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Central-to-Axial Chirality Conversion Approach Designed on Organocatalytic Enantioselective Povarov Cycloadditions: First Access to Configurationally Stable Indole-Quinoline Atropisomers

Giorgiana Denisa Bisag,[a] Daniel Pecorari,[a] Andrea Mazzanti,[a] Luca Bernardi,[a] Mariafrancesca Fochi,[a] Giorgio Bencivenni,[a] Giulio Bertuzzi[a]* and Vasco Corti[a]*

Abstract: The first stereoselective synthesis of enantioenriched axially chiral indole-quinoline systems is presented. The strategy takes advantage of an organocatalytic enantioselective Povarov cycloaddition of 3-alkenylindoles and *N*-arylimines, followed by an oxidative central-to-axial chirality conversion process, allowing access to previously unreported axially chiral indole-quinoline biaryls. The methodology is also implemented for the design and the preparation of challenging compounds exhibiting two stereogenic axes. DFT calculations shed light on the stereoselectivity of the central-to-axial chirality conversion, showing unconventional behaviour.

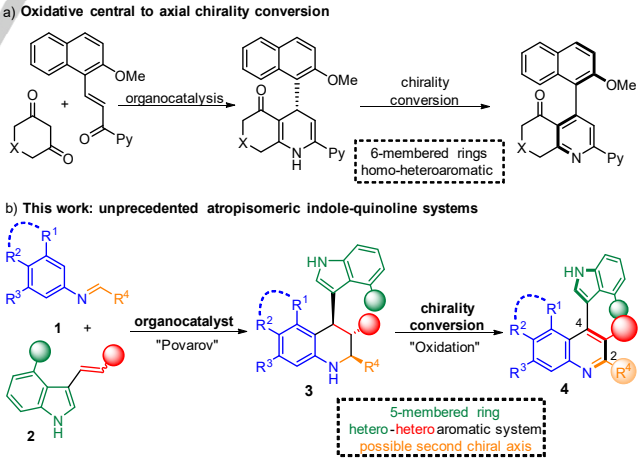
Introduction

Enantioenriched axially chiral compounds are fascinating privileged scaffolds in drug discovery,[1] catalyst design[2] and material science.[3]

Many methodologies for the stereoselective preparation of atropisomeric compounds have been developed,[4] such as atroposelective cross-couplings,[5] cycloadditions,[6] (dynamic) kinetic resolutions[7] and desymmetrizations[8] of stereochemically not defined biaryls. More recently, central-to-axial chirality conversion, hypothesized by Berson in 1955[9] and first demonstrated by Meyers in 1984,[10] has been successfully applied to a restricted number of substrates possessing central chirality, prone to be turned into axially chiral molecules.[11] In this context, a pioneering work by Bressy, Bugaut, Rodriguez and co-workers for the preparation of enantioenriched atropisomeric 4-arylpyridines[11i] [Scheme 1a)] has disclosed the potential of the combination of enantioselective organocatalytic methodologies with the oxidative central-to-axial chirality conversion approach.

The widest class of atropisomeric structures is represented by hindered 6-membered *homo*-biaryls derivatives. On the other hand, axially chiral systems featuring 5-membered rings are intrinsically more challenging structures, requiring higher degrees of demanding constraints to stabilize the stereogenic axis.[12] In addition, the synthesis of optically active *hetero*cyclic architectures, displaying axial chirality, is a prominent goal of current enantioselective catalysis.[13]

In this paper, we show that chiral Brønsted acid catalysed Povarov reactions[14] of *N*-arylimines with specifically designed 3-alkenylindoles **2**[15] provide a convenient route to enantioenriched, highly substituted, 1,2,3,4-tetrahydroquinolines **3**, prone to be oxidized into axially chiral 4-(indol-3-yl)quinolines **4** [Scheme 1, b)] in a central-to-axial chirality conversion approach. Products **4** represent not only a rare and challenging example of axially chiral 5-membered heteroaryl - 6-membered heteroaryl compound, but also, to the best of our knowledge, the first class of atropisomeric indole-quinoline systems. These are indeed privileged structures, that can be found, in tropo-isomeric forms, in several drug candidates.[16] This methodology is also useful for the design of structures exhibiting two stereogenic axes, at the C2 and at C4 positions of the quinoline.[17] The conversion of multiple stereocenters into multiple atropisomeric elements is an important extension of the chirality conversion approach. This was reported for the first time very recently, restricted to the case of proximal chirality axes.[18] In order to achieve this goal, challenges such as the formation of a particularly demanding stereogenic axis, in proximity of a pyridinic nitrogen, lacking any substituent, must be faced.



