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Kinetic Resolution, Dynamic Kinetic Resolution and Asymmetric Desymmetrization by N-Heterocyclic Carbene Catalysis

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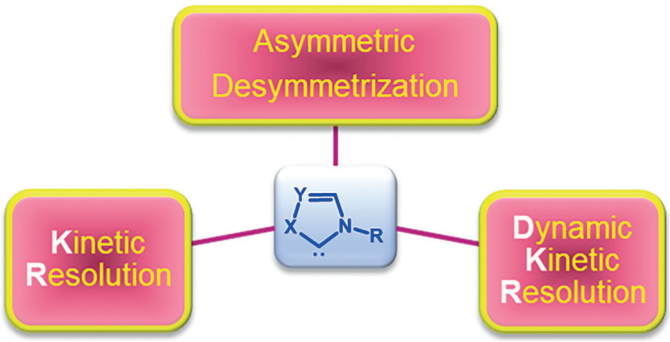

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Abstract N-Heterocyclic carbenes (NHCs) are now well-established organocatalysts for a large number of asymmetric and non-asymmetric transformations. In the last 15 years, there has been significant interest in using NHCs in kinetic resolution (KR), dynamic kinetic resolution (DKR) and asymmetric desymmetrization reactions for the stereoselective synthesis of enantioenriched compounds, with diverse substrates and activation modes being adopted to this end. This short review brings into focus the progress made on NHC-catalyzed KR, DKR, and asymmetric desymmetrization from 2004 until December 2018■■*OK?*■■. The literature discussed in this article is classified on the basis of the type of reaction involving the NHC catalyst.

Key words N-heterocyclic carbenes, kinetic resolution, dynamic kinetic resolution, asymmetric desymmetrization, organocatalysis, asymmetric synthesis

1 Introduction

N-Heterocyclic carbenes (NHCs) represent powerful organocatalysts which mediate a variety of chemical transformations in either chiral or achiral fashion, not just through classical *umpolung* (polarity reversal) reactivity but also via acyl-anion-free reactions.[1]

Driven by the constant search for novel catalysts for non-enzymatic asymmetric transformations, over the last 15 years NHCs have seen their role expand as promoters of stereoselective processes proceeding via kinetic resolution (KR), dynamic kinetic resolution (DKR) and asymmetric desymmetrization.[2]

As laid down in IUPAC recommendations,[3] kinetic resolution is '*the achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)*'.[4] In this process, efficiency is something fundamental being assessed by the selectivity factor (*s*), which has been shown to be related to several parameters, such as the relative reaction rates of the two enantiomers, the reaction conversion (c) and the enantiomeric excess (ee) of either the reaction product or the recovered starting material.[5]

As a type of KR, DKR is distinguished by the equilibration of a mixture of stereoisomers (enantiomers or diastereomers) through an in situ epimerization occurring prior to or during the KR.[6] It should be made clear that DKR could theoretically convert 100% of the starting material into a single stereoisomer of the target product, in contrast to KR which is expected to provide no more than a 50% yield.

Besides, desymmetrization allows for '*the modification of an object which results in the loss of one or more symmetry elements, such as those which preclude chirality (mirror plane, centre of inversion, rotation-reflection axis), as in the conversion of a prochiral molecular entity into a chiral one*' (100% theoretical yield).[7]

In order to correctly apply these principles to NHC-catalyzed KR, DKR and asymmetric desymmetrization, many research efforts have been directed at finding suitable substrates since 2004, when Suzuki and co-workers reported the first example of NHC-promoted enantioselective KR.[8]

In this respect, a broad range of candidates were sought and used very effectively in KR processes, with examples including secondary (tertiary) alcohols, 1,2-diols, axially chiral diols and amino alcohols, secondary amines, sulfoximines and diverse heterocycle-based scaffolds (Figure 1).

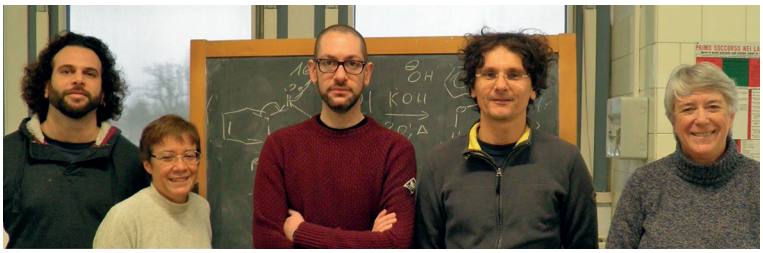
Enolizable α- and β-stereogenic carbonyl compounds along with hemiacetals were suitable starting materials for DKR reactions, while the desymmetrization procedures were conveniently run starting from both *meso* and prochiral compounds via enantiotopic group selection or enantiotopic facial differentiation.

The advances in the application of NHC catalysis to (dynamic) kinetic resolution and asymmetric desymmetrization have been recently collected in three review articles.[2] In such cases, the contents are discussed and organized in terms of (i) the different intermediates involved,[2a] (ii) the deracemization (desymmetrization) method adopted to generate the enantioenriched product(s),[2b] and (iii) the substrate structure.[2c]

However, no systematic survey based on the reaction types involving NHCs has been hitherto reported, to the best of our knowledge. In this short review we have collated■■*change OK?*■■ the literature on the reactions used to achieve KR, DKR and asymmetric desymmetrization under NHC catalysis between 2004 and December 2018.

The different transformations have been organized in sections according to the type of reaction which implicates the NHC catalyst. In detail, Section 2 is dedicated to acylation strategies by distinguishing between *O*-acylation (subsection 2.1), *N*-acylation (subsection 2.2) and *C*-acylation (subsection 2.3). Aldol-acylation processes are detailed in Section 3, while benzoin- and Stetter reactions are covered in Section 4 and Section 5, respectively. Finally, Section 6

Biographical Sketches



Olga Bortolini (right) received a Laurea degree in chemistry from the University of Padova (1979). She was a CNR research fellow (1983–1987), Associate Professor of Organic Chemistry at the University of Ferrara (1987–2003), Professor of Organic Chemistry at the University of Calabria (2003–2010). She is presently Head of the Department of Chemical and Pharmaceutical Sciences at the University of Ferrara■■*change OK?*■■. Her main research interests include studies of reaction mechanisms in solution (metal-catalyzed oxidation systems) and in the gas phase (organocatalyzed reactions), ionic liquids, N-heterocyclic carbenes and bio-equivalents for new C–C bond formation.

Alessandro Massi (2nd from right) received his Ph.D. (1999) from the University of Ferrara. He then joined the group of Prof. S. V. Ley at the University of Cambridge as a postdoctoral fellow (1999–2000). He returned to the University of Ferrara working as Research Associate until 2014 when he became Assistant Professor at the Department of Chemical and Pharmaceutical Sciences. He is the author of more than 100 publications in scientific international journals including patents, review articles and book chapters. His recent research interests include heterogeneous organocatalysis, umpolung catalysis, flow chemistry, and biomass valorization.

Graziano Di Carmine (middle) obtained his bachelor's degree in 2011 from the University of Rome (Tor Vergata), under the supervision of Prof. Barbara Floris. In the same year, he moved to Bologna to complete his master's studies at "Alma Mater Studiorium" (University of Bologna), working on H-bond catalysis under the supervision of Prof. Luca Bernardi. In 2015, after a short period in industry, he joined the group of Prof. Olga Bortolini at the University of Ferrara as a Ph.D. student. His research comprises umpolung reactivity (mediated by both organocatalysis and biocatalysis) and heterogenization of organocatalysts for batch and flow chemistry.

Carmela De Risi (2nd from left) graduated in chemistry at the University of Ferrara (1992) and received her Ph.D. in organic chemistry in 1996. That same year, she joined the group of Prof. P. Vogel at the University of Lausanne where she spent a one-year research period as a grant holder. She then moved back to the University of Ferrara where she performed postdoctoral studies (1997–1999). Since November 1999, she has been a Research Associate at the University of Ferrara. Her main research interests focus on synthesis and modification of biologically active compounds, general synthetic methodologies, organocatalysis, and biomass valorization.

Daniele Ragno (left) received his Ph.D. in chemistry in 2016 from the University of Ferrara, under the supervision of Prof. Alessandro Massi. In 2015 he worked in the research group of Prof. Albrecht Berkessel at the Institute of Organic Chemistry of the University of Cologne as a visiting Ph.D. student. Since 2018, he has been a Research Associate at the Department of Chemical and Pharmaceutical Sciences of the University of Ferrara. His main research interests include organocatalysis, heterogeneous catalysis, flow chemistry and green chemistry.

