Organocatalytic Dynamic Kinetic Resolution: An Update

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Abstract: This is only in the two last decades that the first examples of organocatalytic dynamic kinetic resolutions (DKRs) have been disclosed. These methodologies allow resolving racemic compounds with up to quantitative yield. Today, a variety of chiral organocatalysts are capable of providing excellent enantioselectivities in many types of transformations evolving through DKR. The goal of this review is to update the field of organocatalytic DKRs since 2016. It is divided into six sections, according to the different types of organocatalysts employed in these reactions, such as Brønsted acid catalysts, hydrogen-bonding catalysts, N-heterocyclic carbene catalysts, Lewis base catalysts, phase-transfer catalysts, and cinchona alkaloid-based Brønsted base catalysts.

1. Introduction

The resolution of racemates still constitutes the most employed methodology to prepare chiral products in industry in spite of the huge expansion of asymmetric synthesis and especially enantioselective catalysis. In a simple kinetic resolution, one enantiomer (S_R) of a racemic mixture is more rapidly transformed into the corresponding chiral product (P_R) while the other (S_S) is recovered unchanged, as illustrated in Figure 1.[1]

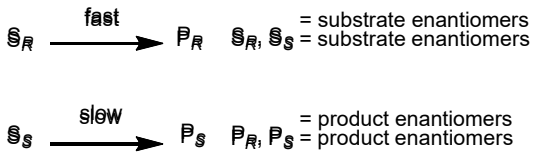


Figure 1. Simple kinetic resolution.

The principal drawback of this methodology is related to the limitation of the yield to 50%. Attempts to overcome this limitation have been undertaken, resulting in the discovery of dynamic kinetic resolution (DKR). Indeed, this methodology allows a quantitative yield of one of the enantiomers to be achieved. Actually, DKR combines the resolution step of a kinetic resolution, with an *in situ* equilibration or racemization of the chirally-labile substrate (Figure 2). The enantiomers of a racemic substrate are induced to equilibrate at a rate that is faster than that of the slow-reacting enantiomer in reaction with the chiral reagent (Curtin–Hammett kinetics). If the enantioselectivity is sufficient, then isolation of a highly enriched non-racemic product is possible with a theoretical yield of 100% based on the racemic substrate. Special requirements have to be fulfilled in order to gain the complete set of advantages of DKR, such as the irreversibility of the resolution step, and the fact that no product racemization should occur under the reaction conditions. In order to obtain products with high enantiopurity, the selectivity (k_{fast}/k_{slow}) of the resolution step should be at least 20. Furthermore, the rate constant for the racemization process (k_{inv}) should be faster than the rate constant of the resolution step (k_{fast}), otherwise a very high selectivity has to be ensured.

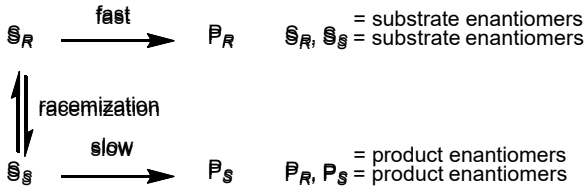


Figure 2. Dynamic kinetic resolution.

Under these conditions, the two starting enantiomers of the racemic mixture can be converted into a single enantiopure product in 100% theoretical yield. The required racemization of the substrate can be performed either chemically, biocatalytically or even spontaneously. However, the conditions must be chosen to avoid the racemization of the formed chiral product. The utility of the DKR is not limited to a selective synthesis of an enantiomer; when the reaction occurs along with the creation of a novel stereogenic center, the stereoselective synthesis of a diastereoisomer is also possible. This powerful concept has been applied to either enzymatic[2] or non-enzymatic reactions.[3] Along with enzymes[2] and metal catalysts,[4] organocatalysts present considerable advantages in addition to be environmentally compatible, since they are non-toxic, inexpensive, robust and often readily available.[5] Especially, their use in the synthesis of drugs is highly appreciated thanks to the exclusion of any trace of hazardous metals in the final products. This type of green catalysts have been applied in the last two decades to describe the first examples of organocatalyzed DKRs, allowing a considerable extension of the synthetic scope of the DKR methodology. In this context, a wide variety of chiral organocatalysts have been successfully investigated in these economic reactions, providing chiral products with very high enantioselectivities.

The goal of this review is to update the field of organocatalytic dynamic kinetic resolution since the beginning of 2016 since this field was most recently reviewed this year.[3m] It must be noted that the same year, a review focusing on DKRs especially promoted by bifunctional (thio)urea- and squaramide-based organocatalysts was published.[6] Moreover, kinetic resolutions, dynamic kinetic resolutions and desymmetrizations catalyzed by N-heterocyclic carbene catalysts were compiled together in two reviews published in 2018 and 2019.[7] The latters only included respectively three and four references ≥2016, concerning N-heterocyclic carbene-catalyzed DKRs. The present review is divided into six sections, according to the different types of organocatalysts employed to promote DKR, such as Brønsted acids, hydrogen-bonding catalysts, N-heterocyclic carbene catalysts, Lewis base catalysts, phase-transfer catalysts, and cinchona alkaloid-based Brønsted base catalysts. In many cases of processes, especially those involving domino reactions, the DKR occurs on intermediates and not directly on starting materials. This review only includes DKRs strictly defined as processes involving reversible racemization of the substrates prior to the selective reaction of one enantiomer with the chiral catalyst.[4k] Closely related dynamic kinetic asymmetric transformations (DyKATs) are not included. The latter also involve an equilibration of substrate enantiomers; however, they differ from DKRs in that a chiral catalyst is responsible for this equilibration.[4k]

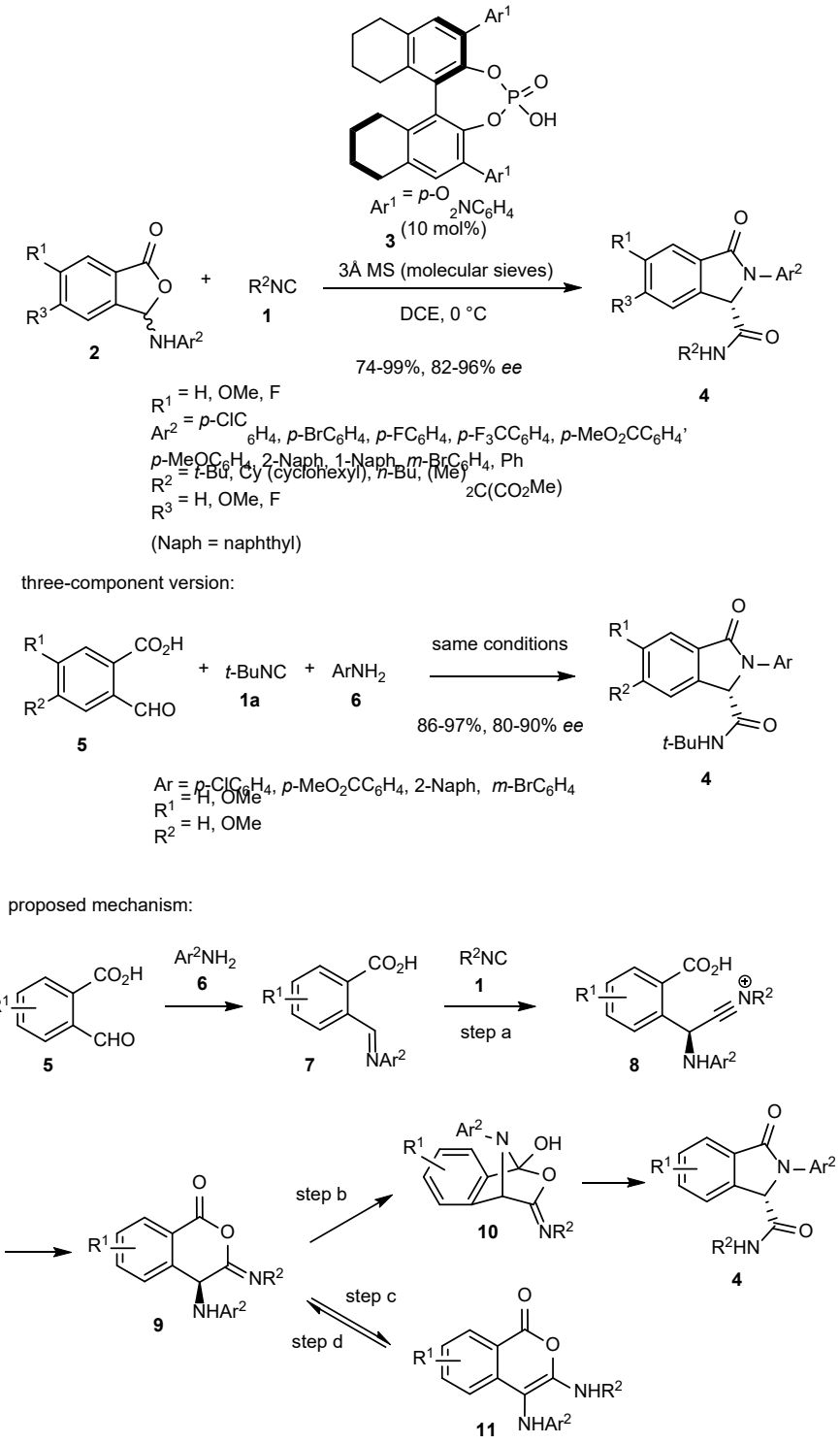
2. Dynamic Kinetic Resolutions Promoted by Brønsted Acid Catalysts

2.1. Domino reactions

Chiral phosphoric acids, often derived from BINOL (1,1'-bi-2-naphthol), have been widely employed as Brønsted acid catalysts in many types of transformations including DKR processes.[8] Among them, many enantioselective organocatalyzed domino reactions[9] have been demonstrated to follow a DKR protocol. In 2006, List et al. reported the first DKR process catalyzed by a chiral phosphoric acid which was derived from BINOL.[10] Excellent enantioselectivities (up to 98% *ee*) combined with high yields (up to 92%) were obtained in these asymmetric reductive aminations of α-branched aldehydes with aromatic amines and Hantzsch esters.

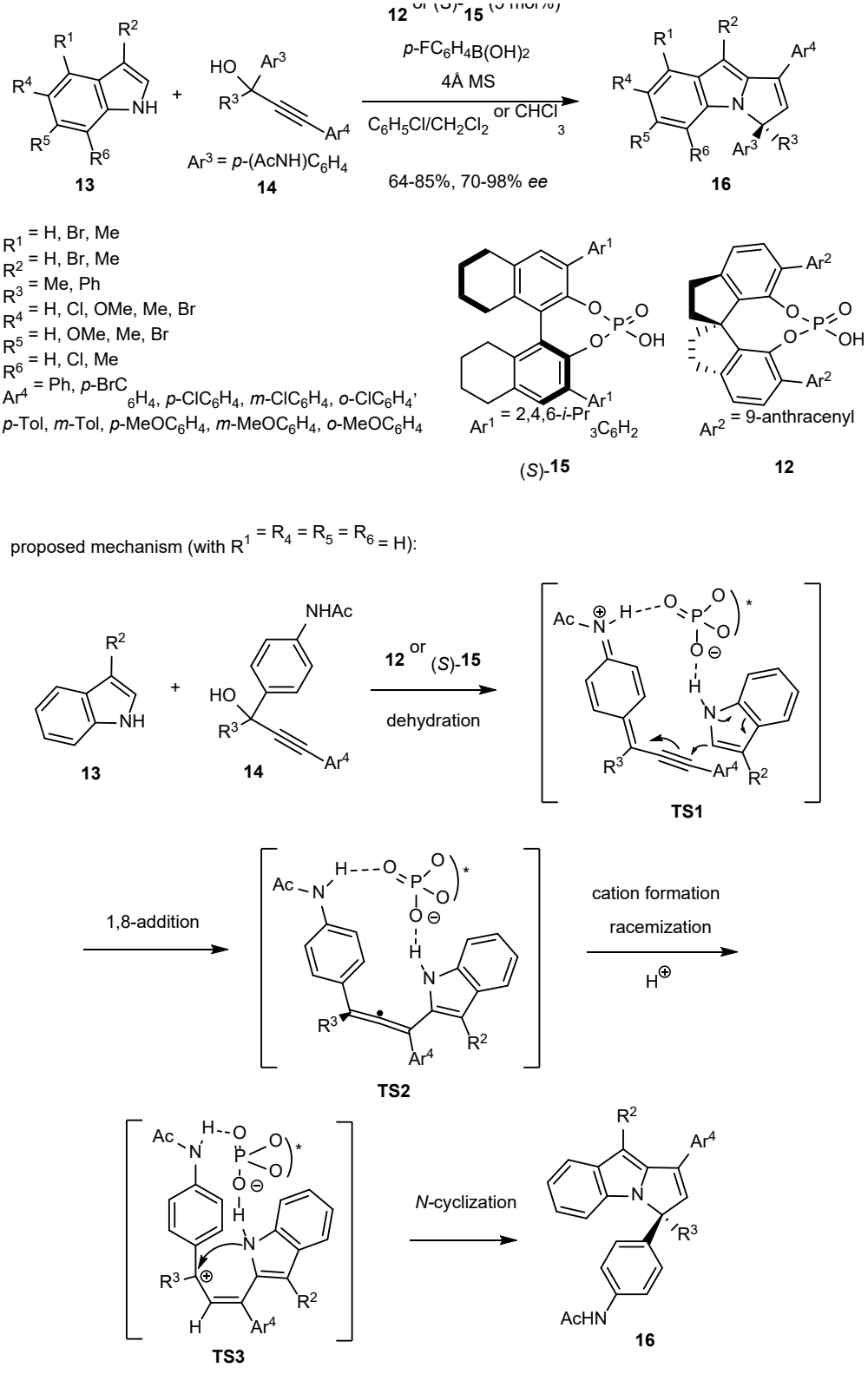
In a more recent example published in 2016 by Wang and Zhu, an enantioselective two-component Ugi-type reaction between isonitriles **1** and 3-(arylamino)isobenzofuran-1(3H)-ones **2** was performed at 0 °C in the presence of 10 mol% of chiral phosphoric acid catalyst **3** in DCE (1,2-dichloroethane) as solvent.[11] As shown in Scheme 1, the process which evolved through DKR afforded the corresponding chiral 3-oxo-2-arylisoindoline-1-carboxamides **4** in both uniformly high yields (74-99%) and enantioselectivities (82-96% *ee*). These heterocyclic compounds represent important products in medicinal chemistry. For example, they constitute the key structural motif in many bioactive products, such as analgesic and anxiolytic drugs (*S*)-(+)-lennoxamine and (*R*)-pazinaclone. As demonstrated by the uniformly excellent results achieved, the catalyst system tolerated the presence of either electron-withdrawing or electron-donating groups (R^1,R^3) on the phenyl ring of substrates **2**. While the presence of electron-poor substituents on the anilines (Ar^2) resulted in excellent ee values (89-94% *ee*), the reaction of an electron-rich aniline (Ar^2 = *p*-$MeOC_6H_4$) afforded the corresponding product with a lower ee value (62% *ee*). Moreover, primary, secondary as well as tertiary alkyl isonitriles were all compatible. On the basis of these excellent results, the authors also developed an unprecedented three-component version of this process, involving 2-formylbenzoic acids **5**, anilines **6** and *tert*-butylisonitrile **1a** as substrates, that led to the same chiral heterocycles **4**. This constituted the first example of an enantioselective Ugi reaction in which a carboxylic acid was incorporated as one of the participating functional groups. In this case, only 3 mol% of the same organocatalyst **3** was sufficient to promote the reaction, which allowed a series of chiral products **4** to be synthesized in both high yields (86-97%) and enantioselectivities (80-90% *ee*). The mechanism proposed by the authors involved the condenzation of

aniline **6** to 2-formylbenzoic acid **5**, leading to iminium salt **7** which subsequently added isonitrile **1** to give nitrilium intermediate **8** (step a). The latter was subsequently trapped by the tethered carboxylate to provide intermediate **9**. Then, rearrangement of **9** via the bridged intermediate **10** (step b) afforded final isoindolinone **4**. In the same time, **9** was submitted to an imine/enamine isomerization (steps c/d) to give isocoumarine **11** through prototropic tautomerization. The fact that this equilibrium was faster than step b was responsible of the DKR.



Scheme 1. Ugi-type reactions.

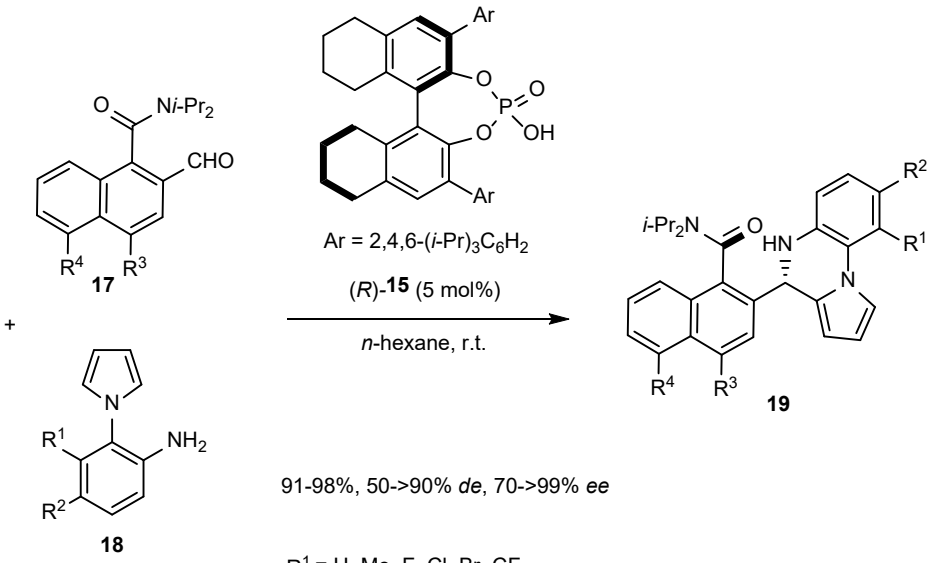
Later in 2020, phosphoric acid catalyst **12** was applied by Li et al. to promote asymmetric formal [3+2] cycloaddition of 3-substituted 1H-indoles **13** with propargylic alcohols **14** exhibiting a NHAc directing group.[12] As shown in Scheme 2, this domino reaction was promoted at room temperature (r.t.) by 5 mol% of chiral phosphoric acid **12** in a mixture of dichloromethane and chlorobenzene as solvent or by the same quantity of other chiral phosphoric acid (*S*)-**15** employed in chloroform as solvent, according to the substrates used. The corresponding chiral pyrrolo[1,2-a]indoles **16** were obtained through DKR of the allene intermediates in both good to high yields (64-85%) and enantioselectivities (70-98% *ee*). A possible mechanism is depicted in Scheme 2, beginning with the *in situ* dehydration of propargylic alcohol **14** which generated in the presence of the chiral catalyst the corresponding aza-*p*-quinone methide shown in transition state **TS1**. In the latter, the organocatalyst activated both this aza-*p*-quinone methide and 3-substituted 1H-indole **13** through hydrogen bonding. Due to the steric hindrance of the aza-*p*-quinone methide at the 6-position, a 1,8-addition of the C2-position of indole **13** occurred, resulting in the formation of the corresponding chiral tetrasubstituted allene (**TS2**). Finally, the hydrogen-bonded chiral allene was protonated to give a benzylic cation (**TS3**) which underwent intramolecular *N*-cyclization to afford the final product. The presence of the NH moiety in the propargylic alcohol was crucial, since it accelerated the dehydration of the propargylic alcohol and also interacted with the catalyst to control the stereoselectivity of the DKR of the allene intermediate.



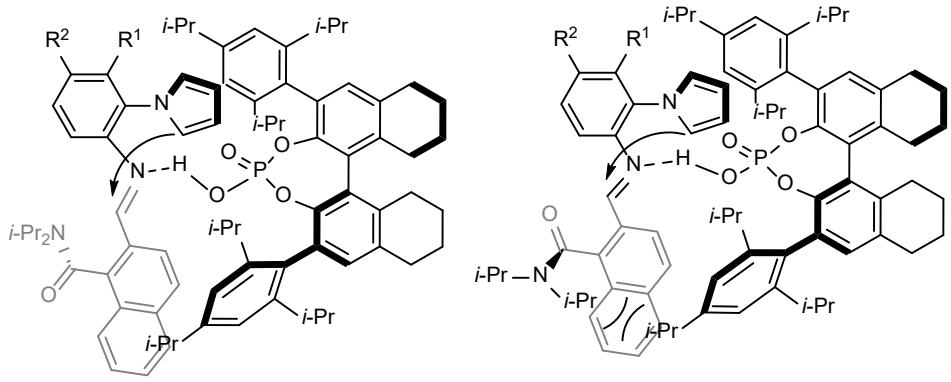
Scheme 2. Domino dehydration/1,8-addition/protonation/*N*-cyclization reaction of 3-substituted 1H-indoles with propargylic alcohols.

In the same year, Hang, Zhang and Jiang reported the first readily scalable phosphoric acid-catalyzed enantioselective domino imine formation/cyclization reaction of simple atropisomeric *ortho*-formyl naphthamides **17** with pyrrolylanilines **18** evolving through DKR.[13] The process performed at room temperature in hexane as solvent was promoted by 5 mol% of chiral phosphoric acid (*R*)-**15**, resulting in the formation of the corresponding chiral pyrrolopyrazines **19** with uniformly

excellent (91-98%) combined with good to very high enantioselectivities (70->99% *ee*) and moderate to excellent diastereoselectivities (50->90% *de*), as presented in Scheme 3. This strategy installed simultaneously a chiral axis, a stereogenic center and a nitrogen-containing heterocycle into an atropisomeric amide to form a new family of potentially biologically active pyrrolopyrazine products. The presence of either electron-deficient or electron-rich substituents at the 2- (R^1) or 3-position (R^2) of the aromatic rings of the pyrrolylanilines was tolerated, providing comparable results. Concerning the scope of the naphthamide partner, the presence of a methyl or a fluorine substituent at the 4-position (R^3 = Me, F) was compatible. Moreover, the reaction of a 1,2-dihydroacenaphthylene-1-aldehyde (R^3,R^4 = $(CH_2)_2$) led to the corresponding product with 98% yield, 82% *de* and 96% *ee*. The DKR process evolved through imine formation followed by nucleophilic addition of the pyrrole to this imine unit in the presence of the organocatalyst. The chiral phosphoric acid could have chiral recognition for each step in the cascade reaction with the synergistic effect beneficial to the final enantioselectivity. To explain the stereoselectivity of the reaction, the authors postulated the catalytic transition state TS-A depicted in Scheme 3. Theoretically, the latter should be more favorable than transition state TS-B in which larger steric impulsion existed between the *N*-isopropyl groups and the catalyst skeleton. On the other hand, the addition of the pyrrole to the intermediate imine would take place from the *anti*-face of the isopropyl groups with lower steric hindrance.



proposed transition states (R^3 = R_4 = H):

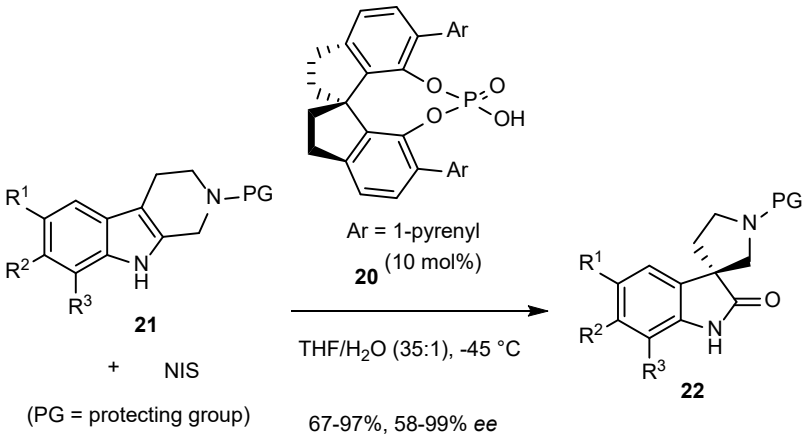


favored transition state TS-A

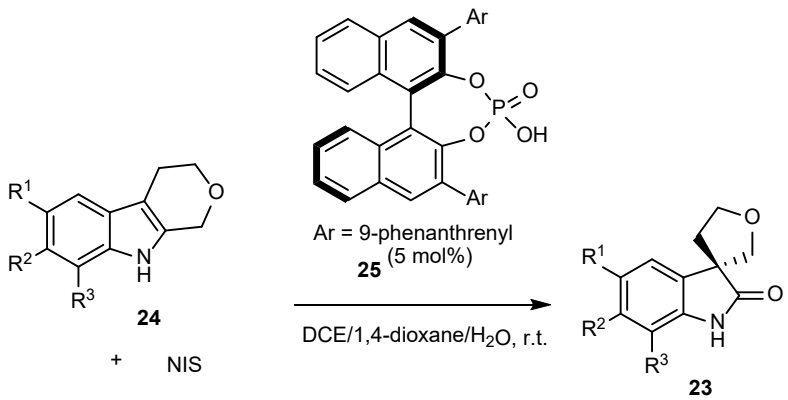
disfavored transition state TS-B

Scheme 3. Domino imine formation/cyclization reaction of *ortho*-formyl naphthamides with pyrrolylanilines.

In 2021, Sun and Li developed an enantioselective oxidative rearrangement of indoles into oxindoles catalyzed by chiral phosphoric acids.[14] This domino iodination/nucleophilic addition/rearrangement reaction allowed a rapid access to a variety of chiral spirooxindoles. It employed *N*-iodosuccinimide (NIS) as the oxidant and a suitable chiral phosphoric acid as the catalyst. For example, in the presence of 10 mol% of catalyst **20** in a mixture of THF (tetrahydrofuran) and water as solvent, a range of tetrahydro-β-carbolines **21** reacted at -45 °C with NIS to form the corresponding chiral pyrrolidinyl-spirooxindoles **22** with good to quantitative yields (67-97%) and generally excellent enantioselectivities (58-99% *ee*), as presented in Scheme 4. The presence of various substituents on the indole ring did not affect the excellent outcome of the reaction since all the ee values were ≥89% *ee* excepted for a substrate bearing a methyl group in R^3. The lowest enantioselectivity (58% *ee*) obtained in the reaction of this indole was probably related to an interference of the adjacent methyl substituent with hydrogen bond interaction in the N1 position. The catalyst system also tolerated diverse functional groups, including aryl halide, ether, silyl-protected alcohol, and ester. Moreover, different *N*-protective groups were also suitable. An extension of this methodology also provided access to analogous chiral tetrahydrofuranyl-spirooxindoles **23** from the corresponding indoles **24**, which constitute another important core found in many bioactive molecules. In this case, the best results were obtained by catalyzing the domino process at room temperature with 5 mol% of related chiral phosphoric acid **25** in a mixture of DCE, 1,4-dioxane and water as the solvent. As shown in Scheme 4, a range of chiral tetrahydrofuranyl-spirooxindoles **23** were synthesized in both high yields (72-90%) and enantioselectivities (74-87% *ee*).



