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REVIEW

Enantioselective Strategies for The Synthesis of N-N Atropisomers

Giovanni Centonze,[a],[b] Chiara Portolani,[a],[b] Paolo Righi[a],[b] and Giorgio Bencivenni*,[a],[b]

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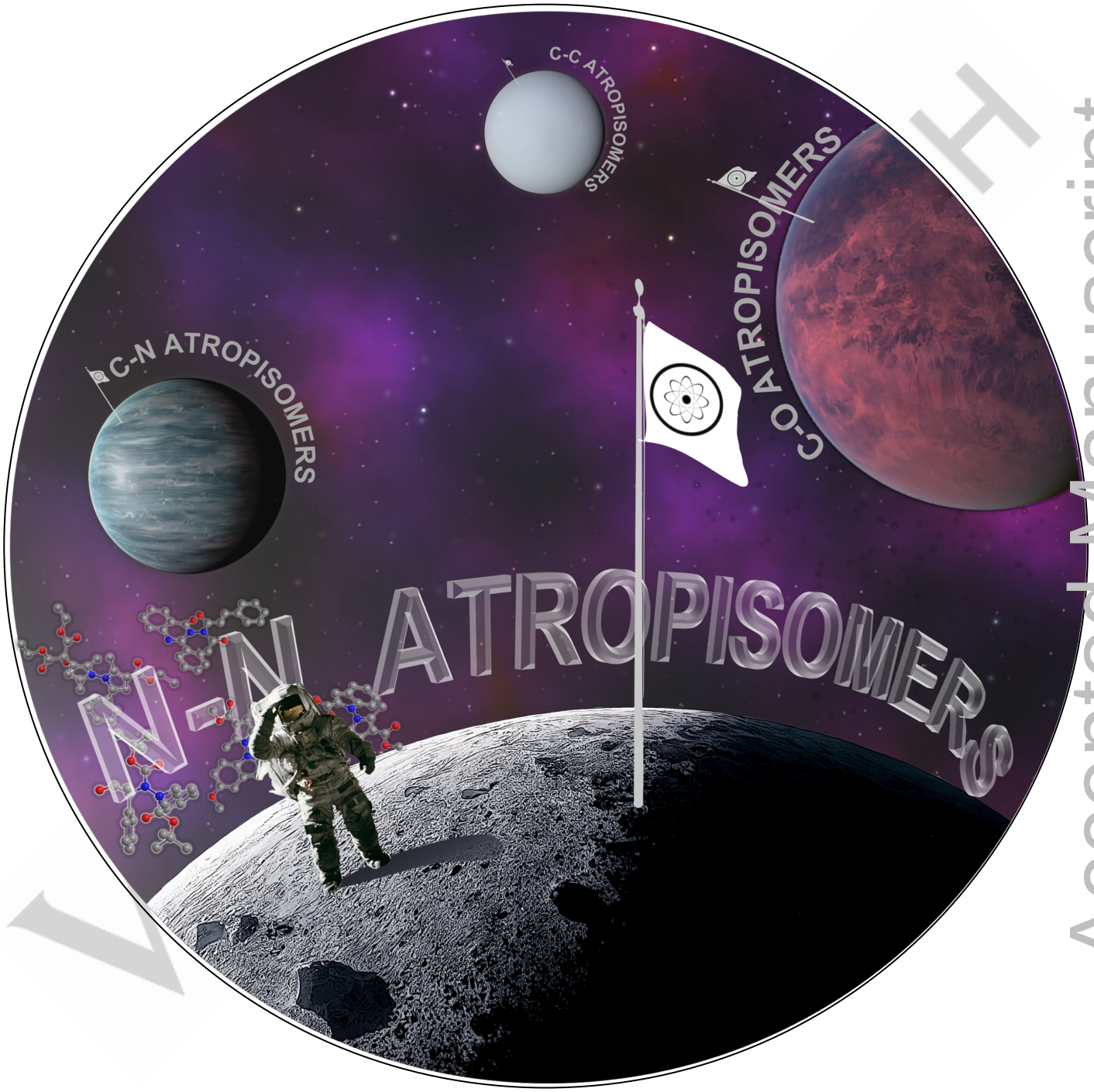

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REVIEW

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Abstract: Axially chiral compounds have been always considered a laboratory curiosity with rare prospects of being applied in asymmetric synthesis. Things have changed very quickly in the last twenty years when it was understood the important role and the enormous impact that these compounds have in medicinal, biological and material chemistry. The asymmetric synthesis of atropisomers became a rapidly expanding field and recent reports on the development of N-N atropisomers strongly prove how this research field is a hot topic open to new challenges and frontiers of asymmetric synthesis. This review focuses on the recent advances in the enantioselective synthesis of N-N atropisomers highlighting the strategies and breakthroughs to obtain this novel and stimulating atropisomeric framework.

1. Introduction

During the last 10 years many research groups have directed their attention to the enantioselective preparation of axially chiral compounds.[1] This has led to the achievement of new frontiers in the field of asymmetric synthesis with the development of programs mainly focused on the preparation of atropisomers,[2] the most representative class of axially chiral molecules, that find large applications in medicinal chemistry and catalysis.[3] Inspired by Nature and by their physical properties or their attitude to be good ligands and catalysts, many methodologies have been used to accomplish the preparation of novel atropisomeric frameworks.[4] In the last years the asymmetric synthesis of atropisomers was mainly targeted at the C-C and C-N series.[5] Novel impulse to the field was achieved after the pioneer works by Clayden, that opened the way to different classes of axially chiral molecules reporting the first enantioselective synthesis of diaryl ethers and sulfones as prototype examples of C-O and C-S atropisomers.[6] Nevertheless, examples of atropisomers where the rotational hampered single bond connects two heteroatoms remained unexplored for many years. A great boost to this challenging research field was observed in the last two years when great attention was given to the enantioselective synthesis of N-N atropisomers. The existence of a restricted rotation of a N-N single bond, in analogy to what is observed in diphenyl series, was advanced and demonstrated by Adams and Chang, that separated the enantiomers of 2,2',5,5'-tetramethyl-[1,1'-bipyrrole]-3,3'-dicarboxylic acid with brucine as the resolving agent in 1931.[7] After this report, no other examples have been reported except some conformational studies on N-N derivatives like *N*-aminocamphorimides,[8] tetraformylyhydrazides[9] and quinazolinones.[10] It was only with the discovery that some N-N atropisomers possess important biological activity, or others displayed important electronic properties and were good ligands for asymmetric synthesis, that the first reports on the stereoselective preparation of N-N atropisomers appeared.

In 1997 Sannicolò realized the synthesis and detailed characterization of atropisomeric ligand BIMIP.[11] Later, Sarker isolated and elucidated the structure of Schischkiniin, an indole alkaloid with potent anticancer activity.[12] In 2014 Baran reported the synthesis of antibacterial Dixiamycin B from Xiamycin A through the direct formation of the hindered N-N single bond by electrochemical oxidation (Figure 1).[13] With this approach it was presented an alternative method to the bacterial synthesis set up by Hertweck one year before.[14]

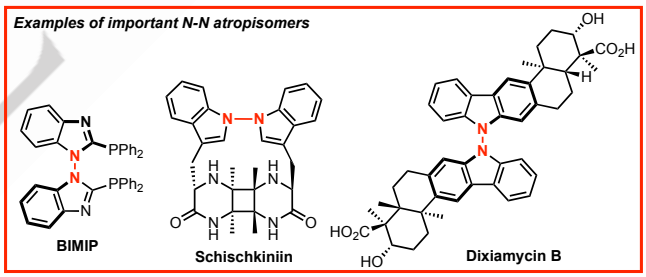

Figure 1. Important N-N atropisomers: BIMIP chiral ligand, Schischkiniin anticancer, Dixiamycin B antibacterial.

Despite the great potentiality expressed, the first examples reporting the catalytic enantioselective preparation of N-N atropisomers appeared only in 2021.[15]

A fundamental criterion to observe atropisomerism is that the rotation along a single bond became even more unfavored. This is usually encountered when the two sides of the molecules tend to assume a coplanar disposition reaching the maximum conformational energy identified with the transition state (TS) of the rotation. In other words, the greater the difficulty of the molecule in assuming a planar conformation due to electronic and steric effects, the greater is the energy required to reach it. The reason for this energy rising is mainly caused by a steric interaction between the spatially close substituents of the molecule. Consequently, as in the case of C-C (biaryls) and C-N (amides) atropisomers, a sp^2 electronic configuration of the atoms connecting the two sides of the molecule favors the existence of

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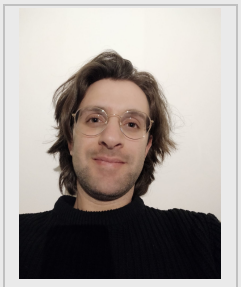
stable atropisomers. Actually, also stable sp^2-sp^3 atropisomers have been successfully prepared in a stereoselective manner, but their synthesis represents a more challenging task that usually requires *ad-hoc* molecular structures to address the atropisomerism criteria.[16] N-N atropisomers are certainly no exception, and in order to synthesize stable N-N atropisomers, the nitrogen atom needs to be sp^2 hybridized. This narrows the field of the accessible molecular architectures to compounds with either a diheteroaromatic or a hydrazide core, where the unpaired electrons conjugate with the aromatic system or with a carbonyl group and the nitrogen atom assumes a stable planar geometry. This review will highlight the state of the art in the asymmetric synthesis of N-N atropisomers focusing on the different strategies employed which gravitate around organo- and metal- catalysis.[17]

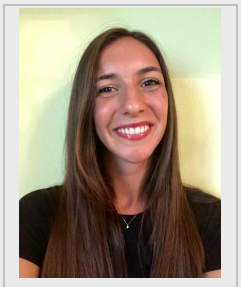
2. Desymmetrization Strategy

Desymmetrization reactions are a powerful tool that successfully found applications in atroposelective synthesis.[18] It is in fact one of the first strategies employed for the synthesis of axially chiral compounds, in particular biaryls. In most of the cases, desymmetrization strategy is realized on substrates which already possess a large rotational energy barrier and fit into the Ōki definition of atropisomers.[2b] This aspect simplifies the synthesis of atropisomers since the direct construction of a stereogenic axis is a problem that found scarce solutions and it often requires harsh reactions conditions.[19] Desymmetrization reactions are performed on functional groups already installed on the prochiral substrate or can be used to functionalize, for instance through C-H activation,[20] one “side” of the molecule thus breaking the symmetry plane in favor of one enantiomer. In the case of N-N atropisomers the desymmetrization strategy was successfully applied for the preparation of highly functionalized bipyrroles.