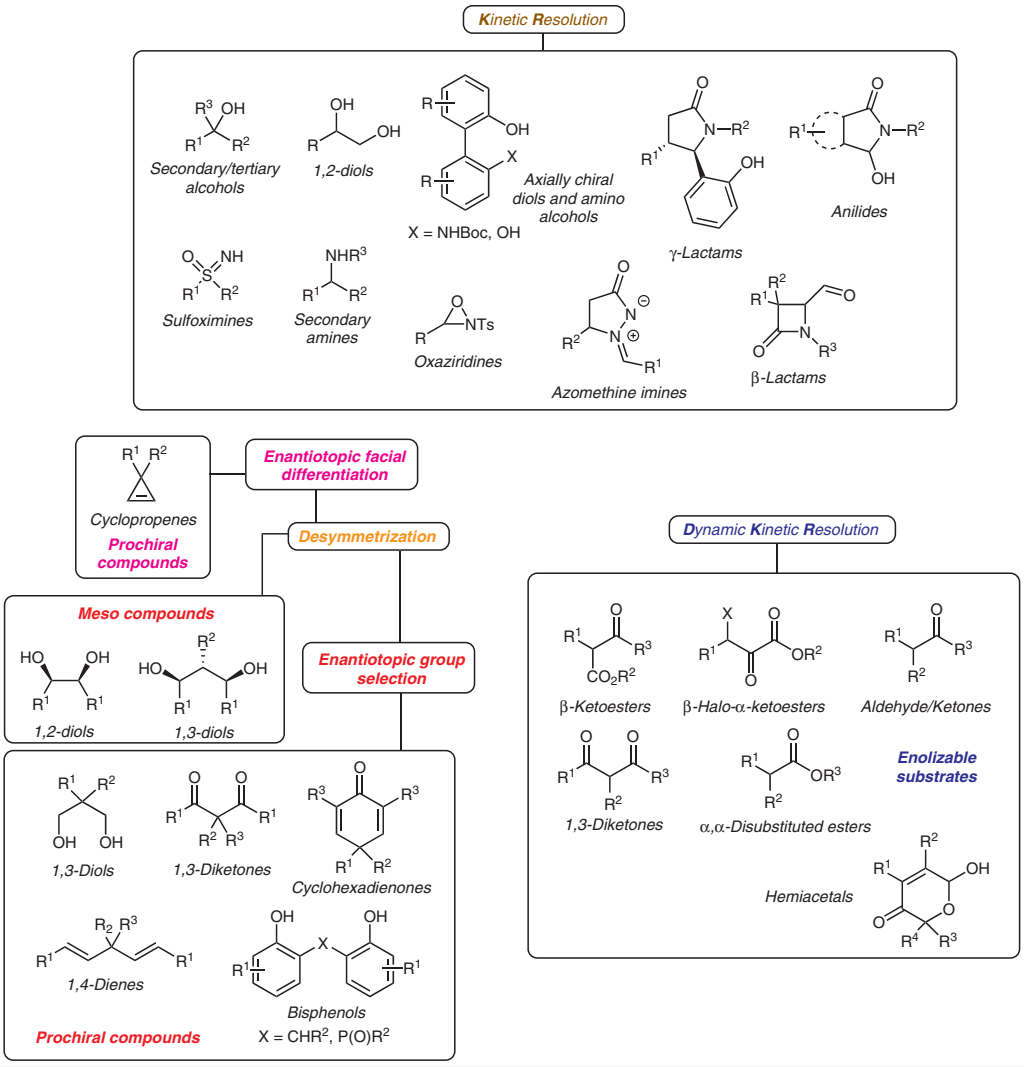


Figure 1 Substrate diversity of NHC-catalyzed KR, DKR and asymmetric desymmetrization reactions

discusses a series of miscellaneous approaches for which there are only a few examples, namely ring expansion, cycloaddition, annulation and transesterification.

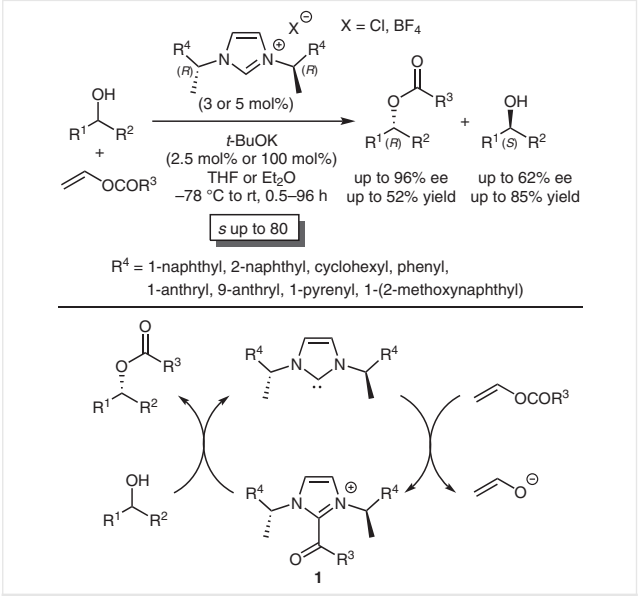
For the sake of clarity, the papers discussed in each section (subsection) have been organized on the basis of two main criteria: chronological order and modus operandi for the generation of the chiral non-racemic target compounds. It also has to be said that alongside synthetic points, wherever possible, particular focus was placed on the most outstanding stereochemical and mechanistic aspects.

2 Acylation Strategies

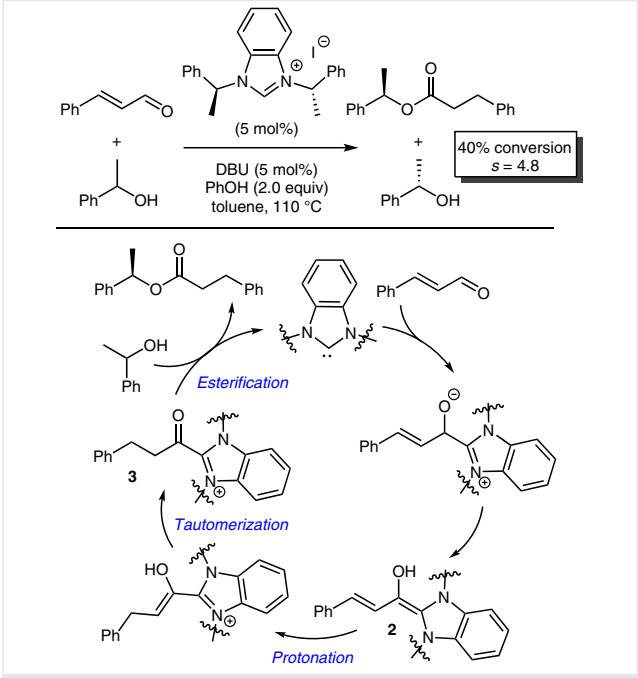
This section presents NHC-catalyzed KR, DKR, and asymmetric desymmetrization reactions proceeding via *O*-, *N*- and *C*-acylation.[9] In this class, traditional acylating agents (i.e., activated derivatives of carboxylic acids) or aldehydes were used as appropriate acyl donors.

2.1 *O*-Acylation

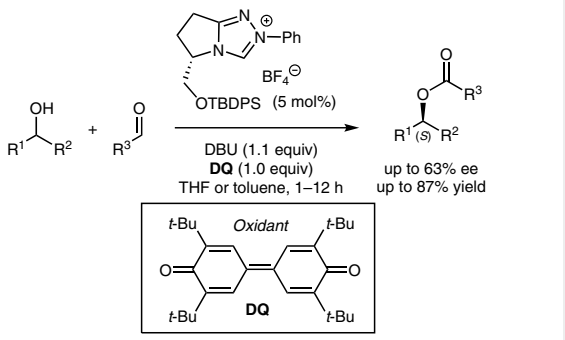
Suzuki[8,10] and Maruoka[11] effectively resolved racemic secondary aryl and cinnamyl alcohols through transesterification with vinyl esters in the presence of chiral NHCs derived from C_2-symmetric 1,3-bis(1-arylethyl)imidazolium salts (Scheme 1).



Scheme 1 NHC-catalyzed KR of racemic secondary alcohols via transesterification with vinyl esters



Scheme 2 NHC-promoted KR of racemic 1-phenylethanol



Scheme 3 NHC-catalyzed KR of secondary alcohols via oxidative esterification

An acylazolium[1k] intermediate **1**, in turn arising from the NHC and the vinyl ester, is presumed to be involved as the key species, which reacts preferentially with one enantiomer of the alcohol substrate. The selectivities depended on both the stereochemical properties and steric hindrance of the *N*-substituents,[8,10] as well as on the bulkiness of the vinyl esters.[11]

As a matter of fact, the best results were obtained using vinyl diphenylacetate in combination with NHCs bearing (*R*)-1-naphthylethyl or (*R*)-1-phenylethyl groups on the nitrogen atoms, with (*R*)-configured acylated products of 87–96% ee (*s* factor = 22–80) being produced.

NHC-catalyzed *O*-acylative KR, DKR and asymmetric desymmetrization have been reported based on the use of aldehydes as acyl donors.[12–15]

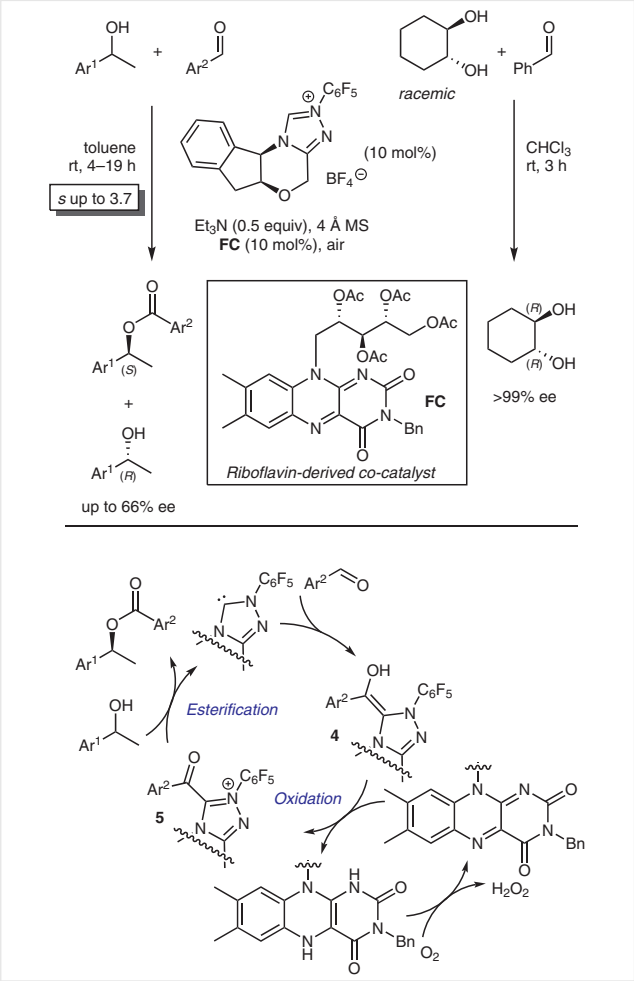
Scheidt and co-workers were able to resolve racemic 1-phenylethanol by reaction with cinnamaldehyde in the presence of the NHC derived from chiral 1,3-bis(1-phenylethyl)imidazolium iodide■■*1,3-bis(1-phenylethyl)-1H-benzo[d]imidazolium iodide?*■■ (Scheme 2).[12,13] Sequential protonation of homoenolate **2** and tautomerization produces the chiral acyl azolium **3**, which preferentially reacts with the (*R*)-enantiomer of 1-phenylethanol.

A NHC-catalyzed oxidative esterification approach has been applied by Studer et al. for the KR of secondary alcohols using aryl, heteroaryl and α,β-unsaturated aldehyde counterparts in the presence of the bisquinone oxidant 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (**DQ**) (Scheme 3).[14]

In Studer's work[14] the selectivity factor was strictly dependent upon the alcohol concentration. In this regard, model studies on racemic 1-(1-naphthyl)ethanol demonstrated that the best result (*s* = 7.3) was achieved when a large excess (25 equiv) of the racemic alcohol was used under conditions that are pseudo first order.