Scheme 1. Combining organocatalytic enantioselective Povarov cycloadditions with the oxidative central-to-axial chirality conversion concept.

With the aim of developing a proper central-to-axial chirality conversion protocol, the initial centrally chiral compound (**3**, in this case) must display free rotation of the sp^3-sp^2 σ-bond that has to be the stereogenic axis of the corresponding atropisomer (**4**).[9] Thus, in order to achieve a highly atropo-selective process, the reaction must discriminate between two conformations (of **3**), leading to opposite enantiomers of the final product (**4**). This

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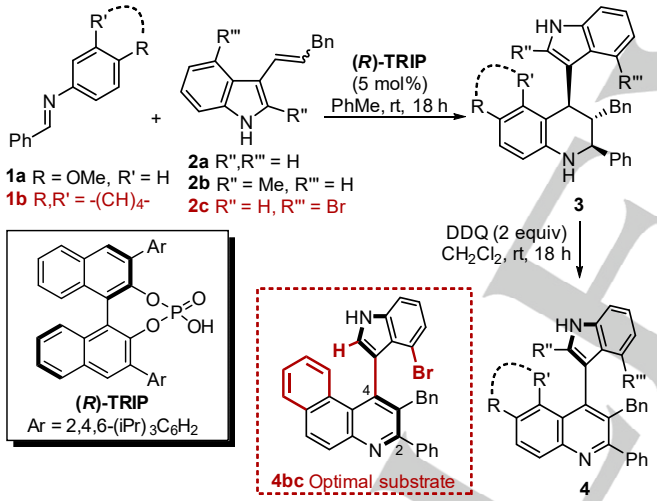
represents indeed the main challenge of such strategies. In most of the oxidative methodologies a kinetical preference for the transformation of the less stable conformer (usually the one displaying the most accessible hydrogen to be removed), is generally observed within a dynamic kinetic resolution process.[10,11h] On the contrary, the system we have studied shows a complementary behavior, with the configuration of the axially chiral product **4** deriving from the major conformer (of **3**). DFT calculations will investigate this aspect, elucidating a "kinetic quench"[19] process, rather than the usual Curtin-Hammett scenario, as a possible alternative mechanism operating in the present case.

Results and Discussion

We set out the investigation of the substrate requirements in order to obtain configurationally stable axially chiral quinolines **4** *via* a Povarov reaction followed by DDQ oxidation (Table 1). Benzyl-substituted 3-alkenylindole **2a**[20] was selected as dienophile for the Povarov cycloaddition with commonly employed imine **1a**, as at least three substituents around the stereogenic axis are mandatory.

Table 1. Search of substrate requirements.[a]



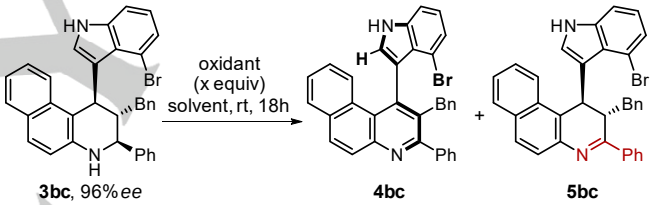
Entry	**3** (yield%)[b]	*ee* [%] **3**[c]	**4** (yield%)[b]	*ee* [%] **4**[c]	$\Delta G^{\ddagger}_{rot}$ [kcal/mol][d]
1	**3aa** (60)	87	**4aa** (30)	-	23.4
2	**3ab** (35)	30	**4ab** (50)	rac	33.1
3	**3ba** (85)	92	**4ba** (55)	-	23.1
4	**3bc** (95)	96	**4bc** (45)	67-90[e]	40.6

[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), PhMe (600 µL), (*R*)-TRIP (0.005 mmol), rt, 18 h. Column chromatography to isolate **3**, then: **3** (0.03 mmol), DDQ (0.06 mmol), CH_2Cl_2 (300 µL), rt, 18 h. [b] Isolated yield after column chromatography. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography. [d] At the B3LYP/6-311g(d,p) DFT level. [e] Range from multiple reactions sharing the same conditions, as a result of scarce reproducibility.

Carrying out the reaction in presence of 5 mol% of a chiral phosphoric acid ((*R*)-TRIP) in toluene, 1,2,3,4-tetrahydroquinoline **3aa** was smoothly obtained as a single all-*trans* diastereoisomer in high yield and enantioselectivity (entry 1). Unfortunately, the corresponding aromatized product **4aa** did not yield stable atropisomers, as confirmed by DFT calculations.

