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Dearomatization with Axial-to-Central Chirality Conversion

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ABSTRACT

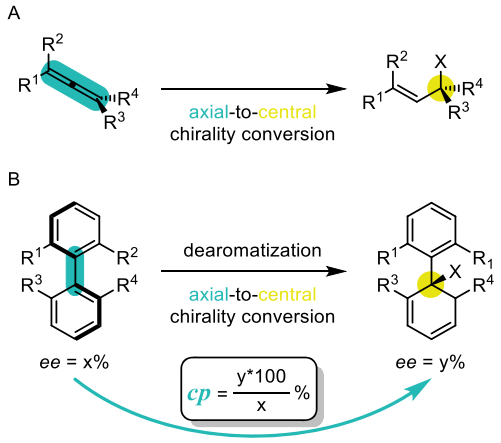
Aromatic atropisomers, that is to say aromatic compounds that exhibit chirality because of a hindered rotation around the bond linking them to one of their substituents, have recently received an increased interest, both as synthetic targets and as molecules of interest for applications as catalysts or in medicinal chemistry. However, despite the easier access to diversified enantioenriched aromatic atropisomers, considering them as substrates is not very frequent, notably in the context of dearomatization reactions. It is even more regrettable, as such transformations can deliver enantioenriched original motifs through an axial-to-central chirality conversion. The goal of this review is to provide a general overview of dearomative transformations of aromatic atropisomers to help the synthetic chemists community identifying new potential research directions in this subfield.

1 | Introduction

The significance of chiral molecules, notably cyclic molecules, no longer needs to be demonstrated, making the discovery of new strategies to develop stereocontrolled reactions still of high interest in organic and medicinal chemistry. The latest decades have seen tremendous developments of enantioselective methodologies, and the importance of those contributions have been recognized by the attribution of several Nobel Prizes, notably the one given to Knowles, Noyori, and Sharpless in 2001 [1–3], or the one given to List and MacMillan in 2021 [4, 5]. The vast majority of those methodologies tackled the control of single or multiple stereogenic centers. However, with the constant need to cover a broader chemical space for diverse applications, the enantioselective preparation of molecules bearing other kinds of stereogenic elements has gradually gained interest, notably stereogenic axes [6–13] or helices [14–18].

Chirality conversion or exchange [19], defined as the stereospecific transformation of a molecule exhibiting one type of stereogenic elements into another one exhibiting another type of stereogenic elements, which is quite less reported in literature. In a strict definition, 'stereogenicity conversion or exchange' would be more accurate than 'chirality conversion or exchange'. Moreover, we tend to prefer 'conversion' or 'exchange' over other words sometimes used in the literature to describe this phenomenon: 'transfer' is more general as it does not imply that the destroyed and created stereogenic elements are of different natures (see S_N2' processes for example) and 'interconversion' would bring an idea of reversibility, which is only rarely present. To finish with, all those terms are often misused to qualify processes that are not of stereospecific nature but rather of diastereoselective nature (for example, transformations that installs a stereogenic center in the vicinity of a stereogenic axis but without destroying the stereogenic axis). This synthetic strategy has at first been implemented with success in the chemistry of allenes, with the conversion of axially chiral allenes into centrally chiral propargylic compounds or the reciprocal transformation (Scheme 1A) [20]. There exists also dearomatization reactions via nonisolated allene intermediates with axial-to-central chirality conversions [21].

Aromatic atropisomers [22–24] represent another family of axially chiral compounds amenable to engage in chirality



SCHEME 1 | Scenarios of axial-to-central chirality conversion. (A) From allenes and (B) from atropisomers (this review).

conversion (Scheme 1B). Their synthesis by aromatization with central-to-axial chirality conversion is already the object of several reviews, (For seminal reports, see Ref. [25,26] For reviews, see Ref. [27–30]) but no general discussion exists on the reverse process of dearomatization of atropisomers with axial-to-central chirality conversion related to the scope of the present review but not included here, some reports exist for axial-to-central chirality conversion without dearomatization. They usually consist in cyclization bridging the atropisomer, thereby lowering its configurational stability [31, 32] Moreover, there are also examples of dearomatizations on compounds that present a restricted rotation around a biarylic bond that is not a stereogenic axis since one of the aromatic rings is symmetrically substituted [33, 34]. Reports using a dearomatization strategy are much less frequent for an obvious reason: this dearomatization step is usually disfavored both kinetically and thermodynamically [35–40]. However, the steric interactions existing between the different substituents surrounding the stereogenic axis might have a positive influence on the dearomatization reaction. Indeed, increasing the energy level of the starting material enables a release of steric interactions when going from rigid and flat aromatic structures to less flexible partially saturated ones. Lastly, dearomatization reactions with axial-to-central chirality conversion have the potential to deliver chiral enantioenriched scaffolds that could not be synthesized using more traditional methods.

As the definition of atropisomerism lies at the frontier of conformational and configurational considerations [22], it appears important to give a precise framework to this review. For the major part of the review, only enantioenriched atropisomeric substrates with barriers to rotation high enough to retain their enantioenrichment in the reaction conditions will be considered. Moreover, the products should be stable dearomatized, centrally chiral compounds, where the stereogenic axis no longer exists. It cannot be excluded that in some cases the stereogenic axis between the Csp^2 and the Csp^3 still exists after dearomatization, which would give rise to diastereomers. However, in cases of very high diastereoselectivities (either kinetic or thermodynamic), this phenomenon could be transparent, explaining why it is scarcely documented. In this vein, recent examples of enantioselective synthesis of products with a Csp^2-Csp^3 stereogenic axis, albeit in a different context have been reported [41, 42]. These conditions grant a stereospecific (and not diastereoselective!) nature to the overall dearomatization process. The quantification of stereospecificity will rely on the use of chirality conversion percentage (*cp*) defined as the ratio between the enantiomeric excess of the product and the one of the substrate [43]. We will start by the description of transformations in which the dearomatization with axial-to-central chirality conversion occurs in intramolecular fashion (the overall transformation being potentially intermolecular). We will then turn our attention to their even more challenging intermolecular counterparts. To complete the discussion, two complementary aspects will be covered: dynamic kinetic resolution processes from atropisomers that are configurationally labile in the reaction conditions, and the enantioselective formation of transient atropisomers with spontaneous chirality conversion. To finish, a few related specific miscellaneous examples will also be discussed.

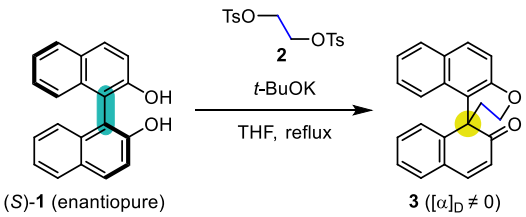
2 | Intramolecular Axial-to-Central Chirality Conversion (Stereospecific Reaction on an Enantioenriched Substrate)

As for many unusual and challenging transformations, the first example of axial-to-central chirality conversions was discovered by serendipity. The story started in 1975 during studies by the group of Cram aiming the preparation of various trimers of BINOL **1** (Scheme 2) [44]. When reacted with ethylene glycol ditosylate **2**, five different compounds were formed, including the dearomatized α-spiroketone **3** resulting from successive *O*-alkylation and intramolecular *C*-alkylation in 45% yield.

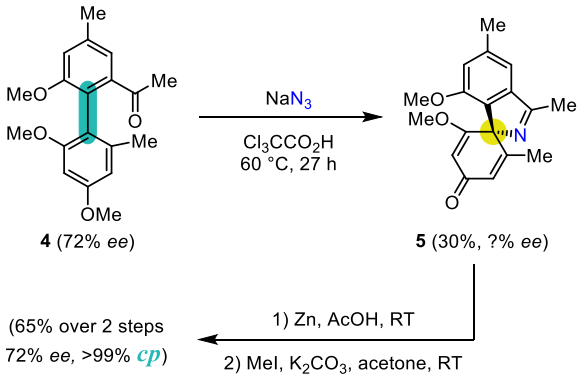
With enantiomerically pure (*S*)-BINOL, the ketone product **3** showed a specific rotation of +628° at 25°C and 546 nm. Even though no information about the enantiomeric excess is provided to allow quantification of the stereospecificity, this observation implies that a centrally chiral enantioenriched product is obtained by dearomatizing the axially-chiral (*S*)-BINOL.