Combination of a chiral-triazolium-salt-derived NHC and a catalyst originating from riboflavin (**FC**) proved effective for the organocatalytic KR of racemic secondary alcohols via oxidative esterification of aldehydes using oxygen as the terminal oxidant (Scheme 4).[15]

1-Phenylethanol, 1-(1-naphthyl)ethanol, and 1-(2-naphthyl)ethanol were selected as the counterparts of benzaldehyde, 1-naphthaldehyde, and 2-naphthaldehyde providing 39–66% ee of the unreacted (*R*)-alcohols (*s* = 2.3–3.7). Excellent results were found for the reaction between *trans*-1,2-cyclohexanediol and benzaldehyde affording the



Scheme 4 KR of secondary alcohols using a chiral NHC/riboflavin-derived catalytic system

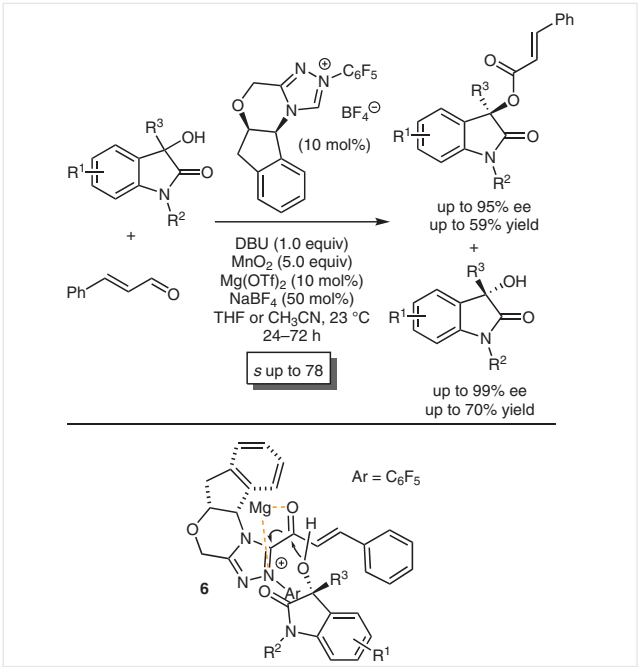
(1*R*,2*R*)-configured diol in >99% ee. In all cases, the chirality of the NHC was solely responsible for the observed enantioselectivities.

Under the optimized reaction conditions found for KR reactions, the chiral NHC/**FC** catalytic system has led to the asymmetric desymmetrization of *cis*-1,2-cyclohexanediol in the presence of benzaldehyde. The corresponding (1*S*,2*R*)-monobenzoate was obtained in 64% ee, albeit the yield was rather modest (30%) due to the concomitant formation of the *meso*-dibenzoate.

It is likely that the oxidative esterification process proceeds via the acyl intermediate **5**, in turn derived by flavin-promoted oxidation of Breslow species **4**, with the flavin catalyst being regenerated from its reduced form by an oxygen-mediated electron transfer reaction.

It is worthy of note that attempts to use the chiral NHC/**FC** couple to perform the oxidative amidation and thioesterification of aldehydes with amines and thiols, respectively, proved unsatisfactory in terms of both efficiency and selectivity (up to 9% ee).

Cooperative catalysis involving a NHC[10] and a Lewis acid paved the way for the KR of 3-hydroxy-3-substituted oxindoles via *O*-acylation with cinnamaldehyde under oxidative conditions (Scheme 5).[16,17] In this process, combination of the NHC, the Lewis acid $Mg(OTf)_2$ and $NaBF_4$ as an additive guaranteed excellent selectivity, giving access to highly enantiomerically enriched 3-hydroxyoxindoles with several different 3-substituents (e.g., alkyl, alkenyl, alkynyl and aryl groups) as well as diverse substitution patterns on either the oxindole ring or the nitrogen atom.

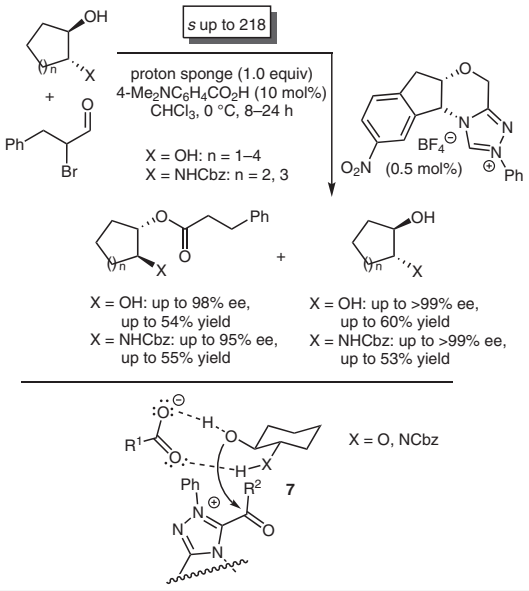


Scheme 5 KR of tertiary alcohols by NHC/Lewis acid catalyzed *O*-acylation

From a mechanistic point of view, it has been postulated that the acyl azolium intermediate **6** suffers nucleophilic attack by the tertiary hydroxy group on the side that is opposite to the backbone of the chiral catalyst, while the Lewis acid activates the substrate in a synergistic fashion. Besides, the substrate conformation is most likely secured by secondary interactions between the aryl ring on the oxindole compound and the styrenyl residue on **6**.

Moreover, as far as the additive is concerned, it most likely interacts with the *N*-pentafluorophenyl group of the catalyst. This effect probably impacts the transition state of the reaction thereby influencing the enantioselectivity.[18]

In 2013, Takasu, Yamada and co-workers applied a chiral NHC/carboxylate salt couple to promote the KR of *trans*-cycloalkane-1,2-diols and *trans*-2-aminocycloalkanols through *O*-acylation in the presence of an α-bromo aldehyde (Scheme 6).[19] High levels of selectivities have been observed for these processes, with *s* values up to 218 and up to >99% ee for the recovered starting materials.

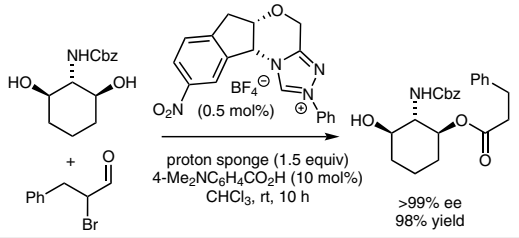


Scheme 6 KR of *trans*-cycloalkane-1,2-diols and *trans*-2-aminocycloalkanols catalyzed by a chiral NHC/carboxylate salt couple

One salient feature of this approach is represented by the enhancement of both rate and enantioselectivity compared to other NHC-catalyzed asymmetric acylations of alcohols appended with adjacent H-bond donor moieties. These effects have been attributed to the presence of the in situ generated carboxylate anion, which likely facilitates the C–O bond formation in the acylation step. Calculations led to the assumption that the carboxylate co-catalyst is involved in a possible transition state **7** wherein it serves as a Brønsted base to deprotonate the hydroxy group and participates in hydrogen bonding interactions with the adjacent moiety.

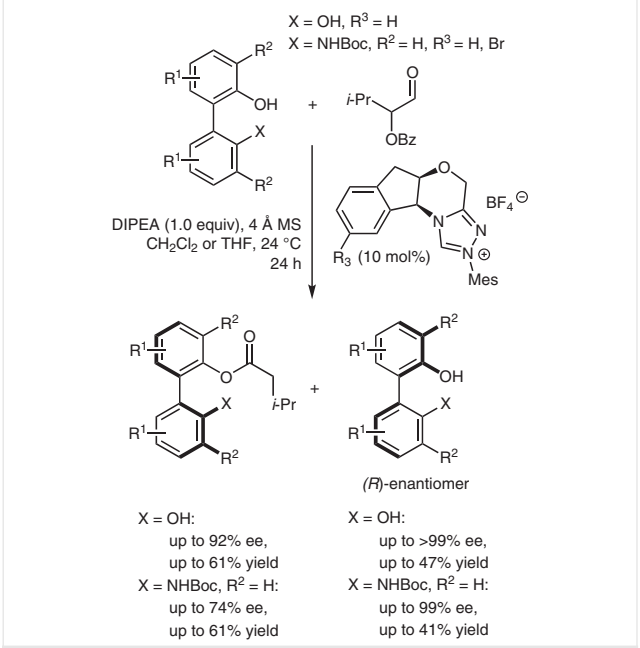
Besides, totally selective *O*-acylation of 2-aminocycloalkanols has been observed, confirming literature data on the ability of acylazolium intermediates to acylate preferentially alcohols instead of amines.[20]

It is striking that the chiral NHC/carboxylate-salt-induced *O*-acylation was also applied to the highly effective asymmetric desymmetrization of *N*-Cbz-protected 2-amino-1,3-cyclohexanediol (Scheme 7).



Scheme 7 Asymmetric desymmetrization of *N*-Cbz-protected 2-amino-1,3-cyclohexanediol catalyzed by a chiral NHC/carboxylate salt system

One year later, the Zhao group reported a chiral NHC-catalyzed atroposelective acylation for the KR of axially chiral diols and amino alcohols using an α-benzoyloxy aldehyde as the acyl donor (Scheme 8).[21] A series of 1,1′-biaryl-2,2′-diols as well as *N*-Boc-protected 2-amino-2′-hydroxy-1,1′-biaryl derivatives were resolved with high selectivity (*s* factor up to 116), with all starting materials being recovered in ≥99% ee.

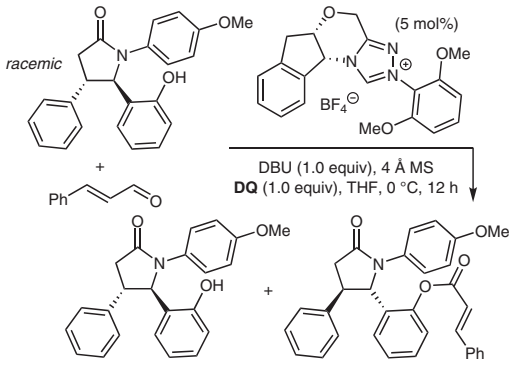


Scheme 8 NHC-catalyzed atroposelective acylation for the KR of axially chiral diols and amino alcohols

These results have been explained by assuming that either phenol–phenol or phenol–amine intramolecular hydrogen bonds may help boost the nucleophilicity of the substrates and (or) organize their active conformations.