Compound **2b**,[20] featuring a methyl group at position 2 of the indole, was found to be poorly suitable for the Povarov reaction with **1a**, delivering the corresponding product **3ab** in low yield and enantioselectivity (entry 2). Oxidation of this compound afforded configurationally stable quinoline **4ab**, although with no retention of the enantiomeric excess. In order to enhance the thermal stability of the atropisomers of **4**, while maintaining high efficiency in the catalytic reaction, we turned our attention to the reaction between *N*-2-naphthylimine **1b** and 3-alkenylindole **2a**, leading to benzo[*f*]-1,2,3,4-tetrahydroquinoline **3ba** and to benzo[*f*]-quinoline **4ba** after oxidation. As shown in entry 3, the Povarov cycloaddition exhibited excellent results;[21] however, no satisfying enhancement of the free rotational barrier of **4ba** was observed. Being imine **1b** an excellent reagent for the first synthetic step, we employed remotely substituted 4-bromo-3-alkenylindole **2c**[22] to raise the value of the rotational barrier of the indole-quinoline system in **4bc** (entry 4).

Table 2. Optimization of the chirality conversion step.[a]



Entry	oxidant	solvent	equiv	**4bc**/**5bc** ratio[b]	*ee* of **4bc**[c] [%]
1[d]	MnO_2	PhMe	20	>2:98	-
2	PCC	CH_2Cl_2	1+1[e]	30:70	63
3	DDQ	CH_2Cl_2	1+1[e]	50:50	67-90[f]
4	DDQ	PhMe	1+1[e]	40:60	75
5	DDQ	THF	1+1[e]	>98:2	50
6	DDQ	CH_3CN	1+1[e]	>98:2	65
7	DDQ	CH_3CN	2	>98:2	40
8	DDQ	CH_3CN	3	>98:2	90
9[g]	DDQ	CH_3CN	3	>98:2[h]	94 (98% *cp*)

[a] Reaction conditions: **3bc** (96% *ee*, 0.03 mmol), oxidant (0.06 mmol), solvent (900 µL), rt, 18 h. [b] Determined on the crude reaction mixture by ^{1}H NMR. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography. [d] MnO_2 (0.6 mmol), PhMe (1.6 mL) [e] One equivalent (0.03 mmol) was added at the reaction start, the other one (0.03 mmol) after 2 h of stirring. [f] Range from multiple reactions sharing the same conditions, as a result of scarce reproducibility (the other results in this table were confirmed by repeating the experiments three times, giving the same values). [g] Reaction run at 0 °C for 48 h. [h] Isolated yield of **4bc** 97%.

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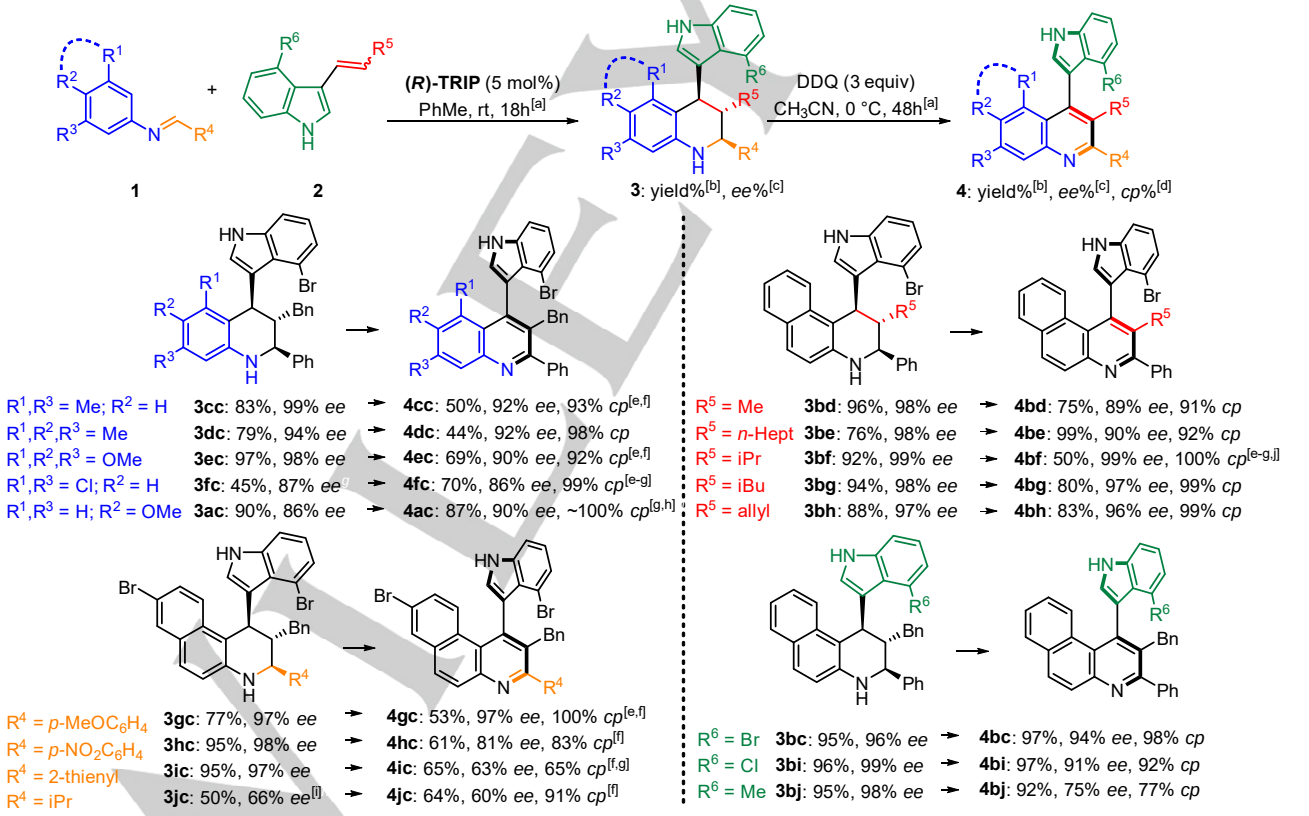
Pleasingly, this modification did not affect the Povarov reaction and simultaneously provided the configurationally stable product **4bc**,[23] with partial retention of the chiral information derived from the parent compound (**3bc**).