More than two decades later, the group of Baker and Sargent also reported an unexpected dearomatization reaction from an atropisomeric substrate (Scheme 3) [45]. Through the study of amide construction by Schmidt rearrangement on enantioenriched atropisomeric ketone **4** (72% *ee*), they isolated the expected product but also a spirocyclic imine **5** in 30% yield. The formation of this product could be ascribed to the interception of the acylium ion by the electron-rich aromatic ring. The authors were not able to attest the enantioenrichment of the centrally chiral side product by experimental characterization.

However, reductive cleavage with Zn in AcOH followed by alkylation of the free phenol transformed **5** back to **4**, which



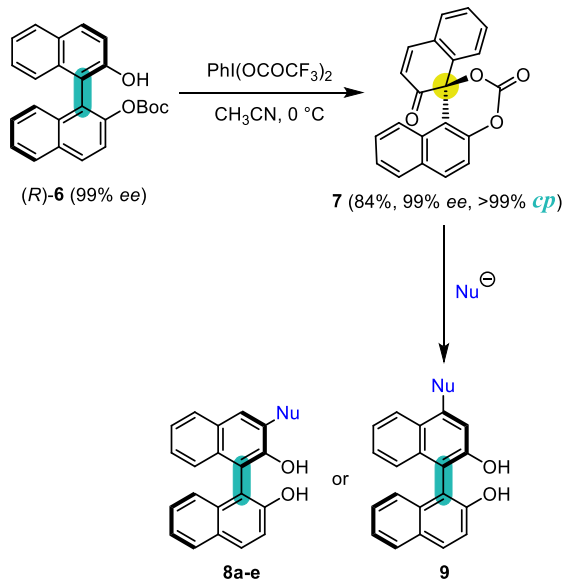
SCHEME 2 | First example of dearomatization with axial-to-central conversion of chirality.



SCHEME 3 | Stereospecific axial-to-central-to-axial chirality conversion cascade through a spirocyclic imine.

had preserved its enantioenrichment (72% *ee*), attesting for a stereospecific axial-to-central-to-axial chirality conversion cascade.

Despite these interesting seminal reports, two other decades passed before other research groups showed an interest for the development, the analysis, and the rationalization of similar processes. In most of those transformations, BINOL or its derivatives have served as starting materials because of their availability in enantiopure form and the phenol functions serving as handles for reactivity. It is only in 2011 that the dearomative cyclization of an axially chiral substrate via an *ortho*-quinol intermediate was described by Suzuki, Matsumoto, and coworkers (Scheme 4) [46]. Herein, enantiopure Boc-protected (*R*)-BINOL **6** (99% *ee*) was used to prevent multiple oxidations during the dearomatization process and form the corresponding cyclic carbonate **7**. The optimized method affords enantioenriched dearomatized product by oxidation with $PhI(OCOCF_3)_2$ in acetonitrile with 86% yield and 99% *ee*. This product appears to be useful to perform *C3*- or *C4*-functionalization with rearomatization of the naphthol unit and full conservation of the *ee* value. The regioselective formation of **8a-e** or **9** depended on the nucleophilic species (alkyl

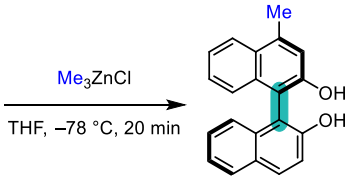
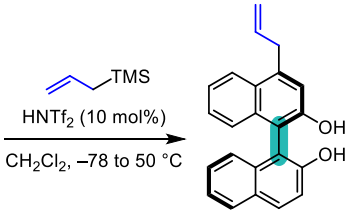
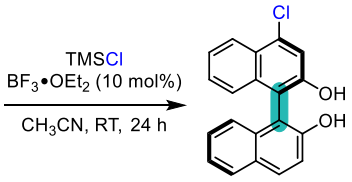
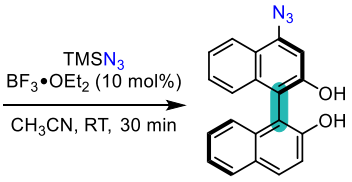
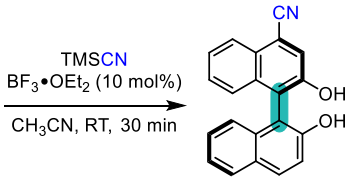
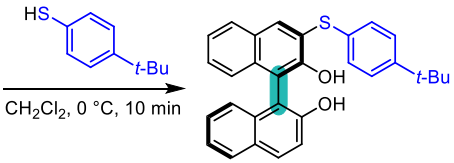


SCHEME 4 | Chirality conversion cascade with oxidative dearomatization of Boc-protected BINOL and subsequent rearomatization.

organometallics, chloride, azide and cyanide ions, aromatic thiol) used for the rearomatization, but could not be fully rationalized (Table 1). All in all, this example describes a rare example of chirality conversion cascade, at first axial-to-central then central-to-axial, which embodies a remote functionalization of BINOL.

Metallation at the position 1 of BINOL naphthyl unit is also feasible. Indeed, while studying the complexation of enantiopure

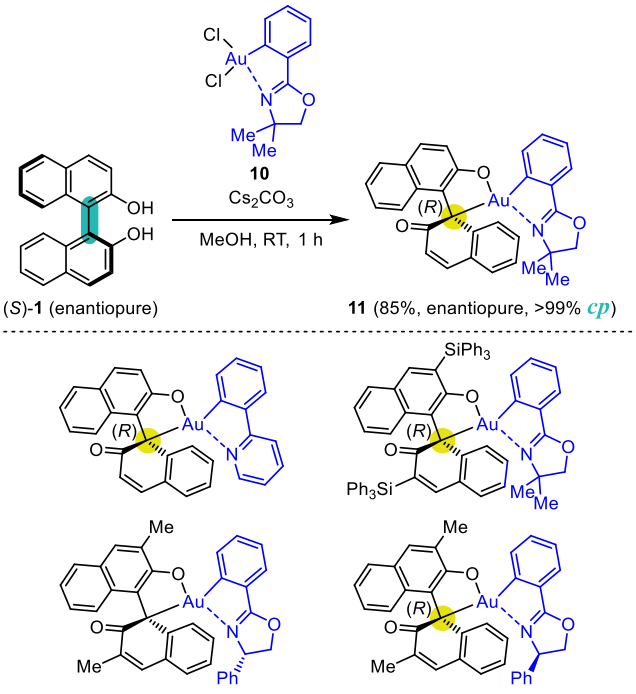
TABLE 1 | Scope of nucleophiles for the rearomatization of 7.

Entry	Nucleophiles, reaction conditions, products and results
1	 **8a** (95%, 99% *ee*, >99% *cp*)
2	 **8b** (95%, 99% *ee*, >99% *cp*)
3	 **8c** (97%, 99% *ee*, >99% *cp*)
4	 **8d** (99%, 99% *ee*, >99% *cp*)
5	 **8e** (99%, 99% *ee*, >99% *cp*)
6	 **9** (97%, 99% *ee*, >99% *cp*)

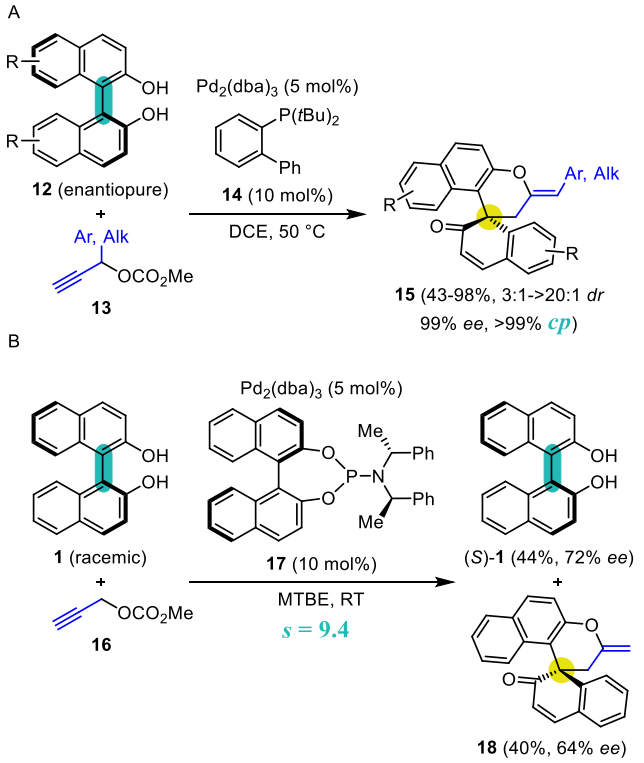
BINOL (*S*)-**1** with Au(III)-oxazoline complex **10**, Man-Kin Wong and coworkers did not isolate *O*,*O*-chelation product but *C*, *O*-chelation product **11** (Scheme 5) [47]. Using the antipode of BINOL resulted in the formation of the enantiomeric product. It was then possible to prepare a library of related catalysts (only a few examples are shown here) by adding substitutions on the BINOL or by replacing the oxazoline ring by other complexing moieties. All the obtained complexes proved to be light-, air- and moisture-insensitive. They were able to catalyze several transformations, showing modest enantioinduction in the only attempt of enantioselective catalysis presented.