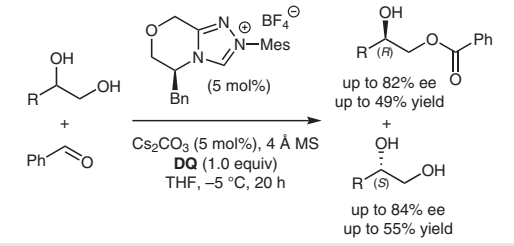
Interestingly, chiral NHC-catalyzed *O*-acylation reactions have been successfully extended to the KR of *trans*-γ-lactams bearing a 2-hydroxyphenyl substituent at C-5 (Scheme 9).[22] In a proof-of-concept study, it has been shown that the phenolic hydroxy group on the lactam substrate could take part in the oxidative esterification of cinnamaldehyde to provide the enantioenriched starting material in 44% yield and 45% ee.

Recently, Chi and co-workers reported the KR of alkyl-, aryl- and heteroaryl-substituted 1,2-diols bearing both secondary and primary alcohol motifs via chiral NHC-catalyzed benzaldehyde oxidative esterification.[23] This process gave rise to selective acylation of the primary alcohol moiety producing chiral enantioenriched 1,2-diols and their corresponding monoester compounds (Scheme 10). It is possible for the secondary alcohol group to participate in



Scheme 9 KR of racemic *trans*-γ-lactams by NHC catalysis

non-covalent interactions that likely control both the selective acylation and the KR process, in line with results already reported for related substrates.[19,21,24]

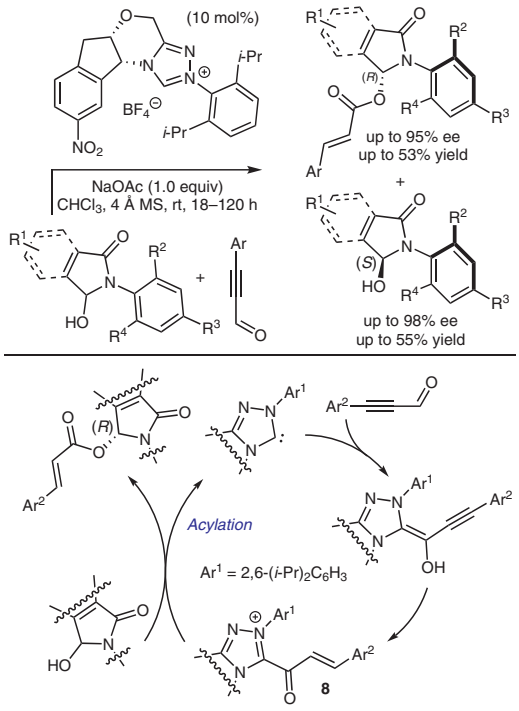


Scheme 10 NHC-catalyzed KR of 1,2-diols by benzaldehyde oxidative esterification

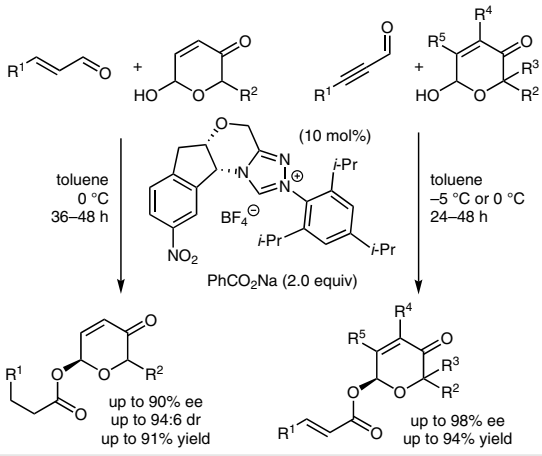
Wang and co-workers have developed a very efficient NHC-catalyzed *O*-acylation strategy for the KR of anilides to generate axially chiral isoindolinones (Scheme 11).[25] A conceivable course for the asymmetric esterification of anilides passes through acyl azolium **8**, which is attacked by the anilide hydroxy group to give the (*R*)-configured *O*-acylated product. It seems convincing that the nucleophilic addition to the carbonyl group of **8** takes place opposite to the catalyst backbone, thereby elucidating the observed stereocontrol.

In the field of DKR reactions, Wang and co-workers have accomplished the asymmetric *O*-acylation of 6-hydroxypyranones through redox esterification with enals or alkynals catalyzed by a chiral NHC (Scheme 12).[26] This method provided structurally diverse 6-acyloxy-3-pyranones in good to high yields and with high stereoselectivities. The compounds obtained were eventually used to prepare carbohydrate derivatives and key precursors for natural products synthesis.

Chiral NHC catalysts were also used for the asymmetric desymmetrization of *meso*-diols[27,28] and dihydroxy prochiral compounds[29–32] via *O*-acylation. In particular, internal oxidative (Scheme 13, a)[27] and external oxidative (Scheme 13, b)[28] protocols have been efficaciously applied to *meso*-



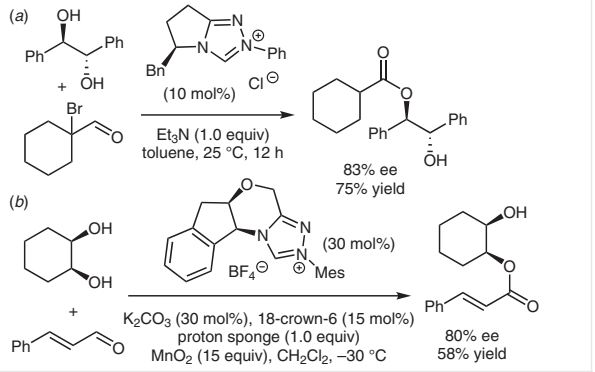
Scheme 11 NHC-catalyzed enantioselective KR of anilides via *O*-acylation



Scheme 12 NHC-catalyzed DKR of 6-hydroxypyranones

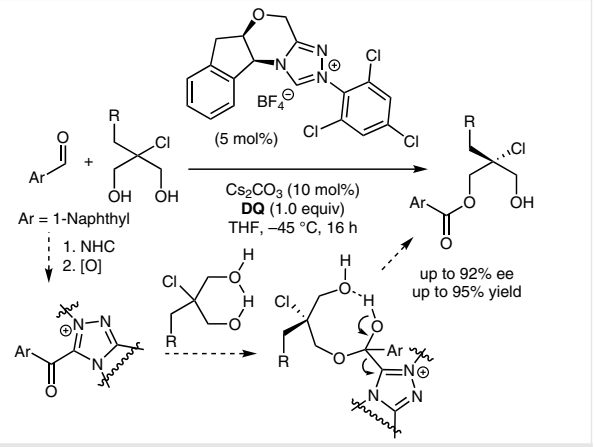
hydrobenzoin and *cis*-1,2-cyclohexanediol using an α-haloaldehyde as well as cinnamaldehyde as suitable reaction partners, respectively.

A chiral NHC-catalyzed oxidative esterification method has opened the way to the asymmetric desymmetrization of prochiral 1,3-diols (Scheme 14).[29] In fact, 2-chloro-1,3-diol derivatives appended with aryl, heteroaryl, alkene and alkyne units have been efficiently transformed into the corresponding monoesters with high yields and enantioselectivities. In this process, a key role is likely acted by the intramolecular hydrogen bonding which can occur between the



Scheme 13 NHC-catalyzed *O*-acylative asymmetric desymmetrization of *meso*-diols

hydroxy groups of the 1,3-diol moiety. It should be noted that further esterification of a model monoester product (R = Ph) did not alter its ee, proving that this value was only due to catalytic desymmetrization of the parent diol.



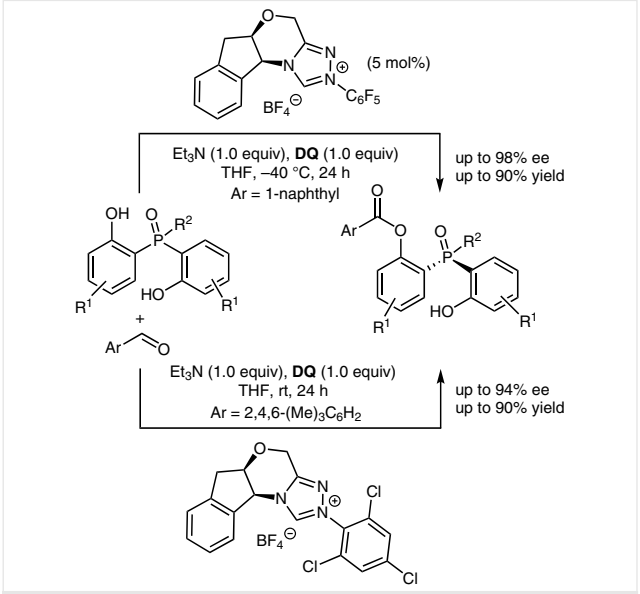
Scheme 14 NHC-catalyzed asymmetric desymmetrization of 2-chloro-1,3-diols■■*show hydrogen bond as H---O in the 1,3-diol shown in the mechanism?*■■

The *O*-acylation strategy has been tested on the asymmetric desymmetrization of prochiral bisphenols.[30–32]

As shown in Scheme 15, chiral NHCs promoted the oxidative esterification of 1-naphthaldehyde or mesitaldehyde with bis(2-hydroxyphenyl)phosphinates to give P-stereogenic phosphinates in enantioenriched form.[30] Similar to prochiral 1,3-diols, the obtained enantioselectivities mainly arose from the catalytic desymmetrization process, as confirmed by controlled KR experiments on a selected racemic monoester compound (Ar = 1-naphthyl).

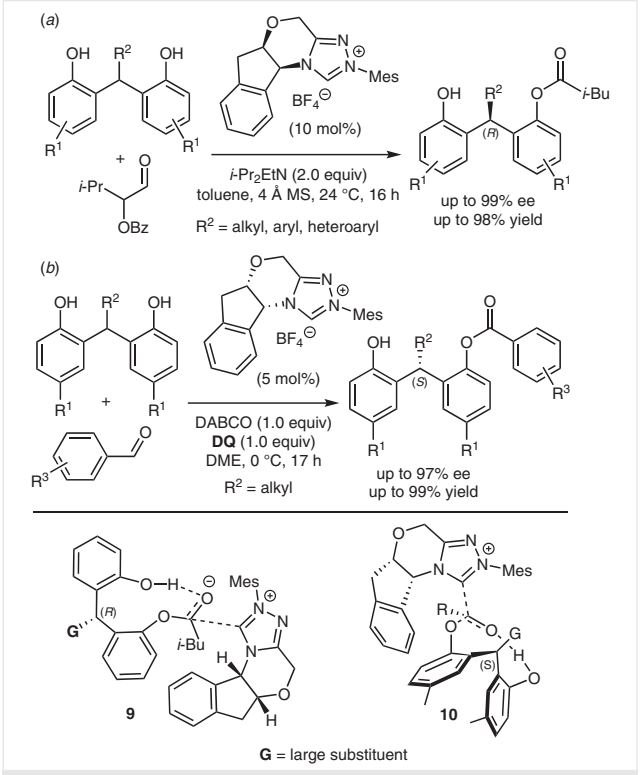
NHC-mediated internal oxidative (Scheme 16, a)[31] and external oxidative (Scheme 16, b)[32] routes have been reported for the enantioselective desymmetrization of triarylmethane and 1,1-diarylalkane bisphenols.