The latter result demonstrated the feasibility of the overall strategy and we thus moved to optimize the central-to-axial chirality conversion step (Table 2). Preliminarily, oxidations of compounds **3** were carried out using DDQ in CH_2Cl_2 at room temperature,[11k] (see Table 1), albeit only moderate reactivity and poorly reproducible results were obtained. Despite compounds **3** were readily consumed, partially oxidized imines **5** (Table 2) were in fact generally observed in the reaction mixtures as major products, or in equimolar ratio with the desired products. Indeed, **5bc** was isolated and proved to be a stable reactive intermediate in the step-wise conversion of **3bc** to **4bc**. (see SI).

Any attempt to employ oxidants different from DDQ led to unsatisfactory results. The use of MnO_2 afforded selectively intermediate **5bc** (Table 2, entry 1), while PCC led to the formation of small amounts of the desired product with low retention of the enantioselectivity (entry 2, for other oxidants see SI). On the other hand, the oxidation with DDQ in CH_2Cl_2 showed better reactivity but lacked reproducibility of the enantiomeric excess of final product **4bc**, ranging from moderate to very good values (entry 3). Many parameters were investigated to shed light on the factors affecting this process. The addition of acids or bases, the concentration of the reaction mixture and the presence of either atmospheric oxygen, water or free radical species, lead to inconclusive results (see SI). On the other hand, the retention of the enantiomeric excess showed a strong dependence on the solvent (entries 3-6) as well as the equivalents of DDQ added (entries 6-8). In particular, polar solvents furnished product **4bc** with excellent reactivity but lower enantiomeric excess, when the oxidant was added portion-wise (entries 5 and 6). Surprisingly, the addition of an excess of DDQ in one portion resulted in reproducible high enantiomeric retention for compound **4bc** (entry 8). The optimized reaction conditions (entry 9) were eventually found by running the reaction at 0 °C and consequently extending the reaction time to ensure full conversion of **5bc**.

We then moved to evaluate the reaction scope of the two-step synthetic sequence [Scheme 2]. In each example, Povarov adduct **3** was isolated and fully characterized prior to the oxidation step in order to evaluate the corresponding *cp* factor[11h] of the atropisomeric quinoline **4**. Variations of the amine portion of *N*-arylimines **1** 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 (**4cc-ec**).



Scheme 2. Scope of the Povarov cycloaddition-oxidative chirality conversion process. [a] Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), PhMe (2 mL), (*R*)-TRIP (0.015 mmol), rt, 18 h. Column chromatography to isolate **3**, then: **3** (0.1 mmol), DDQ (0.3 mmol), solvent (3 mL), 0 °C, 48 h. All compounds **3** were isolated as single regio- and diastereoisomers. [b] Isolated yield after column chromatography. [c] Determined by CSP (chiral stationary phase) HPLC analysis after column chromatography. [d] Ratio between *ee* of **4** and *ee* of **3**. [e] 300 μL CH_2Cl_2 added. [f] Reaction time: 64 h. [g] Reaction run at room temperature. [h] Precipitation of poorly soluble racemic **5ac** intermediate from the reaction mixture may be the reason for the small enantioenrichment with respect to **3ac**. [i] Product obtained through a three-component Povarov reaction (see SI for details). [j] Isolated as a 0.64:1 **5bf**/**4bf** inseparable mixture in 82% overall yield.