To access structures quite similar to those described above, He and collaborators presented a stereospecific Pd-catalyzed dearomatization of substituted BINOL derivatives **12** (Scheme 6A) [48]. Using (*S*)-BINOL and a propargyl carbonate **13** in presence of $Pd_2(dba)_3$ and (2-biphenylyl)di-*tert*-butylphosphine **14** as an achiral ligand, it was possible to isolate more than 30 dearomatized *ipso*-functionalized enantioenriched products **15**, all with 99% *ee*. Generally high diastereomeric ratios were observed for the trisubstituted alkenes, except for some alkyl substituents. Interestingly kinetic resolution of *rac*-BINOL **1** was also investigated (Scheme 6B). Under slightly different conditions (different solvent and temperature and unsubstituted propargyl carbonate **16**), and by using chiral enantiopure phosphoramidite ligand **17** [49], two enantioenriched compounds were obtain: the dearomatized product **18** in 40% yield and 64% *ee* along with unreacted (*S*)-BINOL **1** in 44% yield and 72% *ee*. These results account for a moderate selectivity factor *s* equal to 9.4. Related reactions of kinetic resolutions will also be presented in Section 6.

In 2020, Xingwei Li and coworkers reported an intermolecular enantioselective Rh-catalyzed coupling between *N*-phenyl nitrones **19** and diazoketones **20**, affording spirocyclic nitrones **22** (Scheme 7A) [50]. High enantioselectivities were observed using



SCHEME 5 | Unexpected *C*,*O*-chelation of Au(III) complexes with axial-to-central chirality conversion.



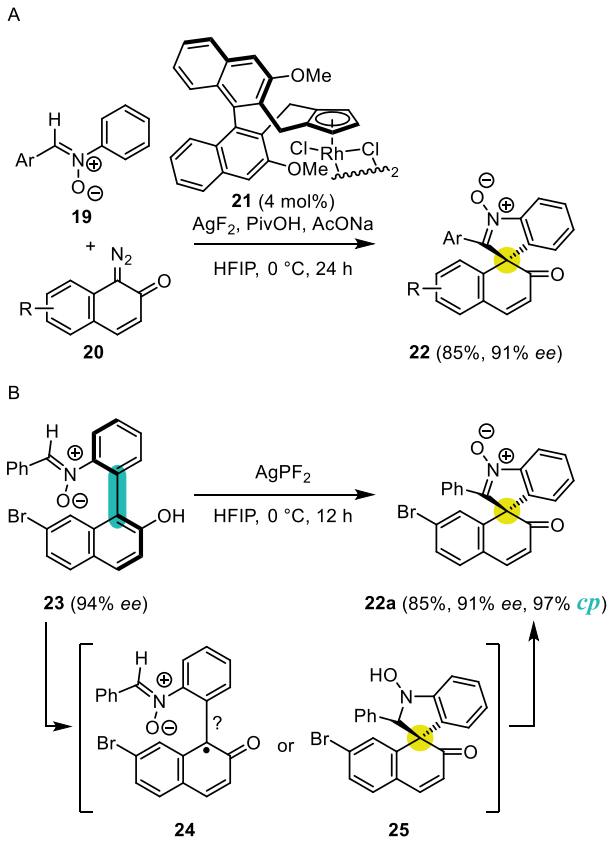
SCHEME 6 | Dearomatization of BINOL derivatives initiated by Pd-catalyzed propargylic substitution: stereospecific and stereoselective scenarios. (A) Sterespecific scenario: axial-to-central conversion of chirality and (B) sterespecific scenario: kinetic resolution (see also Section 6 for related examples).

Cramer's chiral $Cp^xRh(III)$ catalyst **21** [51]. Modified reaction conditions allowed isolating configurationally stable atropisomer **23** as a putative reaction intermediate (Scheme 7B). Pleasingly, it could efficiently be converted to the final product **22a** with 97% *cp*, even in the absence of Rh. The mechanism of the intramolecular dearomatization step is believed to involve a SET oxidation and a cyclization through intermediates **24** or **25**, even though preliminary calculations did not really manage to determine in which order they happen, both reaction pathways being almost isoenergetic. If SET occurs first, there is a striking question around the configurational stability of carbon-centered radical intermediate **24**.

3 | Intermolecular Axial-to-Central Chirality Conversion (Stereospecific Reaction on an Enantioenriched Substrate)

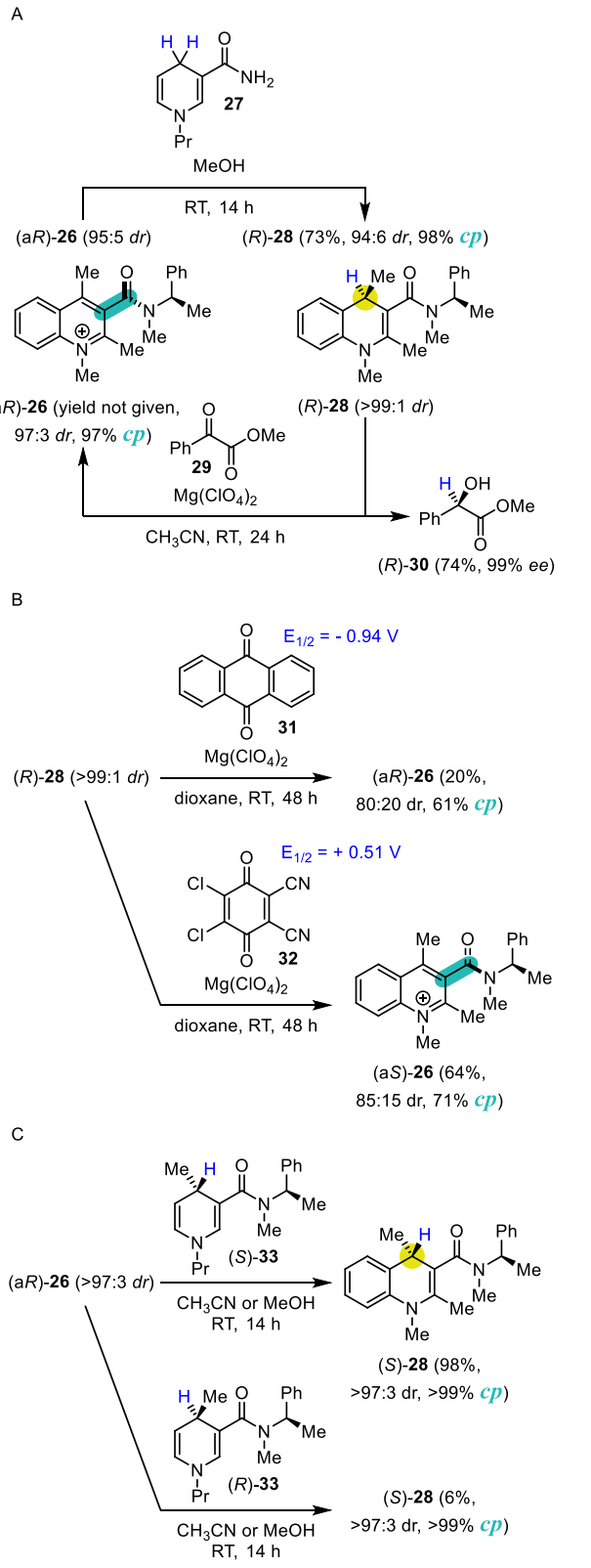
Besides the transformations presented above that involve an intramolecular dearomatization step, there has also been reports of intermolecular dearomatization of atropisomers with axial-to-central chirality conversion. These transformations are fundamentally more challenging, both on reactivity and stereospecificity aspects. They consist mostly, but not exclusively, into formal hydrogenation reactions.