DFT calculations[31] and LFER analysis[32] led to the conclusion that both steric and electronic effects strongly influenced enantioselectivities. Based on the structure of the



Scheme 15 NHC-catalyzed asymmetric desymmetrization of bis-(2-hydroxyphenyl)phosphinates

tetrahedral adduct which arises from nucleophilic addition of the bisphenol substrate to the anticipated acyl azolium intermediate, favored transition state models **9**[31] and **10**[32] were proposed (Scheme 16). In any case, the catalyst moi-



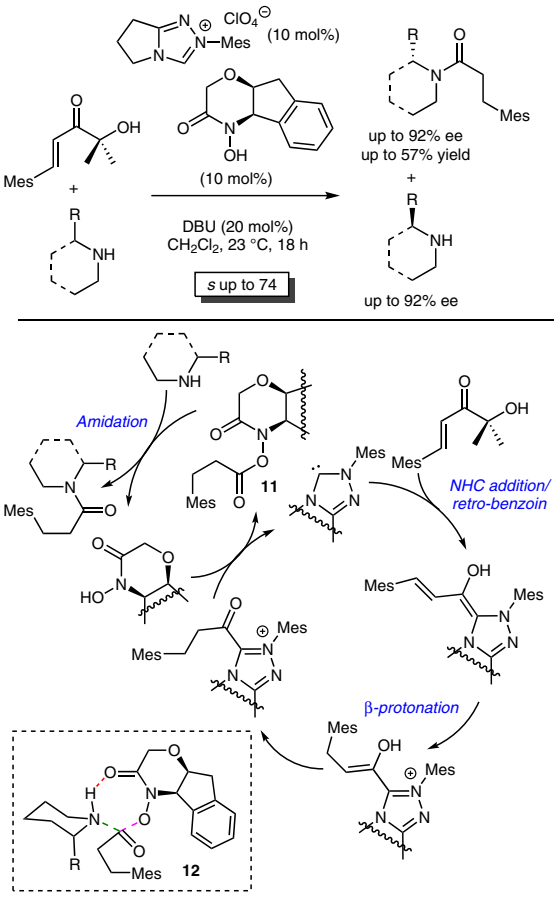
Scheme 16 NHC-catalyzed enantioselective desymmetrization of 1,1-diarylalkane and triarylmethane bisphenols

ety and the large C-1 substituent (**G**) are far apart, whereas the surviving phenolic hydroxy group builds a strong hydrogen bond with the negatively charged oxygen atom.

2.2 *N*-Acylation

NHC-catalyzed amidation reactions have been conveniently used for the KR of cyclic amines and sulfoximines.

Accordingly, co-catalysis between an achiral NHC and a chiral hydroxamic acid[6h] has proved successful when 2-substituted piperidines, piperazines, morpholines, tetrahydroisoquinolines and azepanes were reacted with a mesityl-substituted α′-hydroxyenone, generating enantiomerically enriched amines and amides with *s* factor values of up to 74 (Scheme 17).[33]

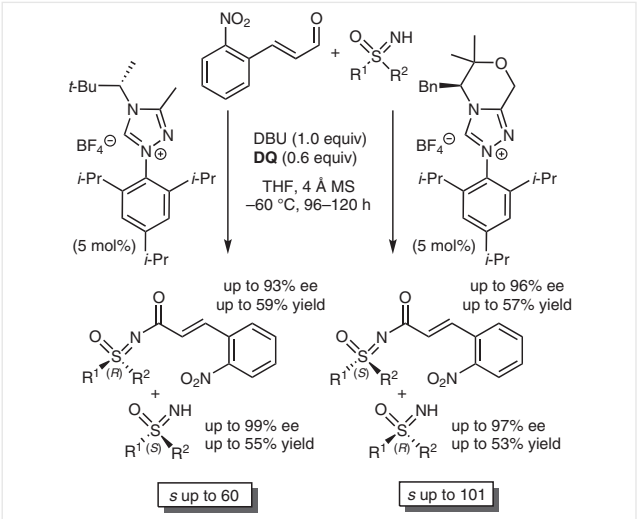


Scheme 17 KR of cyclic amines via NHC/hydroxamic acid co-catalysis

^{1}H NMR and control experiments clearly showed that the hydroxamic acid derived species **11** is the actual acyl transfer agent involved in the amidation step. Importantly, the mesityl residue does not affect the stereochemistry and hampers NHC-catalyzed dimerization reactions.

Furthermore, quantum mechanical calculations suggested that amine acylation proceeds via a seven-membered transition state (**12**) accounting for a concerted nucleophilic addition (C–N bond formation, *green dashed line*)/displacement (C–O bond cleavage, *purple dashed line*)/hydroxamic acid proton transfer (*red dashed line*) pathway.[34] ■■*all colored lines are dashed*■■

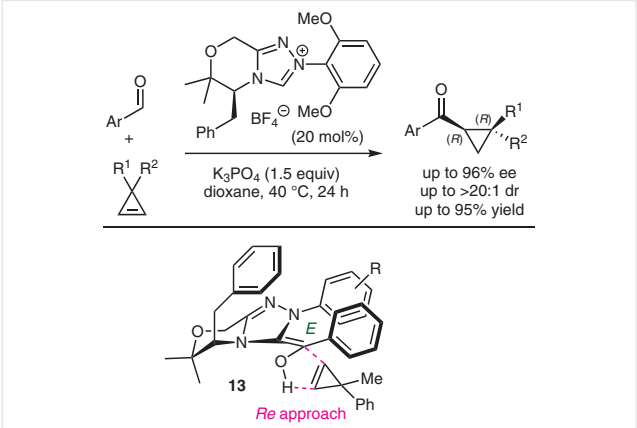
Bolm and co-workers used an oxidative amidation approach for the KR of sulfoximines with enals in the presence of a chiral NHC promoter (Scheme 18).[35] This work led the authors to obtain many diverse sulfoximines in both enantiomeric forms, with the best reactivity and enantioselectivity being observed with 2-nitrocinnamaldehyde.



Scheme 18 NHC-promoted KR of sulfoximines

2.3 *C*-Acylation

An intermolecular hydroacylation reaction has opened the door to the asymmetric desymmetrization of cyclopropenes by formation of the corresponding acyl cyclopropanes in high yield and stereoselectivity (Scheme 19).[36]



Scheme 19 NHC-catalyzed asymmetric desymmetrization of cyclopropenes

A concerted five-membered transition state **13** for the model reaction between benzaldehyde and 3-methyl-3-phenylcyclopropene has been evoked to explain both the (*R*,*R*) configuration and the diastereomeric ratio of the major products.[37] These are consistent with privileged *re* approach of the cyclopropene to the *E*-isomer of the Breslow intermediate.

3 Aldol-Acylation Processes

Scheidt and co-workers developed aldol-acylation reactions catalyzed by chiral NHCs for the asymmetric desymmetrization of 1,3-diketones.[38–40] Typically, these processes provided α,α-disubstituted cyclopentenes starting from 1,3-aryldiketones, while cyclic and acyclic aliphatic 1,3-diketones gave exclusively cyclopentane-fused β-lactone products (Scheme 20).

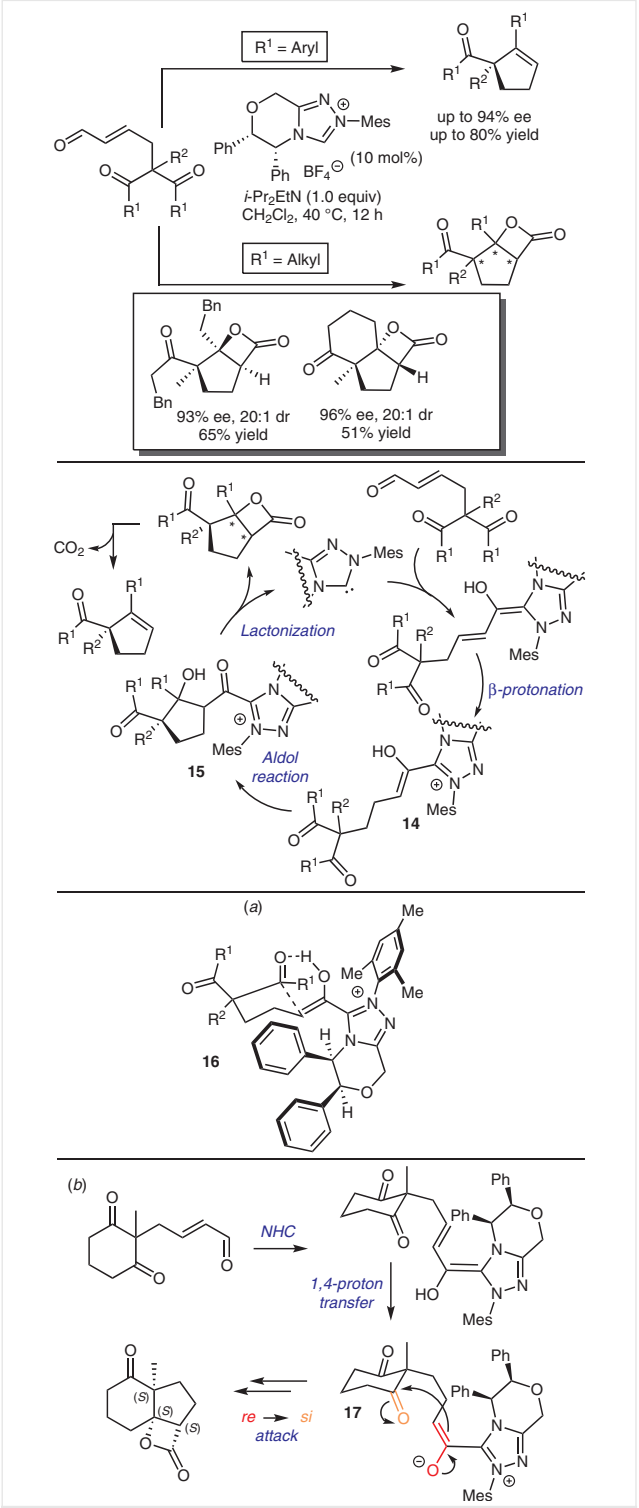
The proposed mechanistic pathway implicates the formation of the key enol intermediate **14** which takes part in an intramolecular aldol reaction to yield the cyclopentane derivative **15**. Subsequent intramolecular lactonization produces a cyclopentane-fused β-lactone species which collapses to give the target molecule by decarboxylation.