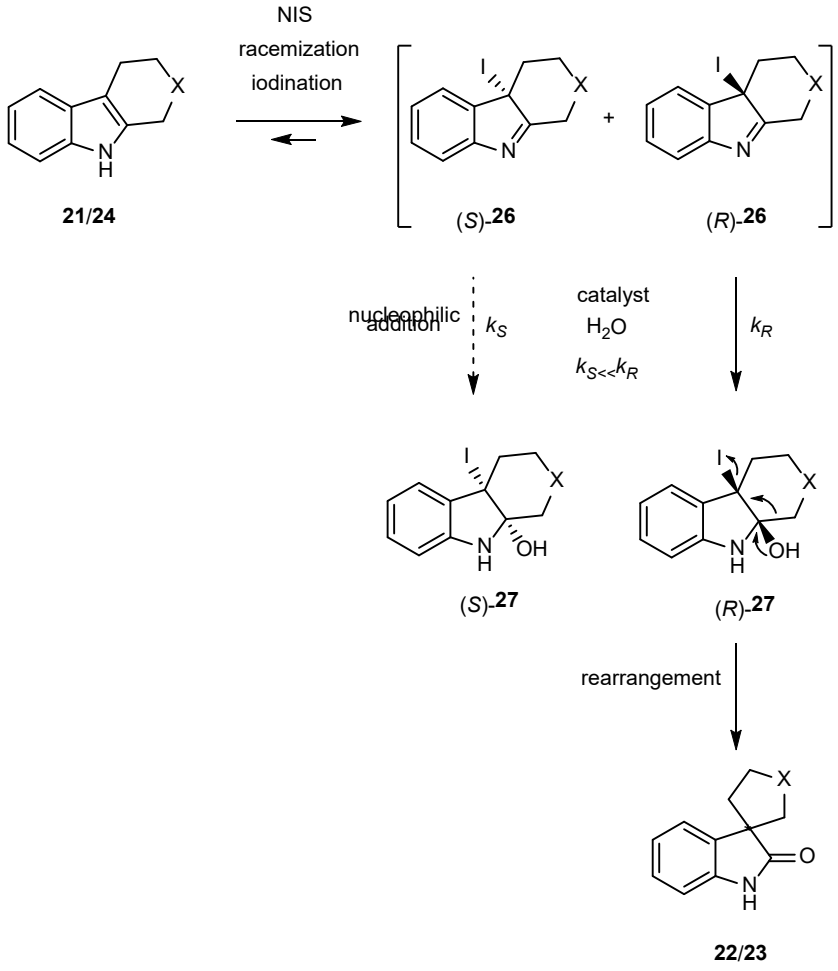
PG = Boc, Ts, Fmoc (9-fluorenylmethoxycarbonyl), Bz (benzoyl), CO_2Me
R^1 = H, Cl, Me, OMe, OBn, OTIPS (TIPS = triisopropylsilyl), OAc
R^2 = H, F
R^3 = H, Me



R^1 = H, F
R^2 = H, CF
R^3 = H, Me, CN

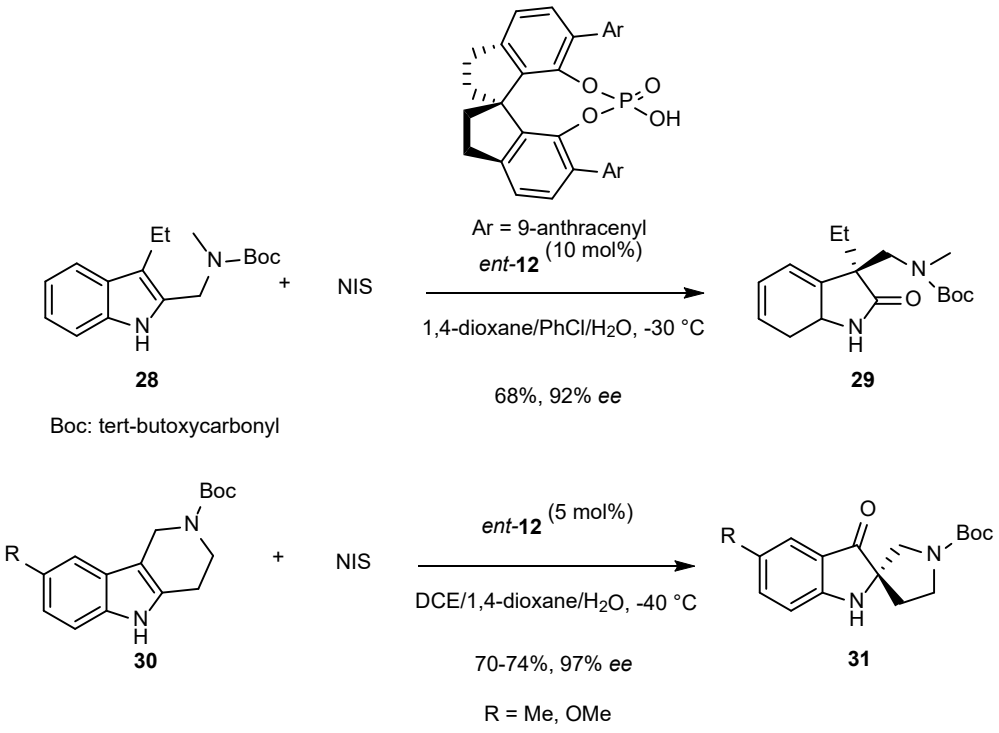
Scheme 4. Domino iodination/nucleophilic addition/rearrangement reactions of indoles with NIS.

As depicted in Scheme 5, the precedent methodology began with the rapid and reversible iodination in the 3-position of indoles **21**/**24**, leading to racemic intermediates **26**.[14] Then, nucleophilic addition of water to the imine motif of **26** generated hemiaminals **27**. The chiral phosphoric acid was supposed to interact as a bifunctional catalyst activating both imine **26** and water. Thus, the two enantiomers of **26** reacted in different rates owing to chiral recognition by the catalyst, with (*R*)-**26** being much faster that (*S*)-**26**. The slow reacting (*S*)-**26** then racemizes via reversible halogenation, thereby allowing a DKR scenario. Finally, the predominant (*R*)-**27** isomer underwent a 1,2-migration to form the enantioenriched final oxindole products **22**/**23**.

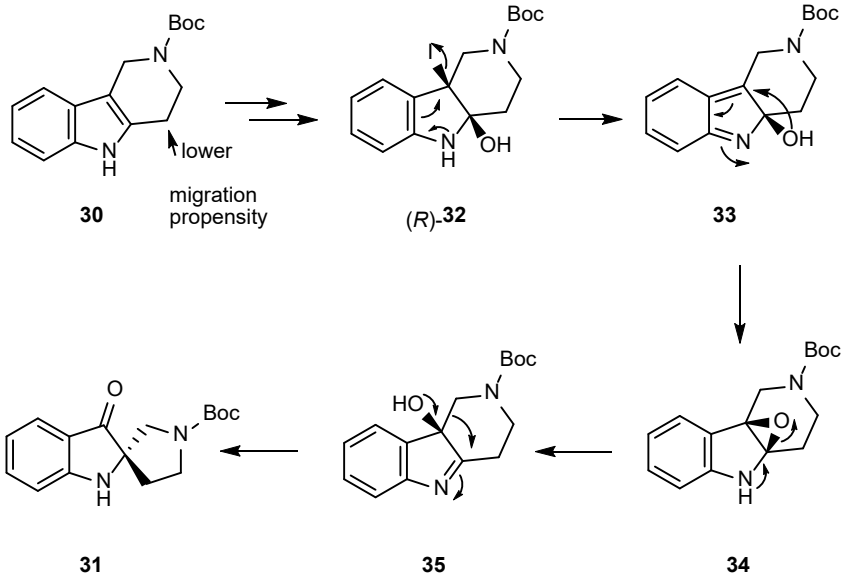


Scheme 5. Mechanism for domino iodination /nucleophilic addition/rearrangement reactions of indoles with NIS.

In addition, another chiral catalyst *ent*-**12** was applied by the same authors to promote the domino iodination/nucleophilic addition/rearrangement reaction of indole **28**.[14] This afforded by reaction with NIS at -30 °C in the presence of 10 mol% of chiral phosphoric acid *ent*-**12** the corresponding chiral oxindole **29** in 68% yield and 92% *ee* (Scheme 6). On the other hand, a distinct selectivity control was observed in the domino reaction of indoles **30**, which resulted in the formation of chiral products **31** arisen from a ring fusion at the 2-position. This inverted rearrangement could be related to the fact that the heteromethyl substituent had a higher propensity to migrate. These chiral products **31** were obtained in good yields (70-74%) and 97% *ee* (Scheme 6). To explain the inverted rearrangement of substrate **30** in which the 3-substituent had a higher migration propensity, the authors assumed that the first few steps followed the same pathway to hemiaminal (*R*)-**32** (Scheme 6). Owing to the low migration ability of the 2-substituent, it cyclized to form epoxide **33**, presumably via azaquinone methide **34**. Subsequent epoxide ring-opening assisted by the amine lone pair generated 3-hydroxy indolenine **35**. Finally, a semi-pinacol type rearrangement afforded final product **31**.



mechanism for the formation of **31** (R = H):

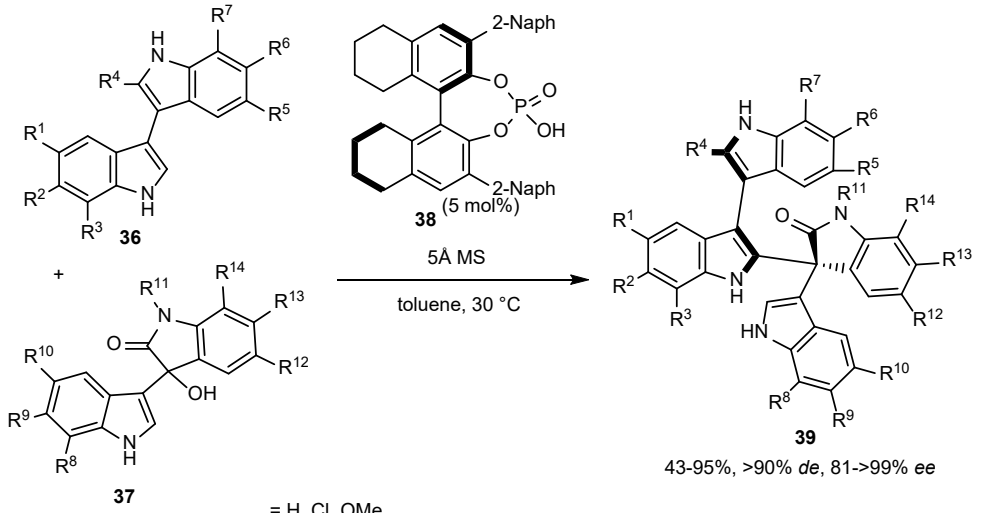


Scheme 6. Domino iodination /nucleophilic addition/rearrangement reactions of other indoles with NIS.

2.2. Coupling reactions

The 3,3'-bisindole skeleton is present in many biologically important products, making their synthesis challenging. In 2019, Shi et al. described the first asymmetric synthesis of chiral 3,3'-bisindoles exhibiting both axial and central chirality on the basis of a DKR process.[15] It involved an asymmetric nucleophilic addition of 2-substituted 3,3'-bisindoles **36** to isatin-derived 3-indolylmethanols **37** promoted at 30 °C in toluene as solvent by 5 mol% of chiral phosphoric acid **38**. The reaction afforded the corresponding chiral 3,3'-bisindoles **39** as almost single diastereomers (>90% *de*) with moderate to quantitative yields (43-95%) and uniformly high enantioselectivities (81->99% *ee*), as illustrated in Scheme 7. It was based

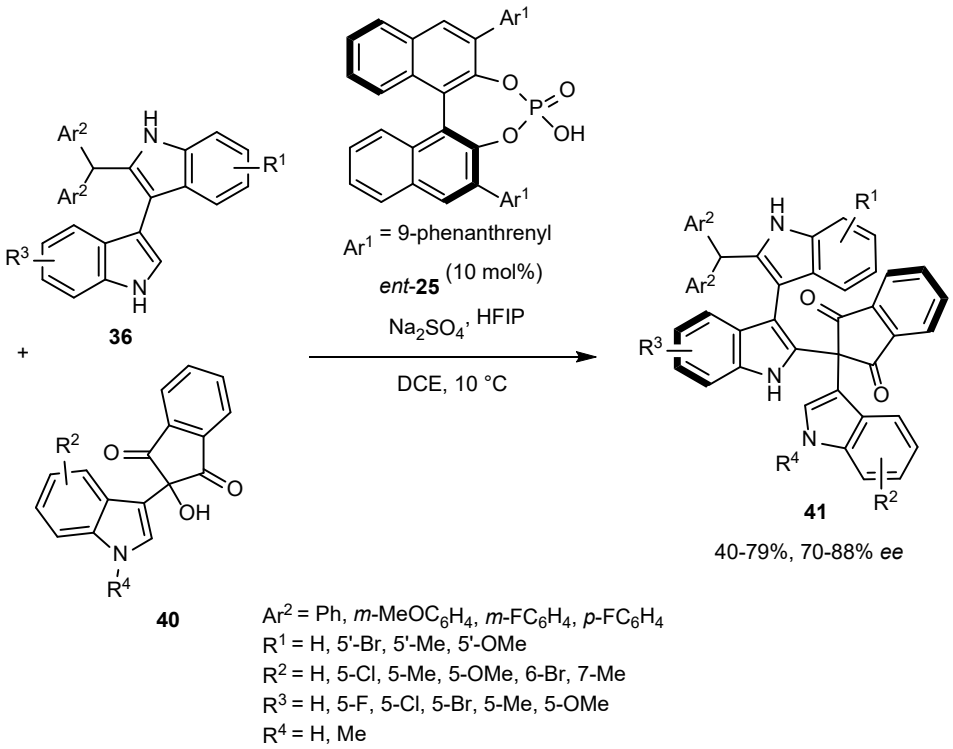
on a strategy of introducing a bulky group to the *ortho*-position (R^4) of prochiral 3,3'-bisindoles **36** for generating axial chirality. When this substrate added to a bulky electrophile, such as 3-indolylmethanol **37**, in the presence of chiral organocatalyst **38**, an axially chiral 3,3'-bisindole skeleton was generated as a result of the steric congestion between the two bulky 2,2'-substituents around the axis.



R^1 = H, Cl, OMe
R^2 = H, Cl, OMe
R^3 = H, Me
R^4 = Ph$_2$CH, (*p*-FC_6H_4)$_2$CH, (*p*-*t*-BuC_6H_4)$_2$CH, (*p*-Tol)$_2$CH, (*m*-FC_6H_4)$_2$CH, (*o*-Tol)$_2$CH, (*m*-$MeOC_6H_4$)$_2$CH
R^5 = H, Cl, OMe
R^6 = H, Br, OMe
R^7 = H, Br
R^8 = H, F, Me
R^9 = H, F
R^{10} = H, OMe, F, Cl
R^{11} = Bn, Ph, Me, H
R^{12} = H, OMe, Me
R^{13} = H, Br, OMe
R^{14} = H, F, Me

Scheme 7. Coupling reaction of 2-substituted 3,3'-bisindoles with isatin-derived 3-indolylmethanols.

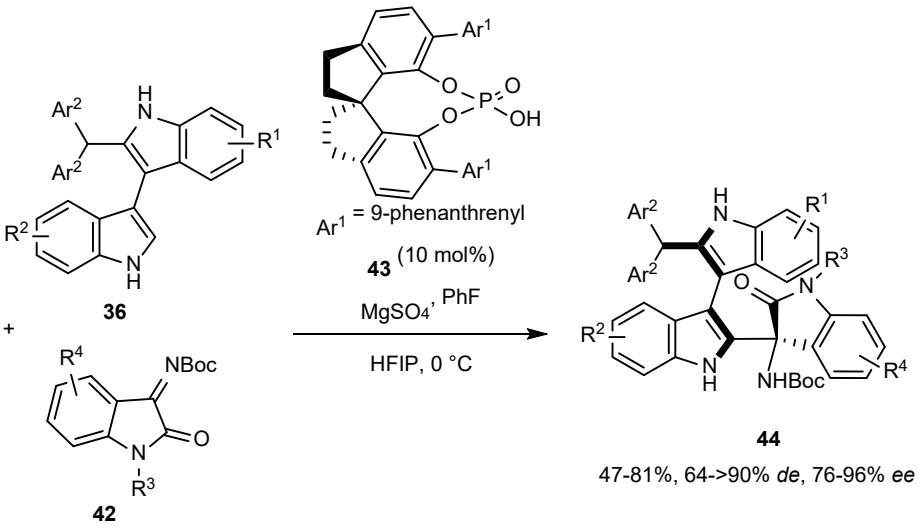
Later in 2020, the same authors employed another types of electrophiles, such as ninhydrin-derived 3-indolylmethanols **40**, in related reactions.[16] As illustrated in Scheme 8, the coupling of these electrophiles with a series of 2-substituted 3,3′-bisindoles **36** was promoted at 10 °C by 10 mol% of chiral phosphoric acid *ent*-**25** in DCE as solvent, resulting in the formation of the corresponding complex products **41** exhibiting single axial chirality with moderate to high yields (40-79%) and good to high enantioselectivities (70-88% *ee*).



Ar^2 = Ph, *m*-$MeOC_6H_4$, *m*-FC_6H_4, *p*-FC_6H_4
R^1 = H, 5'-Br, 5'-Me, 5'-OMe
R^2 = H, 5-Cl, 5-Me, 5-OMe, 6-Br, 7-Me
R^3 = H, 5-F, 5-Cl, 5-Br, 5-Me, 5-OMe
R^4 = H, Me

Scheme 8. Coupling reaction of 2-substituted 3,3'-bisindoles with ninhydrin-derived 3-indolylmethanols.

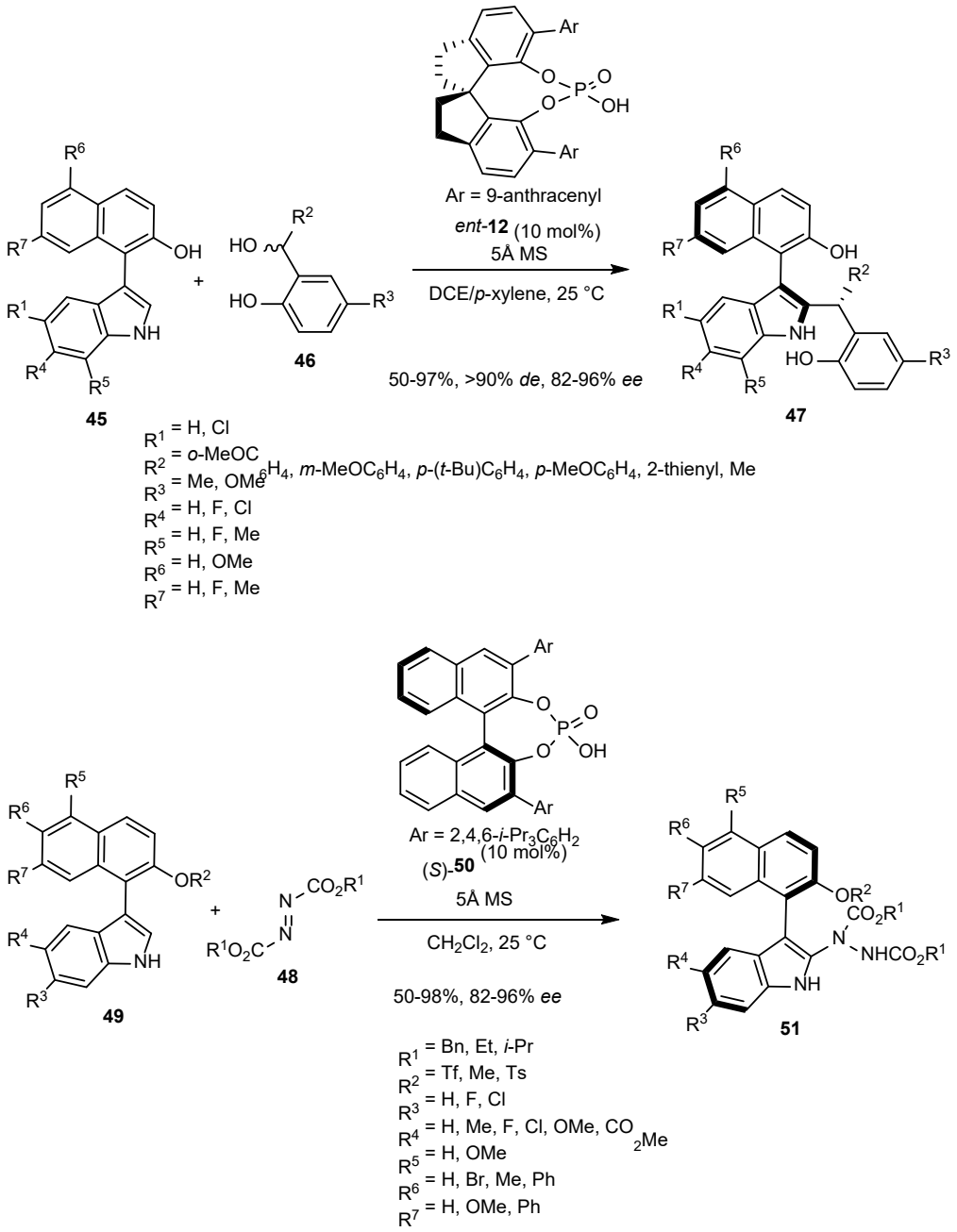
In the same year, these authors also developed coupling reaction between 2-substituted 3,3'-bisindoles **36** and isatin-derived imines **42**.[17] In this case of electrophiles, the optimal organocatalyst was found to be chiral phosphoric acid **43** employed at 10 mol% of catalyst loading in hexafluoroisopropanol (HFIP) as solvent (Scheme 9). The DKR process performed at 0 °C allowed the atroposelective synthesis of a new class of biologically interesting 3,3'-bisindoles **44** with axial and central chirality to be achieved. The presence of various substituents on the phenyl rings of both the two substrates was tolerated. Indeed, a range of highly functionalized complex chiral products **44** were produced with good yields (47-81%), moderate to high diastereoselectivities (64->90% *de*) and good to excellent enantioselectivities (76-96% *ee*).



Ar^2 = Ph, *p*-FC_6H_4, *m*-FC_6H_4, *p*-Tol, *m*-Tol, *o*-Tol
R^1 = H, 7-Br, 6-Cl, 6-OMe, 5-Cl, 5-Me
R^2 = 5'-OMe, 6'-Me, 7'-Me
R^3 = Bn, Me, allyl, Ph
R^4 = H, 7-Cl, 6-Br, 6-OMe, 5-Cl, 5-Me

Scheme 9. Coupling reaction of 2-substituted 3,3'-bisindoles with isatin-derived imines.

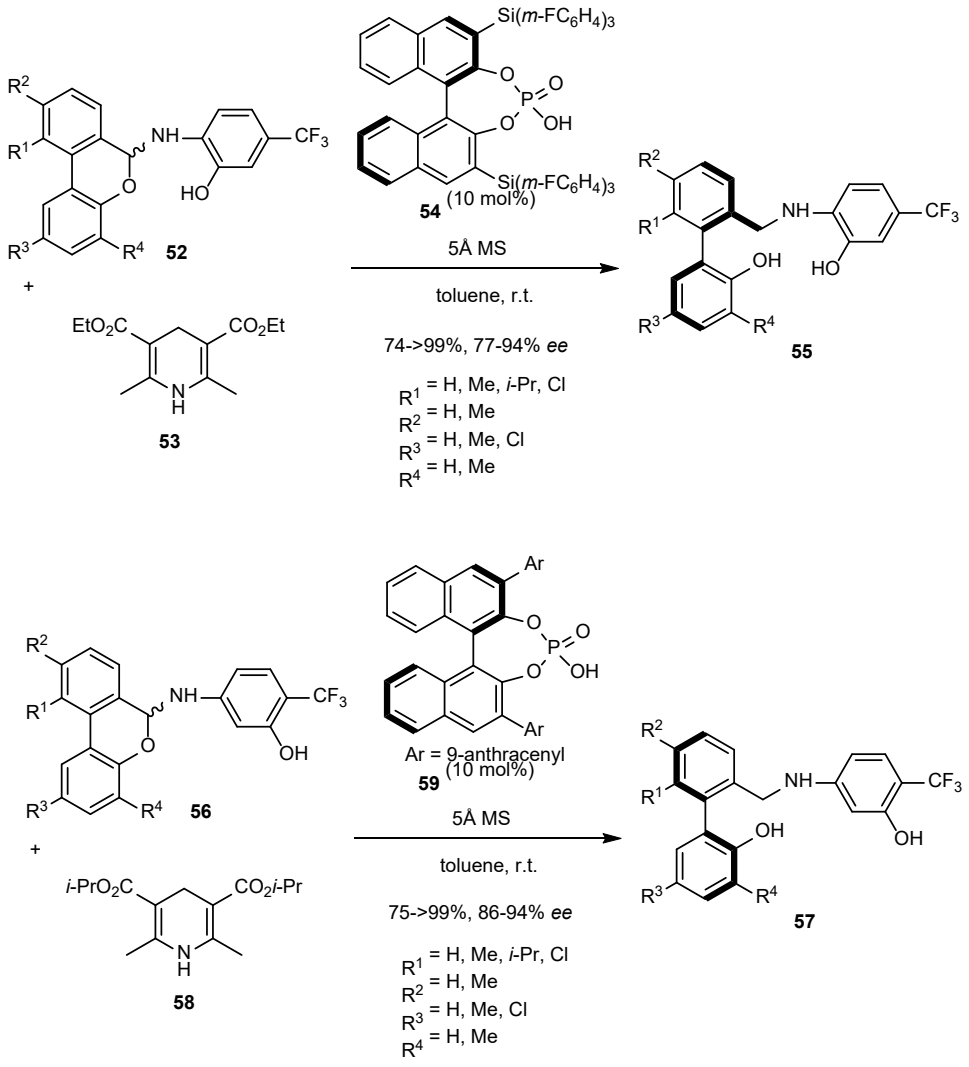
In addition, the same authors applied in 2019 a related methodology to synthesize axially chiral naphthyl-indoles.[18] The latter arose from the asymmetric nucleophilic addition of the corresponding naphthyl-indoles **45** to bulky electrophiles, such as *o*-hydroxybenzyl alcohols **46**, catalyzed by 10 mol% of chiral phosphoric acid *ent*-**12** in a mixture of DCE and *p*-xylene as the solvent (Scheme 10). The DKR process resulted in the formation of a series of axially chiral naphthyl-indoles **47** as almost single diastereomers (>90% *de*) with moderate to quantitative yields (50-97%) and uniformly high enantioselectivities (82-96% *ee*). Furthermore, another type of electrophiles, such as azodicarboxylates **48**, was successfully investigated in related coupling reactions with other naphthyl-indoles **49** (Scheme 10). In this case, the optimal organocatalyst was chiral phosphoric acid (*S*)-**50** employed at the same catalyst loading albeit in dichloromethane as solvent. The resulting axially chiral naphthyl-indoles **51** were thus synthesized with moderate to excellent yields (50-98%) and high enantioselectivities (82-96% *ee*).



Scheme 10. Coupling reactions of naphthyl-indoles with *o*-hydroxybenzyl alcohols/azodicarboxylates.

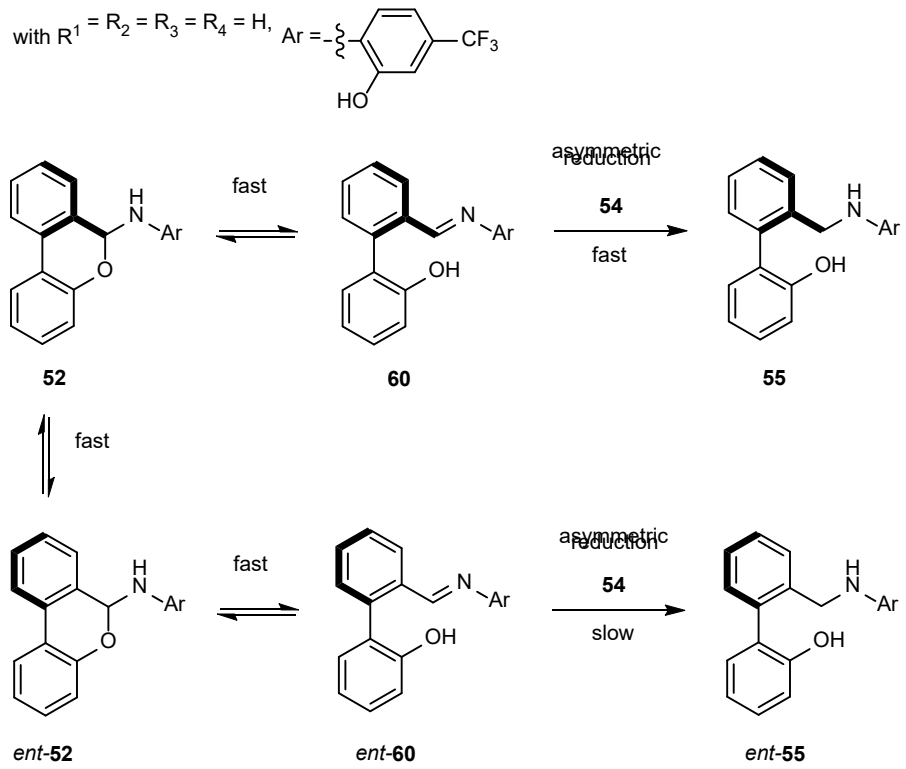
2.3. Transfer hydrogenations

In 2016, Akiyama et al. reported the use of chiral phosphoric acids to promote asymmetric transfer hydrogenations of biaryl lactols with aromatic amines and Hantzsch esters, allowing a novel route to chiral biaryls through DKR.[19] As shown in Scheme 11, the reductive amination of biaryl lactols **52** with Hantzsch ester **53** catalyzed by 10 mol% of organocatalyst **54** led to the corresponding chiral biaryls **55** with both high enantioselectivities (77-94% *ee*) and yields (74->99%). A remarkable feature of this reductive amination reaction was that the atroposelectivity of the formed products was controlled by the choice in the hydroxyaniline moieties of the starting biaryl lactol substrates. Indeed, whereas using *o*-hydroxyaniline derivatives **52** yielded by reaction with Hantzsch ester **53** the corresponding chiral biaryls **55** in favor of the (*R*)-isomers, the use of the *m*-hydroxyaniline derivatives **56** reversed the atroposelectivity of the reaction to provide the corresponding (*S*)-isomers **57** with both high yields (75->99%) and enantioselectivities (86-94% *ee*) by reaction with Hantzsch ester **58**. In the synthesis of (*R*)-products **55**, the optimal catalyst was found to be **54** while the best results achieved in the synthesis of (*S*)-products **57** were obtained by using catalyst **59**. These enantiodivergent atroposelective syntheses of chiral biaryls were performed at room temperature in toluene as solvent in the presence of 10 mol% of catalyst **54** or **59**.