Ten years after the seminal discovery of axial-to-central chirality conversion by Cram, Oka's group studied the stereochemical outcome of the interconversion between the centrally chiral NAD(P)



SCHEME 7 | Enantioselective Rh-catalyzed coupling between *N*-phenyl nitrones **19** and diazoketones **20** involving an intramolecular dearomatization with axial-to-central chirality conversion. (A) Rh-catalyzed coupling between diazoketones and N-phenyl nitrones and (B) intramolecular dearomatization with axial-to-central chirality conversion.

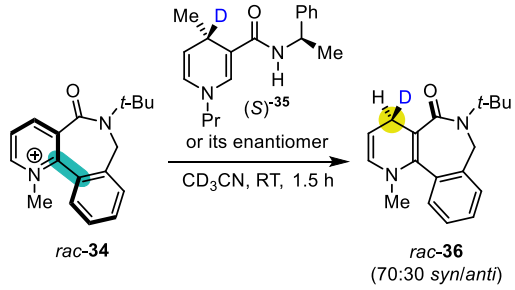
H analog Me_3MQPH **28** and the configurationally stable axially chiral NAD(P)$^+$ analog Me_3MQP^+ **26** (Scheme 8A) [52]. It should be noted that compared to all previous examples, the atropisomerism of this compound is not supported by a biarylic bond but by an arenium–amide bond. On these compounds, the stereogenic center present on the amide *N*-substituent allowed the existence of diastereomers, thereby facilitating the study. However, it does not seem to have any meaningful impact on the stereochemical outcome, since the other diastereomers of **26** and **28** behave similarly in all transformations presented here. On the one hand, when diastereomerically enriched (a*R*)-**26** was treated with 1-propyl-1,4-dihydronicotinamide **27**, the reduced product (*R*)-**28** was obtained with an almost complete chirality conversion. On the other hand, combining (*R*)-**28** with methyl phenylglyoxylate **29** as an oxidizing agent in the presence of $Mg(ClO_4)_2$ delivered the same diastereomer of the quinolinium cation (a*R*)-**26**, without any significant erosion of the diastereomeric ratio. At the same time, the methyl mandelate coproduct (*R*)-**30** was formed in 99% *ee*. It should be noted that the conformation of (*R*)-**28** where the oxygen atom of the amide function points toward the side of the hydride is the reactive one, in agreement with Buck's hypothesis based on



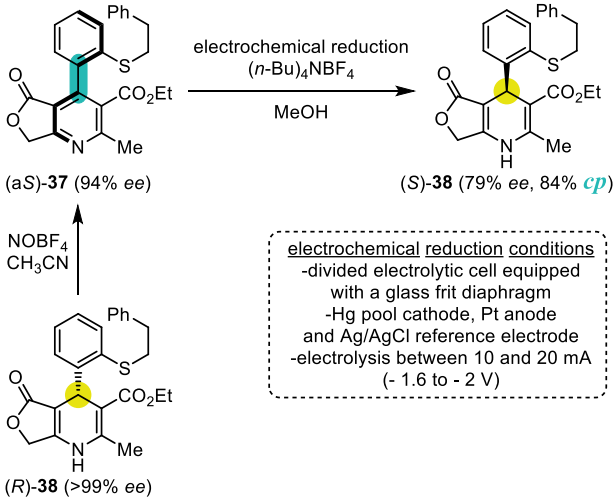
SCHEME 8 | Studies on the stereospecific interconversion of NAD(P)H and NAD(P)$^+$ analogs with chirality conversions. (A) Oxidation and reduction cycle with chirality conversions, (B) dependence of the oxidation's stereospecificity on the oxidant, and (C) match/mismatch effect with a chiral reductant.

quantum-mechanical calculations [53]. Hydride addition to the quinolinium cation (a*R*)-**26** also occurs on the same face. Overall, these results indicate that stepwise cycling of stereospecific events of oxidations and reductions should be feasible.

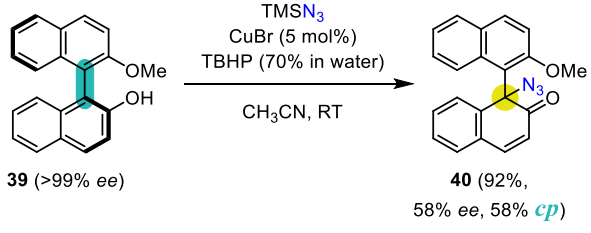
In addition, using anionic reductants ($Na_2S_2O_4$, $NaBH_4$, $LiAlH_4$) or cationic oxidants ($K_3Fe(CN)_6$) annihilated the diastereomeric ratios. Further studies with quinones of different oxidation potentials as alternative oxidants evidenced that the scenario is in fact more complicated: the stereochemical outcome of the reaction is also depending on the organic oxidant, notably its oxidation potential (Scheme 8B) [54]. Indeed, anthraquinone **31** with a low oxidation potential followed the same pathway as methyl phenylglyoxylate **29**, delivering the expected oxidized



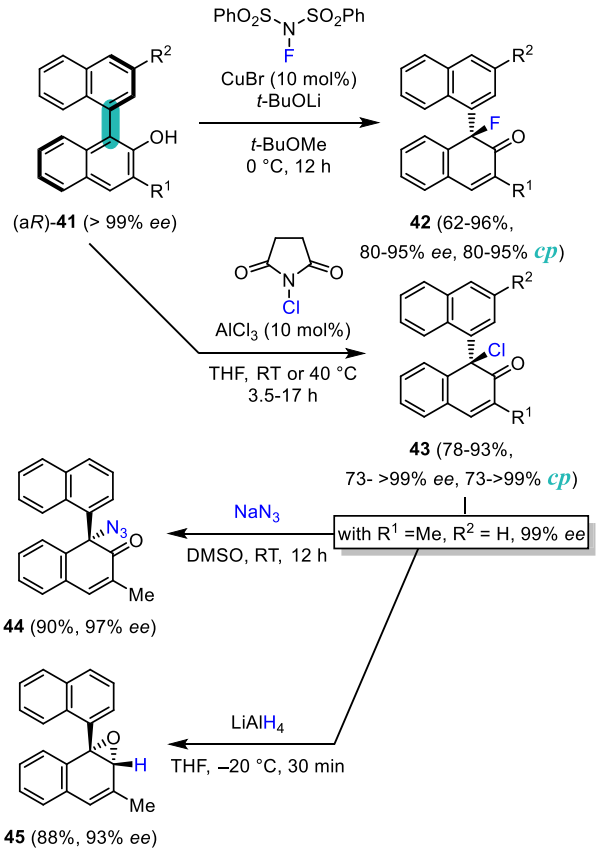
SCHEME 9 | Extension to pyridino[3,2-*d*]-2-benzazepinium salts.



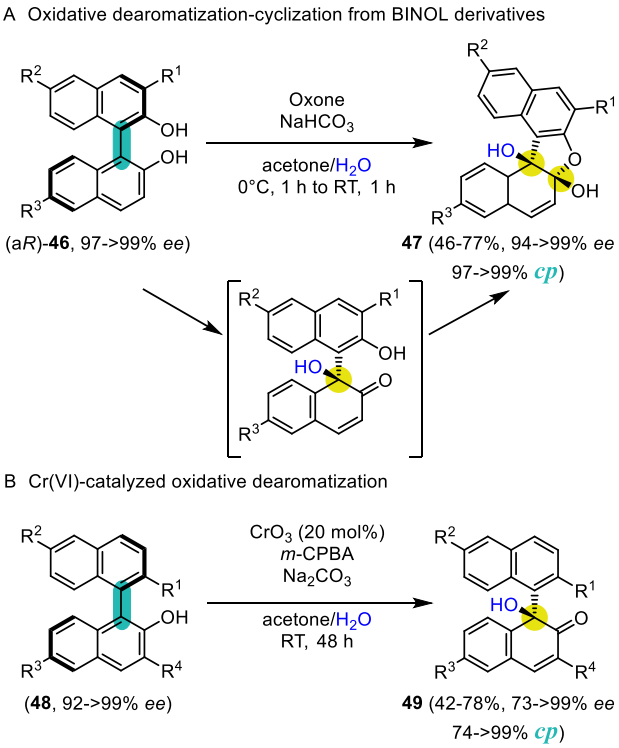
SCHEME 10 | Electrochemical reduction of pyridinium salts with axial-to-central chirality conversion.



SCHEME 11 | Cu-catalyzed oxidative dearomatization of a BINOL derivative in the presence of $TMSN_3$.