With particular regard to the aldol step, a plausible model calls for the formation of the *Z*(*O*)-enol species **16** (Scheme 20, a), where a six-membered hydrogen-bonded network ensues to minimize the non-bonding interactions between the phenyl substituents on the catalyst and the aryl ketone, which does not suffer nucleophilic attack.

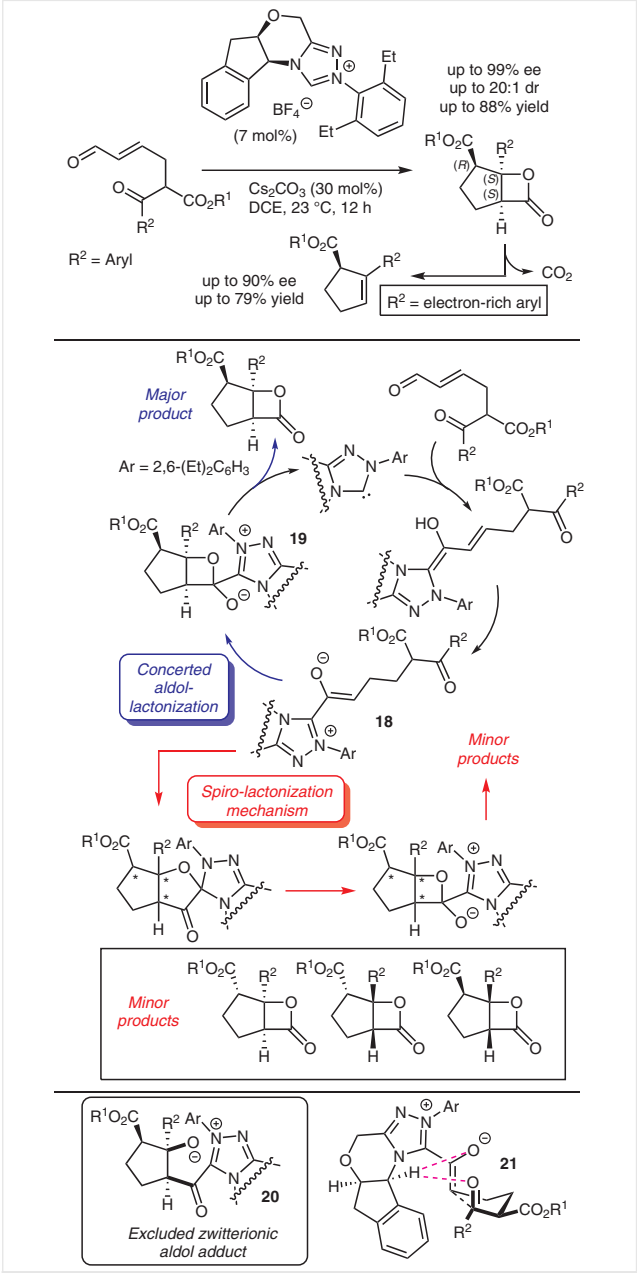
Fruitfully, the tandem aldol–lactonization–decarboxylation procedure has found application in the preparation of a pivotal intermediate for the asymmetric synthesis of bakkenolides I, J, and S.[40,41]

Sunoj and Reddi[42] have studied in great detail the mechanism and the origin of the stereoselectivity in the NHC-catalyzed asymmetric desymmetrization of a substituted cyclohexyl-1,3-diketone. DFT calculations demonstrated that a facile intramolecular 1,4-proton transfer may produce the reactive enolate **17** from the parent Breslow intermediate (Scheme 20, b). The succeeding intramolecular aldol reaction preferentially proceeds via interaction of the enolate *re* face with the *si* face of the reacting carbonyl group, with the aryl moieties of the catalyst (i.e., the mesityl and phenyl groups) being apart from the domain where the new C–C bond is forming. This mode of action would explain the formation of a major β-lactone diastereomer featuring (2a*S*,4a*S*,8′*S*) stereochemistry, which is in accordance with the experimental data.[40]

Further studies on the NHC-catalyzed aldol–lactonization approach enabled the Scheidt group to achieve the DKR of racemic ω-formyl aryl-β-ketoesters to generate cyclopentane-fused β-lactones in high yields and stereoselectivities (Scheme 21), with preferential formation of the (1*S*,4*R*,5*S*)-configured isomers being observed.[43–45]



Scheme 20 NHC-catalyzed asymmetric desymmetrization of 1,3-diketones via an aldol–lactonization sequence



Scheme 21 NHC-catalyzed DKR of ω-formyl aryl-β-ketoesters

It certainly needs emphasizing that the β-lactone products arising from electron-rich aryl ketones underwent a facile decarboxylation giving direct access to cyclopentene derivatives (R^1 = Et■■*CO_2Et now Et–OK?*■■; R^2 = 2-$EtOC_6H_4$, 4-$MeOC_6H_4$, thiophen-3-yl, furan-3-yl).[43]

In-depth computational studies on a model substrate ascertained that the DKR of ω-formyl aryl-β-ketoesters may take place by two divergent pathways passing through the common enolate **18**.[44] In particular, a concerted asynchronous aldol–lactonization route leads to the formation of the major isomer via the catalyst-lactone adduct **19**. Besides, the minor products originate from a stepwise spiro-lactonization mechanism. Interestingly, these findings completely rebutted the original mechanistic model proposed by the same authors,[43] thence excluding the direct involvement of the zwitterionic aldol adduct **20** in a stepwise aldol–lactonization route.

Moreover, it has been demonstrated that stereoselectivity is dictated by two major effects, namely: (i) activation of the reactive carbonyl group by conjugation with its aryl substituent, and (ii) electrostatic stabilizations, i.e., non-classical hydrogen bonding interactions involving the catalyst pyranyl C–H, as shown in the predicted transition state **21** leading to the major product.[44]

Last, but not least, additional experiments led to the conclusion that the NHC-catalyzed DKR of ω-formyl aryl-β-ketoesters is a *non-classical* DKR as the NHC species is exclusively involved in capturing and irreversibly transforming one enantiomer of the substrate, which is in turn racemized by an exogenous base.[44]

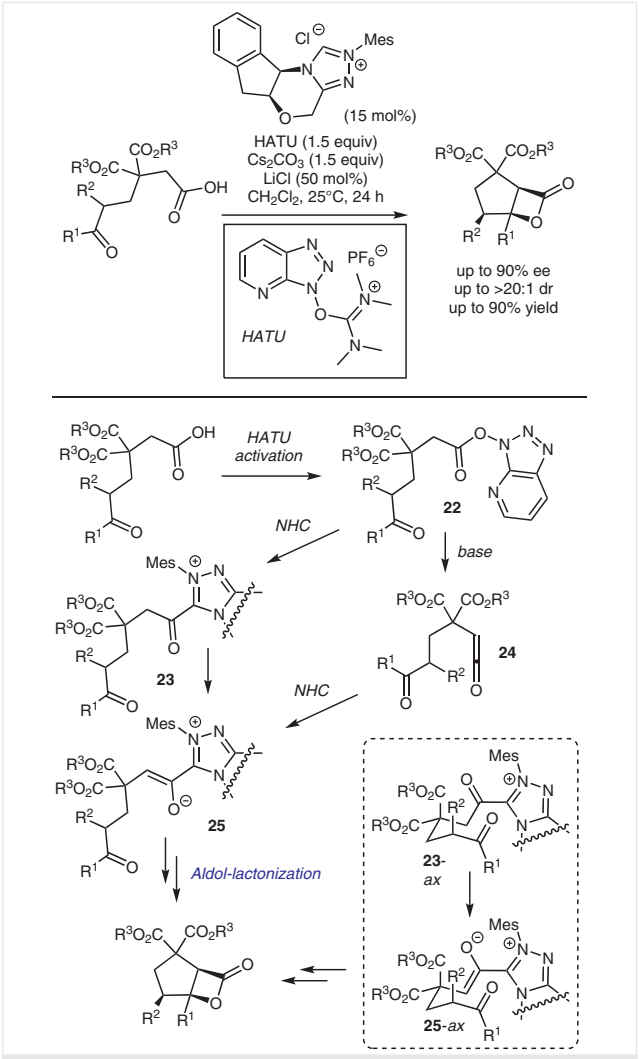
Interestingly, the NHC–DKR–decarboxylation strategy has been very successfully applied as the key step in the enantioselective formal synthesis of an estrogen receptor β-agonist.[45]

A strictly related DKR based on an aldol–lactonization reaction has been developed by Biju and co-workers, starting from acyclic ketoacids, to produce cyclopentane-fused β-lactones with three contiguous stereocenters in diastereo- and enantioselective fashion (Scheme 22).[46] These compounds were eventually subjected to synthetic manipulations of the β-lactone moiety via decarboxylation, methanol-promoted ring opening or reactions with primary amines.