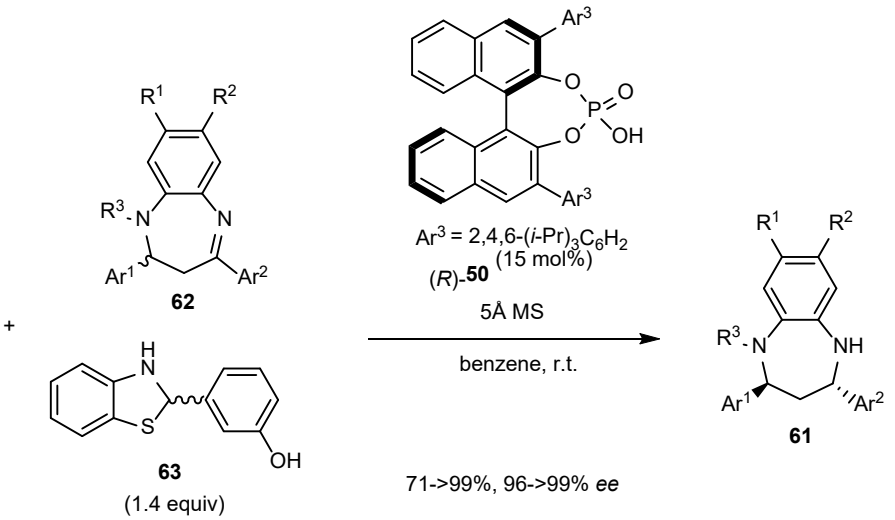
Scheme 11. Transfer hydrogenations of biaryl lactols with aromatic amines and Hantzsch esters.

The DKR process depicted in Scheme 11, leading to biaryls **55**, arose from the ring-opening/ring-closing equilibrium between biaryl *N,O*-acetal **52** and biaryl imine **60**, allowing racemization. Then, a faster subsequent asymmetric transfer hydrogenation of **60** led preferentially to chiral biaryls **55** (Scheme 12).



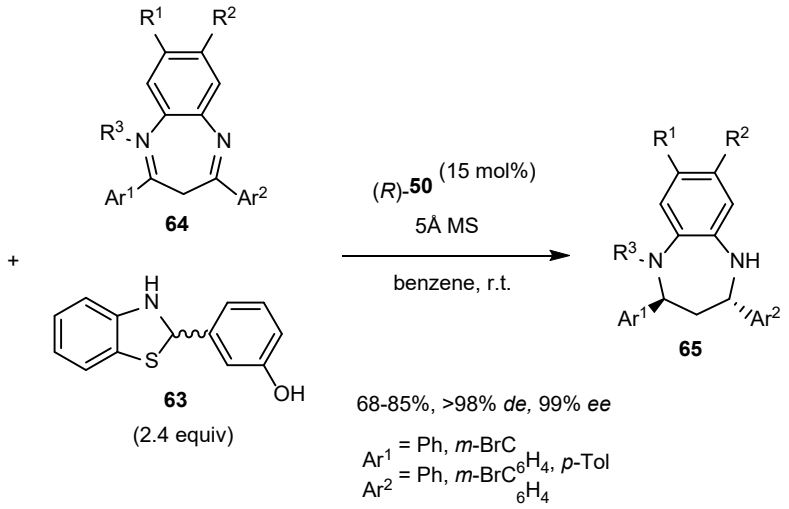
Scheme 12. Mechanism for reductive amination of biaryl lactols.

In 2016, the same authors also described a novel asymmetric synthesis of 2,4-diaryl-1,5-tetrahydrobenzodiazepines **61** achieved by transfer hydrogenation of the corresponding dihydrobenzodiazepines **62** with benzothiazoline **63** as a hydrogen donor evolving through DKR (Scheme 13).[20] Remarkable results were obtained by using 15 mol% of chiral phosphoric acid (*R*)-**50** as catalyst in benzene at room temperature since the products were formed as single enantiopure (96->99% *ee*) *trans*-diastereomers (>98% *de*) in good to quantitative yields (71->99%), as illustrated in Scheme 13. The catalyst system tolerated the presence of various substituents on the aryl groups at the 2,4-positions, including trifluoromethyl and methoxy groups. Moreover, the introduction of a functional group on the fused phenylene ring (R^1 = OMe, Me, R^2 = Me) also led to highly diastereo- and enantioselective transfer hydrogenation, giving the corresponding tetrahydrobenzodiazepines in good yields (95-97%) with excellent enantioselectivities (95-99% *ee*). In addition, the reaction of a *N*-methylated tetrahydrobenzodiazepine (R^3 = Me) also provided excellent results (97% yield, 98% *ee*). The DKR process required the racemization of the starting benzodiazepine derivatives which proceeded through retro-Michael/Michael reactions, as depicted in Scheme 13.



Scheme 13. Transfer hydrogenation of dihydrobenzodiazepines with a benzothiazoline.

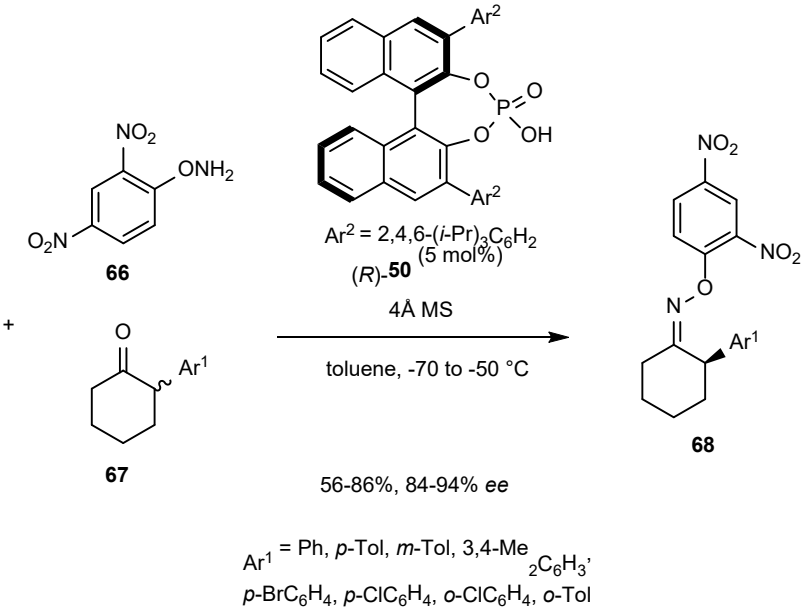
As an extension of the precedent work, these authors investigated the asymmetric transfer hydrogenation of benzodiazepines **64**.[20] Under the same reaction conditions, the latter reacted with 2.4 equivalents of benzothiazoline **63** to give the corresponding enantio- (99% *ee*) and diastereopure (>98% *de*) 2,4-diaryl-tetrahydrobenzodiazepines **65** in good to high yields (68-85%), as shown in Scheme 14. However, 2,4-dialkyl-tetrahydrobenzodiazepines did not react under similar reaction conditions. It must be noted that this result could also be situated in Section 2.1 dealing with enantioselective domino reactions.



Scheme 14. Transfer hydrogenation of benzodiazepines with a benzothiazoline.

2.4. Other reactions

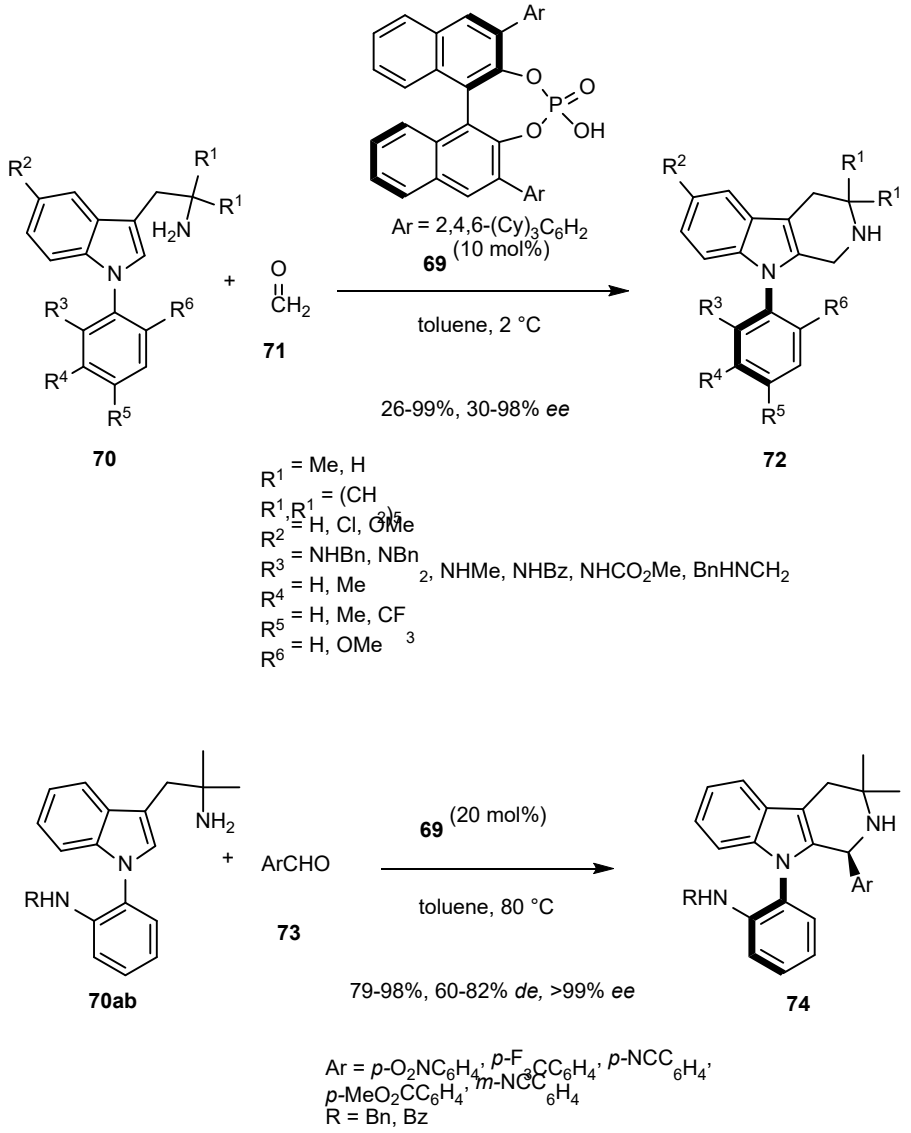
Inspired by the work reported in 2010 by List et al., dealing with asymmetric reductive amination of α-substituted cyclohexanones with *p*-anisidine through DKR catalyzed by a chiral BINOL-derived phosphoric acid,[21] Antilla et al. investigated in 2017 related reactions by using *O*-phenylhydroxylamine **66** as the nucleophilic partner.[22] Therefore, the reaction of a range of α-substituted cyclohexanones **67** with *O*-phenylhydroxylamine **66** performed in toluene at low temperature (-70 to -50 °C) in the presence of 5 mol% of chiral phosphoric acid (*R*)-**50** allowed the corresponding chiral cyclohexylidene oxime ethers **68** to be synthesized in good to high yields (56-86%) and uniformly high enantioselectivities (84-94% *ee*). As presented in Scheme 15, electron-donating groups as well as electron-withdrawing groups were tolerated as substituents on the cyclohexanone moiety.



Scheme 15. Arylhydroxylimination of α-substituted cyclohexanones with an *O*-phenylhydroxylamine.

In 2021, Kwon et al. investigated for the first time atroposelective Pictet–Spengler cyclizations of *N*-arylindoles (Scheme 16).[23] Employing 10 mol% of chiral phosphoric acid **69** as organocatalyst in toluene as solvent allowed the atroposelective Pictet–Spengler reaction of variously substituted *N*-arylindoles **70** with formaldehyde **71** to be achieved,

leading to the corresponding chiral *N*-aryltetrahydro-β-carbolines **72** with low to quantitative yields (26-99%) and variable enantioselectivities (30-98% *ee*). Actually, the ee values were generally excellent (≥92% *ee*) excepted in the reaction of four substrates. Among them, a dibenzyl-substituted *N*-arylindole ($R^3 = NBn_2$, Bn = benzyl) reacted with only 56% *ee* and a methyl carbamate ($R^3 = NHCO_2Me$) with 76% *ee*. The lowest enantioselectivity (30% *ee*) was observed in the cyclization of a substrate exhibiting an additional methyl substituent (R^4 = Me) on the bottom arene ring presumably due to unfavorable steric repulsion with the catalyst. It was found that an homologated benzylamine substrate ($R^3 = CH_2NHBn$) also provided the desired product albeit with a moderate enantioselectivity (70% *ee*). The authors showed that by using a higher catalyst loading (20 mol%) as well as a higher reaction temperature (80 °C), the methodology could be applied to the reaction with benzaldehydes (Scheme 16). Indeed, a variety of benzaldehydes **73** bearing different electron-withdrawing substituents on the phenyl ring reacted with *N*-arylindoles **70ab** to give the desired enantiopure (>99% *ee*) products **74** in high yields (79-98%) and moderate to high diastereoselectivities (60-82% *de*). Given the biological significance of β-carboline derivatives, especially as potential anticancer agents, the thus-formed products were submitted to a biological evaluation which showed an antiproliferative activity.



Scheme 16. Pictet–Spengler reactions of *N*-arylindoles with aldehydes.

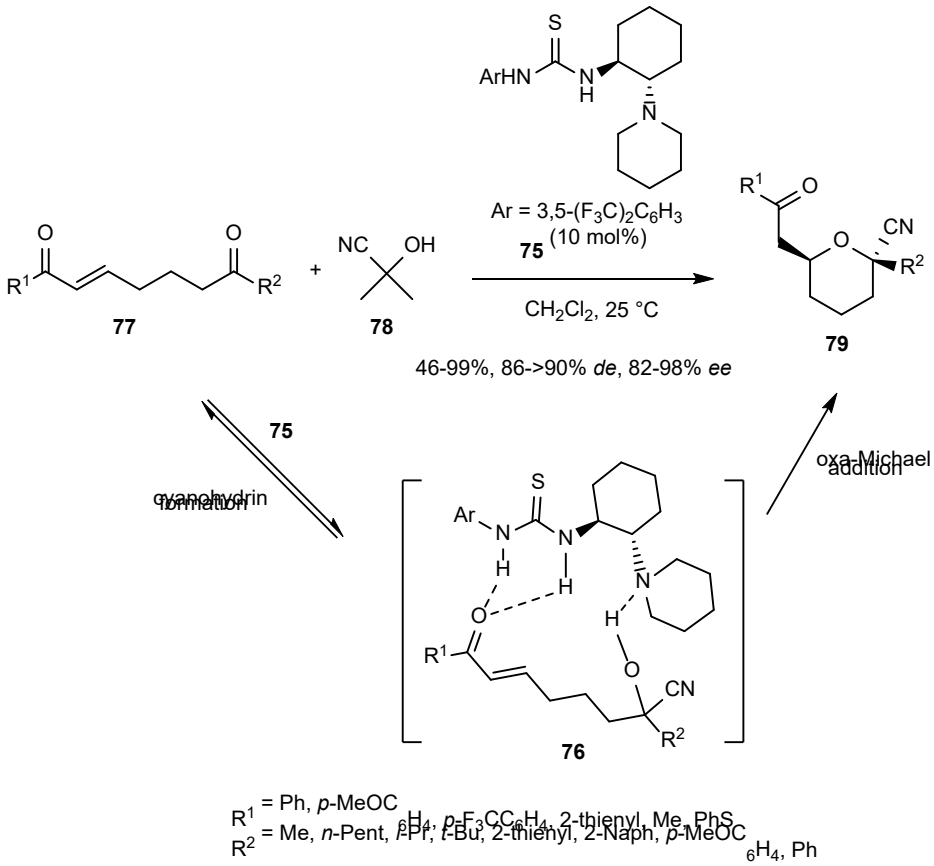
3. Dynamic Kinetic Resolutions Promoted by Hydrogen-Bonding Catalysts

3.1. (Thio)urea catalysts and derivatives

3.1.1. Domino reactions

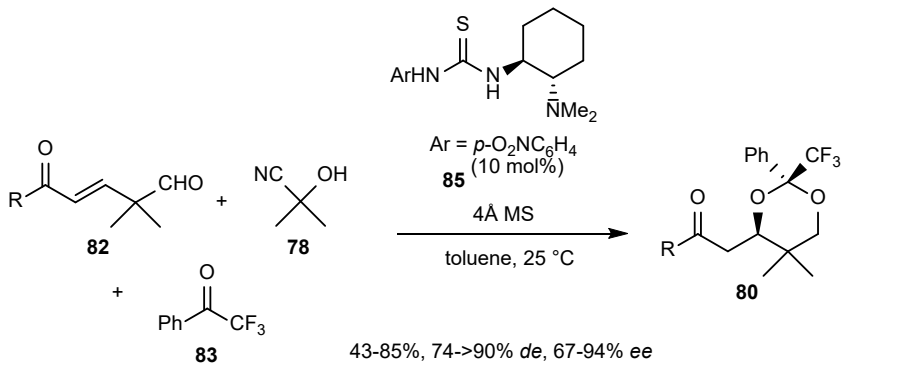
Chiral thioureas constitute ones of the most widely employed chiral hydrogen-bond-donor catalysts.[24] The first example of DKR based on the use of a chiral thiourea catalyst was reported in 2005 by Berkessel et al.[25] It dealt with an asymmetric ring-opening of azlactones with allylic alcohols, leading to chiral α-amino acids with enantioselectivities of up to 95% *ee*.

Ever since, many successful DKR processes have been achieved under catalysis with this type of organocatalysts.[6] For example in 2017, Matsubara and Asano developed a novel asymmetric synthesis of functionalized tetrahydropyrans based on a domino reaction promoted by 10 mol% of chiral bifunctional thiourea **75**.[26] The process involved a DKR of reversibly generated chiral cyanohydrins **76** from the corresponding 1,7-diketones **77** and acetone cyanohydrin **78**. Then, these cyanohydrins **76** were submitted to organocatalyzed cycloetherification through intramolecular oxa-Michael addition, which afforded final chiral tetrahydropyrans **79** exhibiting two stereocenters in moderate to quantitative yields (46-99%) combined with both high diastereo- (86->90% *de*) and enantioselectivities (82-98% *ee*), as shown in Scheme 17.



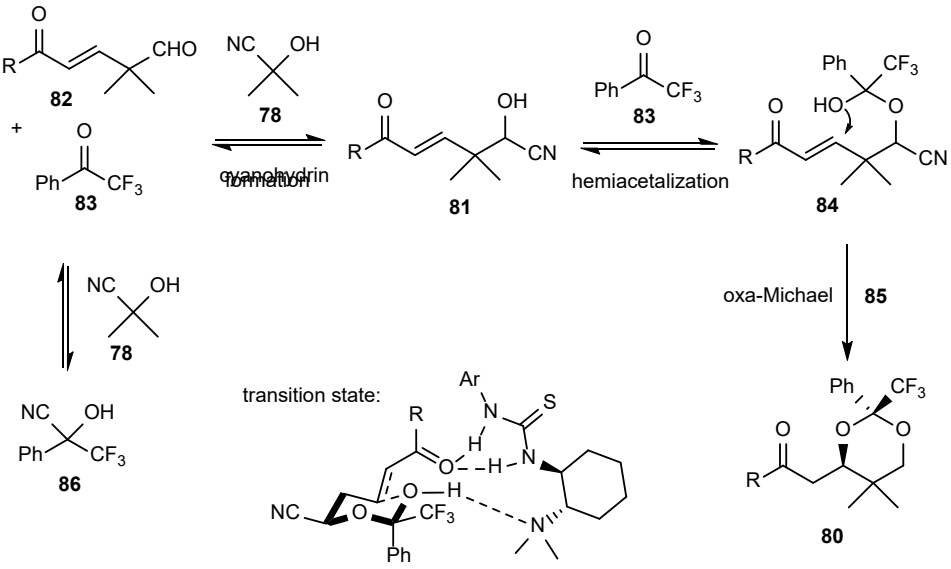
Scheme 17. Domino cyanohydrin formation/oxa-Michael reaction of 1,7-diketones with acetone cyanohydrin.

Later in 2019, the same authors developed a highly efficient synthesis of chiral *syn*-1,3-dioxanes **80** based on an organocatalyzed domino reaction evolving through DKR of *in situ* generated chiral cyanohydrins.[27] As depicted in Scheme 18, this cascade reaction began with a reversible formation of cyanohydrins **81** from the corresponding δ-oxo-α,β-unsaturated ketones **82** and acetone cyanohydrin **78**. The formed cyanohydrins **81** subsequently underwent hemiketalization with phenyl trifluoromethyl ketone **83** to give hemiketals **84**. Then, the latter were submitted to an intramolecular oxa-Michael addition organocatalyzed by chiral bifunctional organocatalyst **85** bearing thiourea and dimethylamino moieties on a chiral 1,2-cyclohexanediamine skeleton, which delivered final chiral 1,3-dioxanes **80** exhibiting two stereocenters. This one-pot process was performed in toluene at 25 °C in the presence of 10 mol% of chiral catalyst **85**. A variety of *syn*-1,3-dioxanes **80** were synthesized in moderate to high yields (43-85%) combined with both high diastereo- (74->90% *de*) and enantioselectivities (67-94% *ee*). In general, the reaction of aromatic ketones (R = aryl) provided the highest enantioselectivities (87-94% *ee*) while lower ee values (70-75% *ee*) were obtained in the reaction of an aliphatic α,β-unsaturated ketone (R = Me) and an heteroaryl α,β-unsaturated ketone (R = 3-pyridyl). Actually, the lowest enantioselectivity (67% *ee*) was observed in the reaction of a substrate bearing an electron-deficient enone (R = *p*-$F_3CC_6H_4$). The mechanism depicted in Scheme 18 shows that acetone cyanohydrin **78** reacted with both α,β-unsaturated ketone **82** and phenyl trifluoromethyl ketone **83** to form the corresponding cyanohydrins **81** and **86**, respectively. Even though the reaction of **78** with trifluoromethyl ketone **83** competed with the reaction of **78** with the formyl group of **82**, the resulting cyanohydrin **86** could take a backward pathway into the main catalytic process. Then, another cyanohydrin **81**, which was reversibly generated from ketone **82**, reacted with **83** to form the corresponding hemiketal intermediate **84**. In the subsequent six-membered ring formation, chiral bifunctional thiourea **85** selectively recognized a specific chair-like conformation of **84** via multipoint interaction through hydrogen bonding; allowing the DKR of **81** and asymmetric oxa-Michael addition to be achieved, thus affording final chiral 1,3-dioxane **80**.



R = Ph, *p*-$MeOC_6H_4$, *p*-$F_3CC_6H_4$, *p*-BrC_6H_4, *p*-PhC_6H_4, 2-thienyl, 3-pyridyl, Me

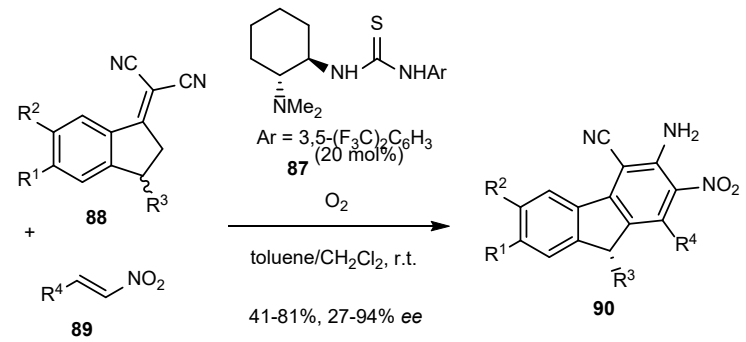
mechanism:



Scheme 18. Three-component domino cyanohydrin formation/hemiacetalization/oxa-Michael reaction of δ-oxo-α,β-unsaturated ketones, acetone cyanohydrin and phenyl trifluoromethyl ketone.

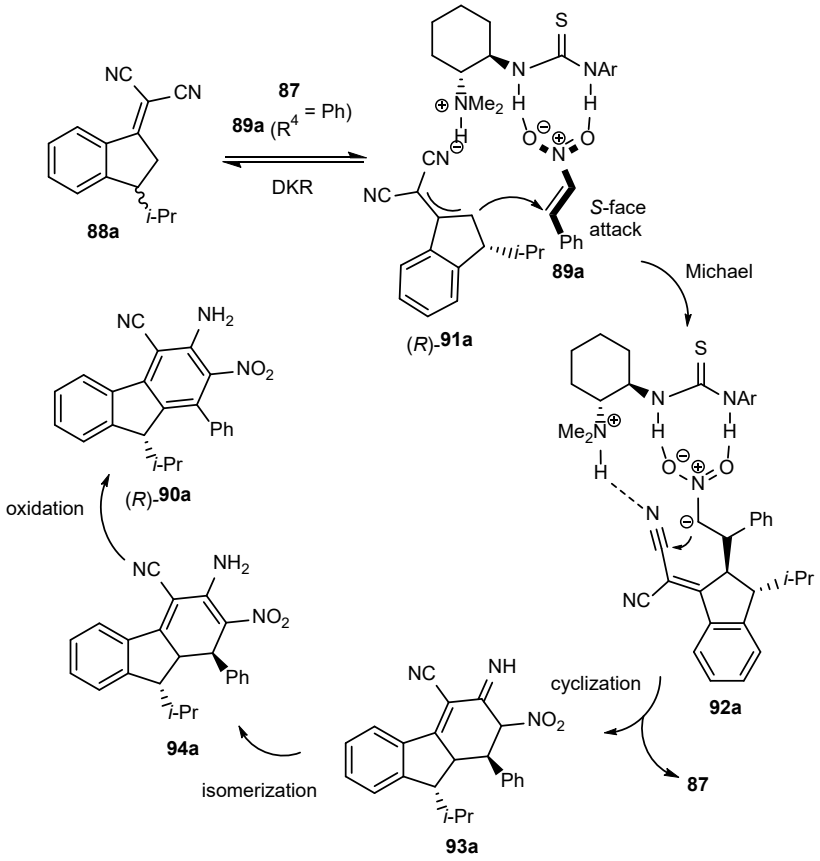
In 2020, Chen and Chen reported the use of a closely related chiral thiourea catalyst **87** at 20 mol% of catalyst loading to promote an enantioselective domino Michael/cyclization/isomerization/oxidation reaction occurring through DKR between dicyanoolefins **88** and nitroolefins **89** under oxygen atmosphere.[28] Indeed, the benzylic C−H group of α,α-dicyanoolefins **88** derived from 3-substituted 1-indanones could be significantly activated via transmission along the aromatic system, thus enabling DKR via a traditional reversible deprotonation/protonation process. The domino reaction of racemic α,α-dicyanoolefins **88** arisen from 3-substituted 1-indanones and malononitrile with nitroolefins **89** resulted in the formation of the corresponding chiral multisubstituted 9H-fluorene derivative **90** in moderate to high yields (41-81%) and variable enantioselectivities (27-94% *ee*), as presented in Scheme 19. Introducing either electron-withdrawing or electron-donating groups into the aryl ring of 1-indanone-derived dicyanoolefins **88** was tolerated, since the corresponding products were obtained with high ee values (77-86% *ee*). On the other hand, the lowest enantioselectivity (27% *ee*) was observed in the reaction of a phenyl-substituted substrate (R^1 = R^2 = H, R^3 = Ph) related to its easy racemization under the catalytic conditions. Moreover, a range of styrenes bearing either electron-withdrawing or electron-donating groups were compatible, providing the corresponding domino products with uniformly high enantioselectivities (81-92% *ee*) while reduced enantiocontrol was observed for products exhibiting a heteroaryl substitution (R^4 = 5-Me-2-furyl, 5-Me-2-thienyl). In addition, nitroolefin derived from *n*-hexanal (R^4 = *n*-Pent) gave the product with a moderate enantioselectivity (75% *ee*). A possible mechanism is depicted in Scheme 19 in which racemic α,α-dicyanoolefin **88a** was activated by chiral catalyst **87** to give the anion intermediate (*R*)-**91a** after a key and simultaneously remote DKR process, and a diastereo- and enantioselective vinylogous Michael addition to nitrostyrene **89a** according to a concerted activation pattern. Then, an intramolecular addition of intermediate **92a** occurred, leading to tricyclic product **93a**. After isomerization to give diene

precursor **94a**, an oxidative aromatization process under oxygen atmosphere finally delivered chiral 9H-fluorene product **90a**.