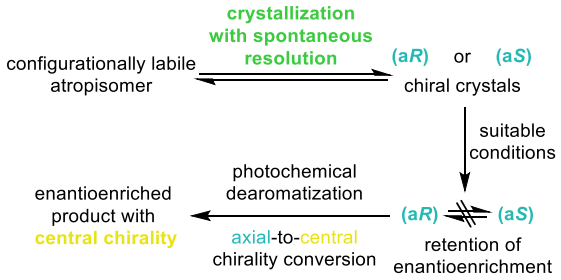
SCHEME 12 | Cu-catalyzed halogenative dearomatization of BINOL derivatives.



SCHEME 13 | Oxidative dearomatization of 2-naphthol derivatives. (A) Oxidative dearomatization-cyclization from BINOL derivatives, (B) Cr(VI)-catalyzed oxidative dearomatization.

product (a*R*)-**26**, albeit with lower stereospecificity. On the contrary, strongly oxidizing 2,3-dichloro-5,6-dicyanoquinone (DDQ) **32** yielded the other diastereomer (a*S*)-**26** as the major one. This observation does not follow completely Buck's hypothesis but is in line with the Benner's hypothesis on the reactivity of NAD(P)H coenzymes based on stereoelectronic control [55]. It sets that the hydride transfer occurs from the most reactive face (the one toward which the oxygen atom is pointing) with rather stable carbonyl groups and from the least reactive face with less stable substrates. This phenomenon could be related to the progressive evolution over time of the enzyme-coenzyme couples to reach the possibility of carrying out reversible transformations in both directions.

Later on, the same authors also studied match/mismatch effects by attempting the reduction of (a*R*)-**26** with the two enantiomers of the chiral dihydropyridine **33** (Scheme 8C) [56]. With (*S*)-**33**, the reaction proceeded smoothly in a match scenario affording the reduced product (*S*)-**28** in 98% yield with no detectable amount of the other diastereomer. On the opposite, a mismatch scenario was observed with (*R*)-**33**: there was almost no reactivity with only 6% yield of the same diastereomer (*S*)-**28**, with the formation of an unidentified byproduct.



SCHEME 14 | General principle for absolute asymmetric synthesis by dearomatization of configurationally labile atropisomers.

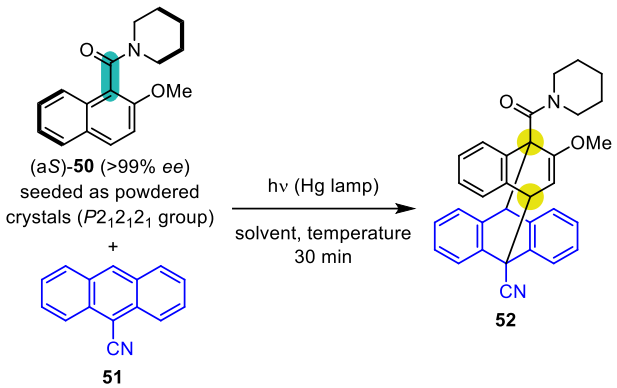
In 1994, the group of Ohno completed its studies on NAD(P)$^+$ analogs by studying pyridino[3,2-*d*]-2-benzazepinium salt **34** exhibiting only biaryl axial chirality (Scheme 9) [57]. The enantiopure starting material could be resolved by HPLC on chiral stationary phase at 5°C but unfortunately **34** tended to racemize at room temperature. Therefore, its reduction was carried out on a racemic sample in the presence of deuteride donor (*S*)-**35** or (*R*)-**35**, which indifferently provided the reduced product **36** in a 70:30 *syn*/*anti* ratio with respect to the position of the deuterium atom to the C = O bond.

The very first enantiomeasured example of intermolecular dearomatization with axial-to-central chirality conversion where the only stereochemical information is brought by the stereogenic axis was reported by Straub and Goehrt in 1996 (Scheme 10) [58].

The electrochemical reduction of atropisomeric pyridinium salt (a*S*)-**37** in the presence of a mercury cathode provided the reduced 1,4-dihydropyridine (*S*)-**38** in good enantiomeric excess (*cp* higher than 98% could even be obtained on other examples not presented here). The authors claim that the heterogenous nature of this transformation may help for the high stereospecificity of the reaction. This work also describes the reverse oxidation with central-to-axial chirality conversion in the presence of a large variety of oxidants with diverse stereochemical outcomes. Overall, this sequence represents a remarkable strategy to achieve the stepwise inversion of configuration of chiral dihydropyridines, a very important family of drugs.

Similarly to the corresponding intramolecular reactions, the field of intermolecular dearomatization with axial-to-central chirality conversion surprisingly remained silent for around two decades. In 2016, the group of Prabhu reported a Cu-catalyzed oxidative dearomatization of 2-naphthols in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant and $TMSN_3$ as a pronucleophile (Scheme 11) [59]. When the reaction was applied to enantiopure BINOL derivative **39**, then the

TABLE 2 | Dearomative photochemical [4 + 4]-cycloaddition of atropisomeric naphthylamide 50 and 9-cyanoanthracene 51 in solution.



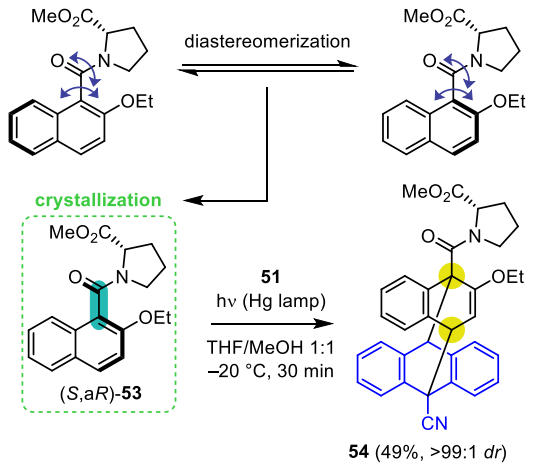
Entry	Solvent	Temperature	Conversion	*ee*
1	THF	−20 °C	52%	95%
2	THF	20 °C	45%	29%
3	THF/MeOH 1:1	−20 °C	40%	88%
4	THF/MeOH 1:1	20 °C	82%	88%

corresponding centrally-chiral dearomatized compound **40** was obtained with a moderate enantiomeric excess.

Based on the same reactivity pattern, an efficient halogenative dearomatization of axially chiral substituted 2-naphthols was also reported recently (Scheme 12) [60]. Fluorination conditions involved a catalytic amount of CuBr and stoichiometric use of *t*-BuOLi and NFSI. It delivered newly formed centrally chiral compounds **42** with high enantiomeric excesses up to 95% starting from functionalized (a*S*)-**41**. Even more satisfying results came from chlorination with NCS in the presence of $AlCl_3$, which allowed the formation of enantioenriched compounds **43** with *ee* up to >99%. However, the corresponding brominated dearomatized product appeared to be unstable and was only isolated for a few days with 53% *ee* (not shown here). Product diversification from the chlorinated compound proceeded smoothly to allow azide introduction to form **44** by a rather unusual S_N2 mechanism at a tertiary carbon atom and ketone reduction-cyclization to obtain epoxide **45**.

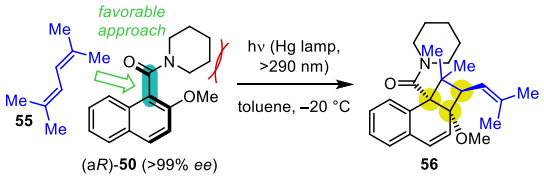
Still in the same outline, Urbano, and coworkers reported in 2020 an oxidative dearomatization-cyclization sequence of substituted enantiopure BINOL derivatives (a*R*)-**46** into pentacyclic centrally-chiral compounds (*R*,*S*)-**47** (Scheme 13A) [61]. Several examples of functionalized BINOLs attest the effectiveness of these mild conditions, stereospecific oxidation with Oxone and $NaHCO_3$ to access highly enantioenriched compounds. Very recently, a similar transformation using Cr(VI) catalysis and *m*-CPBA as the stoichiometric oxidant has been implemented on substrates **48** that lack the second hydroxyl group (Scheme 13B) [62]. In this case, simple hydroxylation products **49** are formed with high stereospecifities.

There is another related oxidative cyclization process of BINOL derivatives in the presence of phenyl iodosobenzene to prepare xanthene derivatives (not shown here) [63]. However, it afforded virtually racemic products, once again highlighting that stereospecificity in those dearomatization processes is not to be taken for granted. To finish with, a very efficient comparable reactivity pattern has been observed from styrenyl atropisomers, but is does not represent a dearomatization [64].