Giovanni Centonze received his MSc (cum laude) in Chemistry from the University of Bologna in 2021. During the internship, he worked on the asymmetric crotylation reactions. Currently, he is spending his second year of Ph.D. in Bencivenni’s group, pursuing new stereoselective strategies for the construction of non-conventional atropisomers.



Chiara Portolani obtained her MSc (cum laude) in Industrial Chemistry from University of Bologna in 2020. She is currently in her third year of PhD with Prof. Giorgio Bencivenni and her research focuses on asymmetric synthesis for novel axially chiral compounds.



Paolo Righi graduated cum laude in Industrial Chemistry at the University of Bologna presenting a Master Thesis on the asymmetric synthesis of cyclic sulfur compounds, under the guidance of Prof. Antonino Fava. He obtained his PhD under the tutorship of Prof. Goffredo Rosini working on synthetic applications of organic nitrocompounds. He is now associate professor at the Department of Industrial Chemistry of the University of Bologna. His interests span from green organic chemistry to asymmetric organic catalysis and study of reactive intermediates and reaction mechanisms by computational methods.

((Author))

Giorgio Bencivenni graduated in Industrial Chemistry at the University of Bologna in 2003. In 2008, he obtained his PhD then he joined Professor G. Bartoli’s group as a postdoctoral associate, studying new organocatalytic reactions under the supervision of Prof. P. Melchiorre. In 2015 he became Fixed-term Senior Assistant Professor and from 2018 he is Associate Professor at the Department of Industrial Chemistry of the University of Bologna. His research interests are focused on atroposelective organocatalytic transformations, radical chemistry and study of reactive intermediates and reaction mechanisms by computational methods.

2.1. Copper(II)-Catalyzed Friedel-Crafts Alkylation

In 2021 the group of Liu and Lu reported the synthesis of enantioenriched bipyrroles **3** by Copper catalyzed Friedel-Crafts alkylation of ketomalonate derivatives **2**.[15a] The authors presented an efficient atroposelective reaction using a combination of $Cu(OTf)_2$ and ^{t}BuBOX ligand **4** which revealed a good promoter for the desymmetrization of prochiral bipyrroles proceeding at the C3 of the electron rich pyrrole unit (Scheme 1).

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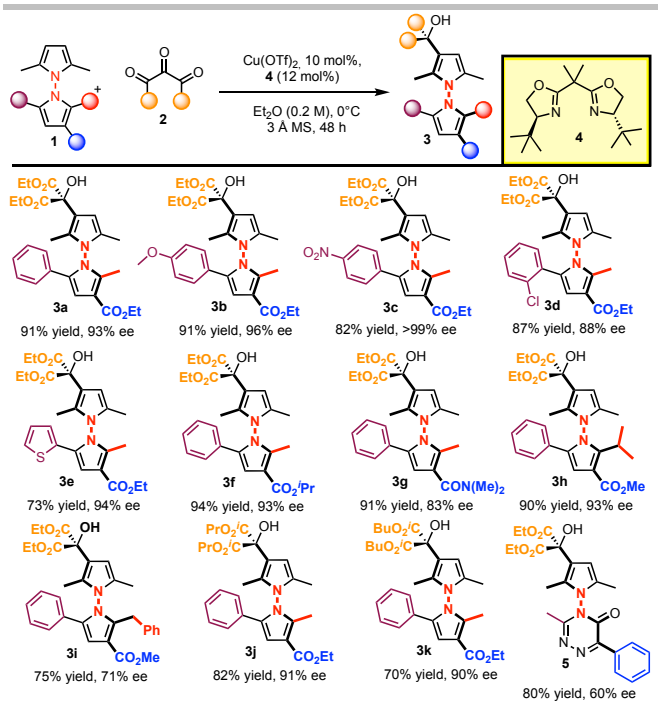
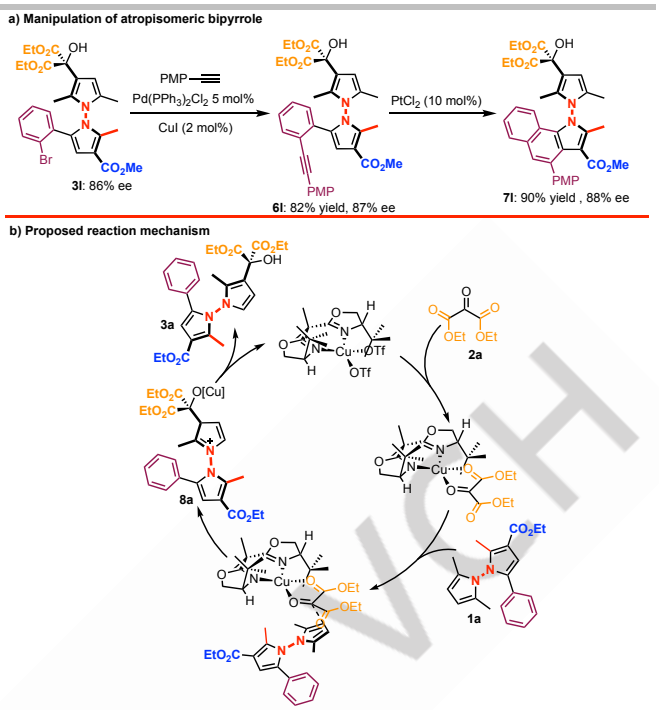


Scheme 1. Representative examples for the atroposelective desymmetrization of pyrroles via Friedel-Crafts alkylation.



Scheme 2. a) Derivatization of atropisomeric pyrroles. b) Proposed reaction mechanism.

A relevant study on the influence of the aromatic and aliphatic substituents revealed the robustness of the protocol that gave high yield and excellent enantioselectivity in most of cases. The presence of electron withdrawing (EWG) and electron donating groups (EDG) did not affect the reaction efficiency (**3a-e**) and good tolerance was observed regarding the carbonyl substituent on pyrrole, as amides and esters with different alkyl functionality could be easily employed (**3f-g**). Furthermore, good performances were observed when the methyl group at C5 was replaced with the bulkier isopropyl substituent (**3h**). On the contrary with benzyl or phenyl group yields and ee dropped dramatically (**3i**). Interestingly, the feasibility of the desymmetrization was demonstrated in the preparation of bisazaheterocycles where two heterocyclic moieties were linked by a N-N bond. For instance, 1,2,4-triazin-5(4*H*)-ones (**5**), indoles, and other heterocycles could be employed obtaining good enantiocontrol and yields. Interestingly the synthetic utility of bipyrroles atropisomers was demonstrated performing useful derivatization reactions with an almost unchanged enantioselectivity (Scheme 2a). The new N-N atropisomers have a great stability to racemization (none was observed after heating at 130°C for 24 h). The mechanism proposed for the reaction is based on the activation of the carbonylic ketone by the chiral copper complex, that interacting with the *t*butyl groups of the BOX ligand drives the addition of the pyrrole unit along the less hindered trajectory, with the second pyrrole ring orients in what is the final axial configuration. The resulting carbenium intermediate (**8a**) then aromatizes to form the 1,1'-bipyrrole product (**3a**) and restore the catalyst.

2.2. Copper(I)-Catalyzed Arylation of Prochiral Pyrroles with Diaryliodonium Salts

One year later the same group realized the asymmetric arylation of pyrroles using diaryliodonium salts.[21] In this case the atroposelective transformation was promoted by a $(CuOTf)_2$·Tol in combination with a Xyl-BINAPO **12** as chiral bis(phosphine) dioxide ligand proceeding through a desymmetrization of prochiral bipyrroles. The impressive number of N-N atropisomers produced accounts for the goodness of the protocol which furnished elevated yields and enantioselectivity employing a diversified typology of substituted pyrroles (**11a-11i**) (Scheme 3a). Also, a broad range of aryliodonium salts could be used except for those bearing an ortho-substituted aryl group that did not react at all. The mechanism is based on an oxidative addition-reductive elimination sequence with the formation of an equilibrating carbenoid species (**13a-13a'**) that controls the arylation step through repulsive interactions between the 3,5-Me_2-Ph group of the ligand and the ester of the bipyrrole (Scheme 3b). An interesting feature of the reaction is the possibility to realize a regioselective double arylation installing a second aromatic ring at C3' of the second pyrrole by using a slightly excess of **10a**. (**14a** Scheme 3c).