R^1 = H, Me
R^2 = H, F, Me, OMe
R^3 = *i*-Pr, Et, Cy, Ph
R^4 = Ph, *p*-FC$_6$H$_4$, *m*-ClC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-F$_3$CC$_6$H$_4$', *p*-Tol, *p*-MeOC$_6$H$_4$, 5-Me-2-furyl, 5-Me-2-thienyl, *n*-Pent

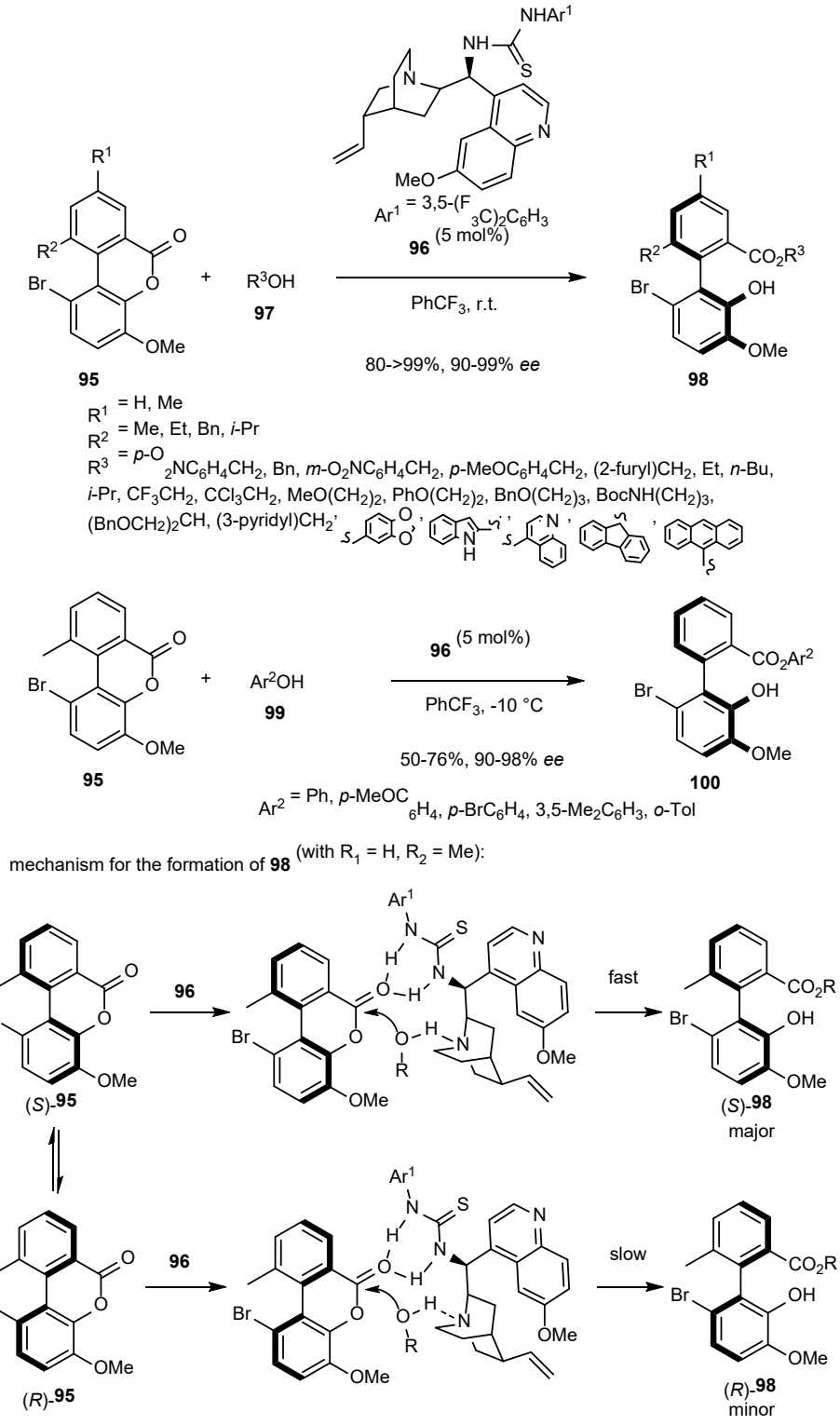
proposed mechanism for formation of **90a** (with R_1 = R_2 = H, R_3 = *i*-Pr, R_4 = Ph):



Scheme 19. Domino Michael/cyclization/isomerization/oxidation reaction of 1-indanone-derived dicyanoolefins with nitroolefins.

3.1.2. Other reactions

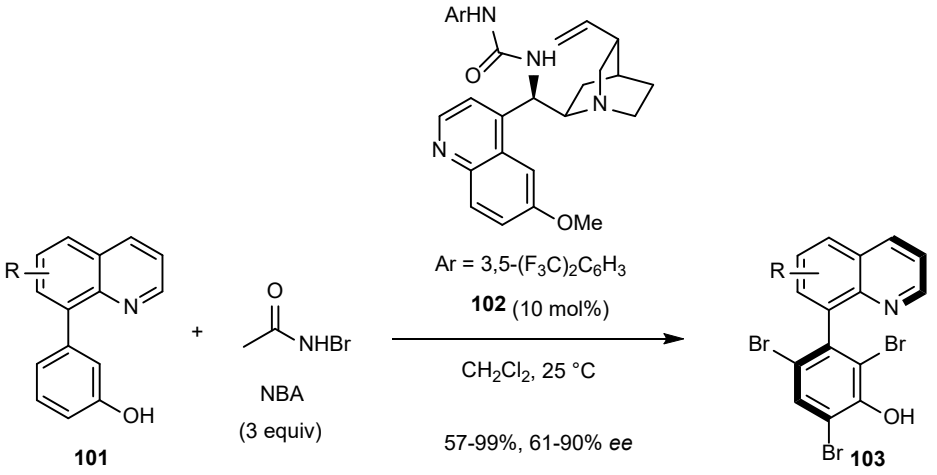
The first example of a metal-free quinine-derived thiourea-promoted atropenantioselective transesterification of Bringmann's lactones[29] was reported by Wang et al., in 2016.[30] As shown in Scheme 20, the DKR of these configurationally labile biaryl lactones **95** was achieved by using only 5 mol% of chiral quinine-derived thiourea **96** in trifluorobenzene as the solvent, thus delivering in the presence of alcohols **97** as the nucleophiles, the corresponding axially chiral biaryl products **98** with uniformly excellent enantioselectivities. Indeed, a remarkable variety of aliphatic alcohols **97** reacted at room temperature to give the desired biaryls **98** with both homogeneously high yields (80->99%) and ee values (90-99% *ee*). Moreover, phenols **99** were also tolerated while requiring a lower temperature (-10 °C) to provide the corresponding chiral products **100** in lower yields (50-76%) than aliphatic alcohols, albeit combined with uniformly excellent enantioselectivities (90-98% *ee*). A mechanism proposed in Scheme 20 shows that the thiourea catalyst activated the strained lactone, while its amine moiety interacted with the hydroxyl group of the alcohol substrate. These interactions directed the nucleophilic attack of the activated lactone by the alcohol through a cooperative atropenantioselective manner, establishing the axial configuration at the resulting now configurationally stable final biaryl product.



Scheme 20. Transesterifications of Bringmann's lactones.

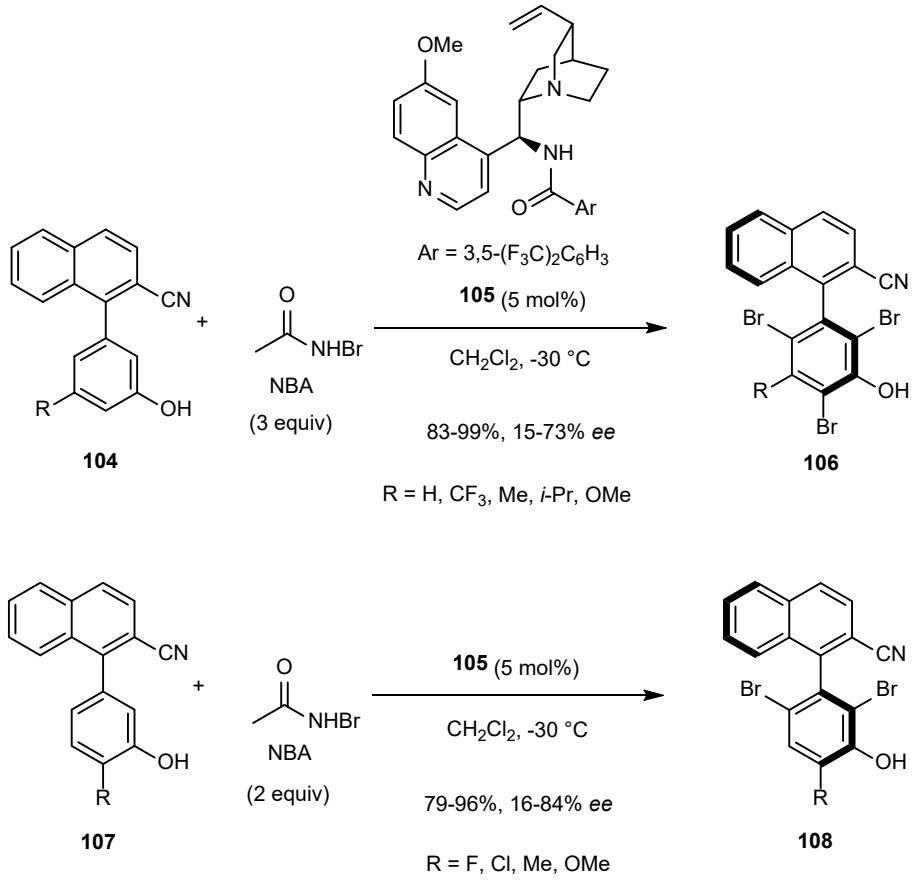
In 2017, the DKR of interconverting 8-aryl-quinolines **101** was disclosed by Asano and Matsubara on the basis of an asymmetric bromination with *N*-bromoacetamide (NBA) as the brominating agent.[31] The process employed 10 mol% of quinidine-derived bifunctional urea catalyst **102** in dichloromethane as solvent. Performed at 25 °C, it resulted in the formation of tribrominated axially chiral quinoline derivatives **103** having a higher rotational barrier than their corresponding substrates **101** due to hydrogen bonding interactions with the bifunctional catalyst locking the chiral axis. The chiral

tribrominated products were obtained with both moderate to excellent yields (57-99%) and enantioselectivities (61-90% *ee*), as illustrated in Scheme 21.



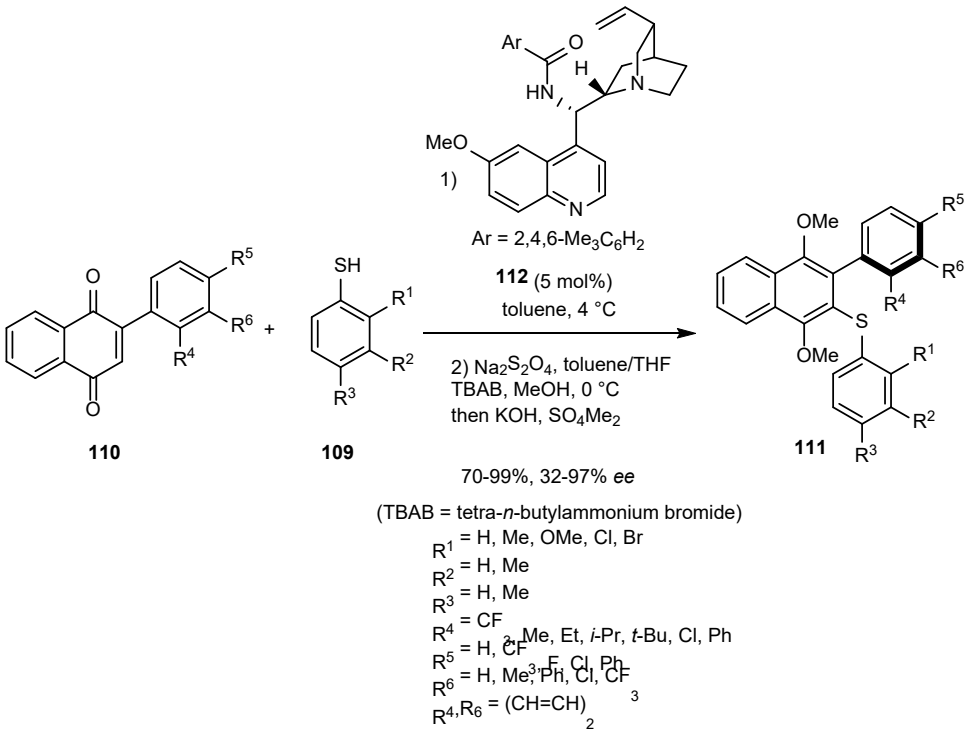
Scheme 21. Bromination of 8-aryl-quinolines with *N*-bromoacetamide.

Later in 2019, related enantioselective brominations of cyanoarenes **104** with *N*-bromoacetamide were developed for the first time by the same authors.[32] In this case, a sequential addition of the brominating agent in several portions was required to improve the enantioselectivity of the reaction. The process was promoted at -30 °C by 5 mol% of quinine-derived bifunctional catalyst **105** in dichloromethane as solvent. The racemization of the substrates at -30 C was fast enough to allow a DKR to occur (Scheme 22). The reaction of 1-(3-hydroxyphenyl)-2-naphthonitrile **104a** (R = H) with three equivalents of *N*-bromoacetamide led to the corresponding tribrominated chiral product **106a** in quantitative yield (99%) and moderate enantioselectivity (51% *ee*). The scope of the reaction was extended to cyanoarenes **104b-e** bearing a substituent (R) at the *meta*-position. While electron-deficient substrate (R = CF_3) reacted with a low enantioselectivity (15% *ee*), the reaction of cyanoarenes bearing aliphatic substituents (R = Me, *i*-Pr) provided improved enantioselectivities (63-73% *ee*). However, a substrate exhibiting a methoxy group (R = OMe) resulted in a low enantioselectivity (19% *ee*). All the tribrominated chiral products were obtained in high yields (83-99%). In addition, the reaction of substrates **107** bearing substituents at the *para*-position of the biaryl axis with only two equivalents of *N*-bromoacetamide led to the formation of the corresponding dibrominated chiral products **108** in uniformly high yields (79-96%) and low to high ee values (16-84% *ee*). The best enantioselectivity (84% *ee*) was achieved in the reaction of a phenol bearing a methyl group (R = Me) while phenols bearing electron-withdrawing groups (R = F, Cl) or a methoxy group led to the corresponding products with lower ee values (16-38% *ee*). These results suggested that aliphatic substituents might efficiently facilitate the racemization of the substrates during the bromination, leading to a better enantioselectivity.



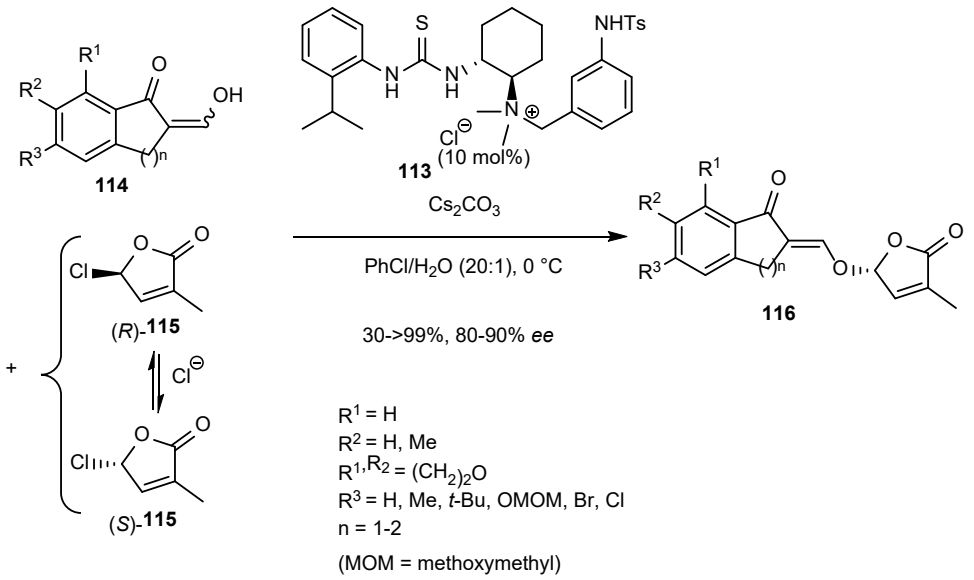
Scheme 22. Brominations of cyanoarenes with *N*-bromoacetamide.

Earlier in 2018, Gustafson et al. reported a DKR process based on the Michael addition of thiophenols **109** to rapidly interconverting arylnaphthoquinones **110**, resulting in the formation of the corresponding chiral stable biaryl sulfides **111** after subsequent reductive methylation (Scheme 23).[33] This atroposelective reaction was performed at 4 °C in toluene as the solvent in the presence of 5 mol% of modified cinchona alkaloid catalyst **112**. The latter was compatible with a range of thiophenols and naphthoquinone substrates, providing the corresponding atropisomers **111** with good to quantitative yields (70-99%) and variable enantioselectivities (32-97% *ee*). Concerning the scope of the thiophenol, the authors found that moving the methyl group (R^1 = Me) on the thiophenol away from the *ortho*-position (R^2 or R^3 = Me) resulted in slightly decreasing the ee values (85% *ee* vs 92% *ee*). Moreover, replacing the *ortho*-methyl group with other groups (MeO, Cl, Br) also led to slightly decrease the enantioselectivity of the reaction (86-88% *ee* vs 92% *ee*). Concerning the scope of the naphthoquinone, the presence of many substitutions on its aryl ring was tolerated. Generally, the presence of substituents at the *para*-position (R^5) had little effect on the enantioselectivity, affording the corresponding products in high enantioselectivities (≥86% *ee*). However, the enantioselectivity was improved with the increasing of the steric bulk of the alkyl substituent at the *ortho*-position (R^4). For example, the lowest enantioselectivities (32-36% *ee*) were obtained in the reaction of a naphthoquinone bearing one methyl or ethyl group at the *ortho*-position (R^4 = Me or Et, R^5 = R^6 = H).



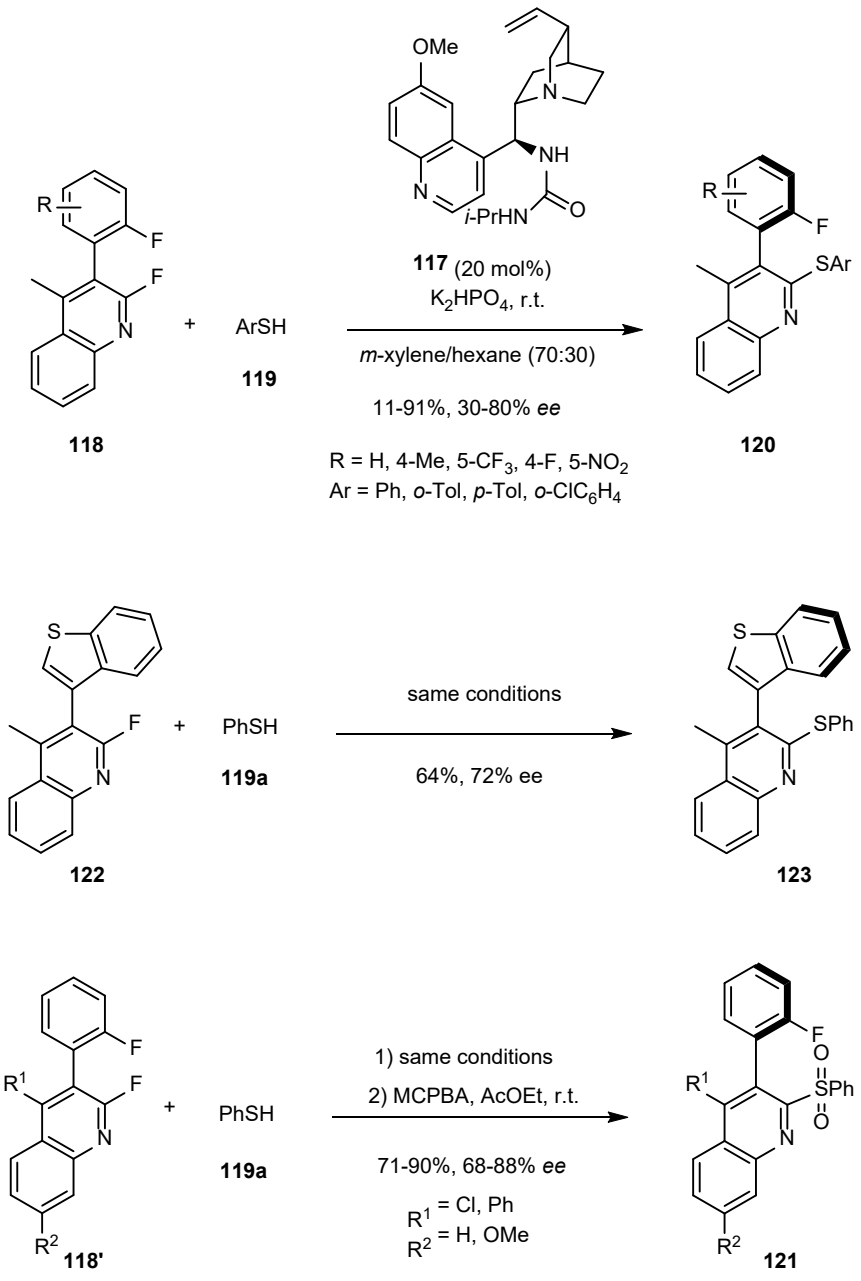
Scheme 23. Michael addition of thiophenols to arylnaphthoquinones.

In 2020, Papai, Takemoto and Tsukano developed novel chiral thiourea-derived quaternary ammonium salt **113** to promote asymmetric S_N2-type acetalization of enols **114** with racemic γ-chlorobutenolide **115**.[34] The latter was submitted to fast racemization because of the presence of chloride anions, allowing DKR to occur (Scheme 24). Performed at 0 °C in a mixture of chlorobenzene and water as the solvent and in the presence of Cs_2CO_3 as a base, the *O*-alkylation afforded a series of chiral acetals **116** with low to quantitative yields (30->99%) and high enantioselectivities (80-90% *ee*). Various substituents in C5-, C6- and C7-positions of the enols were tolerated, providing comparable enantioselectivities. It must be noted that this methodology represented the first example of an organocatalyzed S_N2-type intermolecular asymmetric acetalization.



Scheme 24. S_N2-type acetalization of enols with racemic γ-chlorobutenolide.

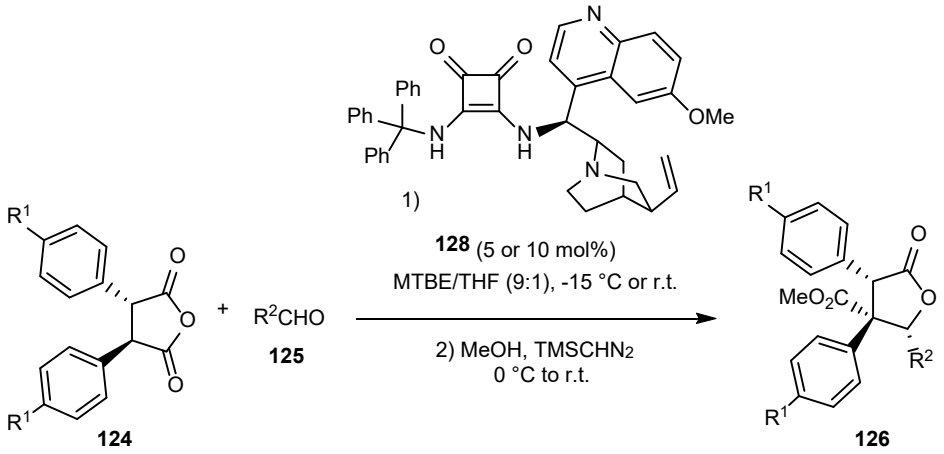
In 2021, Gustafson et al. reported the use of chiral cinchona alkaloid-derived urea catalyst **117** to promote atroposelective syntheses of biologically relevant 3-arylquinolines through nucleophilic aromatic substitution of 3-aryl-2-fluoroquinolines **118** with thiophenols **119**.[35] The processes were performed at room temperature in the presence of 20 mol% of catalyst **117** and K_2HPO_4 in a 70:30 mixture of *m*-xylene and hexane as the solvent (Scheme 25). A series of 3-aryl-2-fluoroquinolines **118** were converted by reaction with thiophenols **119** into the corresponding enantioenriched atropisomerically stable 3-aryl-2-fluoroquinolines **120** with both low to high yields (11-91%) and enantioselectivities (30-80% *ee*). Moreover, the catalyst system could be applied to thiophene substrate **122** which afforded by reaction with thiophenol **119a** the desired chiral product **123** with 64% yield and 72% *ee*. In some cases of substrates **118'** ($R^1 \neq$ Me), an oxidation of the formed unstable sulfide products into the corresponding sulfones **121** by treatment with MCPBA (*meta*-chloroperbenzoic acid) was needed. The latter were obtained from thiophenol **119a** with higher yields (71-90%) and ee values (68-88% *ee*).



Scheme 25. Nucleophilic aromatic substitutions of 3-(hetero)aryl-2-fluoroquinolines with thiophenols.

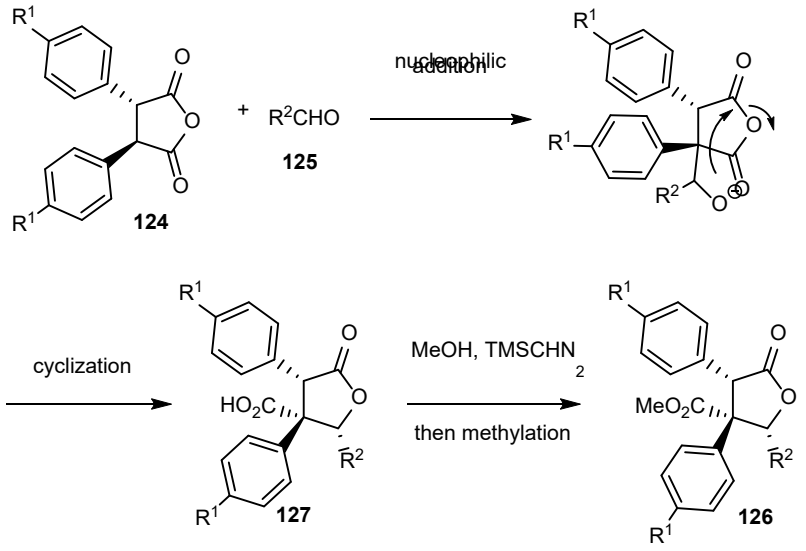
3.2. Squaramide catalysts

In 2018, a squaramide derived from a cinchona alkaloid was applied by Connon et al. for the first time to promote the DKR of disubstituted anhydrides through hydrogen-bonding catalysis.[36] As illustrated in Scheme 26, *trans*-diaryl succinic anhydrides **124** reacted as racemic nucleophilic partners in an asymmetric formal cycloaddition with aromatic and aliphatic aldehydes **125** to afford the corresponding chiral tetrasubstituted γ-butyrolactones **126** bearing three contiguous stereocenters. Actually, the reaction evolved through a domino aldol-type addition/cyclization reaction, leading to carboxylic acids **127**, which were further methylated by treatment with $TMSCHN_2$ (TMS = trimethylsilyl) in methanol to give final γ-butyrolactones **126**. The process was promoted by 5 or 10 mol% of novel bulky bifunctional squaramide **128** in a mixture of MTBE (methyl *t*-butyl ether) and THF as solvent, providing products **126** in moderate to quantitative yields (50->99%), uniformly high enantioselectivities (85->99% *ee*) and variable diastereoselectivities (0-94% *de*). The catalyst system tolerated a range of aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents but also heteroaromatic as well as aliphatic aldehydes. To occur, the DKR required that enolization at both α-carbon atoms of the anhydride had to be significantly faster than the rate of the reaction of the enolate derived from the slow reacting anhydride enantiomer. A dramatic increase in the diastereoselectivity of the process was observed when electron-withdrawing groups were present on the anhydride's aryl substituents, since the latter increased both the rate of the anhydride enolate formation and that of the racemization.