SCHEME 15 | Extension of the dearomative photochemical [4 + 4]-cycloaddition to diastereomeric amides.

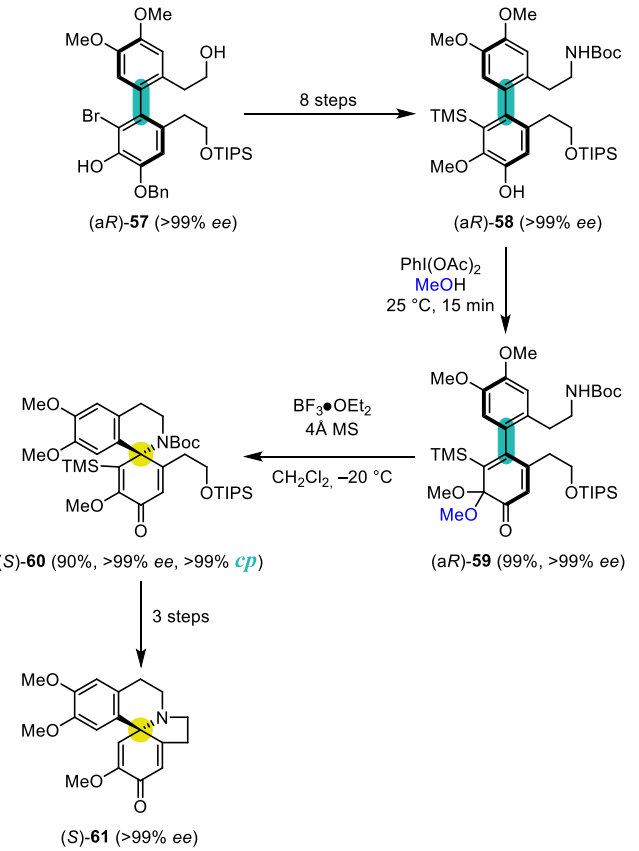
TABLE 3 | Extension of the concept to a dearomative photochemical [2 + 2]-cycloaddition.



Entry	Conversion	Yield	*ee*
1	10%	9%	76%
2	20%	19%	38%
3	45%	42%	20%

4 | Axial-to-Central Chirality Conversion of Transient Atropisomers (Stereospecific Reaction on Configurationally Labile Enantioenriched Substrates Resolved by Crystallisation)

Absolute asymmetric synthesis is a term that has been coined to gather different kinds of transformations that deliver chiral enantioenriched products only using achiral or racemic precursors, reagents, and catalysts [65, 66]. They generally rely on the possibility of some molecules to exhibit transient chirality or associate as chiral edifices, notably during crystallization



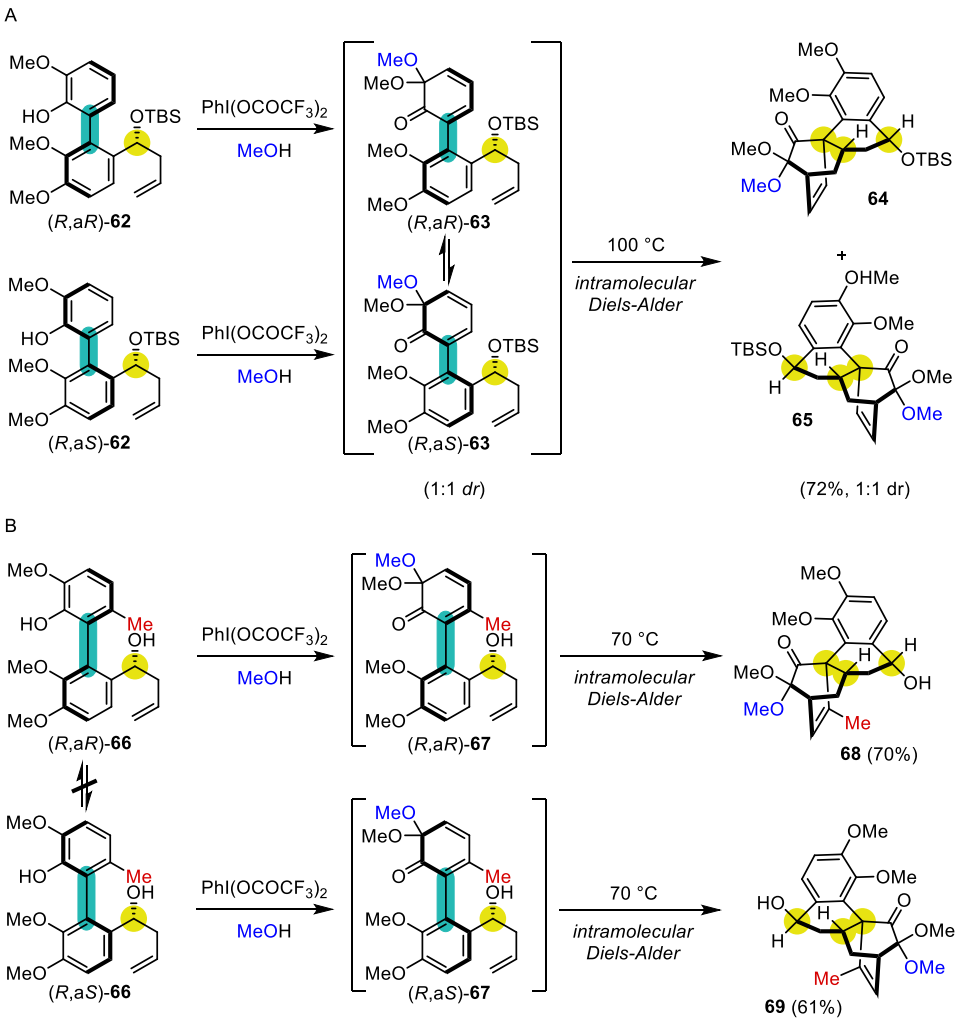
SCHEME 16 | Synthesis of enantiopure erythrinan alkaloid scaffold by successive dearomatization and chirality conversion.

[67]. This transient chirality can then be made permanent through chemical transformation into chiral products, very often by using photochemical reactions. In the context of atropisomers, one can imagine that a molecule with configurationally labile atropisomerism could be resolved during crystallization and reacted by dearomatization, affording enantioenriched centrally chiral products if the reaction occurs faster than the enantiomerization in the selected reaction conditions (Scheme 14). This possibility has been exemplified in a series of publications by the group of Fujita and Sakamoto.

The first application of this concept appeared in 2005 with a study on atropisomeric naphthylamide (a*S*)-**50**, which is not configurationally stable in solution, with a half-time life of less than 12 min in THF at 15°C, but can be crystallized in enantiopure form [68]. Its dearomative photochemical [4 + 4]-cycloaddition with 9-cyanoanthracene (a*S*)-**51** at – 20°C delivered the centrally chiral product **52** with 95% *ee* (Table 2, Entry 1). As expected, a much reduced enantiospecificity was observed at 20°C because of competing enantiomerization (Table 2, Entry 2). Interestingly, when the reaction was performed in THF/MeOH 1:1, high enantiomeric excesses were observed at both temperatures (Table 2, Entries 3 and 4). This is in accordance with an improved half-time life of 128 min in this solvent mixture at 15°C, which could be ascribed to hydrogen bonding and the increased zwitterionic character in the amide group in polar solvents. Although this result is very impressive, it is also inherently limited in scope by the crystallization step. Indeed, the ethoxy- congener of **50** failed to provide chiral crystals.

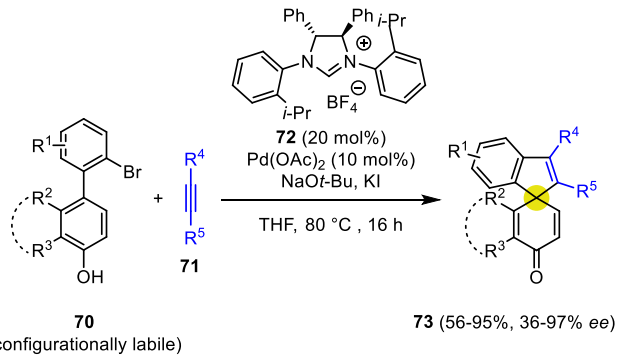
This principle was then extended to diastereoselectivity studies on (*S*,a*R*)-**53** by replacing the piperidine unit of the amide by a proline ester (Scheme 15) [69]. Similar observations were made on the effect of MeOH as polar protic solvent, allowing the formation of **54** as a single diastereomer.