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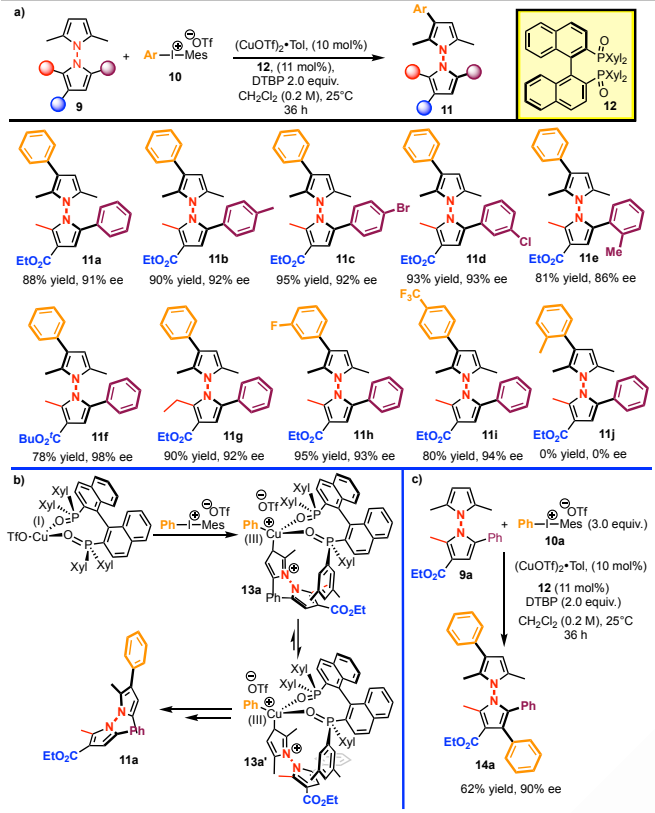


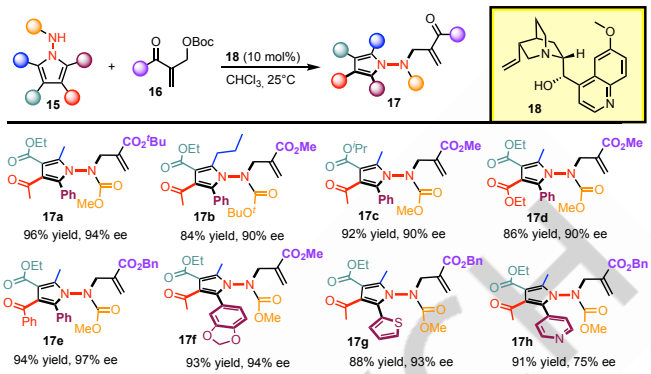
Scheme 3. a) Representative examples for the desymmetrization using aryliodonium salts. b) Proposed reaction mechanism. c) Regioselective double arylation.

3. Direct *N*-functionalization Strategy

The direct functionalization of nitrogen atom always represented a preferred strategy for the preparation of C-N atropisomers. Many examples have been reported using both metal- and organocatalyzed protocols. Seminal manuscripts by Taguchi,[22] Curran,[23] and Maruoka[24] opened the way to the atroposelective functionalization of amide derivatives with aliphatic and aromatic groups. The synthesis of N-N atropisomers by means of alkylation reactions requires that a N-N linkage with a high degree of substitution is already present in the starting material, thus preventing racemization during the alkylation step. *N*-Aminated heterocycles represent valuable substrates for this purpose.

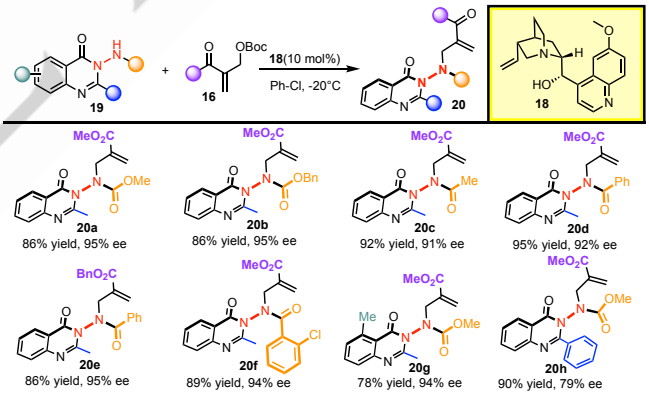
3.1. Asymmetric *N*-alkylation of 1-aminopyrroles and 3-aminoquinazolinones

In 2021 the groups of Lu and Houk described the first example of atroposelective quinidine catalyzed *N*-allylic alkylation of aminopyrroles **15** and aminoquinazolinones derivatives **19**.[15b] The alkylation was efficiently performed on both substrates using a Morita-Bayliss-Hillman protocol that allowed to obtain N-N atropisomeric architectures with a high stability of the new stereogenic axis. In the pyrrole series many combinations of substituents can be easily employed (Scheme 4). In particular, the variation of the alkoxy moiety on the carbamate as well as the longer alkyl chain at C4 and many aromatic substituents at C1 furnished atropisomeric pyrroles with high yields and enantiocontrol (**17a-g**). Indeed, aromatic and aliphatic ketone or ester groups could functionalize the C2 of the pyrrole core with good ee (**17d-e**). Only pyrrole with 4-pyridinyl substituent gave the corresponding product with moderate enantioselectivity (**17h**).



Scheme 4. Atroposelective alkylation of aminopyrroles.

The alkylation reaction of aminoquinazolinones required chlorobenzene as solvent and a temperature of -20°C to obtain optimal results (Scheme 5). In this case the variation of functional groups was mainly focused on the protecting group of the exocyclic nitrogen atom (**20a-d**). A limited number of substituents on the quinazolinone aromatic ring was tested with good results (**20g**), however poor enantiocontrol was observed when a phenyl group at C2 was installed (**20h**).



Scheme 5. Atroposelective alkylation of aminoquinazolinones.

The reaction posed interesting aspects on the catalytic activity of the system. The presence of hydrogen bonding acceptor groups like ketone, ester or amide in both substrates are necessary to reach high enantiocontrol. They furnish an anchorage for the catalyst hydroxy group that, in this way, can exert the remote control on the stereogenic axis orientation (Scheme 6). Computational calculations support the presence of these secondary interactions between **18** and the ketone group in the case of pyrrole unit. This H-bond is found in both TSs corresponding to the enantiomeric products. However, in one case strong repulsive interactions between the quinoline ring and the phenyl group destabilize the TS of 3.0 kcal/mol (Scheme 6). In analogy with the case of pyrroles, the hypothesis on the stereocontrol for aminoquinazolinone atropisomers is based on

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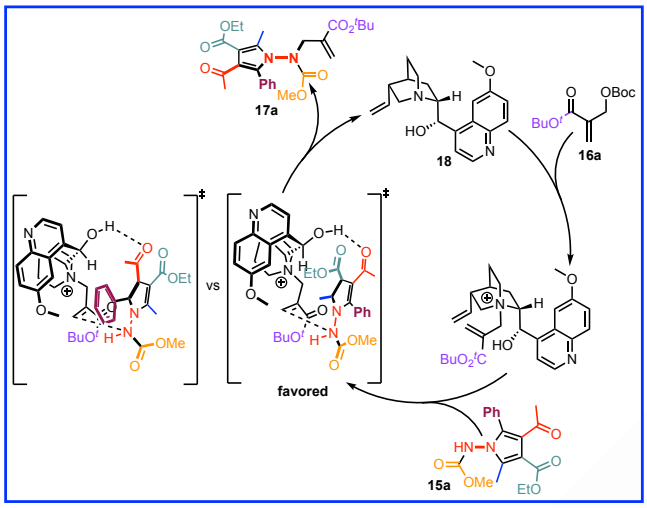
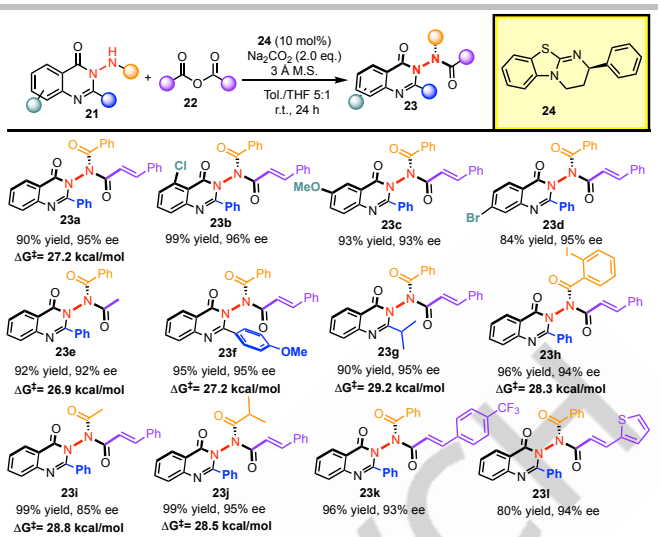
the presence of a hydrogen bond between the amidic carbonyl group and the OH group of the catalyst, that twists the N-N single bond during the alkylation step. Here the less stable TS is the result of a more congested geometry where many repulsive interactions between the catalyst and the acrylate disfavor the addition step. Further computational calculations realized using a simplified model of the catalyst, suggest that the reaction follows a classical MBH mechanism where two consecutive S_N2' processes drive the reaction to the axially chiral adduct.



Scheme 6. Proposed reaction mechanism.