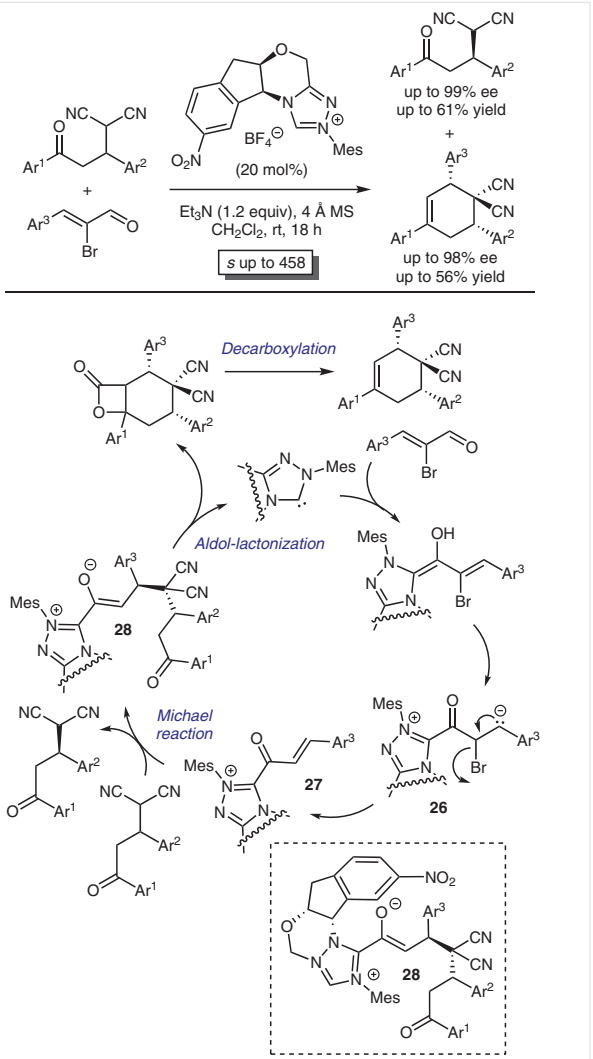
In Biju's approach, activation of the substrate by the peptide coupling reagent HATU generates an activated ester species **22** giving rise to the crucial enolate intermediate **25** via either NHC-bound acyl derivative **23** or ketene **24**. Aldol–lactonization of **25** provides the final lactone compound. It may be assumed that the major β-lactone isomer originates from the pseudo-axial conformer of **25** (**25**-*ax*). It can be expected that aldol–lactonization of the equilibrating pseudo-equatorial conformer (not shown) is less favorable due to steric hindrance effects.

One interesting aspect of Biju's work is that an approximately 1:1 mixture of diastereomers was obtained when the aldol–lactonization reaction was run using either NaCl in THF or LiBr in toluene. This achievement seems to be consistent with a stereodivergent parallel kinetic resolution (PKR),[47] however, a rational interpretation has not been given.

A '*two flies with one swat*' concept was exploited by Enders and co-workers through the blending of an aldol–lactonization–decarboxylation reaction and a Michael addition.[48] As depicted in Scheme 23, reaction of racemic Michael adducts with α-bromoenals under chiral NHC-promotion resulted in the production of highly enantioenriched



Scheme 22 NHC-catalyzed aldol–lactonization of acyclic ketoacids via DKR



Scheme 23 KR of Michael adducts by NHC-catalyzed Michael–aldol–lactonization–decarboxylation reactions

starting substrates and diastereomerically pure cyclohexene derivatives. So, the NHC catalysis proved effective in achieving the KR of Michael adducts, with an efficient asymmetric synthesis of cyclohexenes taking place at the same time.

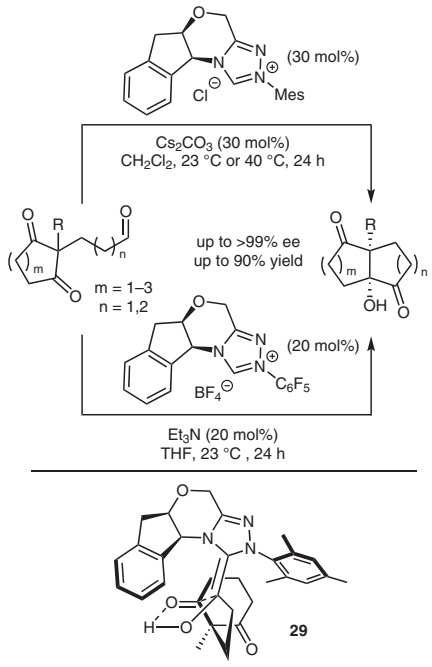
An assumed mechanistic reaction pathway goes through the formation of α,β-unsaturated acyl azolium **27** via the α-bromo acyl azolium intermediate **26**. Michael addition of the racemic substrate to **27** from the side opposite to the catalyst chiral portion gives the azolium enolate **28**, which is then taken to the target compound by an aldol–lactonization–decarboxylation sequence.

It should be noted that this catalytic method could be performed in a one-pot fashion (Michael–Michael–aldol–lactonization–decarboxylation reaction) starting from enones, malononitrile and α-bromocinnamaldehydes. This paved the way to the asymmetric synthesis of polyfunctionalized cyclohexenes (Ar^1 = Ph, 4-MeC_6H_4, Ar^2 = Ph, 4-ClC_6H_4, Ar^3 = Ph) in good yields over the five steps (22–38%) and outstanding stereoselectivities (99% ee).

4 Benzoin Reactions

Benzoin reactions have been reported for both asymmetric desymmetrization and DKR processes under NHC-catalysis.

In this regard, an intramolecular cross-benzoin strategy allowed Ema and co-workers to achieve the asymmetric desymmetrization of cyclic 1,3-diketones appended with an aliphatic aldehyde residue.[49,50] This work produced enantioenriched bicyclic adducts bearing two adjacent quaternary stereocenters at the ring junctions (Scheme 24).



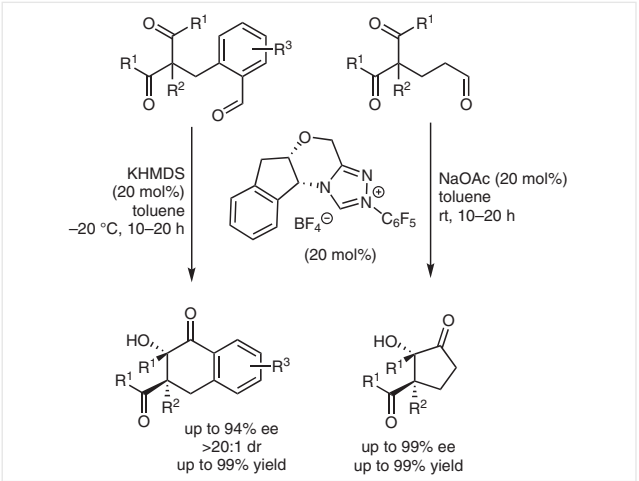
Scheme 24 Asymmetric desymmetrization of cyclic 1,3-diketones by NHC-catalyzed intramolecular cross-benzoin reaction

Generally, the formation of the five-membered rings proceeded with higher yields (up to 90%) than those of the six-membered ones (up to 67% yield), while the trend observed for enantioselectivities was totally opposed (n = 1: up to 78% ee; n = 2: up to >99% ee). In the case of five-membered ring construction, enantioselectivity was influenced by the size of the fused ring (m = 1: up to 26% ee; m = 2: up to 78% ee; m = 3: up to 69% ee).

Transition-state models have been postulated to interpret the observed enantioselectivity. The major enantiomer is likely produced via the favored transition state **29** lacking contact between the mesityl group of the NHC and the substrate ring, thereby allowing C–C bond formation without intense steric hindrance. Moreover, it has been proposed that the mesityl substituent on the NHC interferes with the assembly of a six-membered ring to a greater extent than it does for the five-membered analogue.

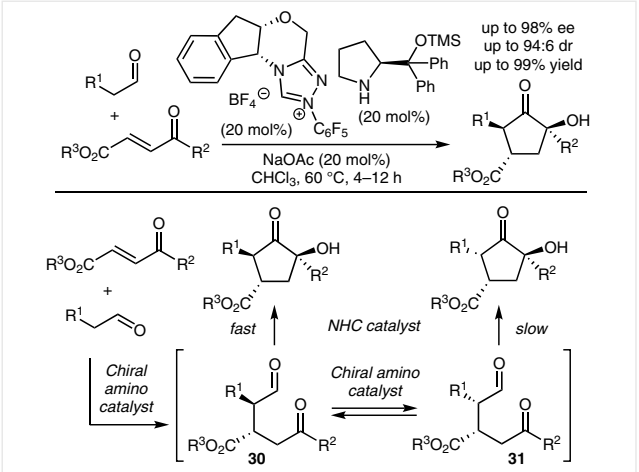
It is notable that Ema's strategy has been used to obtain a precursor for the synthesis of a tricyclic compound with three vicinal tetrasubstituted carbon stereocenters.[50] In addition, Ema's approach was confined to cyclic ketones and aliphatic aldehydes, plus different conditions were exploited with no extensive approach being elaborated.

On the contrary, Du, Fang and co-workers devised a more general method for the NHC-catalyzed asymmetric desymmetrization of 1,3-diketones via intramolecular benzoin reactions.[51] Both aromatic and aliphatic aldehyde moieties as well as aromatic 1,3-diketones were good substrates for this process, which gave access to cyclopentanones and cyclohexanones with two adjacent fully substituted stereogenic centers (Scheme 25). The chiral non-racemic ketone products represent versatile platforms for additional processing, such as Grignard addition, reduction, and Beckmann rearrangement via the corresponding oximes.



Scheme 25 Asymmetric desymmetrization of acyclic 1,3-diketones via NHC-catalyzed intramolecular cross-benzoin reactions

The NHC-catalyzed benzoin reaction was first■■*change OK?*■■ used in organocatalytic DKR processes in 2011, when Rovis and Ozboya reported the stereoselective synthesis of functionalized cyclopentanones from aliphatic aldehydes and activated enones by a dual activation tactic integrating catalysis by a chiral secondary amine and NHC in a cascade (Michael–benzoin) reaction (Scheme 26).[52]

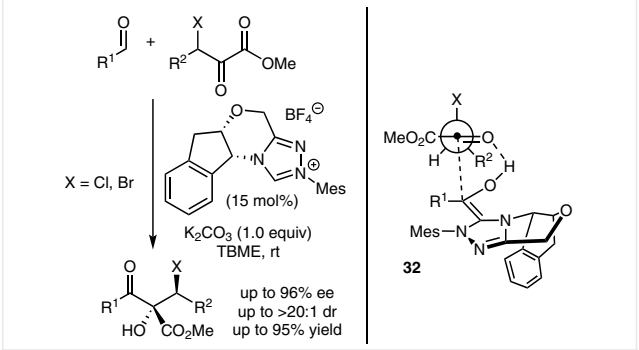


Scheme 26 An organocatalytic DKR process via a Michael–benzoin cascade reaction

Detailed experiments demonstrated that the chiral amino catalyst promotes the initial step, namely a Michael reaction between the aldehyde and enone, and the epimerization of the resulting δ-ketoaldehyde, producing an equilibrating mixture of diastereomers **30** and **31**. At this stage, preferential benzoin cyclization of **30** takes place in the presence of the chiral NHC catalyst, with this second event being analogous to a DKR reaction.