The same group also tried to extend the concept to a [2 + 2]-cycloaddition between atropisomeric naphthylamide (a*R*)-**50** and 2,5-dimethylhexa-2,4-diene **55** (Table 3) [70]. The reaction proceeded slowly at – 20°C and at low conversion, the cycloaddition product **56** that bears three contiguous stereogenic centers was obtained with a decent *ee* of 76% (Table 3, Entry 1). However, attempts to improve the conversion had a strong deleterious impact on the enantiospecificity (Table 3, Entries 2



SCHEME 17 | Synthesis of morphinan scaffolds by successive dearomatization and chirality conversion. (A) Three ortho substituents around the stereogenic axis: no configurational stability, (B) Four ortho Substitutents around the stereogenic axis: configurational stability.

and 3). At first sight, this result appeared surprising, as **50** racemizes really slowly at – 20°C. Mechanistic studies concluded to a photoracemization mechanism with the singlet excited state undergoing twisted intramolecular charge transfer; a phenomenon already known for aromatic amides [71]. Other publications of the same group applied those principles to atropisomeric coumarin- and quinolone-carboxamides [72–74]. Nevertheless, they cannot really be seen as dearomatization reactions, as those substrates only admit a zwitterionic aromatic resonance form. For this reason, they will not be discussed in details in this review.



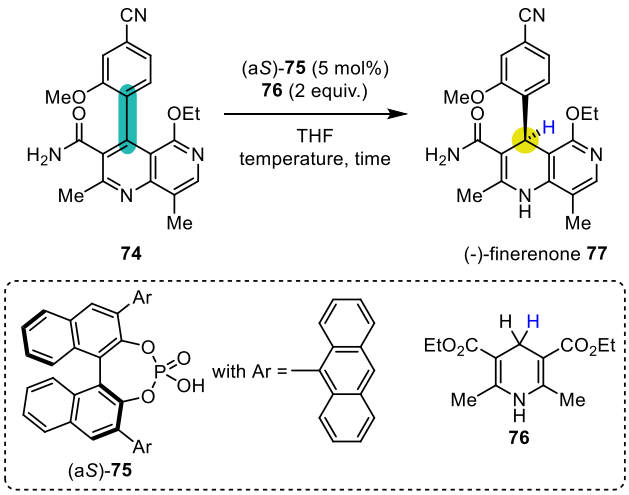
SCHEME 18 | Dearomative Pd-catalyzed dynamic kinetic resolution of configurationally labile atropisomers.

5 | Sequential Dearomatization and Axial-to-Central Chirality Conversion (Stereospecific Reaction on an Enantioenriched Intermediate that Has Just Lost Its Aromaticity)

In addition to the intra- and inter-molecular stereospecific dearomatization methods with *concomitant* axial-to-central chirality conversion discussed above, which constitute the major focus of this review, we also wish to make connections to some examples of related processes. In this section, we will discuss reaction sequences where the dearomatization and the axial-to-central chirality conversion occur in two distinct *successive* steps. In 2004, the group of Matsumoto developed a synthetic route toward enantiopure erythrinan alkaloid scaffold **61** (Scheme 16) [75]. Enantiopure (a*R*)-**57** could be obtained by resolution using HPLC on chiral stationary phase and proved resistant to enantiomerization at room temperature. It was then transformed in 8 steps into intermediate (a*R*)-**58**, which underwent oxidative dearomatization in the presence of $PhI(OAc)_2$. Dearomatized (a*R*)-**59** was also configurationally stable and could undergo cyclization into spirocyclic product (*S*)-**60** with complete enantiospecificity. Three additional steps were then needed to complete the synthesis of tetracyclic erythrinan alkaloid scaffold (*S*)-**61**.

A related stepwise approach where the dearomatization step and the conversion of chirality are disconnected was also described more recently by the group of David Chen, with an application to the synthesis of morphinan scaffolds (Scheme 17) [76]. Several

TABLE 4 | Enantioselective synthesis of (-)-finerenone 77 by enantioselective reduction from atropisomeric naphthyridine 74.



Entry	74	Temperature, time	Yield	*ee*
1[a]	racemic	40 °C, 24 h	37%	96%
2[a]	racemic	40 °C, 72 h	55%	94%
3	(*S*), >99% *ee*	40 °C, 24 h	42%	99%
4	(*R*), >99% *ee*	40°C, 24 h	5%	22%
5	(*S*), >99% *ee*	100 °C, 24 h	74%	96%
6	racemic	100 °C, 24 h	82%	88%

[a]Carried out with (a*R*)-**74** affording *ent*-**77** as the major enantiomer.

systems were successively studied to finally obtain series of compounds that retain their stereochemical integrity during the whole reaction sequence. Diastereomeric compounds (*R*,a*R*)-**62** and (*R*,a*S*)-**62** with three *ortho* substituents around the stereogenic axis could be individually prepared (Scheme 17A). However, their oxidative dearomatization followed by thermal intramolecular Diels-Alder cycloaddition resulted in the formation of the same 1:1 mixture of diastereomers **64** and **65**. This result was ascribed to a potential epimerization of the nonaromatic atropisomers (*R*,a*R*)-**63** and (*R*,a*S*)-**63**, whose barriers to rotation are likely to be lower than those of the aromatic precursors. On the opposite, adding a fourth *ortho* substituent (methyl group) enabled stereospecificity (Scheme 17B). Diastereomeric compounds (*R*,a*R*)-**66** and (*R*,a*S*)-**66** resisted epimerization even at 120°C and their dearomatized counterparts (*R*,a*R*)-**67** and (*R*,a*S*)-**67** were also sufficiently configurationally stable. As a consequence, tetracyclic target products **68** and **69** could be obtained as pure diastereomers. Moreover, those results indicate that only the stereogenic axis, and not the stereogenic center, is involved in the stereospecificity of the sequence.

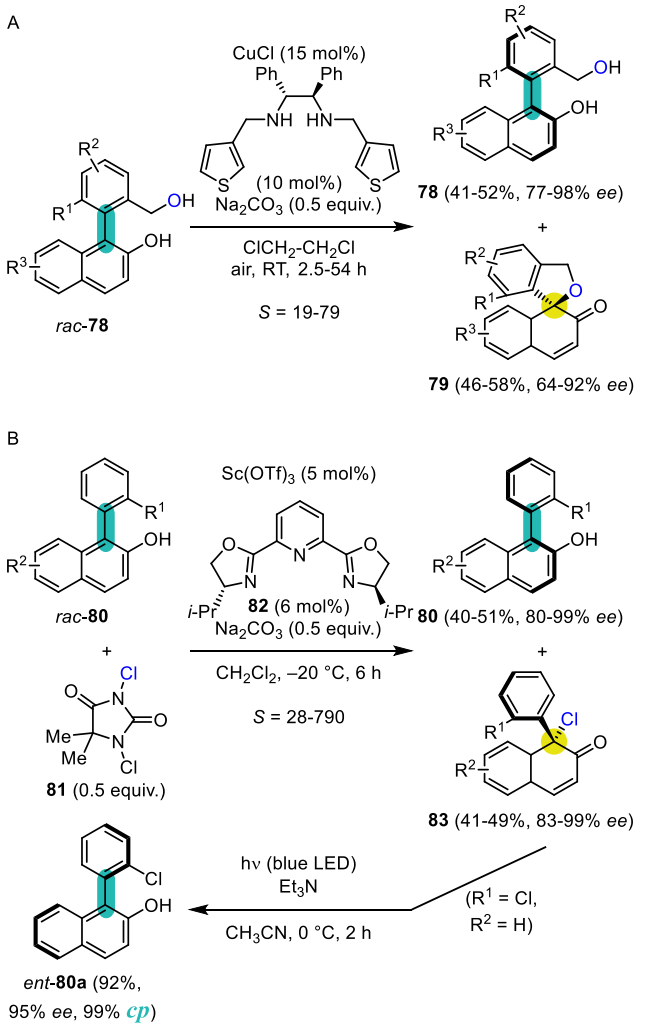
6 | (Dynamic) Kinetic Resolution (Stereoselective Reaction on Racemic or Configurationally Labile Atropisomers with a Chiral Catalyst)

To finish this review, we now wish to present a few processes related to all the ones discussed above but that are not stereospecific. They are rather stereoselective and proceed through (dynamic) kinetic resolutions. Those transformations do not start from an enantioenriched starting material but either from a racemic one (kinetic resolution) or from a configurationally labile one (dynamic kinetic resolution). In addition to the examples discussed below, the one depicted in Scheme 6B also belongs to this category [48].