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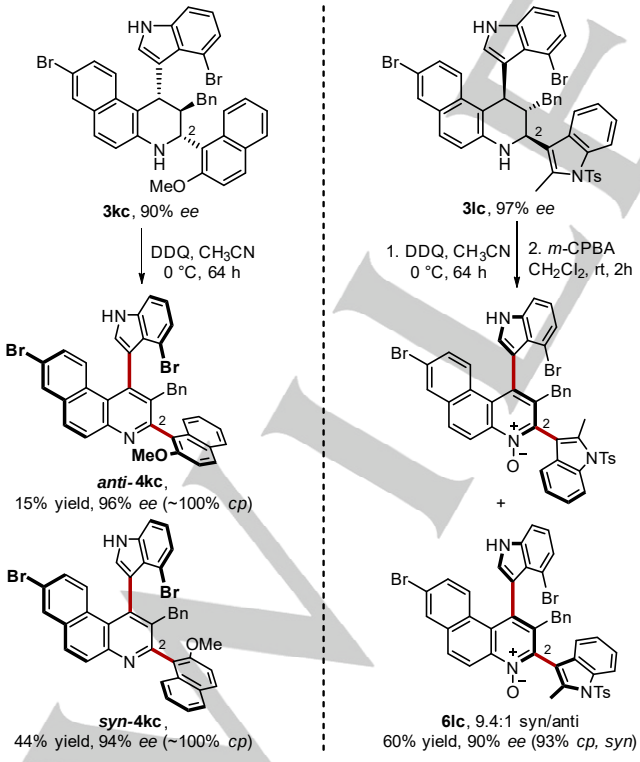
Electron-poor imine **1f** showed sloppy reactivity in the cycloaddition, but oxidation of corresponding **3fc** proceeded with full retention of the enantiomeric excess. Pleasingly, substituent R^1 on quinolines **4** was not strictly necessary to provide configurational stability. Indeed, compound **4ac** (R^1 = H) was obtained in good yield and enantioselectivity.[24] By modification at the aldehyde portion on imines **1**, we observed that an electron-rich substituent (**1g**) afforded good results in both synthetic steps,[25] while an electron-poor and a heteroaromatic one delivered adducts **3hc** and **3ic** in high yields and selectivities but caused less satisfactory retention of the chiral information in the following oxidation step (see SI for details).[26] On the contrary, product **3jc**, derived by a three-component protocol , was obtained with modest results but behaved efficiently in the subsequent aromatization reaction. Variation of the terminal substituent of the vinyl group on compounds **2** was smoothly carried out achieving excellent results in both Povarov and oxidation reactions (**4bd**, **4be**, **4bg**, **4bh**); notably, only encumbered product **3bf** could not reach full conversion into the desired quinoline **4bf**. Modifications at the 4-position of the indole moiety, crucial for the configurational stability of atropisomeric products **4**, were also possible, with no substantial detriment of the final enantiomeric excess (**4bi-bj**).

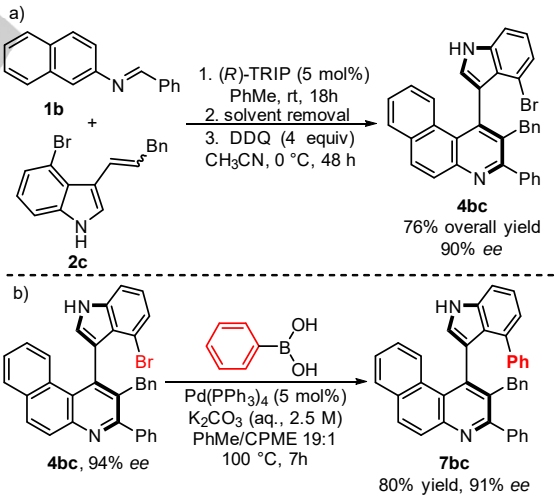
Rational design of quinolines **4**, possessing two stereogenic axes was also possible upon introduction of specifically hindered aromatic substituents at C2. This was accomplished following two different strategies. First, product **4kc** was prepared in high enantiomeric excess, starting from imine **1k**, bearing a 1-(2-methoxynaphthyl) group, and indole **2c** through a slightly modified Povarov cycloaddition[27]-oxidation sequence.



Scheme 3. Povarov cycloaddition-chirality conversion strategy towards doubly axially chiral substrates (***syn*-4kc**/***anti*-4kc** = 3:1 in the crude mixture).