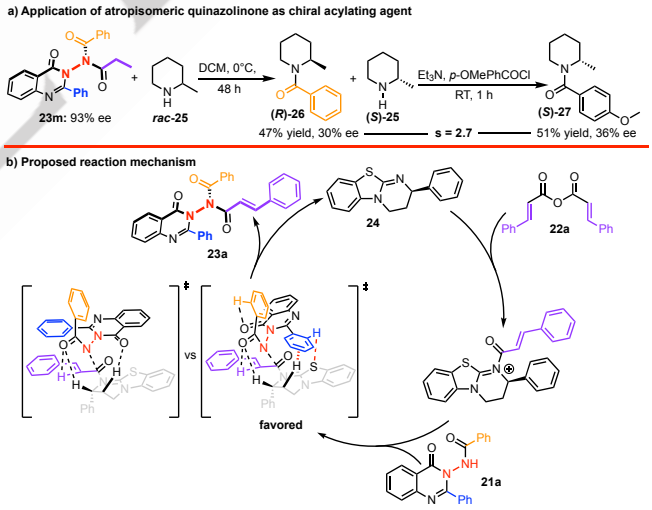
3.2. Asymmetric *N*-acylation and Alkylation of 3-Aminoquinazolinones

In 2022 the Li group reported the synthesis of novel type of N-N atropismers via isothiourea catalyzed acylation of *N*-(4oxoquinazolin-3(4*H*)-yl)amides with anhydrides.[25] Unlike what accomplished by Houk, Li mainly focused on quinazolinone skeletons bearing aromatic substituents at C2. This resulted in lowering the rotational energy barrier of 4-5 kcal/mol on average, nevertheless the high reactivity imparted by the catalyst ensured high enantioselectivity at room temperature. Many *N*-(4oxoquinazolin-3(4*H*)-yl)amides were tested under optimized conditions which required a 5:1 mixture of toluene and THF (Scheme 7). Good functional group tolerance and variability was demonstrated by the high yields and enantioselectivities (**23a-l**). Cinnamic anhydrides have been mostly employed as acylating agents, but good results could be obtained also with saturated ones (**23e**). An accurate study on the racemization of the N-N stereogenic axis evidenced a strong dependence of the rotational energy barrier on the steric hindrance of the alky amides and the substituents at the C2 of the quinazolinone rather than the acyl group of the anhydride (compare **23a** with **23i** and **23j**, and **23a** with **23g** and **23e**). An important aspect regarding possible applications of these new atriposomeric quinazolinones is their use as chiral resolving agents in acylation reactions of racemic secondary amines (Scheme 8a). The reaction conducted on 2-methylpiperidine (**25**), showed good preliminary results and the *N*-benzoylamide (**26**) was isolated in 47% yield and 30% ee. Unreacted 2-methylpiperidine was acylated in 36% ee and 51% yield with *p*-OMePhCOCl (**27**).



Scheme 7. Representative examples for the *N*-acylation of *N*-(4oxoquinazolin-3(4*H*)-yl)amides with anhydrides.

Computational DFT methods have been used to elucidate the origin of the atroposelective. The two competitive TSs leading to the two enantiomers are strongly stabilized by hydrogen bonding interactions between the carbonyl of the quinazolinone, the benzoyl group on the amidic nitrogen and the *N*-acylated catalyst (Scheme 8b).



Scheme 8. a) Use of quinazolinone as acyl transfer reagent for chiral secondary amines. b) Proposed reaction mechanism. Productive secondary interactions are depicted in red.

However, the exclusive presence of two non-covalent C-H···π and C-H···S interactions stabilized more the TS leading to the atropisomer with the R_a absolute configuration at the N-N axis. In the same manuscript Li and co-authors anticipated the results of an atroposelective phase-transfer-catalyzed *N*-alkylation on the same *N*-(4oxoquinazolin-3(4*H*)-yl)amides, that was then developed later in the same year (Scheme 9).[26] In this reaction the amidic proton of **28** was easily deprotonated using aqueous KOH, that after a cation exchange formed a chiral system that

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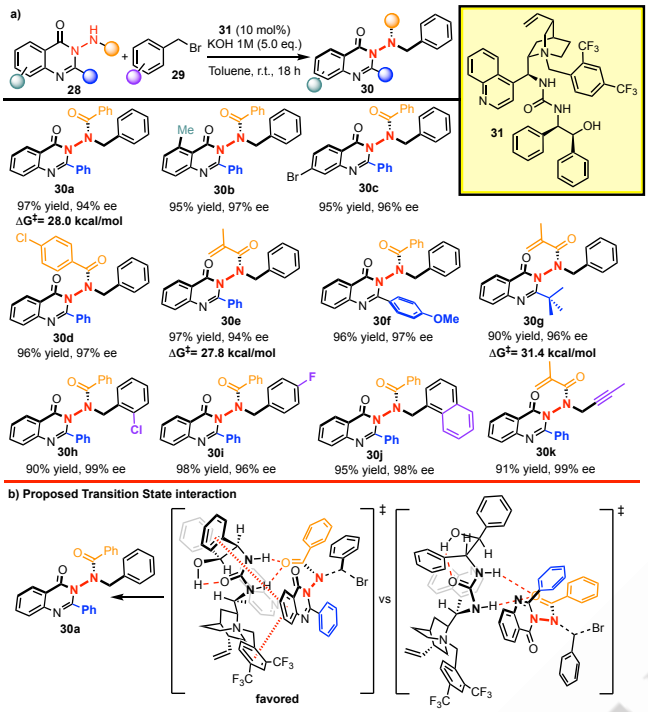
underwent an atroposelective alkylation with primary halides. A powerful cinchona alkaloid catalyst **31** with a chiral amino-alchol unit acting as hydrogen bonding donor enabled a robust alkylation pathway with a very large scope, high yields and ee's (**30a-k**).



Scheme 9. a) Selected examples for the *N*-alkylation of *N*-(4oxoquinazolin-3(4*H*)-yl)amides. b) Proposed Transition State with secondary interactions highlighted.

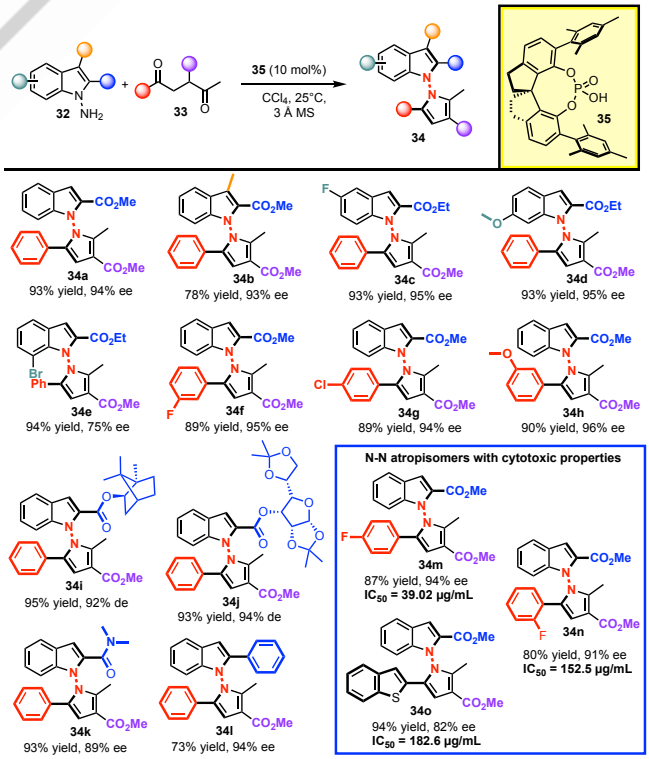
Compared with the previous atroposelective acylation reported by the same authors, the rotational barriers of the N-N stereogenic axis are slightly higher (**30a**, **30e**) suggesting a stronger contribution of the benzylic substituent, whilst a further increment was measured with alkyl substituents at C2 (**30g**). This protocol could be extended to other alkylating agents such as allyl- and alkynyl bromides with excellent enantiocontrol (**30k**). The new *N*-allyl and *N*-propargyl atropisomers are characterized by the highest rotational barrier making the stereogenic axis stable at 130°C for many hours. DFT calculations helped to understand the factors determining the stereocontrol and showed the fundamental role of a π-π stacking interaction between the aromatic unit of **28** and the aromatic ring of the *N*-benzyl group and one of the two phenyl of catalyst **31** (Scheme 9b).

4. De Novo Ring Formation

De novo ring formation represents a powerful strategy for the construction of biaryl atropisomers because it allows to overcome the challenges connected to the direct C-C and C-N coupling reaction. After seminal work by Sparr[27] on the synthesis of binaphthyl atropisomers via aldol reaction, many examples of C-N atropisomers were investigated using cyclization protocols based on metal- or organocatalysis.[28] Cyclization strategy reveals appropriate to synthesize N-N atropisomers since it can be performed on substrates with an already installed N-N single bond. For instance C2 substituted *N*-aminoindoles and *N*-aminopyrroles or 2-amino-*N*'-(2-aminobenzoyl)benzohydrazide) represent privileged structures for N-N atroposelective ring formation. In fact, substituents at C2 will give the necessary steric hindrance to ensure conformational stability, while the exocyclic nitrogen guarantees the right reactivity for the asymmetric cyclization reaction.

4.1. Synthesis of N-N Axially Chiral Indoles and Pyrroles.

Indole and pyrrole core is the main structural feature of many natural and synthetic compounds and recently great attention has been devoted to the preparation of axially chiral indole- and pyrrole-based architectures due to their important applications as bioactive compounds or ligands for symmetric synthesis.[29] For these reasons the developments of innovative methodology for the discovery of novel privileged axially chiral indoles and pyrroles represents an hot topic in atroposelective synthesis. The group of Zhang and Shi realized the synthesis of novel bisheteroaromatic scaffolds using a CPA **35** catalyzed Paal-Knorr cyclization between *N*-aminoindoles **32** and pyrroles **36** and aryl substituted 1,4-diketones **33**.[30] The protocol was highly enantioselective for both series of atropisomers with a vast range of substituents suitable in the reaction conditions (Scheme 10). The reaction showed a good generality, and many functional groups on the indole core could be easily used (**34a-e**). The same trend was observed by varying the substituents of 1,4 diketone from electron poor to electron rich aromatic and heteroaromatic functional groups (**34f-h**, **34m-o**). Interestingly, at C2 of the indole core, amide and aromatic substituents or functional groups with multiple stereocenters could be used with excellent yields and ee (**34i-l**).