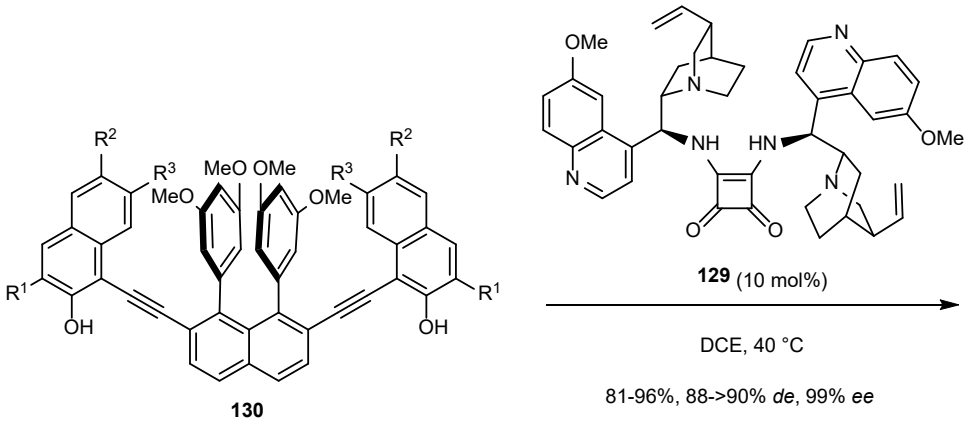
R^1 = H, Br, CF_3, NO_2
R^2 = $BnCH_2$, Ph, *p*-$MeOC_6H_4$, *p*-$O_2NC_6H_4$, $BocNH(CH_2)_2$, *m*-$O_2NC_6H_4$, *o*-$O_2NC_6H_4$, *p*-ClC_6H_4, *m*-ClC_6H_4, 2-Naph, Cy, *p*-$F_3CC_6H_4$, 2-thienyl

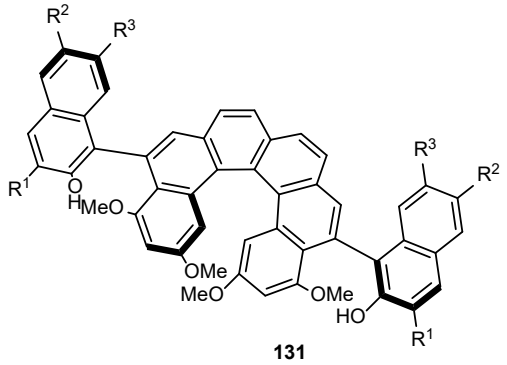
proposed mechanism:



Scheme 26. Domino aldol-type reaction/cyclization reaction of *trans*-diaryl succinic anhydrides with aldehydes followed by methylation.

In 2019, another cinchona alkaloid-derived squaramide **129** was employed by Yan et al. to develop an unprecedented synthesis of complex chiral products exhibiting both helical and axial stereogenic elements.[37] The DKR process evolved at 40 °C through an intramolecular domino double cyclization reaction of substrates **130** submitted to 10 mol% of squaramide **129** in 1,2-dichloroethane (DCE) as the solvent. As shown in Scheme 27, it resulted in the formation of a range of enantiopure helicenes **131** (99% *ee*) with both uniformly high diastereoselectivities (88->90% *de*) and yields (81-96%). These homogeneous excellent results were obtained irrespectively to the nature of substituents exhibited on the naphthol moiety of the substrates.

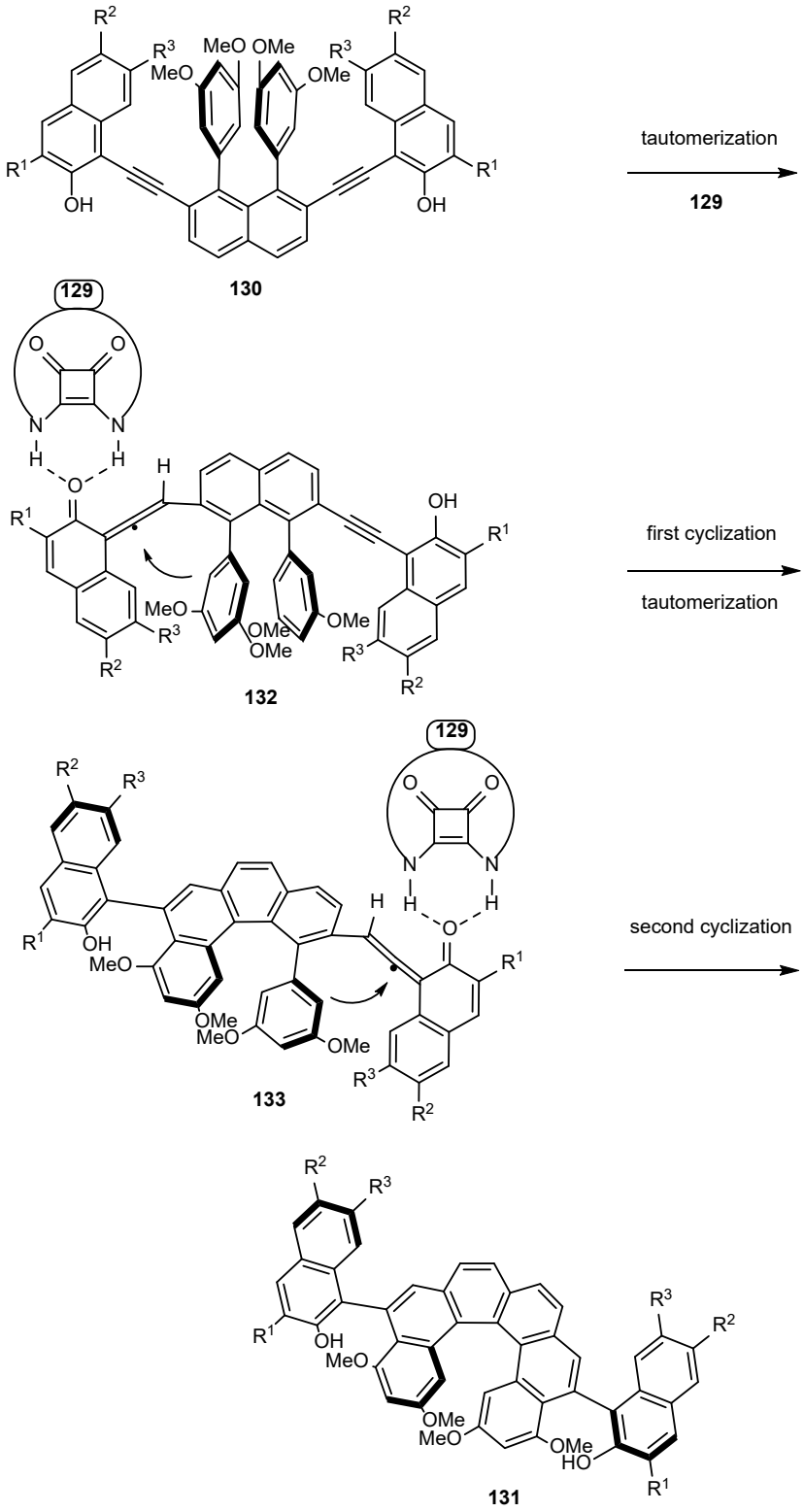




R^1 = H, OMe
R^2 = H, Ph, 2,6-Me$_2$C$_6$H$_3$, 3,5-Me$_2$C$_6$H$_3$, *p*-(*i*-Pr)C$_6$H$_4$
R^3 = H, Ph, *p*-(*i*-Pr)C$_6$H$_4$, *p*-ClC$_6$H$_4$, 2,6-Me$_2$C$_6$H$_3$, 3,5-Me$_2$C$_6$H$_3$

Scheme 27. Synthesis of helicenes exhibiting both helical and axial stereogenic elements through domino double cyclization reaction.

The authors assumed that the precedent domino reaction (Scheme 27) proceeded via two sequential cyclizations activated through hydrogen bonding. As depicted in Scheme 28, substrate **130** underwent a tautomerization to give intermediate **132**. The latter was subsequently submitted to a first cyclization. A following tautomerization provided intermediate **133** exhibiting a stereogenic axis, which subsequently underwent a second cyclization to generate final helicene **131** including another stereogenic axis.

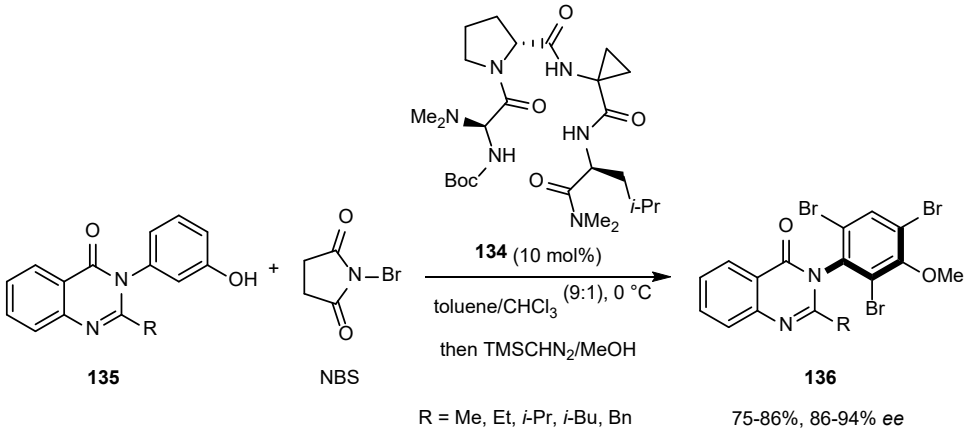


Scheme 28. Mechanism for the domino double cyclization reaction depicted in Scheme 27.

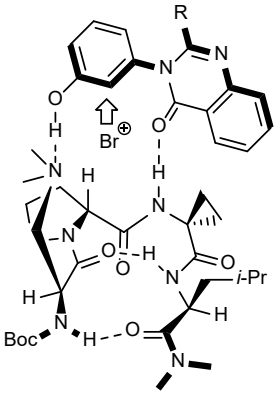
3.3. Peptide-based catalysts

In the last decade, Miller et al. demonstrated that peptide-based catalysts[38] were highly efficient organocatalysts to promote atroposelective brominations of both biaryl[39] and tertiary benzamide scaffolds.[40] Later, related reaction conditions could be applied to the atroposelective bromination of heterobiaryl atropisomers.[41] In this case, the authors

selected peptide **134** as optimal catalyst employed at 10 mol% of catalyst loading in the bromination of 3-arylquinazolinones **135** with *N*-bromosuccinimide (NBS) as the brominating agent. Performed at 0 °C in a 9:1 mixture of toluene and chloroform as solvent, the DKR process of variously substituted quinazolinones **226** afforded the corresponding chiral tribromides **136** in both high yields (75-86%) and enantioselectivities (86-94% *ee*), as presented in Scheme 29. On the basis of NMR (nuclear magnetic resonance) studies, the authors proposed the transition state depicted in Scheme 29 consistent with multidentate association through H-bonding between the substrate and the peptide catalyst. According to structural and mechanistic studies more recently published, the observed enantioselectivity of the reaction was actually found to arise from different transition states in which the peptide adopted multiple conformations.[42]

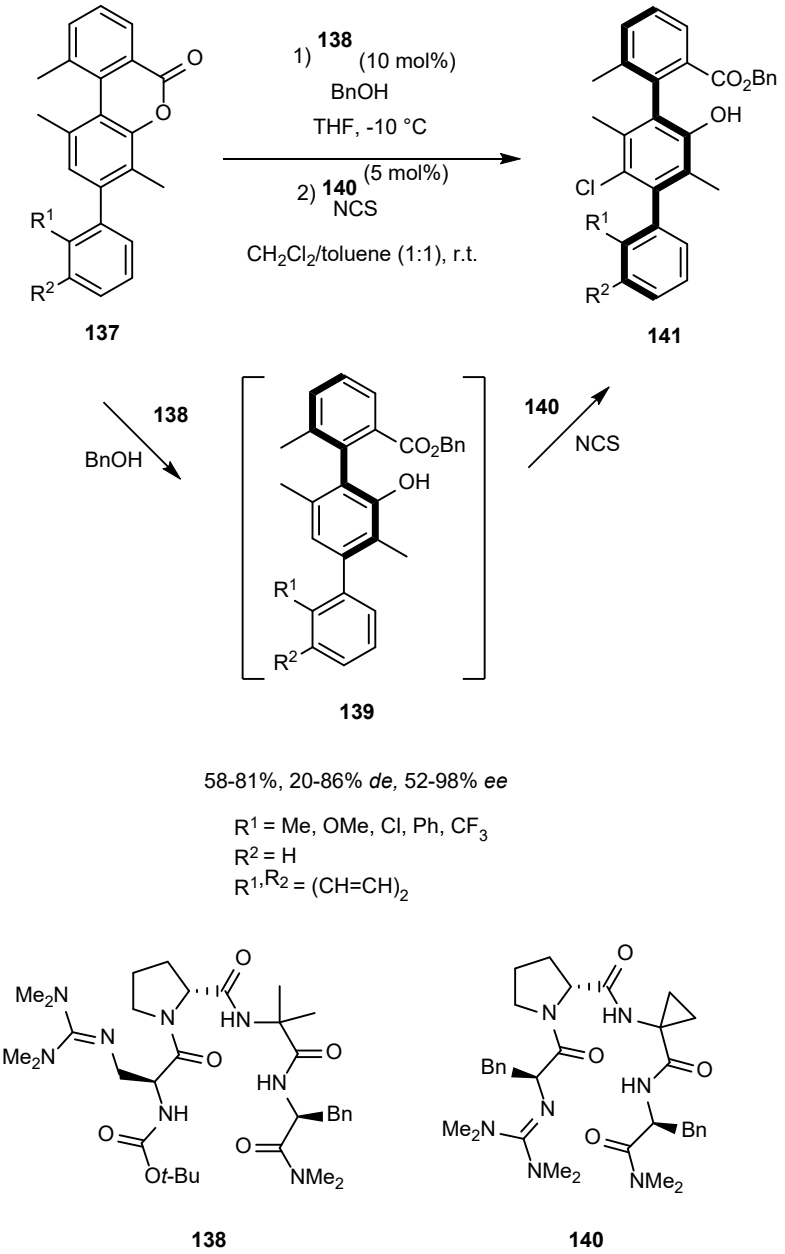


proposed transition state:



Scheme 29. Bromination of heterobiaryls with NBS.

In 2020, Miller and Toste described a tandem ring-opening/chlorination reaction involving two successive DKR processes in one-step which was applied to the synthesis of chiral two-axis terphenyl atropisomers.[43] This methodology was catalyzed by novel strongly Brønsted basic guanidine peptide catalysts. It involved in a first step the atroposelective ring-opening of Bringmann-type terphenyl lactones **137** exhibiting two configurationally labile axes with benzyl alcohol promoted by 10 mol% of chiral guanidinylated catalyst **138** performed at -10 °C in THF as solvent, which led through DKR to the corresponding intermediate products **139** with one established axis of chirality. The latter were subsequently submitted to atroposelective chlorination with *N*-chlorosuccinimide (NIS) in the presence of 5 mol% of related chiral peptide **140** which occurred at room temperature in a 1:1 mixture of dichloromethane and toluene as solvent (Scheme 30). This second DKR process described for the first time allowed to establish the second axis of chirality, thus delivering the desired two-axis terphenyls **141** in good to high yields (58-81%), low to high diastereoselectivities (20-86% *de*) and moderate to excellent enantioselectivities (52-98% *ee*). Very high ee values (90-98% *ee*) were generally achieved in the tandem ring-opening/chlorination reaction of terphenyl lactones bearing various substituents at the *ortho*-position of the arene ring (R^1 = Me, OMe, Cl, Ph) with the exception of a trifluoromethylated substrate (R^1 = CF_3) which provided the lowest enantioselectivity (52% *ee*).



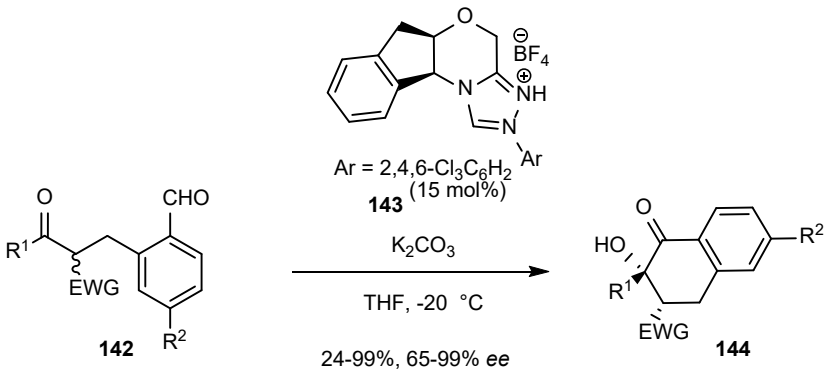
Scheme 30. Tandem ring-opening/chlorination reaction of terphenyl lactones.

4. Dynamic Kinetic Resolutions Promoted by N-Heterocyclic Carbene Catalysts

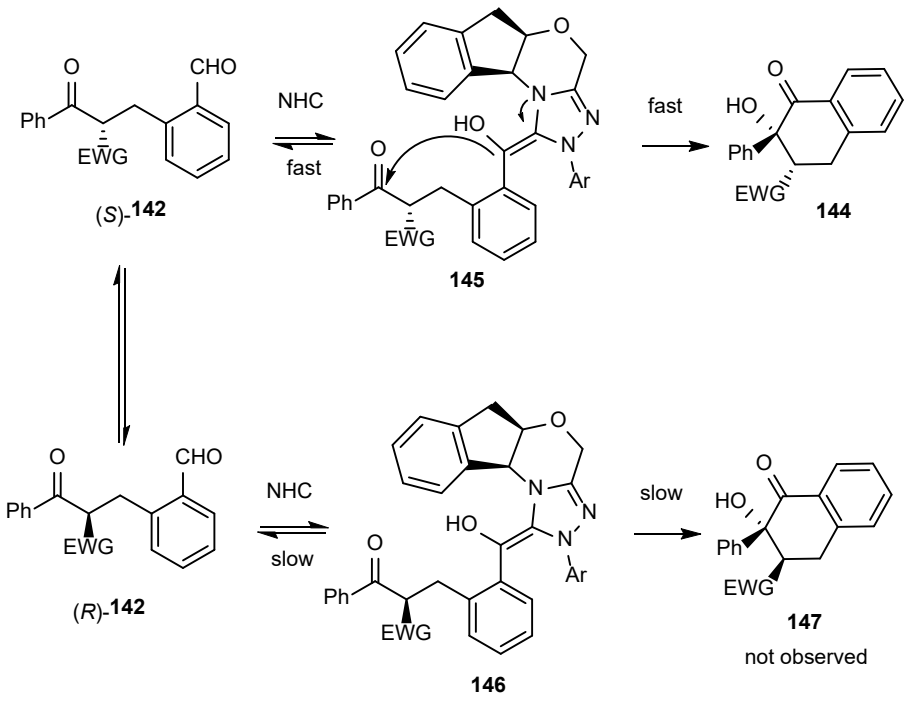
4.1. Benzoin condenzations

N-Heterocyclic carbenes (NHCs) are widely employed organocatalysts.[44] The first example of DKR promoted by this type of catalysts was described by Scheidt et al., in 2012.[45] It occurred through an intramolecular domino aldol/acylation reaction of α–substituted-β-ketoesters to provide the corresponding chiral bicyclic β-lactones with moderate to good yields (53-88%) and diastereoselectivities (66-90% *de*). Ever since, a range of these organocatalysts have encountered many successes in DKR methodology.[7] For example, a highly regio-, diastereo- and enantioselective DKR of β-ketoesters **142** was disclosed by Fang et al. in 2016 on the basis of an asymmetric intramolecular benzoin reaction catalyzed by chiral NHC catalyst **143**.[46] The latter was employed at 15 mol% of catalyst loading in THF at -20 °C, allowing the synthesis of a range of chiral tetralone derivatives **144** bearing two contiguous stereocenters to be achieved as single diastereomers in low to quantitative yields (24-99%) and moderate to excellent enantioselectivities (65-99% *ee*), as presented in Scheme 31. Generally, the reaction of (hetero)aromatic ketones (R^1 = (hetero)aryl) bearing either electron-donating or electron-withdrawing substituents provided very high ee values (89-99% *ee*) while the lowest enantioselectivities (24-39% *ee*) were obtained in that of aliphatic ketones (R^1 = Me, Et). Along with β-ketoesters, a β-phenyl-substituted ketone (EWG (electron-withdrawing) = Ph) was also compatible, giving the corresponding product with a high ee value (95% *ee*) and moderate yield (60%). The DKR process involved a fast and reversible equilibrium between the two enantiomers of starting β-

ketoester **142** in the presence of K_2CO_3 as base. This was followed by the rapid formation of enol intermediate **145** from (*S*)-**142** and NHC catalyst. The latter subsequently underwent irreversible and fast intramolecular benzoin reaction to afford final product **144** while (*R*)-**142** acted on the NHC catalyst much more slowly to give **146** and, consequently, the minor diastereomer **147** was not detected.

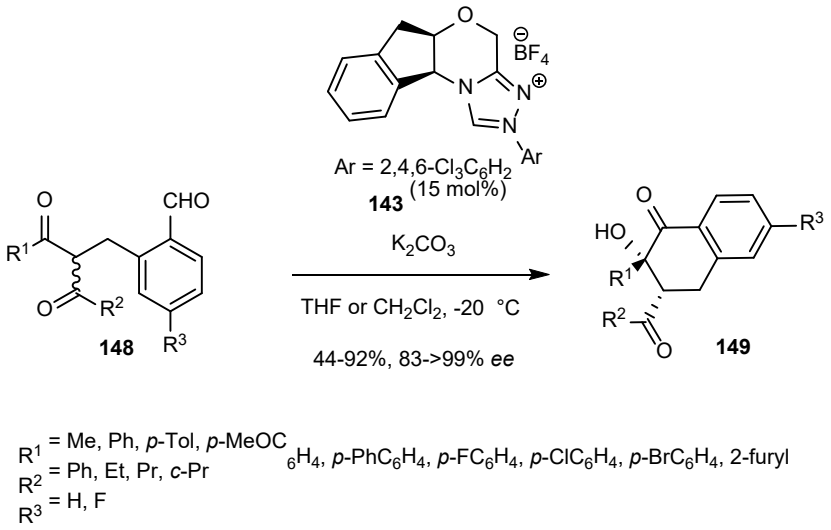


mechanism (with R^1 = Ph, R_2 = H):



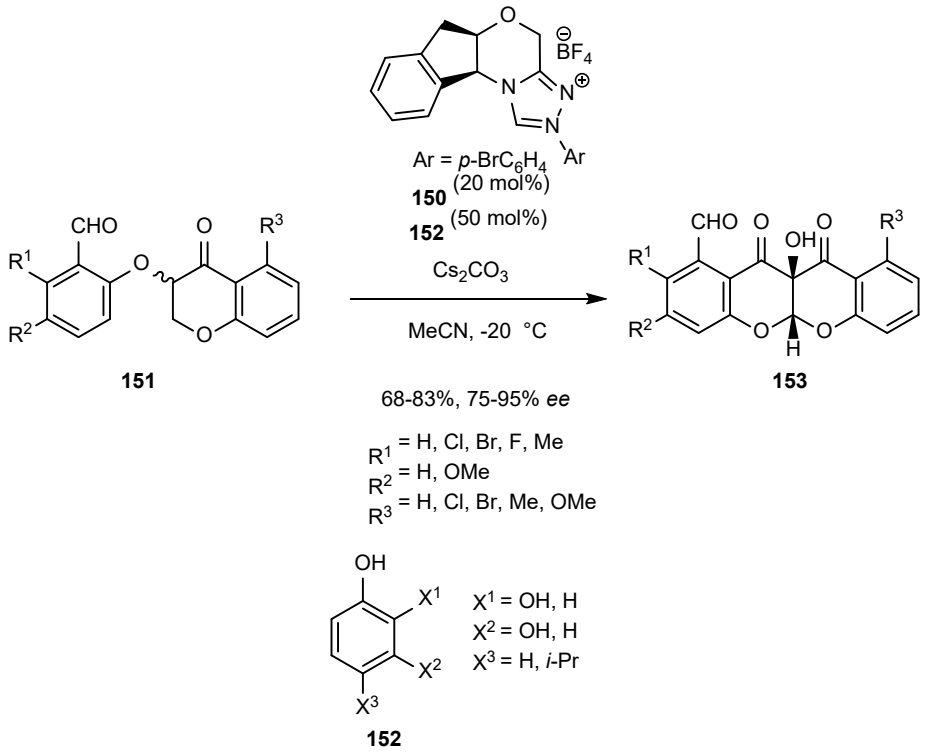
Scheme 31. Intramolecular benzoin reaction of β-ketoesters/β-phenyl-substituted ketones.

The same reaction conditions were also applied to 1,3-diketones **148**, which led to the corresponding chiral tetralone derivatives **149** as single diastereomers with moderate to excellent yields (44-92%) and uniformly high enantioselectivities (83->99% *ee*), as depicted in Scheme 32.[46] Especially, remarkable ee values (96->99% *ee*) were achieved in the reaction of a range of (hetero)aromatic 1,3-diketones (R^1 = (hetero)aryl) performed in THF as solvent while a lower enantioselectivity (83% *ee*) was obtained in the reaction of an aliphatic 1,3-diketone (R^1 = Me) carried out in dichloromethane instead of THF as solvent.



Scheme 32. Intramolecular benzoin reaction of 1,3-diketones.

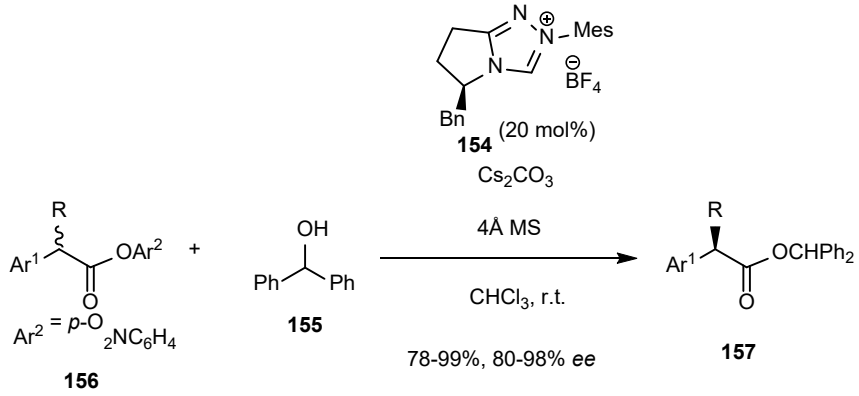
Later in 2019, the same authors employed related chiral NHC catalyst **150** to promote the intramolecular benzoin reaction of ketoaldehyde **151**.[47] The process was performed at -20 °C in acetonitrile as solvent in the presence of 20 mol% of organocatalyst **150** and 50 mol% of phenol additives **152**. As depicted in Scheme 33, the transformation resulted in the formation of chiral rotenoid *cis*-fused tetrahydrochromeno[3,4-b]chromenes **153** in both good to high yields (68-83%) and enantioselectivities (75-95% *ee*). The catalyst system was compatible with the presence on the substrates of a series of substituents with different electronic properties. The utility of this methodology was demonstrated by its application in the total synthesis of biologically relevant rotenoid natural products, such as tephrosin, milletosin, 12a-hydroxymunduserone and 12a-hydroxyrotenone.