This substituent allowed the stable formation of a particularly demanding axis, in proximity of an unsubstituted nitrogen (experimental $\Delta G^{\ddagger}_{rot}$ = 30.5 kcal/mol, see SI for further details). Easy isolation and characterization of the two diastereoisomers was indeed possible.[28] In this case, the simultaneous formation of the two axes was accomplished. We then undertook the challenge to synthesize a compound having two stereogenic axes, both featuring a five-membered ring. A 3-(2-methylindolyl) group was found to be suitable to this purpose, being well tolerated in the Povarov reaction and the subsequent oxidation step. Unfortunately, HPLC analyses showed a slowly equilibrating mixture of diastereoisomers. This indicates that in our case, a five membered ring is not bulky enough to stabilize a stereogenic axis around a non-substituted nitrogen. Thus, transformation of **4lc** to the corresponding *N*-oxide was performed to circumvent this issue, generating a stable chirality axis in compound **6lc** in good yield, high diastereoselectivity and excellent retention of the starting enantiomeric excess. In this case, the two stereogenic axes were formed in separate synthetic steps in a stepwise manner.

A one-pot protocol, leading from **1b** and **2c** to **4bc**, without purification of **3bc**, was also developed without any significant variation from the two-step procedure, affording very satisfactory results [Scheme 4, a)]. Finally, the synthetic utility of products **4** was demonstrated by exploring the possibility to perform a palladium catalysed cross-coupling on the 4-bromoindole moiety. Suzuki reaction with phenylboronic acid towards compound **7bc** proceeded smoothly at 100 °C, with almost complete retention of the enantiomeric excess, as a result of the excellent thermal stability of the stereogenic axis [Scheme 4, b)].



Scheme 4. a) One-pot protocol and b) Synthetic elaboration on **4bc**.

The *aS* absolute configuration of **4gc** and that of **3ic** (2*S*,3*R*,4*S*) were unambiguously determined by X-Ray crystallography.[25,26] Analysis of the structure of **3ic** suggested that the *aS* atropisomer derives from the same conformation observed in the solid state. The rotation of 4-bromoindole yields two conformers with different energies (*syn* and *anti* periplanar, *sp* and *ap* as in Scheme 5).

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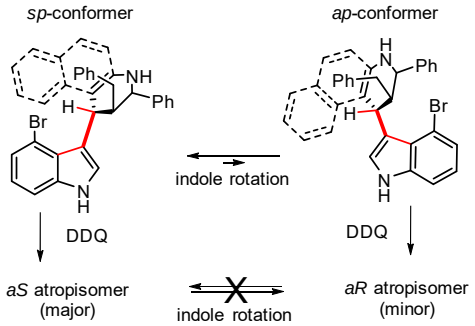

Scheme 5. *sp*- and *ap*-conformers of **3bc** and general pathway for the oxidation process.

DFT calculations at the M06-2x/6-31G(d) level suggested that the *sp* conformer (observed in the solid state) is much more stable than the *ap* (9.5 kcal/mol), whose concentration in solution is negligible. This implies that oxidation by DDQ takes place on the more stable conformation.

A DFT computational study was carried out to rationalize the stereoselectivity of the central-to-axial chirality conversion, that is in sharp contrast with the reported literature examples[10,11h] (see SI for full details). As from the experimental results, the first oxidation of the Povarov adduct to the imine is not the rate-determining step of the reaction. Thus, the proposed mechanism was modelled starting from the imine intermediate (Figure 1).

When the imine is reacted with DDQ, the first stage of the reaction is the formation of a DDQ-complex, as evident by the formation of a deep-coloured solution. Calculations on the DDQ complexes revealed a large stabilization with respect to the isolated compounds, with the *sp* conformer still more stable than the *ap*. When the DDQ complex is formed, the imine can be converted to enamine by proton relay from C3 to the nitrogen. Therefore, the same complexes were then calculated for the enamines, and they were found to be more stable than the corresponding imines (-7.7 kcal/mol for the *sp* and -5.5 kcal/mol for the *ap* conformer, respectively). The removal of the H4 hydrogen by hydride transfer to oxygen (HTO)[29] was calculated to be higher in energy for the imines with respect to enamines, thus suggesting that the oxidation mechanism should take place on the enamine. Due to the less steric hindrance, the HTO TS was calculated to be easier on the less stable *ap*-enamine with respect to the more stable *sp*-enamine, in contrast to the experimental results (but in agreement with literature examples).[10,11h] However, to achieve *sp*/*ap* interconversion, the *sp* enamine must overcome a rotational energy barrier of 19.2 kcal/mol (calculated at the M06-2x/6-31G(d) level). The same energy barrier, calculated on the free enamine is sensibly lower (15.1 kcal/mol, see SI). Indeed, the presence of DDQ hampers the free rotation of the sp^2-sp^3 dihydroquinoline-indole bond in the complex, due to the restricted rotational freedom of the benzyl group at C3, that is instead required to make easier the rotation of the indole moiety.

