(^{79}Br) + H^+], 507 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 10.3; t_{major} = 63.1 min).

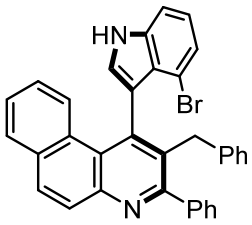
(*aS*)-2-allyl-1-(4-bromo-1*H*-indol-3-yl)-3-phenylbenzo[*f*]quinoline 4bh



4bh

Following the general procedure (48 h) from tetrahydroquinoline **3bh**, product **4bh** was obtained as a white solid in 83% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +64 (c = 0.2 in $CHCl_3$) for 96% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 9.23 (bs, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.70 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.50 – 7.34 (m, 5H), 7.30 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.04 (ddd, *J* = 8.7, 7.0, 1.5 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 5.49 (ddt, *J* = 17.2, 10.1, 5.9 Hz, 1H), 4.67 (dq, *J* = 10.1, 1.6 Hz, 1H), 4.27 (dq, *J* = 17.1, 1.8 Hz, 1H), 3.52 (ddt, *J* = 15.7, 5.9, 1.7 Hz, 1H), 3.28 (ddt, *J* = 15.7, 6.1, 1.7 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.2, 146.9, 142.1, 141.3, 137.1, 136.6, 133.3, 133.2, 131.0, 130.7, 129.1 (2C), 128.6, 128.5, 128.2 (2C), 128.0, 127.2, 126.2 (2C), 125.8, 125.1, 124.5, 123.9, 123.7, 116.1, 115.2, 114.7, 111.1, 35.2. **ESI-MS**: 489 [M(^{79}Br) + H^+], 491 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{minor} = 13.3; t_{major} = 42.2 min).

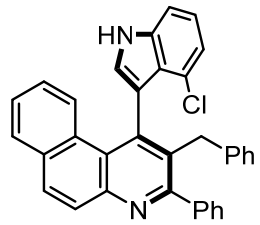
(*aS*)-2-benzyl-1-(4-bromo-1*H*-indol-3-yl)-3-phenylbenzo[*f*]quinoline 4bc



4bc

Following the general procedure (48 h) from tetrahydroquinoline **3bc**, product **4bc** was obtained as a white solid in 97% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +154 (c = 0.2 in $CHCl_3$) for 94% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.88 (d, *J* = 1.9 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.86 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.70 (dd, *J* = 8.4, 0.5 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.42 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.39 – 7.27 (m, 5H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.02 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.97 – 6.90 (m, 3H), 6.48 – 6.41 (m, 2H), 6.38 (d, *J* = 2.5 Hz, 1H), 4.25 (d, *J* = 15.9 Hz, 1H), 3.91 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.5, 147.1, 142.5, 141.4, 141.3, 137.0, 134.5, 133.2, 131.1, 130.8, 129.1 (2C), 128.6, 128.5, 128.2 (2C), 128.0, 127.9 (2C), 127.6 (2C), 127. 4, 126.22, 126.21, 125.7, 125.2, 124.8, 124.6, 124.0, 123.6, 116.1, 114.6, 111.1, 36.7. **ESI-MS**: 539 [M(^{79}Br) + H^+], 541 [M(^{81}Br) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{major} = 13.1 min; t_{minor} = 40.3 min).

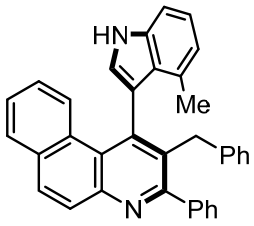
(*aS*)-2-benzyl-1-(4-chloro-1*H*-indol-3-yl)-3-phenylbenzo[*f*]quinoline 4bi



4bi

Following the general procedure (48 h) from tetrahydroquinoline **3bi**, product **4bi** was obtained as a white solid in 97% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +206 (c = 0.2 in $CHCl_3$) for 91% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.86 (bs, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.45 – 7.38 (m, 1H), 7.38 – 7.27 (m, 4H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.02 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.97 – 6.91 (m, 3H), 6.49 – 6.34 (m, 3H), 4.25 (d, *J* = 15.9 Hz, 1H), 3.95 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.5, 147.2, 142.7, 141.5, 141.3, 137.3, 134.1, 133.2, 131.1, 130.7, 129.1 (2C), 128.58, 128.55, 128.2 (2C), 127.93, 127.89 (2C), 127.6 (2C), 127.3, 126.6, 126.2, 126.0, 125.7, 125.2, 123.8, 123.6, 123.3, 121.1, 115.3, 110.4, 36.6. **ESI-MS**: 495 [M(^{35}Cl) + H^+], 497 [M(^{37}Cl) + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 80:20, flow-rate 0.75 mL/min; t_{major} = 7.1 min; t_{minor} = 14.8 min).

(*aS*)-2-benzyl-1-(4-methyl-1*H*-indol-3-yl)-3-phenylbenzo[*f*]quinoline 4bj



4bj

Following the general procedure (48 h) from tetrahydroquinoline **3bj**, product **4bj** was obtained as a white solid in 92% yield after column chromatography on silica gel (*n*-hexane/Et_2O = 1:1). $[\alpha]_D^{25}$ = +116 (c = 0.2 in $CHCl_3$) for 75% *ee*. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.32 (bs, 1H), 8.11 (d, *J* = 9.0 Hz, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.45 – 7.33 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.23 – 7.15 (m, 1H), 7.05 – 6.93 (m, 4H), 6.88 (dd, *J* = 7.1, 0.9 Hz, 1H), 6.52 – 6.46 (m, 2H), 6.44 (d, *J* = 2.5 Hz, 1H), 4.18 (d, *J* = 15.7 Hz, 1H), 3.93 (d, *J* = 15.7 Hz, 1H), 2.03 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 159.6, 147.4, 144.3, 141.6, 141.3, 136.4, 133.7, 133.2, 131.3, 131.2, 130.7, 129.0 (2C), 128.9, 128.6, 128.2 (2C), 127.97 (2C), 127.94, 127.7 (2C), 127.3, 126.3, 125.9, 125.8, 125.2, 125.0, 122.9, 121.9, 121.5, 115.9, 109.4, 36.4, 19.3. **ESI-MS**: 475 [M + H^+]. **HPLC**: OD-H (*n*-hexane/iPrOH 90:10, flow-rate 0.75 mL/min; t_{major} = 6.8 min; t_{minor} = 16.4 min).

6. Bibliography

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