Scheme 10. Representative examples for the 1,1'-indole-pyrrole synthesis via Paal-Knorr reaction.

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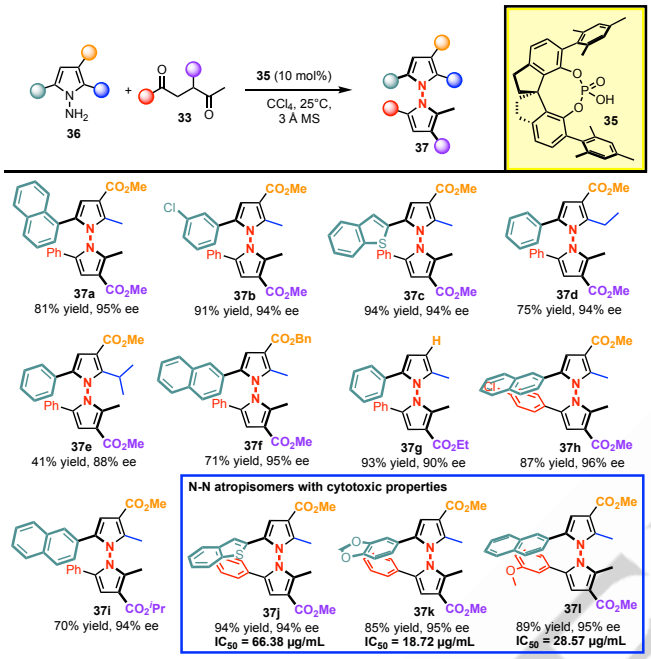
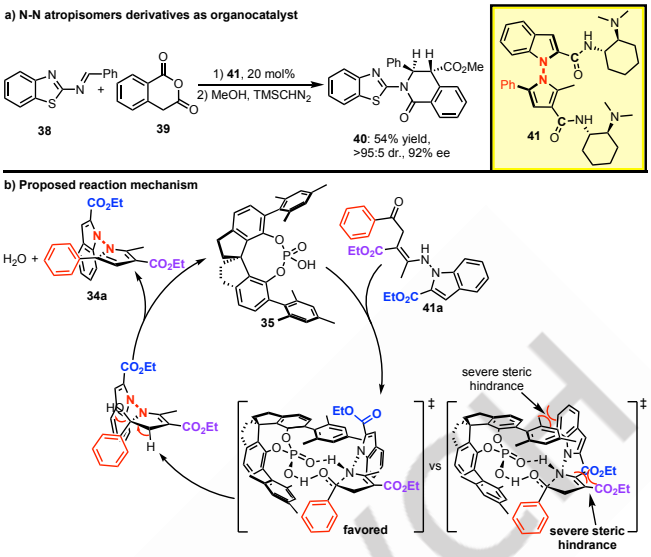
Also for aminopyrroles **36** a vast numbers of N,N-atropisomers were efficiently prepared revealing the robustness and the versatility of the method (Scheme 11). Many functional groups with different electronic properties have been installed and high atroposelectivity was always guaranteed even with large functional groups at both 2 and 2' position of the two pyrrole units (**37a-l**). Notably the ester group at C3 is not fundamental for the reactivity and heteroaromatic groups did not affect yields and enantioselectivities (**37g**).



Scheme 11. Selected examples for the axially chiral 1,1'-bipyrroles via Paal-Knorr reaction.

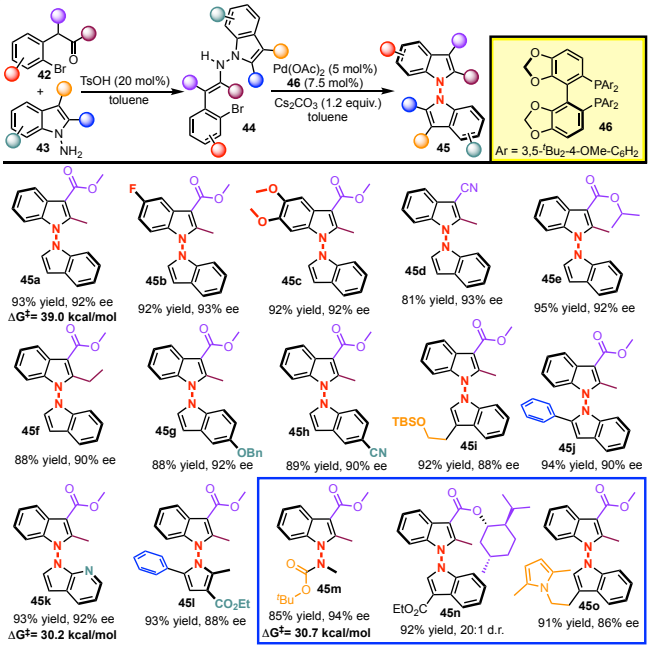
Indole-pyrroles and bipyrroles atropisomers possess an haigh configurational stability. No racemization was observed for compounds **34** and **37** after heating at 110 °C in toluene for 12 hours. DFT methods agreed with this experimental observation and for compounds **34a** and **37h** a rotational barrier value of 47 kcal/mol and 52 kcal/mol respectively was calculated. For these classes of new atropisomers the potential applications in medicinal chemistry were provided by the good results obtained by testing the cytotoxic properties of selected scaffolds against QGP-1 cancer cells (**34m-o** scheme 10 and **37j-l** scheme 11). Another important practical aspect was their use as organocatalyst after easy chemical transformation of the carbonyl groups moieties. For instance, the N-N axially chiral organocatalyst **41** was applied successfully for the (2+4) cyclization of 2-benzothiazolimine **38** with homophthalic anhydride **39** (Scheme 12a). The reaction mechanism is believed to follow a classical Paal-Knorr pathway where the chiral catalyst drives the cyclization of the enaminic nitrogen of **41a** on the activated aromatic ketone. This event that creates a "transient" stereocenter should also control the axis orientation, resulting in the final (S_a) absolute configuration (Scheme 12b).



Scheme 12. a) Use of 1,1'-bipyrroles atropisomers as organic catalyst. b) Hypothesis on the reaction mechanism.

4.2. Synthesis of N-N Axially Chiral Bisindoles via Pd-Catalyzed De Novo Ring Construction.

In 2022 the group of Li and Liu reported the enantioselective synthesis of bisindoles **45** using a Pd catalysed de novo construction of one indole skeleton.[31] The process was based on the use of aminoindoles derivatives **43** to prepare stable Z-enamines **44** via TsOH catalyzed condensation with α-arylketoesters **42**. These enamines were used for the catalytic asymmetric *N*-arylation with a chiral Pd-DTBM-SEGPHOS complex obtained from ligand **46** and $Pd(OAc)_2$. A wide variety of structurally diverse N-N bisindole atropisomers was synthesized in high yields and with good ee's (Scheme 13, **45a-o**).



Scheme 13. Selected examples for the axially chiral 1,1'-bisindoles via Pd catalyzed N-arylation.

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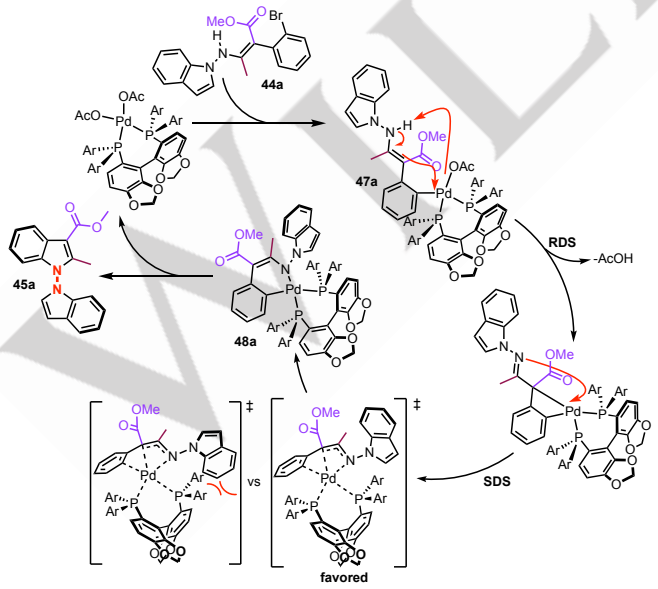
In particular, the bromoaryl ketone **42** could be functionalized with EWG and EDG groups on the aryl unit without affecting yields and enantioselectivity (**45a-c**). The same behaviour was encountered when isopropyl ester or a cyano group were employed (**45d-e**) while ethyl ketone did not compromise the reactivity of the indolization pathway (**45f**). Furthermore, the introduction of different substituents on the amino indole core were well tolerated (**45g-h**). Representative examples showed in scheme 13 revealed a good sustainability of the process using alkyl and aryl substituents at the C2 and C3 position of indole (**45i-j**). The reaction could be successfully performed also using 1-amino-7-azaisoindole and 1-aminopyrroles (**45k-l**). Additionally, *N*-Boc-methylhydrazine were optimal nucleophilic partner, readily reacting with aryl-ketones to give non-biaryl-indole atropisomers (**45m**) with excellent results. The versatility of the protocol was demonstrated using natural product derivatives such as amino-tryptamine and L-menthol as coupling partners (**45n-o**).