Ten year ago, the group of Xinjun Luan reported the first dynamic kinetic resolution of racemic biaryls proceeding through a dearomatization reaction (Scheme 18) [77]. This methodology is based on an annulation between brominated substrate **70**, whose stereogenic axis bearing only two *ortho* substituents is configurationally labile, and disubstituted acetylenes **71** (mostly with aryl substituents). The stereoselectivity of this reaction is controlled by Pd-complex bearing a NHC ligand derived from a chiral imidazolinium salt **72**, which allowed obtaining dearomatized spirocyclic compounds **73** with *ee*'s up to 97%.

Last but not least, the kinetic resolution of racemic atropisomers can also be a powerful strategy that has notably been applied to the synthesis of the drug (-)-finerenone **77**, known as a mineralocorticoid receptor antagonist used for the treatment of chronic kidney disease associated with type-II diabetes (Table 4) [78]. Enantioenriched **77** can be prepared in a very straightforward manner by partial transfer hydrogenation of racemic atropisomeric naphthyridine **74** with Hantzsch ester **76** as the hydride donor and a chiral phosphoric acid catalyst **75**. At 40°C in THF for 24 h, **77** was obtained in 37% yield and 96% *ee* (Table 4, Entry 1). Interestingly, even when extending the reaction time to 72 h in the presence of an excess of reducing agent **76**, it was difficult to overpass half conversion (Table 4, Entry 2). This could be ascribed to a strong kinetic bias in the presence of catalyst **75** with the matched enantiomer reacting 30 times faster than the mismatched enantiomer. Indeed, when the same reaction conditions were applied separately to enantiopure (*S*)-**74** and (*R*)-**74** with (a*S*)-**75** as catalyst, the expected product was obtained in 42% yield and 99% *ee* in the first case versus 5% yield and 22% *ee* in the second case (Table 4, Entries 3 and 4). Pleasingly, when increasing the temperature to 100°C, the conversion of (*S*)-**74** could be markedly improved with only a minor erosion of the enantioselectivity (Table 4, Entry 5). An interesting property of atropisomers is that they can often interconvert when increasing the temperature. In the case of **74**, interconversion is slow at RT but is complete within 24 h at 100°C. All the aspects discussed above made it possible to envisage a dynamic kinetic resolution process by reacting racemic **74** at 100°C affording both a high yield (82%) of **77** and a good enantioselectivity (88% *ee*) (Table 4, Entry 6).

Very recently, two other methods for kinetic resolution of 1-aryl-2-naphthols have been published (Scheme 19). In the first one, the groups of Xiang Cheng and Can Zhu report a dearomative cyclization of racemic stable atropisomers **78** catalyzed by a Cu-chiral diamine complex (Scheme 19A) [79]. The reaction proceeds by aerobic single electron transfer (SET) onto the



SCHEME 19 | Recent dearomative metal-catalyzed kinetic resolution of 1-aryl-2-naphthols. (A) Cu-catalyzed intramolecular dearomatization, (B) Sc-catalyzed intermolecular dearomatization.

naphthoyl unit, followed by intramolecular trapping of the intermediate radical species by the alcohol function present on the other aromatic ring. The reaction delivered enantioenriched spirocyclic products **79** with moderate to good enantiomeric excess and unreacted atropisomeric starting material **78** with notably higher enantiomeric excesses. Complete mechanistic studies, including EPR analyses, control experiments, and density functional theory calculations helped proposing a suitable mechanism.

In parallel, Yicong Ge, Xin Hong, Jingjing Liu, Xinjun Luan, and coworkers developed an intermolecular Sc-catalyzed dearomatization of configurationally stable functional 1-aryl-2-naphthols **80** (Scheme 19B) [80]. Dichlorohydantoin **81** was used as a half-stoichiometric electrophilic chlorine atom source and PyBox ligand **82** to achieve enantiocontrol. For most examples, high enantiomeric excesses were obtained for both unreacted atropisomeric substrate **80** and dearomatization chlorinated product **83**, in accordance with selectivity factors *S* generally above 100. Substrates bearing additional fuzed rings could also take part in this transformation (not shown). Moreover, in addition to its stereogenic center, compounds **83** also exhibited a strong conformational bias around the bond linking the two cyclic moieties, with equilibrations toward the depicted conformation, which is more than 7 $kcal.mol^{-1}$ more stable than the other one. This observation opened the way for a stereospecific photochemical dechlorinative rearomatization to afford highly enantioenriched *ent*-**80a**.

7 | Summary and Outlook

In this review, we have discussed existing methods for the dearomatization of atropisomers with axial-to-central chirality conversion. They consist in intra- and intermolecular reactions, generally occurring on configurationally stable atropisomers but sometimes also on configurationally labile ones, with different strategies used to ensure obtaining enantioenriched centrally chiral products. This strategy can also appear as an efficient way to access challenging quaternary or tetrasubstituted stereocenters with a good enantiocontrol. Moreover, on a few occasions, it has opened the way to the synthesis of biologically-relevant compounds.

Our general survey of the literature highlights a fundamental difference between intra- and inter-molecular chirality conversion. On the one hand, for intramolecular examples, the molecular constraint of having the reactive function at the origin of the dearomatization tethered to the aromatic ring controls regioselectivity at the *ipso* position providing spirocyclic scaffolds. Moreover, the same phenomenon forces the reaction to occur on one face of the aromatic ring, explaining why very high *cp*'s are observed. On the other hand, intermolecular methods actually showed more variable *cp*'s depending on the atropisomeric precursor and the reaction conditions. However, these intermolecular reactions led to more diversified scaffolds with less rigidity than spirocycles. In addition to this, a handful of chirality conversion cascades (aromatization with central-to-axial chirality conversion followed by dearomatization with axial-to-central chirality conversion, or the reverse) has also been designed.

Nevertheless, despite the fact that the first report of dearomatization of atropisomers with axial-to-central chirality conversion is now 50 years old, the number and variety of such process is still somewhat limited. Moreover, most examples use only three families of precursors: (i) pyridine and pyridinium salts; (ii) BINOL derivatives or related structures; and (iii) crystallized naphthylamides. In the last two decades, both the synthesis of enantioenriched atropisomers and the development of dearomatization reactions have received a renewed interest. Based on these two observations, all the required background seems now present in the literature to envisage a strong development of the sub-field of dearomatization with axial-to-central chirality conversion in the near future.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Biographies

Morgane Mando received her M.Sc in chemistry in 2018 from the University of Strasbourg and her PhD in 2022 from the University of Reims Champagne-Ardenne under supervision of Dr. E. Riguet and Dr. F. Grellepois. She worked on asymmetric allylic alkylation and studied the Aromatic Cope rearrangement. She then joined the group of Prof. X. Bugaut at the University of Strasbourg for postdoctoral research to work on organocatalyzed

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Clément Lemaitre studied chemistry at Aix-Marseille Université and then at the Ecole Nationale Supérieure de Chimie Montpellier. He came back to Aix-Marseille Université to carry out his doctoral research under the supervision of Dr. Xavier Bugaut and Prof. Thierry Constantieux, working on the development of new synthetic methods to access atropisomers by central-to-axial chirality conversion. Following his PhD defense in 2021, he was hired as at Sanofi as a research engineer focusing on the development of new synthetic routes for pharmaceutical active compounds.

Thierry Constantieux completed his PhD at University Bordeaux I under the supervision of Dr. J.-P. Picard and Dr. J. Dunoguez in 1994. In 1995, he was appointed as an assistant professor at University of Aix-Marseille III, completed his habilitation in 2004 and is currently Full Professor of organic chemistry. His main research interest is focused on the development of new eco-compatible synthetic methodologies, especially enantioselective organocatalyzed cascades and domino multicomponent reactions from 1,3-dicarbonyl compounds and their applications in heterocyclic chemistry. Since 2024, he is the director of the "Institut des Sciences Moléculaires de Marseille" (iSm2).

Xavier Bugaut carried out his doctoral work under the supervision of Dr. E. Roulland at the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette. After a postdoctoral stay in the group of Prof. F. Glorius at the Universität Münster (Germany), he was appointed as an assistant professor at Aix-Marseille Université in 2011. Ten years later, he joined the Université de Strasbourg as a full professor and was nominated as a junior fellow of the Institut Universitaire de France in 2022. His current research interests focus on enantioselective organocatalysis, notably its use for the synthesis of atropisomers.