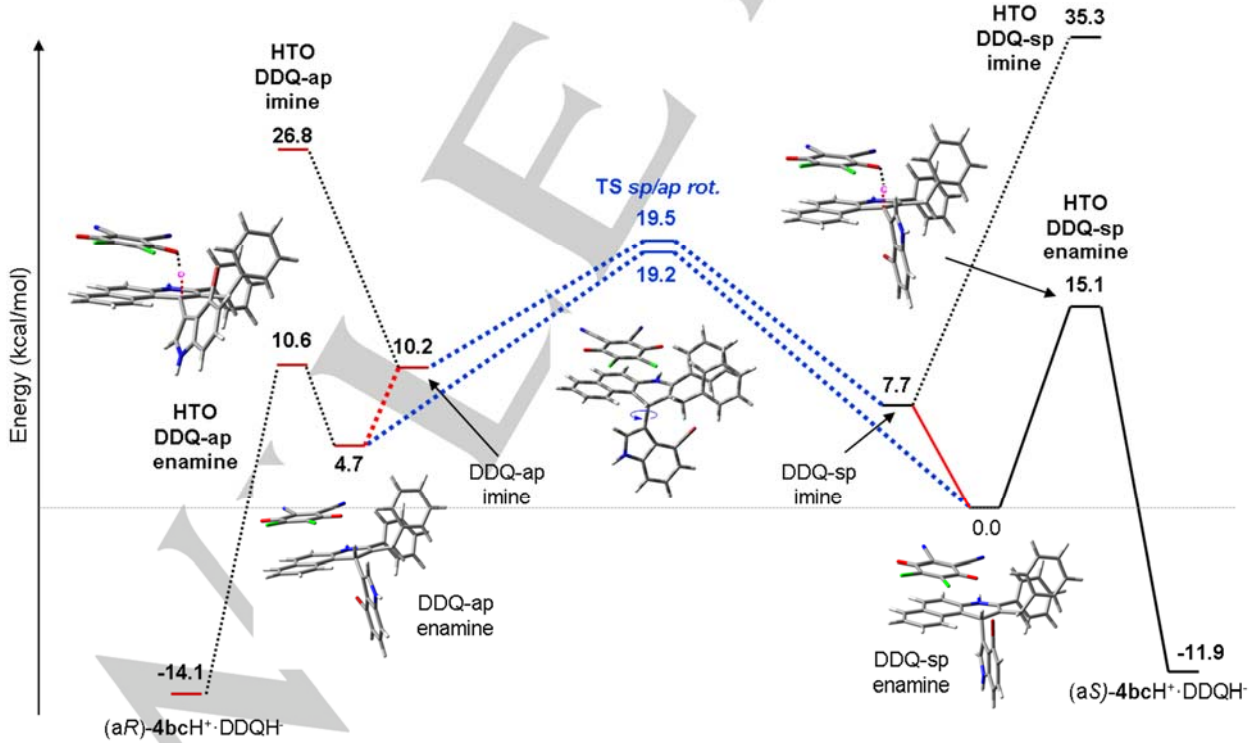

Figure 1. Proposed reaction pathway. Blue lines indicate rotations, red lines indicate tautomerism. The continuous line indicates the enantioselective pathway.

With this constraint, the classic Curtin-Hammett reaction scheme is not applicable. We therefore propose that the reaction proceeds by tautomerism from the imine-DDQ complex to enamine-DDQ, followed by kinetic quench of the more stable *sp* enamine *via* the HTO TS. Within this framework, the role of DDQ is not restricted to a mere oxidant species, but seems to play a crucial role in the stereoselection of the process. It is indeed responsible of the increment of the rotational barrier between the two conformers, a key feature for the retention of the selectivity in such a reactive scenario. The formed $DDQH^-$ complex of the benzoquinolinium ion undergoes deprotonation by $DDQH^-$ to yield the final compound and $DDQH_2$.It should be noted that the intermediates a*S*-4bcH$^+$·$DDQH^-$ and a*R*-4bcH$^+$·$DDQH^-$ are indeed diastereoisomers because of the presence of the stereogenic axis coupled with the position of $DDQH^-$ (leading to a transient element of planar chirality), thus they have different energies (see Figure 1).