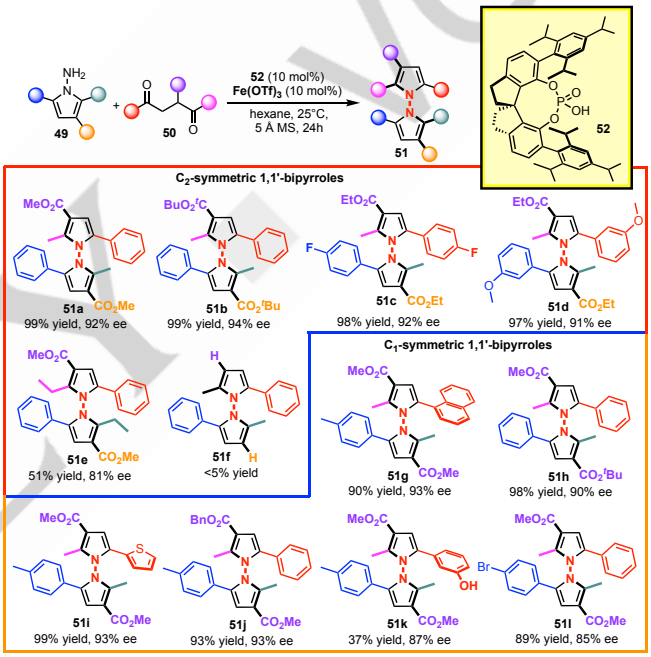
In general, the rotational energy barrier was assumed to be very high because at 130 °C no racemization was observed over 24 hours. Only for compounds **45k** and **45m** the rotational barrier was experimentally determined to be 30.2 kcal/mol and 30.7 kcal/mol respectively, while DFT calculations suggested an energy barrier for derivative **45a** of 39.0 kcal/mol. A deep computational analysis of the reaction mechanism was furthermore conducted. It was hypothesized that the reaction could follow a classical Buchwald-Hartwig *N*-arylation via an oxidative addition-reduction elimination sequence. Based on the energy profile obtained, the deprotonation of the enamine intermediate **47a** was identified as the rate-determining step (RDS) while the stereo-determining step (SDS) was located on the migration of the nitrogen of the imine on the Pd atom. The stereochemistry of the migration is under the control of the chiral catalyst which drives the reaction to the favoured axially chiral configuration by means of the steric interactions between ligand's substituents and indole in the TS (Scheme 14).



Scheme 14. Proposed reaction mechanism for the aryl amination reaction.

4.3. Synthesis of N-N Axially Chiral Bipyrroles via Cooperative Lewis Acid Assisted-Brønsted Acid Catalysis.

The group of Yang and Zhao synthesized 1,1'-bipyrrole atropisomers **51** through a Lewis acid assisted-CPA catalyzed Paal-Knorr reaction from *N*-aminopyrroles **49** and 1,4-diketones **50**.[32] Initially tested as an auto-relay catalytic process[33] that under the control of a CPA **52** could generate the axially chiral 1,1'-bipyrrole from hydrazine and an excess of 1,4-diketone, the process was turned to the construction of the novel N-N atropisomers from preformed *N*-aminopyrroles. Interestingly, during the optimization study it was observed that the addition of $Fe(OTf)_3$ as Lewis acid co-catalyst improved the reaction rate and it switched the configuration of bipyrroles from S_a to R_a. This result is a rare example of enantiodivergent synthesis that gave access to C_2- and C_1-symmetric 1,1'-bipyrrole atropisomers in high enantiocontrol. The efficiency of the process has been explored with a wide range of substituents on the 1,4-diketone and aminopyrrole (Scheme 15).



Scheme 15. Selected examples for the atroposelective dual catalyst promoted Paal-Knorr reaction.

Excellent results have been obtained in the preparation of C_2- and C_1-symmetric bipyrroles. In every case, aromatic substituents with EWG and EDG functionalities as well as different aliphatic groups were well tolerated. (**51a-l**). The ester group was fundamental for the reactivity of pyrrole derivatives, its absence completely compromised the formation of the product (**51f**). The reaction could be conducted also with the use of 1,4-diketone with a thiophene as carbonyl substituent showing impressive yield and enantiocontrol (**51i**). Novel 1,1'-bipyrroles underwent easy functionalization and derivatization such as bromination and Wittig olefination. Interestingly a diacid derivative **53m**, easily prepared from **51m** by Grignard addition followed by oxidation, could be employed as catalyst in the enantioselective allylation of aromatic aldehyde using allyl-Bpin reagent (Scheme 16a). This class of atropisomers showed a very high rotational energy barrier. No racemization was observed after heating **51m** at 150°C for 72 hours. To support the experimental analysis, DFT calculations

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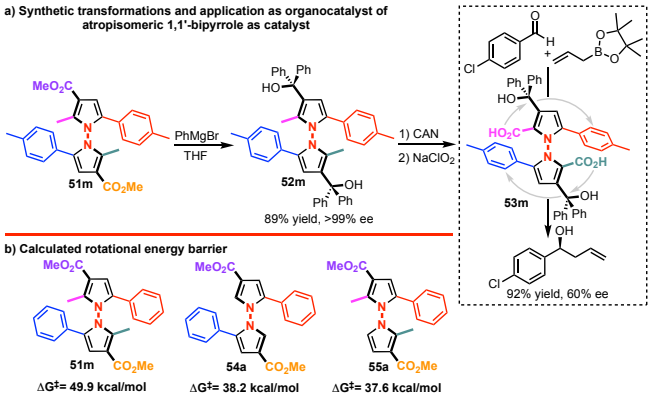
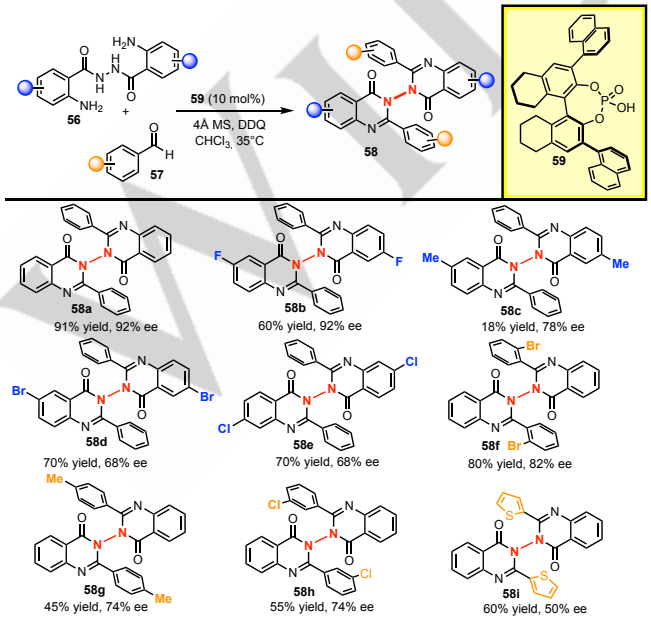
predicted a rotational barrier of 49.9 kcal/mol at 150 °C and evidenced the fundamental role of C2 and C5 substituents. The removal of one of them drastically reduced the $\Delta G^{\neq}_{rot}$ to 38.2 kcal/mol for **54a** (removal of methyl) and 37.6 for **55a** kcal/mol (removal of phenyl).



Scheme 16. a) Derivatization and practical application of 1,1'-bipyrroles atropisomers. b) Calculated rotational barrier by DFT methods.

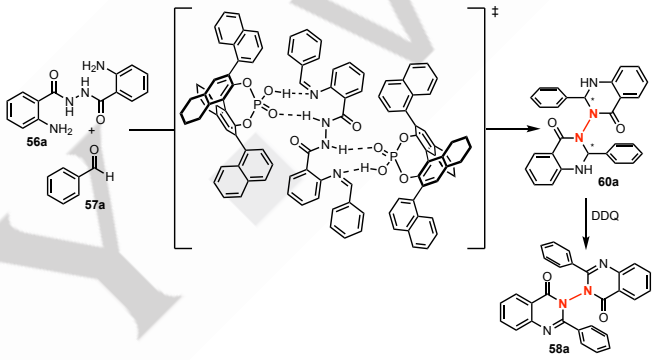
4.4. Asymmetric Synthesis of 3,3'-Bisquinazolinones via Dual Ring Formation.

In contrast with the procedures reported so far, Liu and Teng's group developed the first example of a dual ring formation leading to N-N axially chiral 3,3'-bisquinazolinones **58**.[34] The strategy is based on the reaction between 2-amino-*N*'-(2-aminobenzoyl) benzohydrazides **56** and different type of benzaldehydes **57** catalyzed by H8-CPA catalyst **59** (Scheme 17). During the scope of benzoylhydrazide it was observed that the yields and enantioselectivity were influenced by the electronic properties and the size of the substituents respectively.



Scheme 17. Selected examples for the synthesis of 3,3'-bisquinazolinones via dual ring formation.

With large substituents on the benzohydrazide core high yields and poor enantioselectivity were observed (**58a-e**). Authors ascribed this behaviour to the presence of hydrogen bonding interactions with the catalyst that could alter the optimal stereochemical and reactivity pathway. In the case of aldehydes, the electronic nature of the substituents had a more evident effect on the yields rather than on enantioselectivities (**58f-i**). The absolute configuration could be determined to be S_a by single-crystal X-ray diffraction analysis and the stability of the N-N axis was confirmed to be very high by thermal heating at 150 °C for 12 hours. No hypothesis based on experimental or computational data were reported on the reaction mechanism, which is nevertheless supposed to follow a CPA catalyzed condensation of the benzohydrazide **56a** with the aromatic aldehyde **57a**. The resulting imine undergoes two intramolecular cyclization with the formation of a centrally chiral intermediate **60a** which is rapidly oxidized by DDQ that fix the stereogenic axis of **58a** through a chirality transfer pathway (Scheme 18).



Scheme 18: Proposed reaction mechanism.