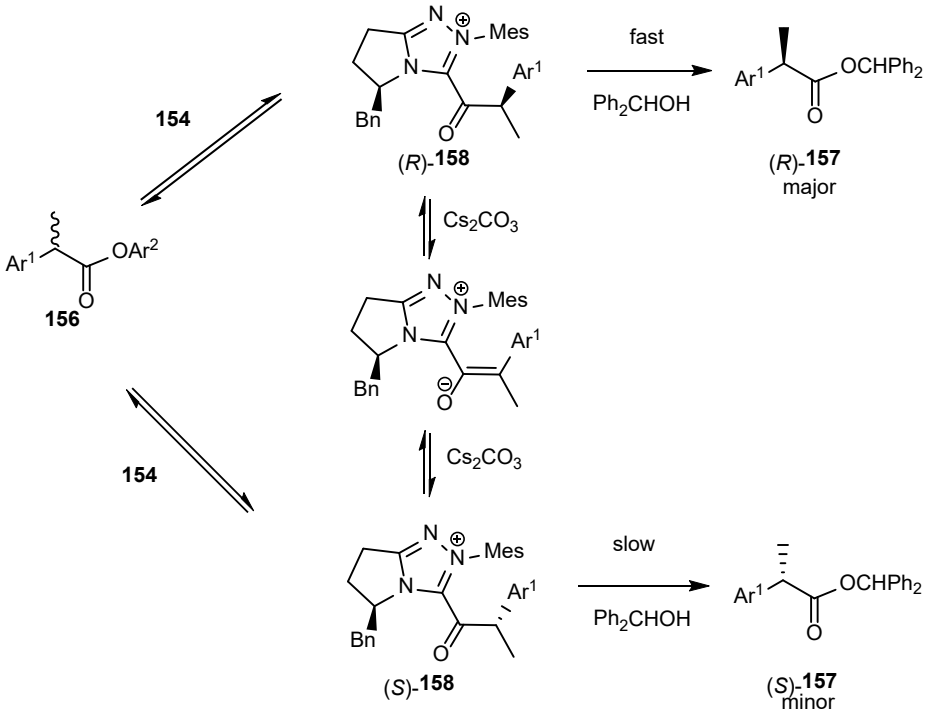
Scheme 33. Synthesis of rotenoid *cis*-fused tetrahydrochromeno[3,4-b]chromenes through intramolecular benzoin reaction.

4.2. Other reactions

In 2016, Chi et al. developed the first NHC-catalyzed DKR of α,α-disubstituted carboxylic esters (Scheme 34).[48] The reaction was promoted at room temperature by 20 mol% of *N*-mesyl-substituted triazolium catalyst **154** in chloroform as solvent. By reacting with diphenylmethanol **155** as alcohol, a series of α,α-disubstituted carboxylic esters **156** resulted in the formation of the corresponding α,α-disubstituted chiral carboxylic esters **157** in uniformly high yields (78-99%) and enantioselectivities (80-98% *ee*). Generally, the best ee values were achieved in the reaction of α-methyl substituted carboxylic esters (R = Me). For example, when the methyl group was replaced with an ethyl substituent (R = Et), a lower ee value (80% *ee*) was obtained. Given the importance of chiral α-aryl propionic acids as bioactive molecules, the utility of this novel methodology is obvious. The mechanism of the DKR involved the addition of chiral NHC catalyst **154** to the racemic starting ester **156** to give the corresponding diastereomeric intermediates (*R*)-**158** and (*S*)-**158**. Then, intermediate (*R*)-**158** reacted faster than (*S*)-**158** with diphenylmethanol **155** to give (*R*)-**157** preferentially.

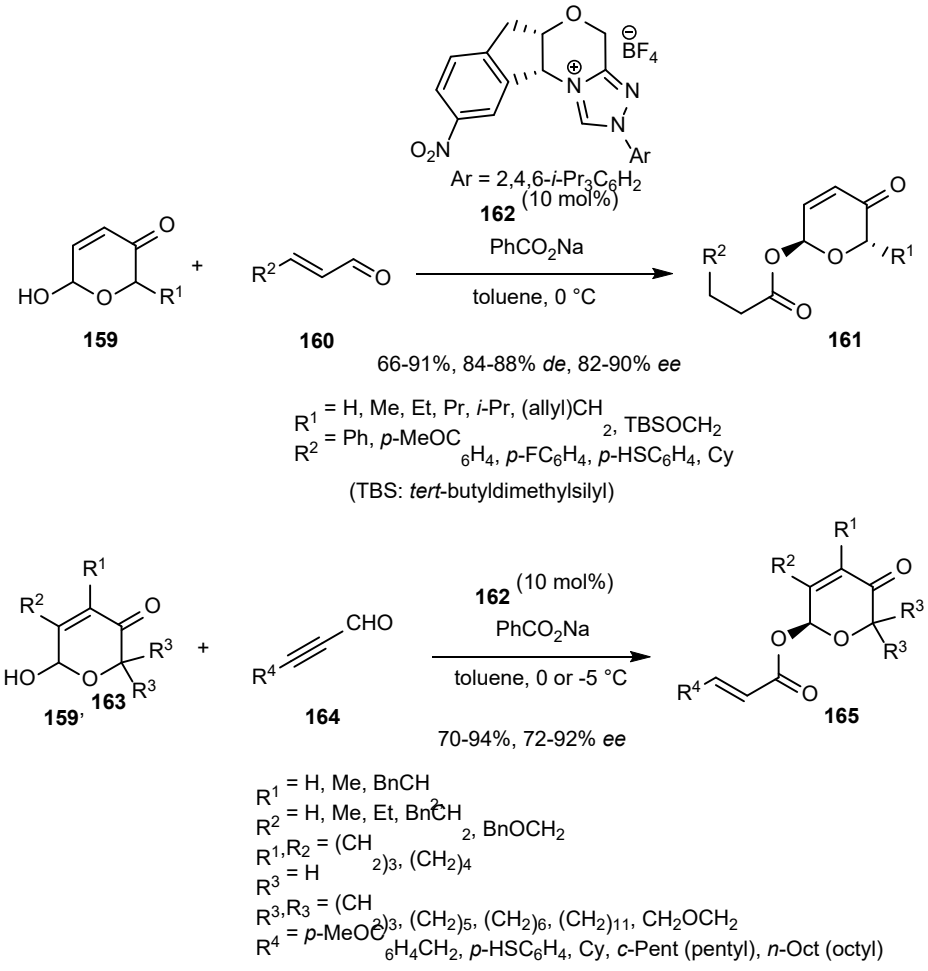


mechanism (with R = Me):



Scheme 34. Transesterification of α,α-disubstituted carboxylic esters with diphenylmethanol.

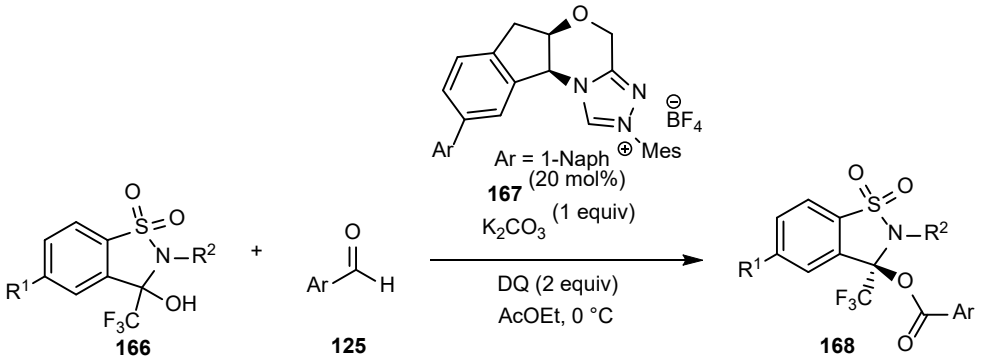
In the same year, Wang et al. described the first NHC-catalyzed DKR of 6-hydroxy-3-pyranones **159**.[49] As illustrated in Scheme 35, the latter reacted with α,β-unsaturated aldehydes **160** through a redox esterification to give the corresponding chiral esters **161** in good to excellent yields (66-91%) combined with high diastereo- (84-88% *de* with $R^1 \neq H$) or enantioselectivities (82-90% *ee* with $R^1 = H$). The reaction was performed at 0 °C in toluene as solvent in the presence of 10 mol% of optimal novel indanol-derived triazolium catalyst **162**. Both electron-donating and electron-withdrawing aryl substituents in the β-position of the enal were well tolerated (R^2) as well as an alkyl group (R^2 = Cy). Moreover, a variety of 2,6-disubstituted hydroxypyranones ($R^1 \neq H$) were compatible, leading to the corresponding esters in good yields and diastereoselectivities (84-88% *de*). The scope of the process was extended to another class of α,β-unsaturated aldehydes, such as alkynals **164**. The latter reacted with 6-hydroxy-3-pyranones **159**/**163** to afford under the same reaction conditions the desired esters **165** in both good to high yields (70-94%) and enantioselectivities (72-92% *ee*), as shown in Scheme 35. The utility of this novel methodology was applied to the syntheses of a variety of sugar derivatives.



Scheme 35. Redox esterifications of 6-hydroxy-3-pyranones with enals and alkynals.

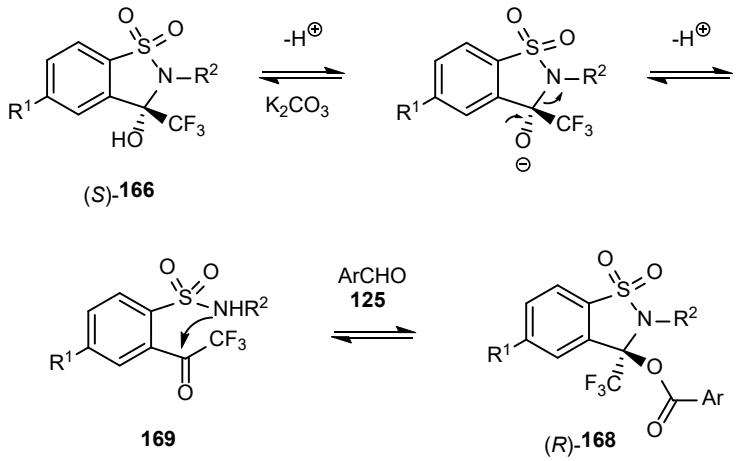
In 2021, Ye et al. developed the first DKR of hemiaminals without α-hydrogen.[50] The process involved an asymmetric *O*-acylation of 3-hydroxy-3-trifluoromethylbenzosultams **166** with aromatic aldehydes **125** catalyzed at 0 °C by 20 mol% of NHC catalyst **167** in ethyl acetate as the solvent. It was performed in the presence of K_2CO_3 as a base and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (DQ) as the oxidant, which allowed a range of chiral benzosultam derivatives **168** to be produced in high yields (75-98%) and moderate to excellent enantioselectivities (66-97% *ee*), as illustrated in Scheme 36. Benzaldehydes bearing either electron-donating or electron-withdrawing groups at the *para*- or *meta*-position were all compatible, providing both high yields and ee values. A high enantioselectivity (94% *ee*) was also achieved in the reaction of β-naphthaldehyde (Ar = 2-Naph), while that of α-naphthaldehyde (Ar = 1-Naph) provided a decreased enantioselectivity (86% *ee*). An heteroaromatic aldehyde, such as thiophene-2-carbaldehyde (Ar = 2-thienyl), was also well tolerated (93%

ee). Unfortunately, aliphatic aldehydes were uncompatible. Concerning the scope of the 3-hydroxybenzosultams, *N*-benzyl substrates provided excellent enantioselectivities but also *N*-alkyl benzosultams (90-92% *ee*). Moreover, along with a *tert*-butyl group on the phenyl ring of benzosultams, both electron-withdrawing groups and electron-donating groups were tolerated but gave the products with some decreased enantioselectivities (66-80% *ee*). The DKR protocol required the racemization of hemiaminals **166** via ketones **169** under basic conditions (Scheme 36). The electron-withdrawing *N*-sulfonyl and *N*-trifluoromethyl groups could enhance the acidity of the α-hydroxyl in hemiaminals, thus facilitating the racemization.



R^1 = *t*-Bu, *m*-MeOC$_6$H$_4$, *m*-MeO$_2$CC$_6$H$_4$, Ph, CF$_3$, OMe, Me
R^2 = Bn, *p*-TolCH$_2$, Ph, *p*-MeOC$_6$H$_4$CH$_2$, *m*-TolCH$_2$, *m*-MeOC$_6$H$_4$CH$_2$'
o-TolCH$_2$, 2-NaphCH$_2$, Cy, *n*-Bu
Ar = Ph, *p*-Tol, *p*-MeOC$_6$H$_4$, *p*-ClC$_6$H$_4$, *p*-BrC$_6$H$_4$, *p*-MeO$_2$CC$_6$H$_4$, *m*-MeOC$_6$H$_4$'
m-ClC$_6$H$_4$, 3,5-(*t*-Bu)$_2$C$_6$H$_3$, 2-Naph, 1-Naph, 2-thienyl, *m*-MeO$_2$CC$_6$H$_4$

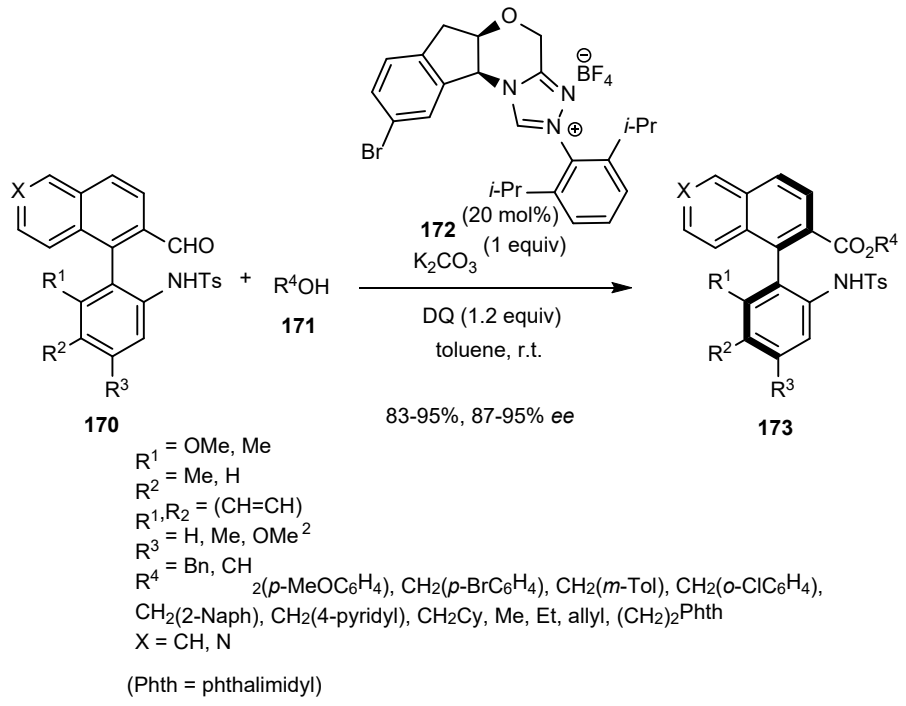
racemization of the hemiaminals:



Scheme 36. *O*-Acylation of 3-hydroxy-3-trifluoromethylbenzosultams with aromatic aldehydes.

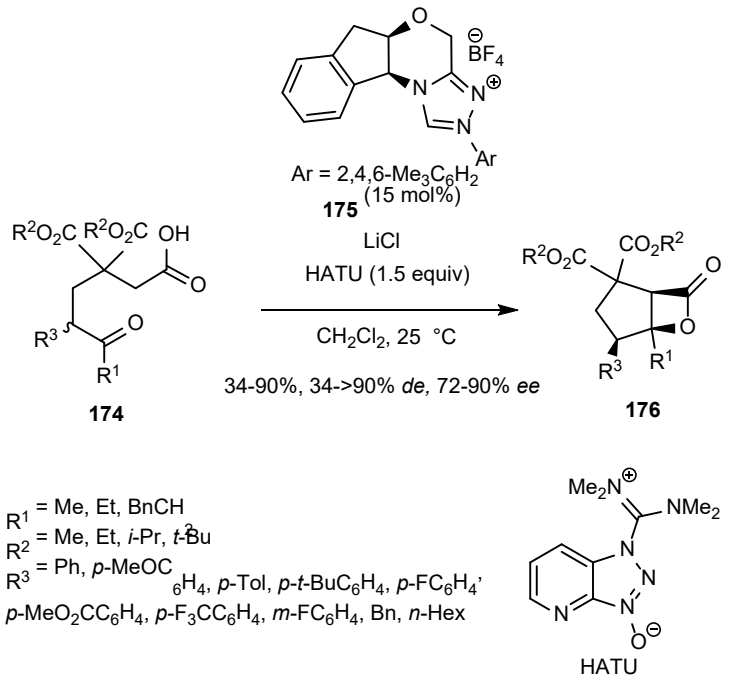
In the same year, Wang et al. developed oxidative esterification of biaryl amino aldehydes **170** with alcohols **171** catalyzed by 20 mol% of chiral NHC catalyst **172**, evolving through DKR.[51] The reaction employed DQ as the oxidant and K_2CO_3 as the base in toluene as the solvent. This novel reaction performed at room temperature involved the in situ formation of hemiaminals which led to axially chiral biaryl amino esters **173** with both uniformly high yields (83-95%) and enantioselectivities (87-95% *ee*), as illustrated in Scheme 37. A range of substituted biaryl substrates were well tolerated both on the phenyl and naphthalene rings regardless of the electronic nature of the substituents. Even an heteroaromatic ring (X = N) was compatible with the catalytic system, providing the corresponding product with 82% yield and 87% *ee*.

Concerning the alcohol partners, the electronic effect of substituents on the aryl ring have limited effects on the enantioselectivity of the reaction. Moreover, aliphatic alcohols reacted smoothly to give the corresponding products with both high yields (85-90%) and enantioselectivities (83-95% *ee*).

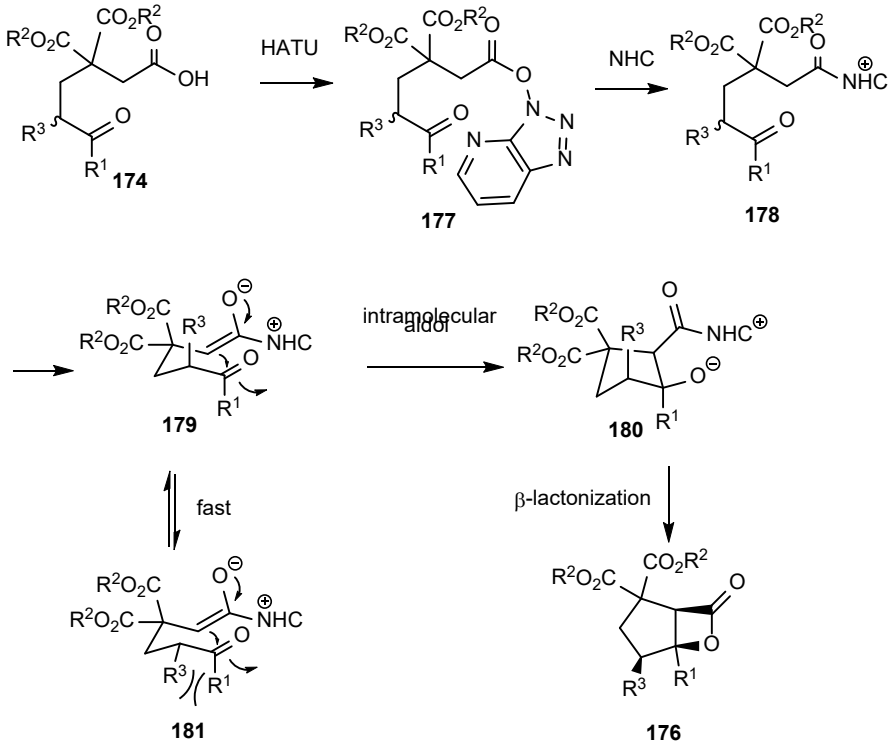


Scheme 37. Oxidative esterification of biaryl amino aldehydes with alcohols.

Earlier in 2017, Biju et al. developed asymmetric domino aldol/lactonization reaction of acyclic ketoacids **174** evolving through DKR.[52] The reaction was catalyzed at 25 °C by 15 mol% of chiral NHC catalyst **175** in dichloromethane as the solvent. Hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU) was used as a coupling reagent. The process led to the corresponding chiral cyclopentane-fused β-lactones **176** exhibiting three contiguous stereocenters in both variable yields (34-90%) and diastereoselectivities (34->90% *de*) along with good to high enantioselectivities (72-90% *ee*), as illustrated in Scheme 38. It must be noted that generally the diastereoselectivity of the reaction was high excepted when the α-aryl keto moiety (R^3 = aryl) was replaced by an α-alkyl group (34% *de* with R^3 = Bn, *n*-Hex (*n*-hexyl) vs ≥82% *de* with R^3 = aryl). Moreover, the reaction of methyl ketones (R^1 = Me) provided higher yields than other alkyl ketones (67-90% with R^1 = Me vs 34-40% with R^1 = Et, $BnCH_2$). The reaction proceeded via the formation of the activated ester **177** arisen from the addition of HATU to ketoacid **174**. The subsequent addition of NHC to intermediate **177** generated the NHC-bound acyl azolium intermediate **178**, which, under basic conditions, yielded NHC-enolate **179**. The latter underwent intramolecular aldol reaction to give cyclopentane intermediate **181**, which, upon further β-lactonization, afforded the final cyclopentane-fused β-lactone **176** along with regenerated catalyst. Intermediates **179** and **181** (Scheme 38) were in rapid equilibrium because of the basic reaction conditions. The major diastereomer **176** arose from enolate **179** in which the aryl group R^3 was in pseudo-axial orientation. This conformation was more favorable than **181** destabilized by the sterically hindered interaction between the aryl (R^3) and the alkyl (R^1) groups.



mechanism:



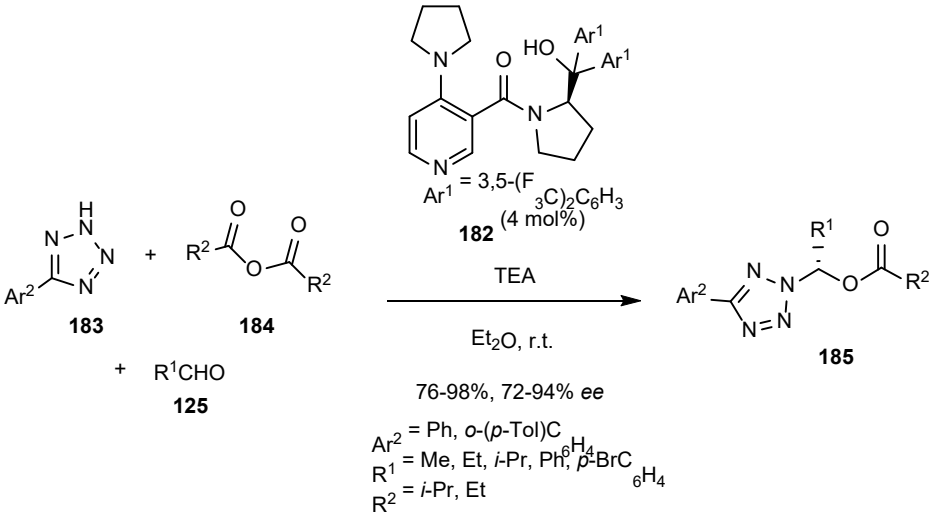
Scheme 38. Intramolecular domino aldol/lactonization reaction of acyclic ketoacids.

5. Dynamic Kinetic Resolutions Promoted by Lewis Base Catalysts

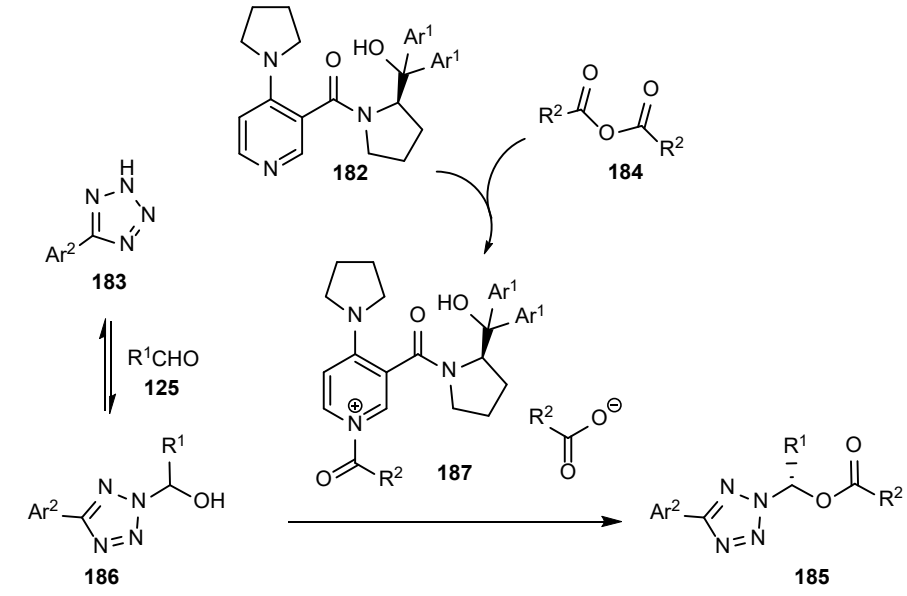
5.1. Pyridine-based Lewis bases

5.1.1. Three-component domino reactions

In 2016, Piotrowski and Kamlet investigated chiral *N,N*-dialkylaminopyridine catalyst **182** as Lewis base catalyst in a three-component reaction between tetrazoles **183**, aldehydes **125** and anhydrides **184** (Scheme 39).[53] Carried out at room temperature in diethyl ether as the solvent in the presence of only 4 mol% of organocatalyst **182** and TEA (triethylamine) as a base, the process afforded the corresponding chiral tetrazole-derived hemiaminals **185** through DKR in both homogeneous high yields (76-98%) and enantioselectivities (72-94% *ee*). A mechanism involving a Lewis base-assisted acylation is proposed in Scheme 39. It began with the reversible addition of tetrazole **183** to aldehyde **125**, generating transient hemiaminal species **186**. Alternatively, chiral acylpyridinium cation **187** was generated from anhydride **184** and Lewis base catalyst **182**. The latter reacted with hemiaminal species **186** to give final hemiaminal **185**.



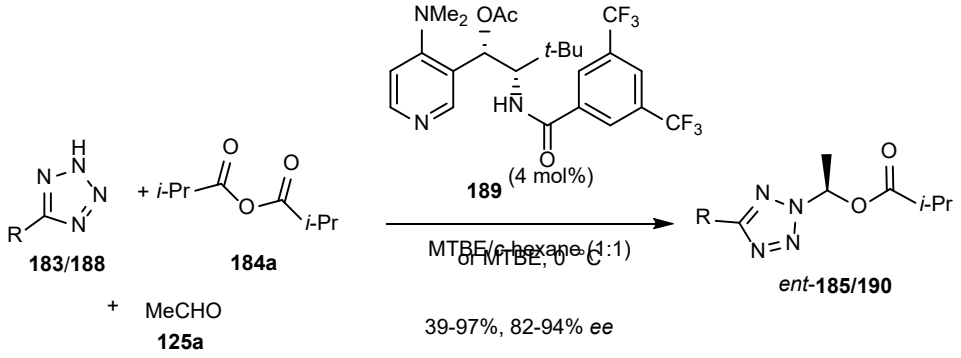
proposed mechanism:



Scheme 39. Three-component reaction of tetrazoles, aldehydes and anhydrides.