Conclusion

In conclusion, we have developed the first stereoselective synthesis of enantioenriched axially chiral indole-quinoline systems, following a central-to-axial oxidative strategy. We have thus proved that organocatalytic enantioselective Povarov cycloadditions of 3-alkenylindoles and *N*-arylimines provide a reliable tool for the preparation of highly hindered tetrahydroquinolines in excellent yields and enantiomeric excesses, tolerating exquisitely the high steric demand required to provide stable atropisomeric quinolines after oxidation. The oxidation reaction has been optimized to a high level of efficiency and retention of the enantiomeric excess. This allowed a high-yielding synthesis of a broad range of optically active atropisomeric 4-(indol-3-yl)quinolines. The methodology was implemented for the design and the preparation of challenging compounds exhibiting two chirality axes following two different approaches. The process has been shown to be feasible in a one-pot (Povarov cycloaddition – oxidation) protocol with optimal results, and the axially chiral products have been subjected to some synthetic elaborations. DFT calculations elucidated the unconventional behaviour of the central-to-axial chirality conversion. The observed absolute configuration of the axially chiral compounds, reflecting the one possessed by the major conformers of the tetrahydroquinolines, has been proposed to arise from the kinetic quench of the more stable enamine intermediate *via* HTO, occurring faster than the conformational rearrangement between the two conformers due to the indole rotation.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 300, Mercury 400 or Inova 600 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvents signals[30] for ^{1}H and ^{13}C NMR. ^{13}C NMR were acquired with 1 H broad-band decoupled mode. Chromatographic purifications were performed using 70-230 mesh silica. Mass spectra were recorded on a Waters Xevo Q-TOF spectrometer. Optical rotations were measured on a Perkin Elmer 241 Polarimeter provided with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T(^{\circ}C)}$ (c = g/100 mL, solvent). 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. Products **3**, **4**, **5bc, 6lc** and **7bc** 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.

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.

General procedure for the synthesis of products 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 (see Supporting Information). 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.

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Keywords: chirality conversion, atropisomerism, Povarov cycloaddition, asymmetric catalysis, indoles, quinolines.

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[20] Synthesized according to: S. Sahu, A. Banerjee, M. S. Maji, *Org. Lett.* **2017**, *19*, 464 and obtained as a single *trans*-isomer.

[21] A single regioisomer was produced, according to the literature (ref. 15a).

[22] Synthesized following a modified literature procedure (C. Gioia, A. Hauville, L. Bernardi, F. Fini, A. Ricci. *Angew. Chem. Int. Ed.* **2008**, *47*, 9236) through Wittig reaction and obtained in 65:35 *cis*/*trans* ratio. Preliminary studies revealed that *cis*-**2c** did not take part in the Povarov cycloaddition but underwent an acid-promoted equilibration to reactive *trans*-**2c** (see SI and ref. 14c for more details).

[23] The thermal stability of the stereogenic axis was confirmed by refluxing a toluene solution of **4bc** for one week without significant decrease in the *ee*. As suggested with the calculations, the $\Delta G^{\ddagger}_{rot}$ is too high to be evaluated experimentally.

[24] $\Delta G^{\ddagger}_{rot}$ = 42.6 kcal/mol.

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[25] The absolute and relative configurations (along with the regiochemistry) of compound **3ic** was assigned by single-crystal X-ray diffraction analysis and extended to all products **3** for analogy. CCDC-1940646.

[26] The absolute configuration of compound **4gc** was assigned by single-crystal X-ray diffraction analysis and extended to all products **4** for analogy CCDC-1940645.

[27] The phosphoric acid derivative of (*R*)-6,6'-di(anthracen-9-yl)-1,1'-spirobi[indane]-7,7'-diol was used as catalyst, delivering **4kc** with opposite configuration with respect of the product derived from (*R*)-TRIP (for which 70% *ee* was observed). See supporting information for more details.

[28] Precipitation of poorly soluble racemic intermediate **5kc** from the reaction mixture may be the reason for the small enantioenrichment with respect to **3kc** observed for both diastereoisomers.

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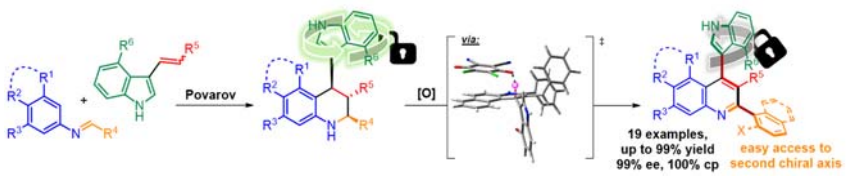

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Title

The Atropovarov reaction: The first stereoselective synthesis of enantioenriched axially chiral indole-quinoline systems is presented. The strategy takes advantage of an organocatalytic enantioselective Povarov cycloaddition of 3-alkenylindoles and *N*-arylimines, followed by an oxidative central-to-axial chirality conversion process