4.5. Synthesis of N-N Axially Chiral indolyl-Carbazoles by Pd Catalyzed 5-*endo*-Hydroaminocyclization.

Inspired by the synthesis of atropisomeric indoles by Kitagawa,[35] the group of Sparr reported the synthesis of bisindoles based on the atroposelective Pd catalyzed intramolecular 5-endo-hydroamino-cyclization of *N*-(2-phenyethynyl)amino carbazoles.[36] After a comprehensive optimization of the reaction conditions (transition metals, ligands, solvent and additives), the best results were obtained when $Pd(CH_3CN)Cl_2$ was combined with (*R*)-DM-SEGPHOS ligand and the reaction performed in ethanol at 60°C for 66 hours. Nevertheless, the process revealed some limits showing in general moderate yield and enantioselectivities (Scheme 19). On the amino carbazole scaffold three strategic sites were identified as key structural positions where install the substituents in order to have an efficient atroposelective transformation. When the 2-position of the carbazole was occupied with large groups a general increment of the enantioselectivity was observed (**62a-62d**). The alkyne moiety with para substituted aromatic ring gave the best results in term of yields and selectivity without influences by the electronic nature of aryl substituent (**62e-62f**).

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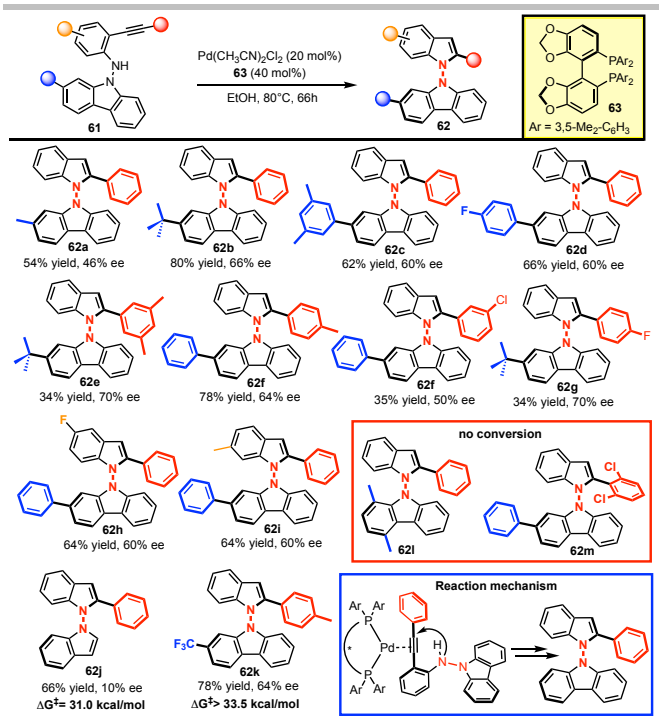
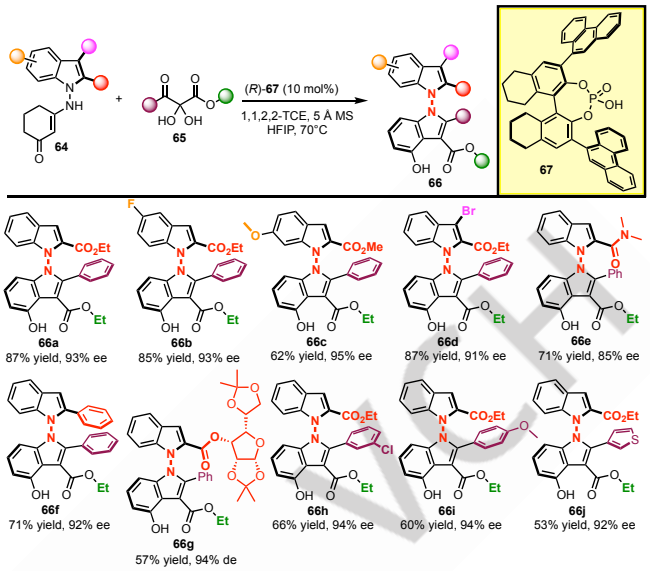


Scheme 19. Selected examples for the synthesis of N-N axially chiral Indolyl-Carbazoles.

The introduction of both EWG and EDG groups on the arylamine moiety gave the desired N-N axially chiral indolyl-carbazoles in good yields and enantiocontrol (**62h-63i**). These atropisomers showed an elevated thermal stability during the racemization experiments. A rotational energy barrier of 31 kcal/mol was found for **62j**, while **62k** was configurationally stable at 160°C for 7 hours with $\Delta G^{\neq}_{rot}$ >33.5 kcal/mol. No reaction was observed when carbazoles with severe steric hindrance were employed (**62l-62m**). The process revealed some drawback due to the partial instability of the starting material to the reaction conditions. It was demonstrated that **61** derivatives furnished the undesired carbazole as side product via a Pd catalyzed N-N cleveage that competed with the alkyne-Pd complex formation during the cyclization pathway.

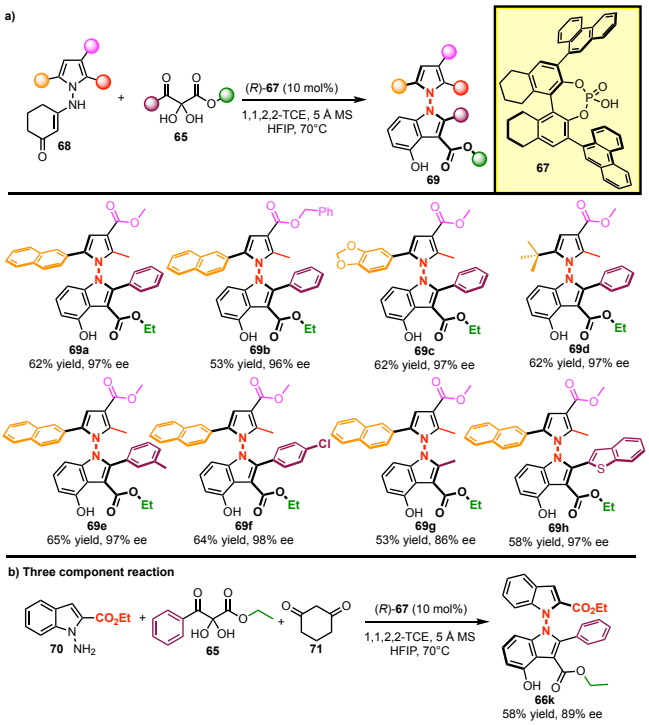
4.6. Synthesis of N-N Axially Chiral Bisindoles by CPA Catalyzed Formal (3+2) Cycloaddition of Indole-based Enaminones.

The group of Shi and Zhang realized the synthesis of axially chiral bisindoles using a phosphoric acid catalyzed (3+2) cycloadditions of indolyl-enaminones with 2,3-diketoesters.[37] The group faced successfully the challenges of designing a new organocatalytic reaction for the construction of atropisomeric *N,N'*-bisindoles furnishing a valuable alternative to the Pd catalyzed version developed by Li and Liu. During the optimization of the reaction conditions, many different CPA have been tested. Initially, the use of (*R*)-**67** in 1,1,2,2-TCE at 90°C revealed the best choice but lowering the temperature to 70°C and using 5 Å molecular sieves and hexafluoroisopropanol (HFIP) as additives improved yield and the enantioselectivity. Enaminenones **64** with electronically different groups on the indole core gave the corresponding axially chiral *N,N'*-bisindoles in high yield and enantioselectivity (Scheme 20).



Scheme 20. Selected examples for the enantioselective synthesis of axially chiral *N,N'*-bisindoles via CPA catalysis.

Amide, aryl substituents and ester derived from natural products can be employed at C2 and C3 of indole with high enantio and diastereoselectivity (**66e-66g**). Also, variation of the 2,3-diketoester precursor led to highly enantioenriched novel axially chiral bisindoles in high yields (**66h-66j**). The generality of the reaction was successfully demonstrated preparing *N,N'*-pyrroleindoles **69** from pyrrole-based enaminones **68** using aromatic, heteroaromatic and alkyl substituents on the pyrrole unit (Scheme 21, **69a-69d**).



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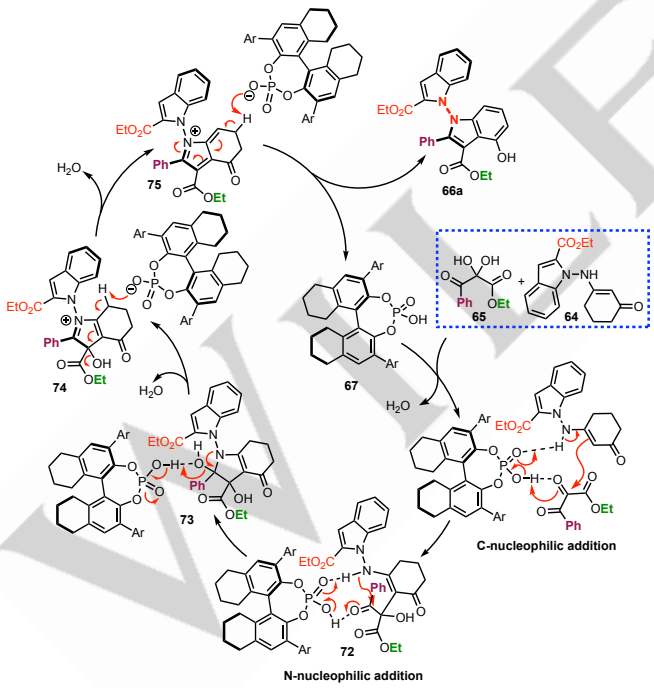
Scheme 21. a) Selected examples for the enantioselective synthesis of axially chiral *N,N'*-bispyrroles via CPA catalysis. b) Selected example for the three-component reaction.