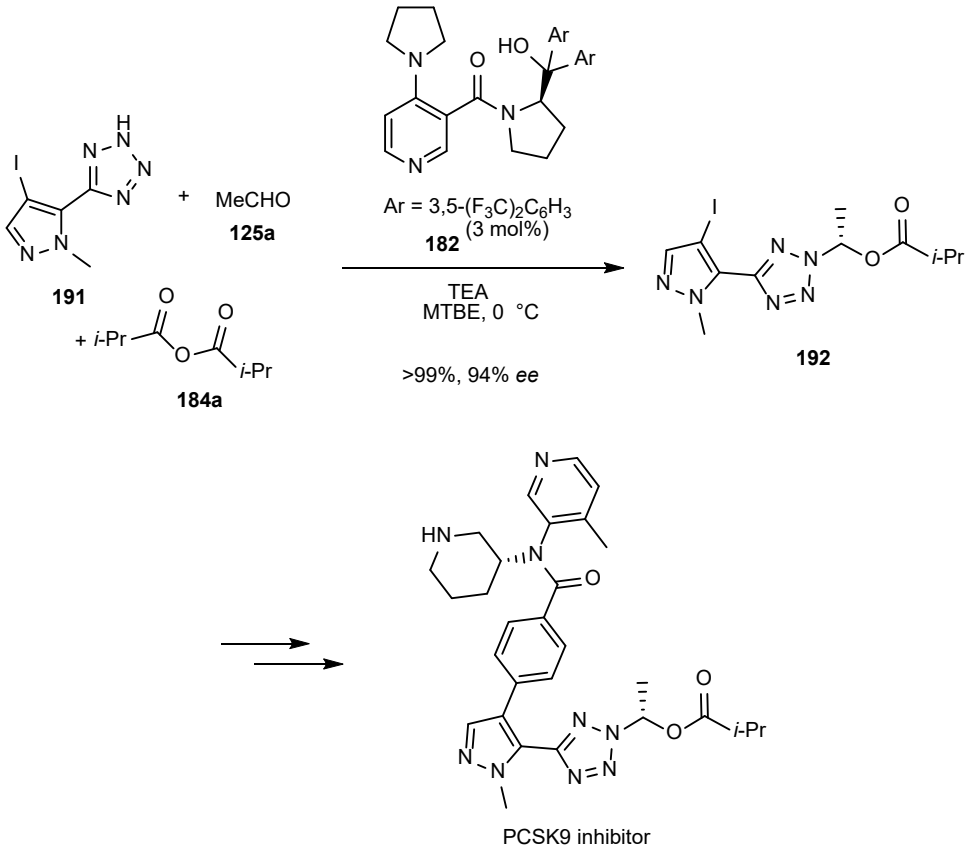
In 2017, Piotrowski and Suna reported the synthesis of a novel chiral *N,N*-dimethylaminopyridine catalyst to be applied in comparable reactions.[54] As shown in Scheme 40, in this case the three-component reaction between tetrazoles **183**/**188**, acetaldehyde **125a** and isobutyric anhydride **184a** was performed at 0 °C in a 1:1 mixture of MTBE and cyclohexane as the solvent (or pure MTBE in some cases). Catalyzed by 4 mol% of chiral catalyst **189** in the absence of an external base, the transformation resulted in the regio- and enantioselective formation of the corresponding chiral azole-

derived hemiaminal esters *ent*-**185**/**190** in moderate to excellent yields (39-97%) and high enantioselectivities (82-94% *ee*). A variety of substituents (R) on the tetrazole partner was compatible, spanning from (hetero)aromatic to aliphatic ones, providing uniformly high enantioselectivities (84-94% *ee*). Moreover, the reaction of 5-unsubstituted tetrazole (R = H) led to the corresponding product with a comparable ee value (82% *ee*).



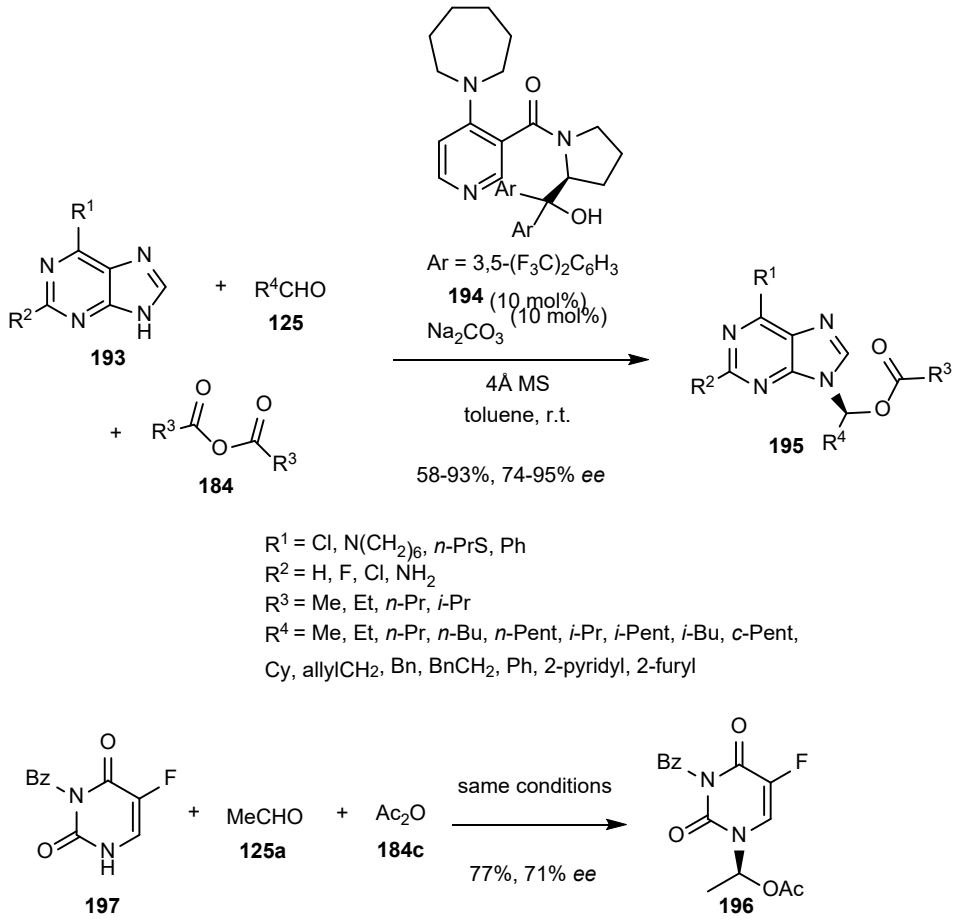
Scheme 40. Three-component reaction of tetrazoles, acetaldehyde and isobutyric anhydride.

A comparable methodology was applied by the same authors to synthesize an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9).[55] In this case, an even lower catalyst loading of 3 mol% of pyridine-based Lewis base **182** was found optimal to promote the three-component reaction of tetrazole **191** with acetaldehyde **125a** and isobutyric anhydride **184a** in MTBE as the solvent. Performed at 0 °C in the presence of TEA as a base, the DKR process afforded the corresponding chiral tetrazole-derived hemiaminal **190** in quantitative yield and 94% *ee* (Scheme 41). The latter was further converted into the desired PCSK9 inhibitor.



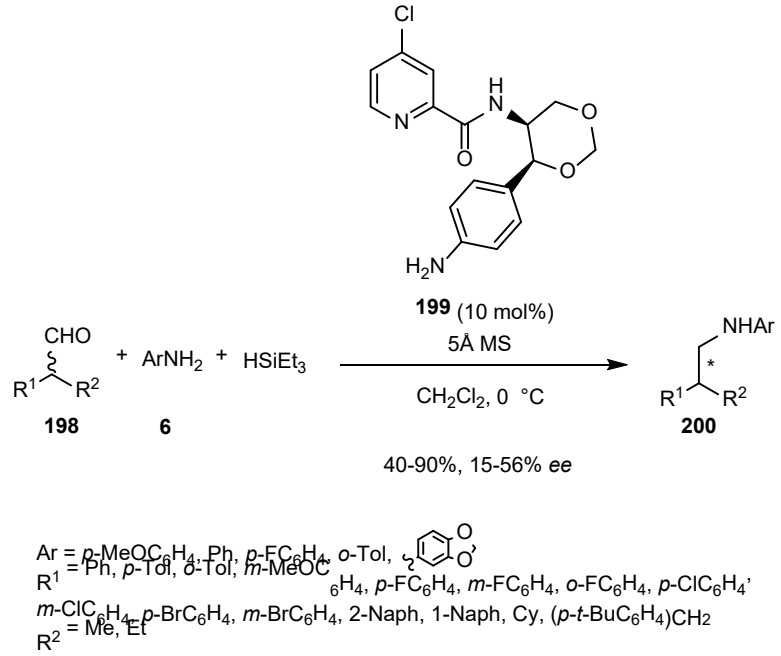
Scheme 41. Three-component reaction of a tetrazole, acetaldehyde and isobutyric anhydride and synthesis of a PCSK9 inhibitor.

In the same area, Xie and Guo developed in 2018 a novel route to chiral acyclic purine nucleosides containing a hemiaminal ester moiety evolving through DKR.[56] The latter arose from the regio- and enantioselective three-component reaction of purines **193**, aldehydes **125** and anhydrides **184** catalyzed at room temperature by 10 mol% of chiral 4-azepanyl-derived pyridine **194** in toluene as the solvent. Performed in the presence of Na_2CO_3 as a base, the DKR process led to a wide range of chiral acyclic purine nucleoside analogues **195** with good yields (58-93%) and enantioselectivities (74-95% *ee*), as illustrated in Scheme 42. The catalyst system tolerated various aliphatic aldehydes, including straight-chain, α- and β-branched, as well as cyclic aliphatic aldehydes, which provided the corresponding products with uniformly high ee values (91-95% *ee*). In addition, (hetero)aromatic aldehydes were also found compatible, leading to the desired products with slightly lower enantioselectivities (83-89% *ee*). The scope of the methodology was extended to the synthesis of potent antitumor chiral (acyloxyalkyl)-5-fluorouracil **196** which arose from the reaction of benzoyl-protected 5-fluorouracil **197**, acetaldehyde **125a** and acetic anhydride **184c** achieved with 77% yield and 71% *ee*.



Scheme 42. Three-component reactions of purines/protected 5-fluorouracil, aldehydes and anhydrides.

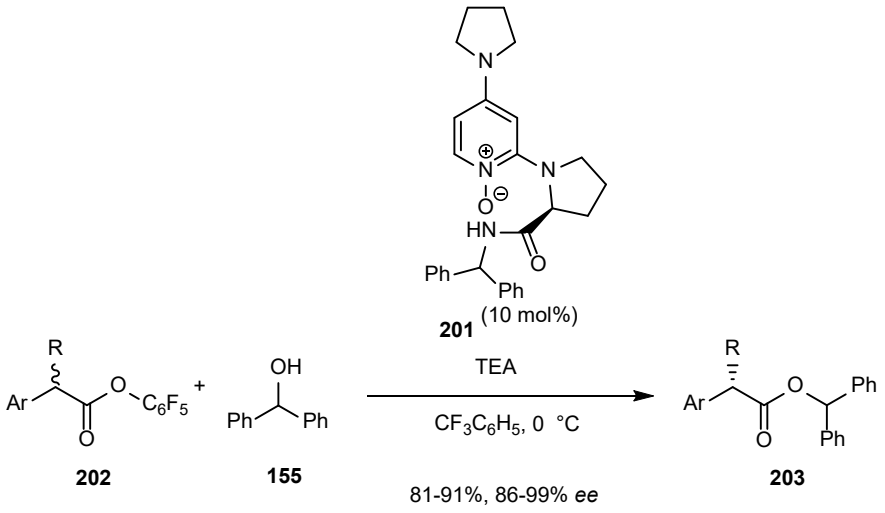
Earlier in 2017, an enantioselective reductive amination of α-branched aldehydes evolving through DKR was described by Zhang et al.[57] It involved the asymmetric three-component reaction between α-branched aldehydes **198**, aromatic amines **6** and triethylsilane as the reductant agent. The process was catalyzed at 0 °C by 10 mol% of chiral pyridine-derived Lewis base **199** in dichloromethane as the solvent. As depicted in Scheme 43, the corresponding β-branched chiral amines **200** were formed in moderate to high yields (40-90%) combined with low to moderate enantioselectivities (15-56% *ee*).

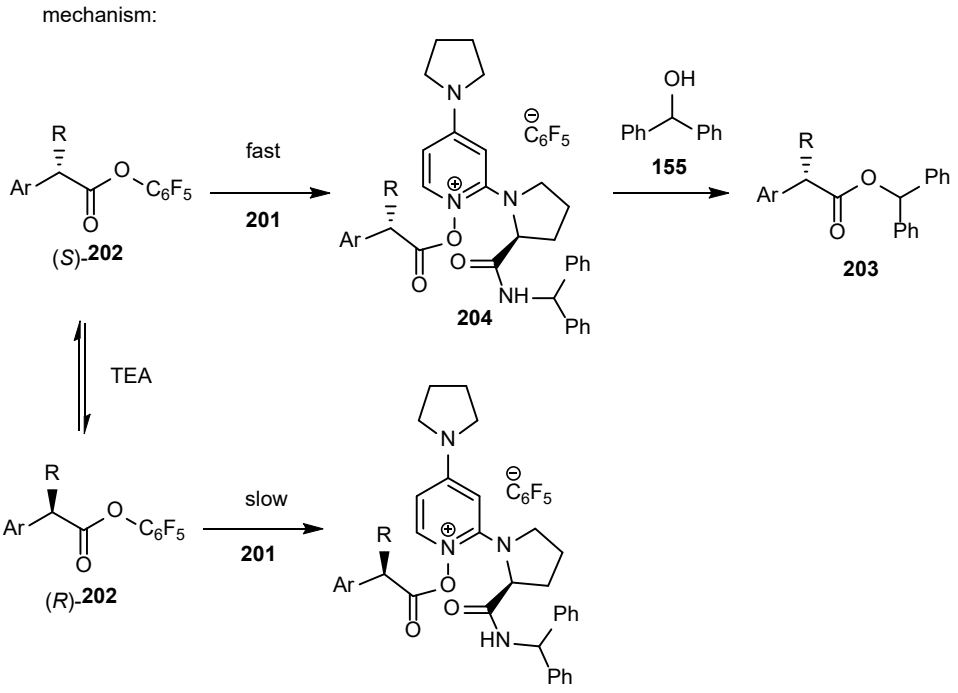


Scheme 43. Three-component reductive amination of α-branched aldehydes, aromatic amines and triethylsilane.

5.1.2. Other reactions

Very recently, Guo, Tian and Xie reported that bifunctional chiral 4-pyrrolidinopyridine *N*-oxide catalyst **201** promoted the DKR of pentafluorophenol esters **202** through transesterification with diphenylmethanol **155**.[58] As presented in Scheme 44, a range of esters reacted with this alcohol in the presence of TEA as a base and 10 mol% of chiral catalyst **201** at 0 °C in trifloromethylbenzene as the solvent to give the corresponding chiral α-aryl α-alkyl carboxylic esters **203** in both uniformly high yields (81-91%) and enantioselectivities (86-99% *ee*). The substrate was supposed to be racemized in the presence of TEA (Scheme 44). The (*S*)-enantiomer reacted faster with the catalyst to form the corresponding *O*-acylated pyridinium cation intermediate **204**, which further underwent a nucleophilic substitution with diphenylmethanol **155** to give the final product. To demonstrate the utility of the process, it was successfully applied to the synthesis of several esters of nonsteroidal anti-inflammatory drugs, such as (*S*)-ibuprofen ester, (*S*)-ketoprofen ester, (*S*)-fenaprofen ester, (*S*)-flurbinprofen ester, and (*S*)-naproxen ester.



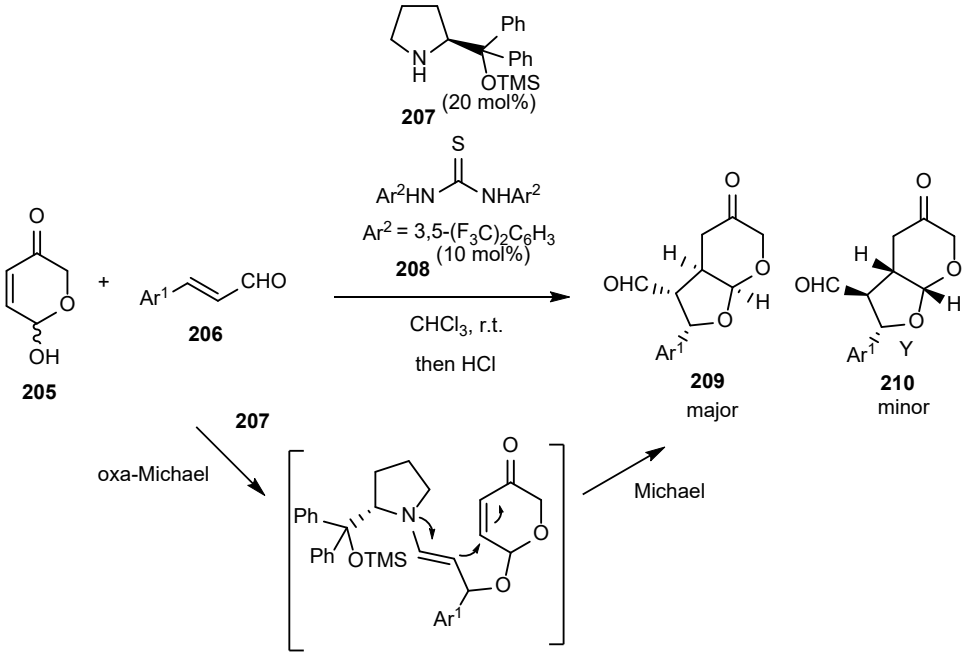


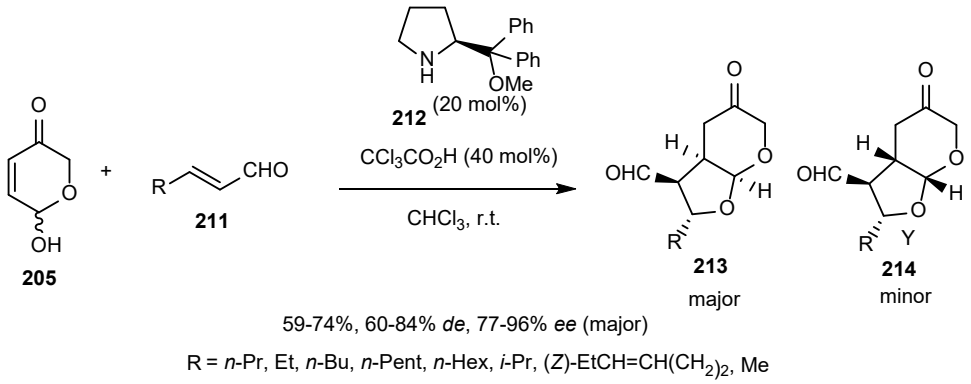
Scheme 44. Transesterification of pentafluorophenol esters with diphenylmethanol.

5.2. Proline-derived Lewis bases

L-Proline derivatives constitute simple, cheap and readily available aminocatalysts employed in many asymmetric transformations.[59] The first use of L-proline to promote a DKR process was reported by Walsh et al., in 2004.[60] It dealt with asymmetric aldol reactions of atropisomeric amides, such as benzamides and naphthamides, with acetone performed with enantioselectivities of up to 95% *ee*. Ever since, many proline derivatives have been successfully applied to promote other types of DKR through imine/enamine catalysis. In an example reported in 2017, Vicario and Merino employed chiral proline derivatives to promote an asymmetric domino oxa-Michael/Michael reaction between hydroxypyranone **205** as unconventional *O*-nucleophile and α,β-unsaturated aldehydes, evolving through DKR and iminium/enamine activation (Scheme 45).[61] When β-aryl substituted α,β-unsaturated aldehydes **206** were involved as electrophiles, the best results were obtained by using 20 mol% of proline-derived catalyst **207** in chloroform as the solvent in the presence of achiral thiourea **208** as an additive. Performed at room temperature, the cascade reaction afforded mixtures of two diastereomers **209** and **210** with good yields (61-87%), moderate to high diastereoselectivities in favor of diastereomers **209** (34-82% *de*)

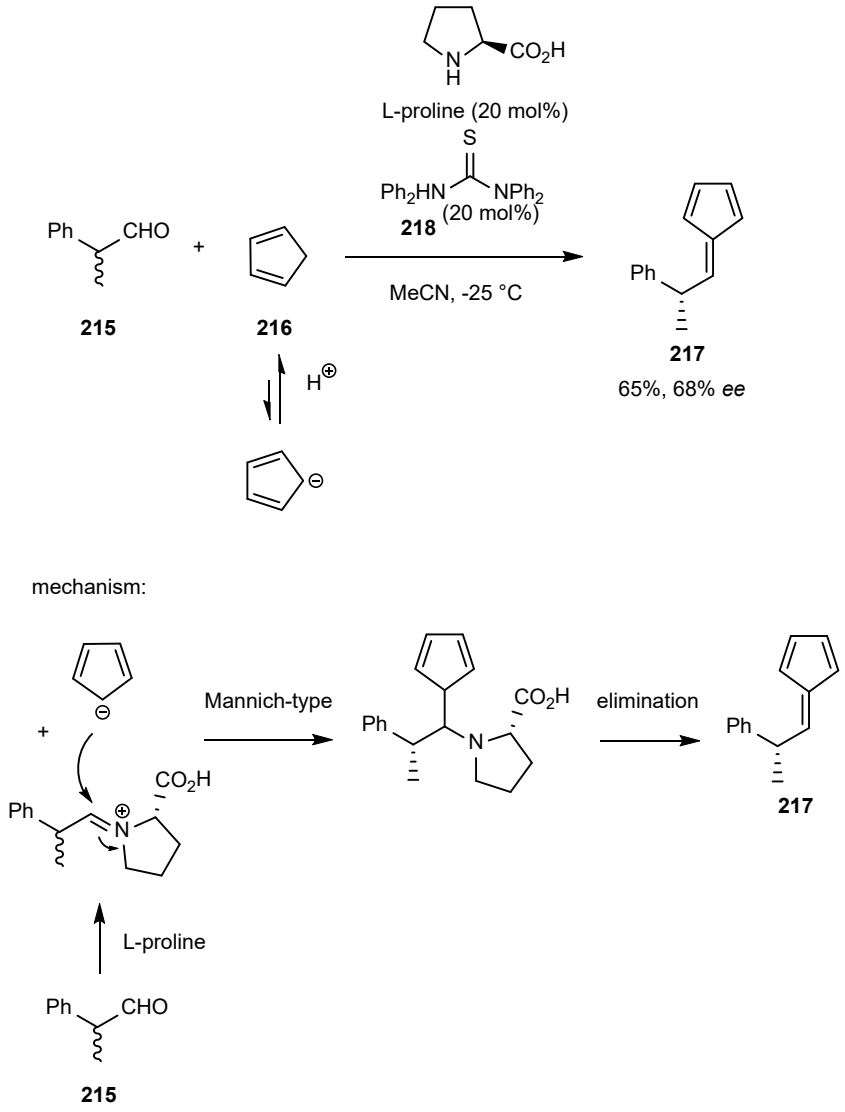
and high enantioselectivities (86-97% *ee*). Cinnamaldehyde derivatives bearing either electron-withdrawing or electron-donating groups at the β-aryl substituent all provided high ee values (86-95% *ee*) as well as a β-heteroaryl substituted substrate (Ar^1 = 2-furyl, 97% *ee*). In the case of β-alkyl substituted α,β-unsaturated aldehydes **211**, the reaction with hydroxypyranone **205** required the use of closely related proline-derived catalyst **212** at 20 mol% of catalyst loading in the presence of trichloroacetic acid as an additive. Under these optimal conditions, the domino process occurred at room temperature in chloroform as solvent to yield major diastereomers **213** along with minor ones **214** in good yields (59-74%), moderate to good diastereoselectivities (60-84% *de*) and high enantioselectivities (77-96% *ee*). The catalyst system tolerated α,β-unsaturated aldehydes containing alkyl chains of different length and size. The DKR was based on the fact that one enantiomer of hydroxypyranone **205** reacted faster than the other.





Scheme 45. Domino oxa-Michael/Michael reactions of hydroxypyranone with β-aryl/alkyl-substituted α,β-unsaturated aldehydes.

In 2018, Kögerler et al. described the first catalytic asymmetric formation of a fulvene derivative from a racemic α,α-disubstituted aldehyde.[62] As illustrated in Scheme 46, 2-phenylpropanal **215** reacted with cyclopentadiene **216** in the presence of 20 mol% of simple L-proline in acetonitrile as the solvent to provide the corresponding chiral fulvene **217** in moderate yield (65%) and enantioselectivity (68% *ee*). The DKR reaction required the use of *N,N*-diphenylthiourea **218** as an additive and a low temperature (-25 °C) to prevent isomerization of the product. Its mechanism evolving through iminium catalysis is depicted in Scheme 46.

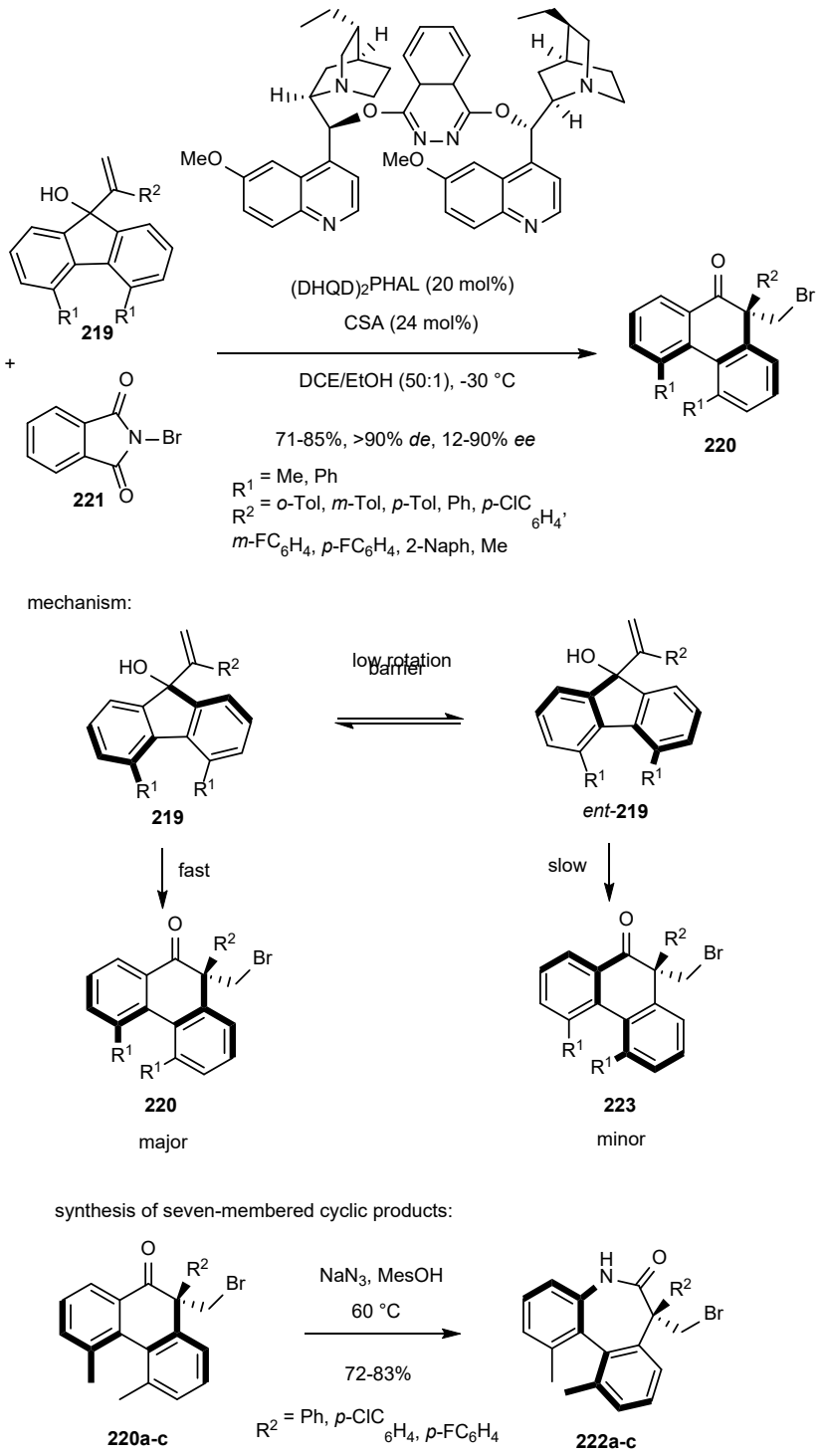


Scheme 46. Domino Mannich-type/dehydration reaction of 2-phenylpropanal with cyclopentadiene.

5.3. Other Lewis bases

In 2017, Yeung et al. disclosed the use of organocatalyst $(DHQD)_2PHAL$ (DHQD = dihydroquinidine, PHAL = 1,4-phthalazinediyl) as promotor of a semi-pinacol rearrangement of fluorenes **219** into chiral 9,10-dihydrophenanthrenes **220** evolving through DKR (Scheme 47).[63] The reaction employed *N*-bromophthalimide **221** as the brominating agent and camphor sulfonic acid (CSA) as an additive. It was performed at -30 °C in a 50:1 mixture of DCE and ethanol as solvent in the presence of 20 mol% of hydroquinidine-derived organocatalyst $(DHQD)_2PHAL$. A range of fluorenes **219** were compatible, leading to the corresponding chiral biaryl products **220** in good yields (71-85%) as almost single diastereomers (>90% *de*) and variable enantioselectivities (12-90% *ee*). A quaternary stereocenter as well as axial chirality were generated in a single operation. Substrates bearing electron-donating substituents all provided high enantioselectivities (80-90% *ee*) with the best ee value (90% *ee*) in the reaction of a bulkier *ortho*-tolyl(Tol)-substituted substrate (R^2 = *o*-Tol). Moreover, the presence of electron-withdrawing groups on the substrates was also tolerated, affording the corresponding products **220** in good to high enantioselectivities (72-88% *ee*). The observed enantioselectivity was slightly lower (74-78% *ee*) in the reaction of 2-naphthyl- and methyl-substituted substrates (R^2 = 2-Naph, Me). The lowest ee value (12% *ee*) was obtained when changing methyl (R^1 = Me) to phenyl substitution (R^1 = Ph). The utility of this novel methodology was demonstrated by converting some products **220a-c** (R^1 = Me, R^2 = Ph, *p*-ClC_6H_4, *p*-FC_6H_4) into biologically relevant seven-membered cyclic dibenzolactams **222a-c** through ring expansion by treatment with sodium azide and methanesulfonic acid at 60 °C (Scheme 47). The DKR process was explained by a low rotation barrier in the 4,5-dimethylfluorene system, resulting in a rapid racemization between atropisomers **219** and *ent*-**219**. Then, the asymmetric ring expansion occurred

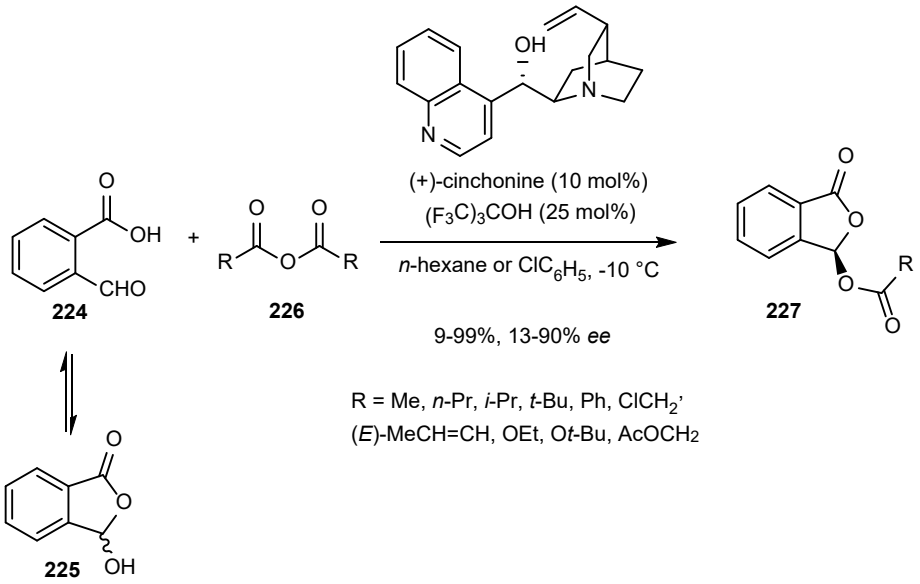
faster on enantiomer **219**, leading preferentially to configurationally stable atropisomer **220** instead of minor product **223** arisen from *ent*-**208** (Scheme 47).



Scheme 47. Semi-pinacol rearrangement of fluorenes with *N*-bromophthalimide.

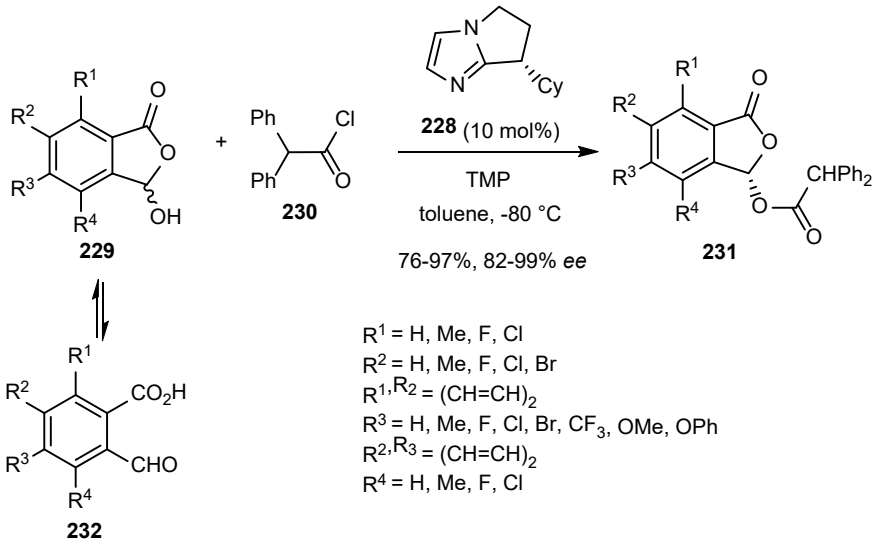
Also in 2017, Schreiner et al. employed 10 mol% of (+)-cinchonine as Lewis base catalyst to promote the reaction of 2-formylbenzoic acid **224** or its tautomeric form 3-hydroxyphthalide **225** with anhydrides **226** to produce the corresponding chiral phthalides **227**.[64] The acylation reaction occurred through DKR at -10 °C in *n*-hexane or chlorobenzene as solvent in the presence of 25 mol% of nonafluoro-*tert*-butanol as an additive. As shown in Scheme 48, a series of acylated 3-

hydroxyphthalides **227** were synthesized with both low to excellent yields (9-99%) and enantioselectivities (13-90% *ee*). The worst result (9% yield, 13% *ee*) was obtained in the reaction of 2-formylbenzoic acid with an α,β-unsaturated anhydride (R = (*E*)-MeCH=CH). When the solubility of the carboxylic anhydrides (R = *t*-Bu, CH_2Cl) was low in *n*-hexane, the enantioselectivities were found higher by using chlorobenzene as solvent (78-80% *ee* vs 42-52% *ee*).



Scheme 48. Acylation of 2-formylbenzoic acid with anhydrides.

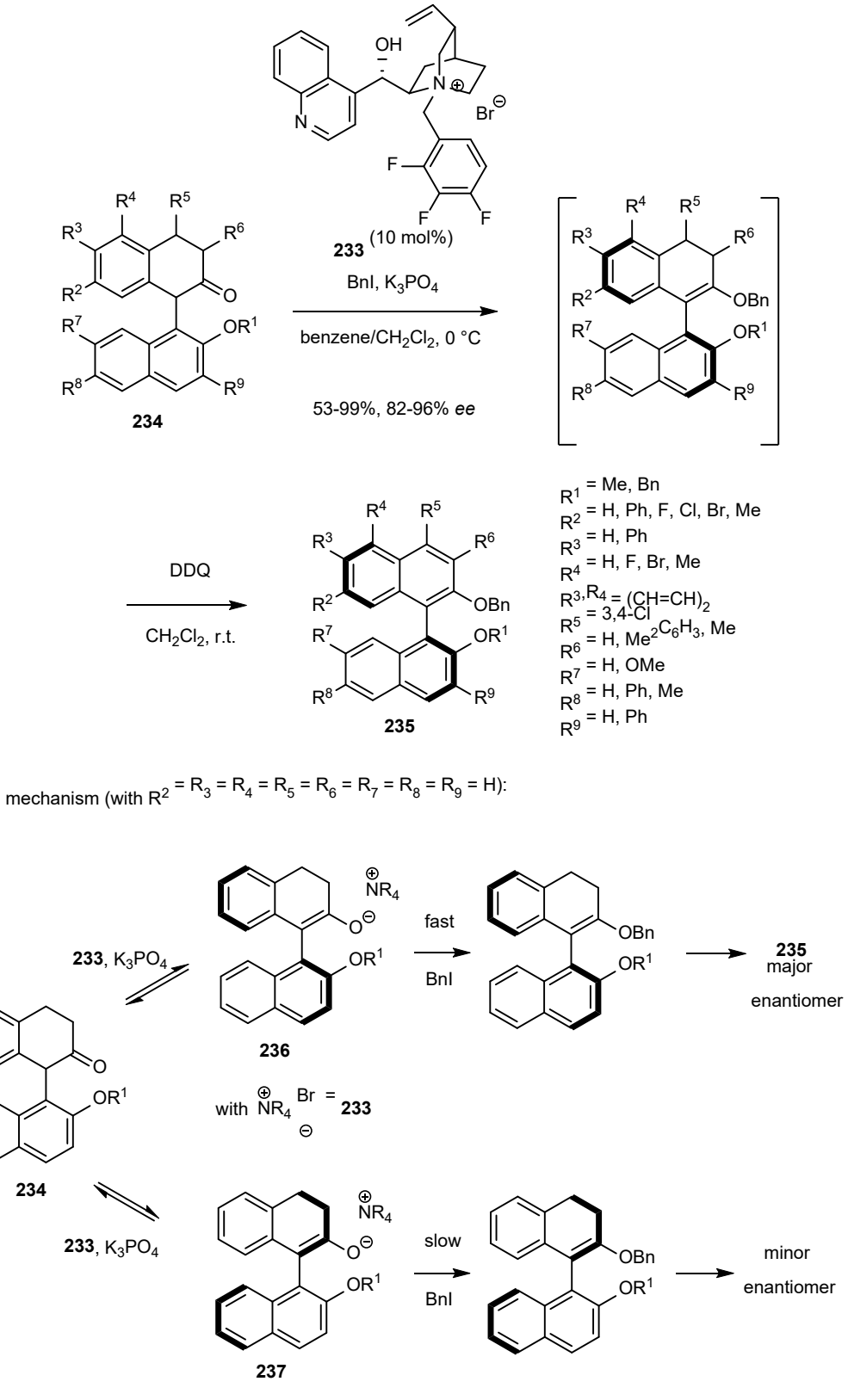
In 2021, Zhang et al. employed chiral bicyclic imidazole organocatalyst **228** to promote asymmetric acylation of 3-hydroxyphthalides **229** with diphenyl acetyl chloride **230**.[65] The reaction evolving through DKR was carried out at -80 °C in toluene as the solvent in the presence of a sterically bulky secondary amine as a base, such as tetramethylpiperidine (TMP). Promoted by 10 mol% of chiral organocatalyst **228**, it resulted in the formation of a wide range of variously substituted chiral phthalidyl esters **231** in both uniformly high yields (76-97%) and enantioselectivities (82-99% *ee*). The spontaneous equilibrium between 3-hydroxyphthalides (*R*)- and (*S*)-**229** and their corresponding aldehyde **232** allowed the DKR to be achieved (Scheme 49).



Scheme 49. Acylation of 3-hydroxyphthalides with diphenyl acetyl chloride.

6. Dynamic Kinetic Resolutions Promoted by Phase-Transfer Catalysts

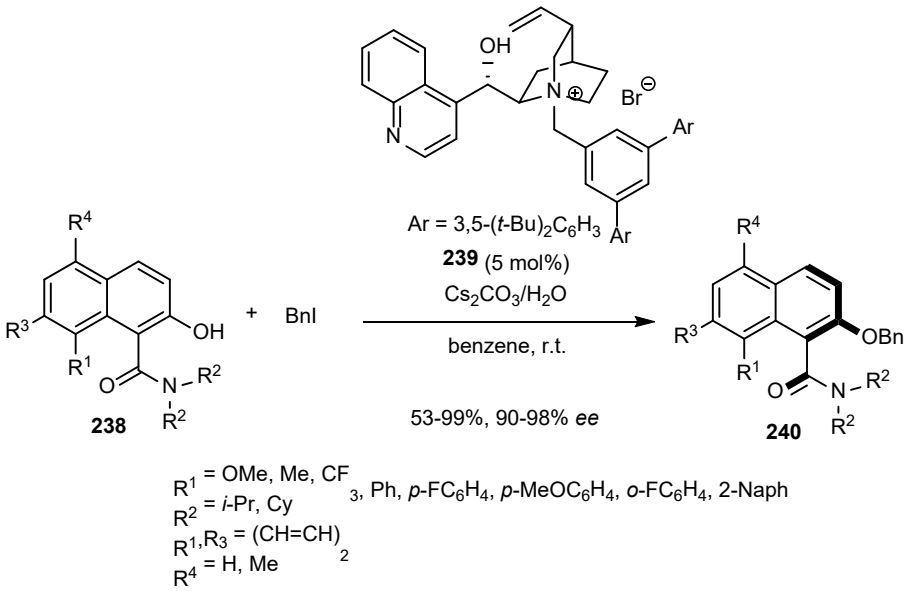
Smith et al. developed in 2017 a highly enantioselective organocatalytic synthesis of atropisomeric biaryl derivatives based on a cation-directed *O*-alkylation (Scheme 50).[66] In the presence of 10 mol% of chiral quinidine-derived ammonium salt **233** under basic conditions, racemic 1-aryl-2-tetralones **234** reacted with benzyl iodide through *O*-alkylation to give, after subsequent oxidation by treatment with DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone), the corresponding chiral BINOL derivatives **235** with moderate to quantitative yields (53-99%) and uniformly high enantioselectivities (82-96% *ee*). To explain the DKR process, the authors proposed that the reaction began with an initial interfacial deprotonation of racemic 2-tetralone **236** with K_3PO_4 to generate axially chiral and racemic potassium enolates. These stereoisomeric enolates could interconvert through rapid and reversible protonation and deprotonation via tetralone **234**. Counterion metathesis with chiral ammonium salt catalyst **233** generated soluble diastereoisomeric ion pairs **236** and **237**, which were alkylated with benzyl iodide at different rates to provide atroposelectivity, with product **235** as the major enantiomer.

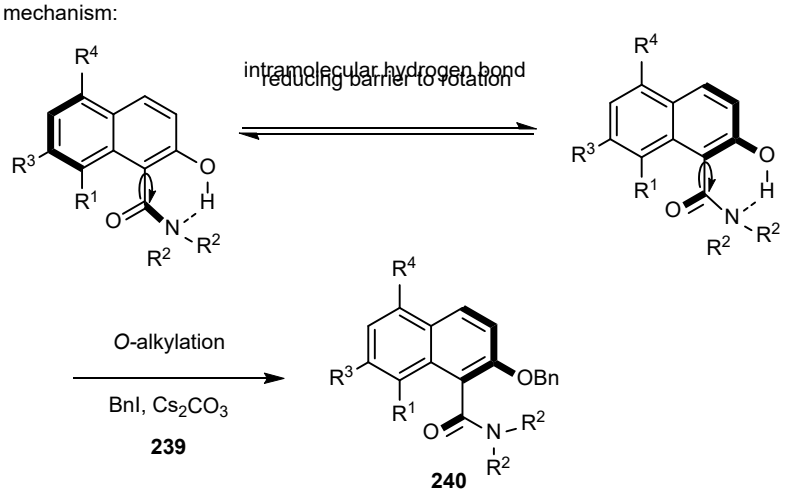


Scheme 50. *O*-Alkylation of 1-aryl-2-tetralones.

Later in 2019, these authors disclosed an asymmetric *O*-alkylation of naphthamides **238** with benzyl iodide evolving through DKR.[67] It was based on the use of 5 mol% of *N*-benzyl cinchoninium bromide **239** as organocatalyst and aqueous Cs_2CO_3 as base (Scheme 51). Performed in benzene at room temperature, it generated the corresponding axially chiral

napthamides **240** with uniformly high enantioselectivities (90-98% *ee*) and moderate to quantitative yields (53-99%). The DKR was enabled by the involvement of an intramolecular hydrogen-bond between the 2-hydroxy group and the amide nitrogen of the starting naphthamide favoring the interconversion between its two enantiomeric forms (Scheme 51). This racemization allowed an enantioselective synthesis of axially chiral amides via atroposelective *O*-functionalization. The increased barrier to rotation of the formed *O*-alkylated products precluded their racemization, enabling DKR. Studying the scope of the process, the authors found that changing the *N*-alkyl group (R^2) from an isopropyl to a cyclohexyl group maintained both high yield (87%) and enantioselectivity (96% *ee*). Moreover, the presence of a methyl group at the 4-position of the phenanthrenyl system (R^4 = Me) was also tolerated, leading to the corresponding product in 83% yield and 94% *ee*. In addition, the reaction of a range of 8-substituted naphthyl systems (R^1) provided homogeneously excellent ee values (90-98% *ee*).



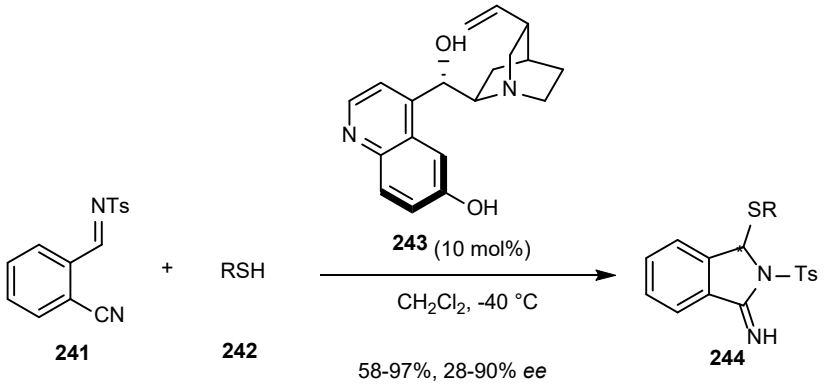


Scheme 51. *O*-Alkylation of naphthamides with benzyl iodide.

7. Dynamic Kinetic Resolutions Promoted by Cinchona Alkaloid-Based Brønsted Base Catalysts

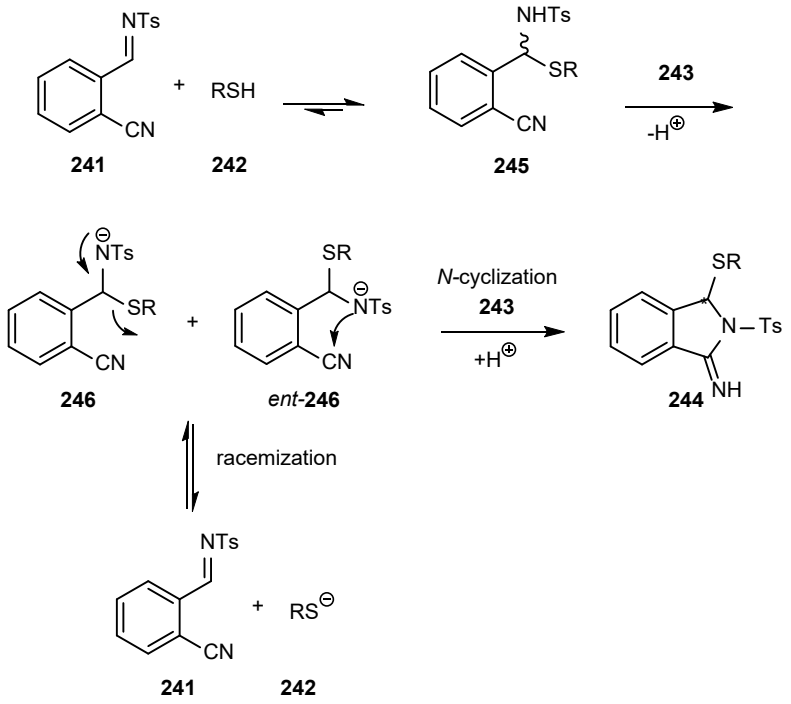
Basic cinchona alkaloids are simple Brønsted bases not particularly stereoselective, probably due to the rather loose nature of nonbonded interactions between extended organic anions and quaternary ammonium salts. On the other hand, activation by bifunctional species including both a hydrogen-bond donor and a Brønsted base moiety has evolved into a general strategy in asymmetric catalysis. The most applied bifunctional hydrogen-bond donor/Brønsted base catalysts are cinchona alkaloids containing a hydrogen-bond donor.[68] This type of robust and tunable catalysts has been widely applied to promote DKRs. The first organocatalytic DKR catalyzed by modified cinchona alkaloid-derived catalysts was reported

by Deng and Hang, in 2003.[69] It dealt with an alcoholytic ring-opening of *N*-carboxyanhydrides, leading to the corresponding chiral amino esters with good enantioselectivities (up to 75% *ee*) and yields (up to 87%). Ever since, many types of DKRs have been developed in the presence of other cinchona alkaloid-derived Brønsted base catalysts. In an example reported in 2017 by Palombi et al., a novel route to an unprecedented class of multiheteroatomic chiral products exhibiting an *N,S*-acetal functionality was opened on the basis of a domino nucleophilic addition/heterocyclization reaction evolving through DKR (Scheme 52).[70] It involved an asymmetric heterocyclization of 2-cyano-*N*-tosyl(Ts)benzylidenimine **241** with thiols **242** organocatalyzed at -40 °C by 10 mol% of cinchona alkaloid **243** in dichloromethane as solvent. The one-pot reaction afforded the corresponding products **244** in good to quantitative yields (58-97%) and low to high enantioselectivities (28-90% *ee*). The best enantioselectivities were generally achieved in the reaction of substituted aryl thiols bearing electron-donating (74-90% *ee*) and relatively electron-neutral groups (64-76% *ee*). On the other hand, lower ee values (28-54% *ee*) were obtained in the addition of aryl thiols exhibiting electron-withdrawing substituents (28-44% *ee*), but also alkyl- (54% *ee*) and benzylthiols (36% *ee*). Moreover, the catalyst system was found compatible with thioglycolate (R = CH_2CO_2Me) and 3-mercaptopropionate (R = $(CH_2)_2CO_2Me$), which allowed the corresponding heterocyclic products to be synthesized in moderate to good enantioselectivities (70-84% *ee*). To explain the results, the authors proposed the mechanism depicted in Scheme 52, beginning with the nucleophilic addition of thiol **242** to 2-cyano-*N*-tosylbenzylidenimine **241** to give intermediate **245**. Then, the latter was deprotonated in the presence of the catalyst to provide a mixture of enantiomers **246** and *ent*-**246**. Subsequently, an irreversible heterocyclization of the enantiomer kinetically favored occurred, while the opposite enantiomer underwent a rapid racemization through the equilibrium with starting materials, thus allowing the DKR to occur.



R = *p*-Tol, *m*-Tol, *o*-Tol, 2,4,6-*i*-$Pr_3C_6H_2$, 2-Naph, Ph, Cy, *p*-$Me_2NC_6H_4$, *p*-$MeOC_6H_4$, *p*-$MeSC_6H_4$, *p*-$MeOC_6H_4CH_2$, *o*-BrC_6H_4, *p*-BrC_6H_4, MeO_2CCH_2, $MeO_2C(CH_2)_2$

proposed mechanism:



Scheme 52. Domino nucleophilic addition/heterocyclization of 2-cyano-*N*-tosylbenzylidenimine with thiols.

8. Conclusions

Although asymmetric catalysis has encountered extensive development during the last decades, the simplest industrial methodology to prepare chiral products is still the resolution of racemates, in spite of its major default related to the limitation of the yield to 50%. By solving this major disadvantage, DKR has undoubtedly become a serious alternative to conventional methods for asymmetric synthesis, providing up to 100 % yield. Concomitantly, asymmetric green organocatalysis plays an increasing and central role in synthetic organic chemistry applicable to a wide variety of transformations, including those evolving through DKR. This is only in the last two decades that the first examples of organocatalyzed DKRs have been described, triggering an impressive growth of this special field. The present review collecting the developments published in the last six years demonstrates the blooming of this special field joining the two powerful concepts that are DKR and organocatalysis. A wide variety of organocatalysts, including phosphoric acids, (thio)ureas, squaramides, peptides, N-heterocyclic carbenes, Lewis bases, phase-transfer catalysts, and cinchona alkaloid-based Brønsted bases among other catalysts, are today capable of promoting DKRs of many types.

For example, significant enantioselectivities have been recently described in a wide variety of complex domino reactions evolving through DKR. Among them, domino nucleophilic addition/heterocyclization reactions of 2-cyano-*N*-tosylbenzylidenimine with thiols catalyzed by cinchona alkaloid-based catalysts provided enantioselectivities of up to 90%

ee. Domino aldol-type reaction/cyclization reactions of *trans*-diaryl succinic anhydrides with aldehydes and domino double cyclization reactions to synthesize helicenes were also found highly enantioselective when mediated by squaramides (up to >99% *ee*). Furthermore, phosphoric acid catalysts were also demonstrated to be highly efficient to promote different types of domino reactions, including Ugi-type reactions with up to 96% *ee*, domino dehydration/1,8-addition/protonation/*N*-cyclization reactions of 3-substituted 1H-indoles with propargylic alcohols with 98% *ee*, domino imine formation/cyclization reactions of *ortho*-formyl naphthamides with pyrrolylanilines with >99% *ee*, and domino iodination/nucleophilic addition/rearrangement reactions of indoles with NIS to give chiral spirooxindoles in 99% *ee*. Another type of organocatalysts, such as N-heterocyclic carbenes, were also applied to the DKR of acyclic ketoacids through intramolecular domino aldol/lactonization reactions with up to 90% *ee*. Moreover, pyridine-based Lewis bases promoted with 94-95% *ee* three-component reactions of tetrazoles or purines with aldehydes and anhydrides. Other domino reactions evolving through DKR, such as domino cyanohydrin formation/oxa-Michael reactions of 1,7-diketones with acetone cyanohydrin; domino cyanohydrin formation/hemiacetalization/oxa-Michael reactions of δ-oxo-α,β-unsaturated ketones, acetone cyanohydrin and phenyl trifluoromethyl ketone; along with domino Michael/cyclization/isomerization/oxidation reactions of dicyanoolefins and nitroolefins under oxygen atmosphere were performed with 94-98% *ee* in the presence of thiourea catalysts. Moreover, proline derivatives were used to promote with up to 97% *ee* domino oxa-Michael/Michael reactions of hydroxypyranone with β-aryl/alkyl-substituted α,β-unsaturated aldehydes. In addition, tandem ring-opening/chlorination reactions of terphenyl lactones were catalyzed by peptides with up to 98% *ee*.

Along with domino reactions, many other types of DKR processes could be highly efficiently organocatalyzed, including brominations of axially chiral biaryls, such as 8-aryl-quinolines and cyanoarenes, mediated by cinchona alkaloid-derived urea catalysts and bifunctional cinchona alkaloids, respectively, with high enantioselectivities (84-90% *ee*). Bifunctional cinchona alkaloid catalysts also provided excellent enantioselectivities (97% *ee*) in Michael additions of thiophenols to arylnaphthoquinones. Other cinchona alkaloid-based catalysts provided high enantioselectivities in semi-pinacol rearrangements of fluorenes with *N*-bromophthalimide (90% *ee*); acylations of 2-formylbenzoic acid with anhydrides (90% *ee*); and *O*-alkylations of 1-aryl-2-tetralones and naphthamides (96-98% *ee*). Moreover, phosphoric acids were applied to promote coupling reactions between 2-substituted 3,3'-bisindoles and isatin-derived 3-indolylmethanols (>99% *ee*) and that of naphthyl-indoles with *o*-hydroxybenzyl alcohols/azodicarboxylates (96% *ee*). This type of organocatalysts also allowed transfer hydrogenations of biaryl lactols with aromatic amines and Hantzsch esters (94% *ee*) or dihydrobenzodiazepines with benzothiazoline (>99% *ee*) to be achieved as well as DKR of α-substituted cyclohexanones by reaction with *O*-phenylhydroxylamine with up to 94% *ee*. Other types of transformations, spanning from benzoin condensations (95->99% *ee*) to transesterifications of α,α-disubstituted carboxylic esters (98% *ee*), redox esterifications of 6-hydroxy-3-pyranones with enals or alkynals (92% *ee*) or the first DKR of hemiaminals without α-hydrogen achieved through *O*-acylation of 3-hydroxy-3-trifluoromethylbenzosultams with aldehydes (97% *ee*) were developed in the presence of N-heterocyclic carbenes catalysts. Moreover, thiourea catalysts allowed the first transesterification of Bringmann's lactones to be achieved with 98% *ee* along with enantioselective S_N2-type acetalization of enols with γ-chlorobutenolide (90% *ee*). An excellent level of enantioselectivity (99% *ee*) was also disclosed in using a chiral bicyclic imidazole catalyst to promote the acylation of 3-hydroxyphthalides with diphenyl acetyl chloride. In addition, excellent enantioselectivities of up to 94% *ee* were also described by using peptide catalysts to mediate atroposelective brominations of (hetero)biaryl and non-biaryl compounds.

It is obvious that the field of organocatalytic DKR will still expand its scope with the employment of already known but also novel organocatalysts to even more types of (novel) transformations. Furthermore, these powerful economic and ecologic strategies will be more and more applied in the near future to the synthesis of biologically relevant molecules and natural products.

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Keywords: Asymmetric catalysis; Asymmetric synthesis; Chirality; Dynamic kinetic resolution; Organocatalysis.

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