The new indole core formed after formal (3+2) cycloaddition can be obtained with good stereocontrol employing **65** derivatives bearing aromatic rings with electronically different substituents as well as alkyl and heteroaryl functional group (**69e-69h**). Interestingly both N-N atropisomers can be synthesized in high yield and enantioselectivity through a three components reaction using respectively *N*-aminoindole or *N*-aminopyrrole derivatives with 1,3-cyclohexadienone **71** (Scheme 21b). Importantly, these new axially chiral compounds are characterized by a very high rotational energy barrier that was estimated to be higher than 50 kcal/mol via DFT computational methods. This indication was confirmed by the experimental results that revealed no racemization of compounds **66a** and **69a** after heating at 150°C for 10 hours. Indeed, investigation on the cytotoxicity of selected products revealed promising results against PC-3 cancer cells thus confirming once more the prominent role of indole and pyrrole derivatives in biological applications. The mechanism of the reaction is based on the initial dehydration of **65** resulting in the 2,3-diketoester **65'** which undergoes a sequence of CPA promoted carbon and nitrogen nucleophilic additions. The resulting intermediate **73** is then transformed into cationic **75** after two dehydrations under the control of (*R*)-**67** which promotes also the consecutive aromatization and isomerization to **66a** fixing the final R_a absolute configuration observed (Scheme 22).[38]



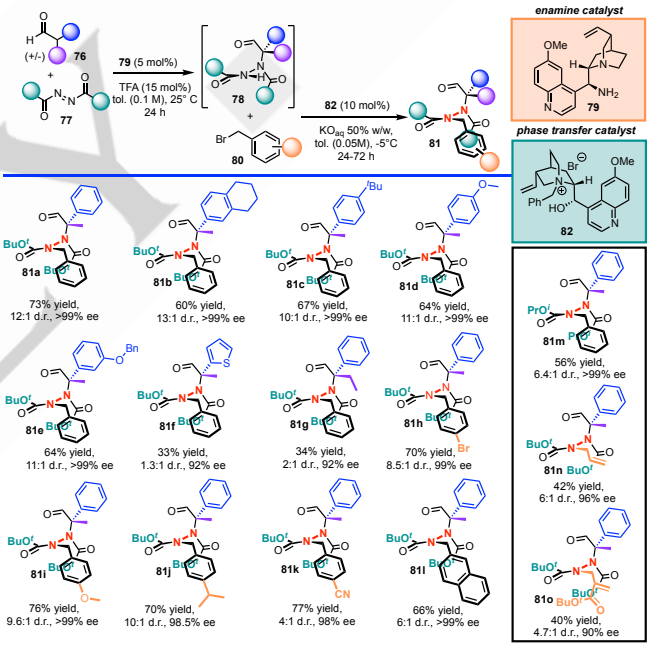
Scheme 22. Proposed reaction mechanism for the formal (3+2) cycloaddition catalyzed by CPA.

5. Sequential Catalysis Strategy

In the context of the asymmetric synthesis of atropisomers, the use of catalytic strategies envisaging the creation of two or more independent catalytic cycles suitable for building a high molecular complexity are very rare if not completely absent. The synthesis of novel N-N atropisomeric architectures N-N atropisomers like hydrazides can be realized applying this kind of strategy starting from simple commercially available substrates such as hydrazines and azodicarboxylates with properly sized substituents.

5.1. Synthesis of Atropisomeric Hydrazides by One-Pot Sequential Enantio- and Diastereoselective Catalysis

In 2022 we performed the first catalytic stereoselective synthesis of hydrazides containing a rotationally stable N–N single bond (Scheme 23).[39] Our catalytic strategy was based on a sequence of two catalytic events occurring in a single reaction pot. Azodicarboxylate **77** was chosen as the source for the rotationally hindered N–N single bond. After an enantioselective amination via enamine catalysis and a subsequent enantioselective phase transfer catalyzed alkylation, the N=N double bond of the achiral **77** was transformed into the N-N single bond of a tetrasubstituted hydrazide **81** displaying axial chirality.



Scheme 23. Selected examples for the enantio- and diastereoselective synthesis of atropisomeric hydrazides via sequential relay catalysis.

The first enantioselective alkylation was performed using chiral racemic α-branched aldehydes **76** using 9-*epi*-9-amino-9-deoxyquinine primary amine **79** as the catalyst and the following PT alkylation was conducted with the commercially available benzylquinidinium bromide salt **82**. The asymmetric synthesis of atropisomeric hydrazides was run on a large series of branched aldehydes and benzyl bromides bearing substituents with different EWG and EDG groups with in general high yields and enantioselectivities and good diastereoselectivity (**81a-l**). The scope of the reaction can be extended to different type of electrophiles such as isopropyl azodicarboxylate (**81m**) in the enantioselective amination and allyl iodide (**81n**) or Morita–Bayliss–Hillman carbonate (**81o**) in the alkylation, albeit with poor

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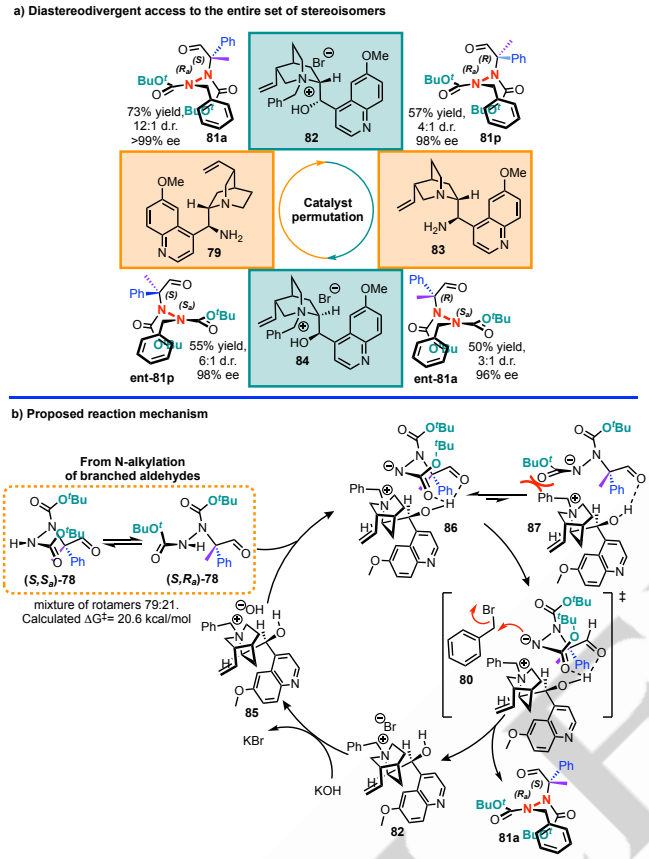
yields and diastereoselectivity. Interestingly, with this sequential relay catalysis the entire set of stereoisomers of hydrazides was achievable by a simple catalyst permutation (Scheme 24a). By changing the catalyst enantiomer of each single reaction, it was therefore possible to obtain each stereoisomer of the atropisomeric hydrazide with high stereocontrol of both elements of chirality.



Scheme 24. a) Catalyst permutation gives access to the entire set of stereoisomers. b) Proposed reaction mechanism.

The rotational energy barrier was experimentally determined to be 28.3 kcal/mol for compound **ent-81p** and X-Ray analysis showed an R_a absolute configuration of the stereogenic axis. The reaction mechanism that generates the stereogenic axis is supposed to be strictly dependent on the bifunctional nature of the catalyst (Scheme 24). After anion exchange reaction between **82** and KOH in the water phase, the resulting catalytic salt **85** migrates in toluene where deprotonation of **78** occurs. The chiral ammonium cation, via ionic and hydrogen bond interactions, stabilizes the anionic rotamer that gave the less steric interaction resulting in the preferential formation of complex **86**. The following alkylation with benzyl bromides **80** liberates the axially chiral hydrazide **81a** restoring the PTC catalyst.

6. Conclusion and outlook

In this review we have highlighted the recent development of the enantioselective preparation of axial chirality based on the N-N single bond. Several synthetic strategies including desymmetrization, direct functionalization or *de novo* ring formation and sequential catalysis have proven to be effective for this purpose, exploiting metal catalysis as well as the powerful use of organocatalysis. N-N atropisomers represent a stimulating frontier in the panorama of axial chirality and asymmetric synthesis, offering a new and easily accessible framework that we believe will receive increasing attention hereafter for novel syntheses and applications.

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Keywords: N-N atropisomers • indoles • pyrroles • alkylation • hydrazides

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[38] During the final stage of the preparation of this manuscript an interesting example of a Pd catalyzed atroposelective synthesis of indole-pyrroles atropisomers have been reported: W. Yao, C.-J. Lu, L.-W. Zhan, Y. Wu, J. Feng, R.-R. Liu *Angew. Chem. Int. Ed.*, **2023**, doi.org/10.1002/anie.202218871.

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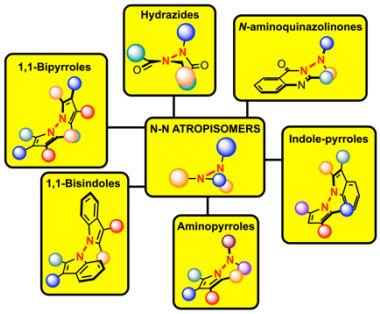

Recent advances in the enantioselective synthesis of N-N atropisomers are highlighted and discussed within this Review. In particular, the strategies and breakthroughs to obtain this novel and stimulating atropisomeric architecture are presented while a particular attention is given to mechanistic aspects.

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