Johnson and Goodman[53] reported the DKR of racemic β-halo α-ketoesters by chiral NHC-catalyzed intermolecular umpolung addition of aldehydes giving rise to β-halo glycolic esters with excellent degrees of stereoselectivity (Scheme 27). High chemoselectivity was also observed, certainly due to the higher electrophilicity of the α-ketoester toward the Breslow intermediate compared to the aldehyde.

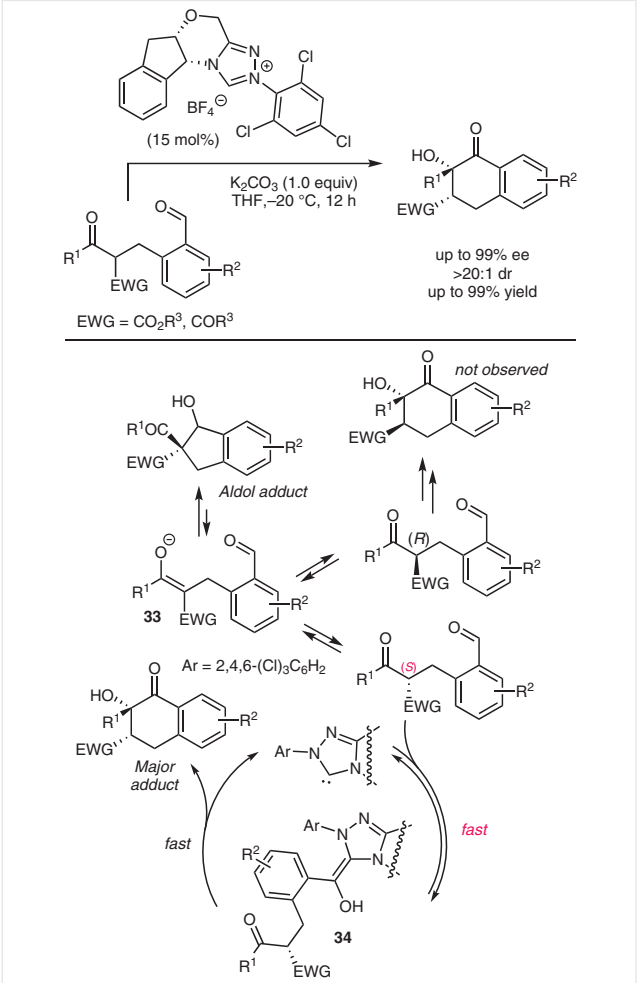
The stereochemistry of the cross-benzoin adduct conforms with both a polar Felkin–Anh[54] and a Cornforth[55] model for the addition of the nucleophilic Breslow intermediate to the electrophilic carbonyl group, as shown by the possible transition state **32**. Potent facial differentiation due to the indane backbone of the catalyst together with orientation/activation by the enolic hydroxy group[56] are the most likely effects that allow the Breslow species to discriminate between α-ketoester enantiomers.



Scheme 27 DKR of β-halo α-ketoesters by NHC-catalyzed cross-benzoin reaction

A chiral NHC-catalyzed intramolecular cross-benzoin reaction has been developed to achieve the DKR of β-ketoesters and 1,3-diketones via the formation of 1-tetralones in a highly stereo- and regioselective manner (Scheme 28).[57]

Extensive investigation allowed the mechanistic features of this process to be established. In detail, both enantiomers of the substrate rapidly equilibrate with enolate **33**, which may participate in a reversible aldol reaction. At the same time, the (*S*)-enantiomer is quickly and reversibly converted into Breslow species **34** going through an irreversible benzoin reaction that produces the major cross-benzoin adduct. In contrast■■*change OK?*■■, its diastereomer is not observed on the grounds of a slow action of the NHC catalyst on the (*R*)-enantiomer.

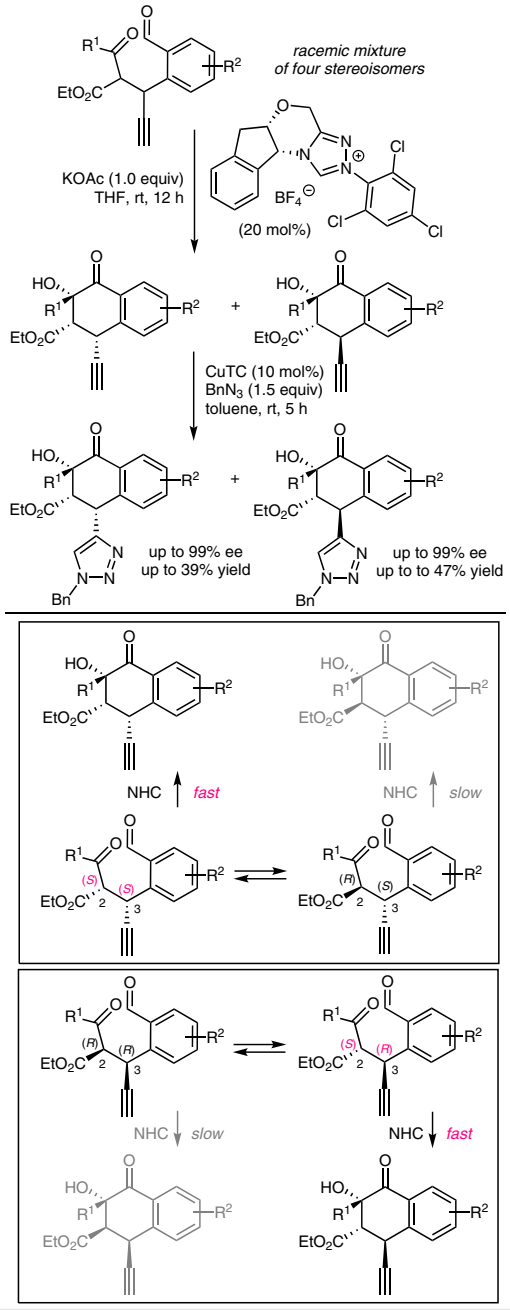


Scheme 28 DKR of β-ketoesters and 1,3-diketones via cross-benzoin reaction under NHC catalysis

So that aldol and benzoin reactions coexist, the reversibility of the aldol reaction prepares the way to a retro-aldol–benzoin sequence enabling the predominant formation of the benzoin compound.

Other than that, it has been demonstrated that the presence of an *N*-electron-withdrawing residue on the NHC catalyst speeds up the rate of the benzoin process rather than suppressing the aldol reaction through reduction of the carbene catalyst basicity.

Most recently, a NHC-catalyzed benzoin reaction has been used as a channel for the resolution of racemic mixtures of four stereoisomers via divergent dynamic kinetic resolution (DDKR).[58] This new resolution technique was applied to alkynyl-substituted β-ketoesters yielding exclusively two enantioenriched diastereomeric tetralone derivatives, which were directly involved in a copper-catalyzed azide–alkyne cycloaddition reaction for ease of separation (Scheme 29).

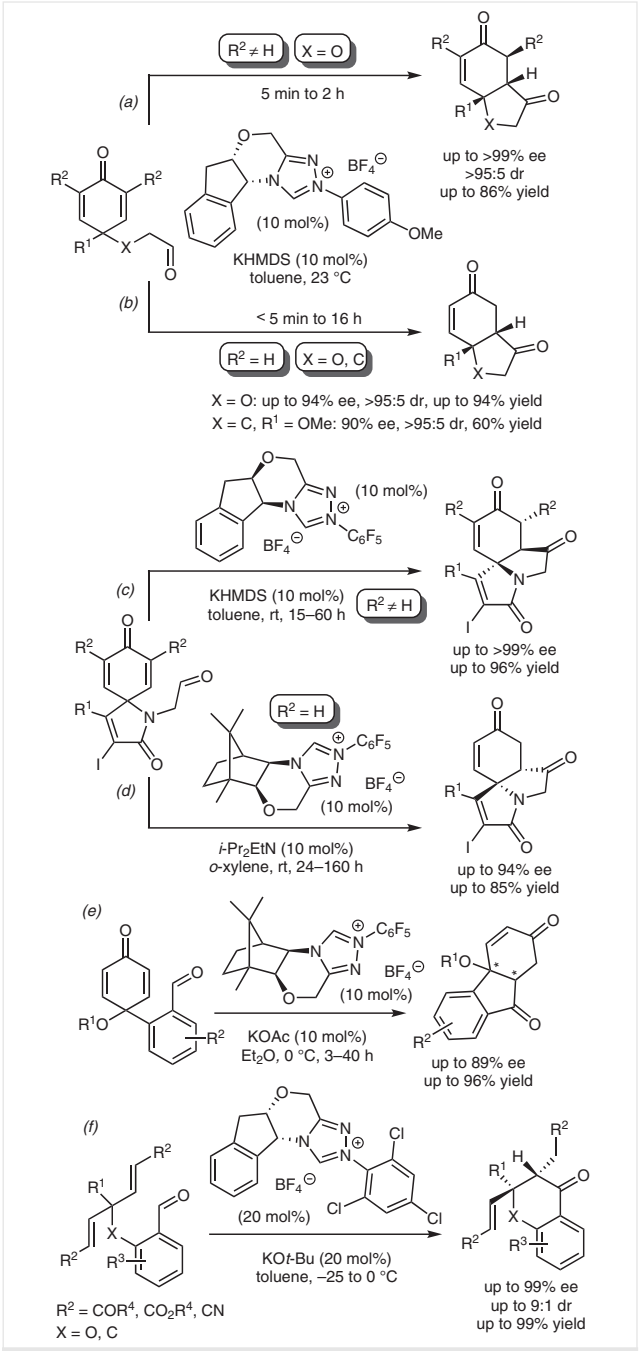


Scheme 29 NHC-promoted DDKR of a racemic mixture of four stereoisomers

A possible mechanism for the DDKR reaction was proposed under the assumption that diastereomers (2*S*,3*S*)/(2*R*,3*S*) and (2*R*,3*R*)/(2*S*,3*R*) constantly interconvert throughout the process; in the meantime, both the (2*S*,3*S*) and (2*S*,3*R*) species undergo fast intramolecular benzoin reactions to produce the corresponding annulation compounds. Thus, it is as if two DKR reactions are taking place in parallel resulting in the divergent formation of the observed final products.

5 Stetter Reactions

Intramolecular Stetter reactions mediated by chiral NHCs enable the asymmetric desymmetrization of cyclohexadienones[59–63] and 1,4-dienes[64] (Scheme 30).

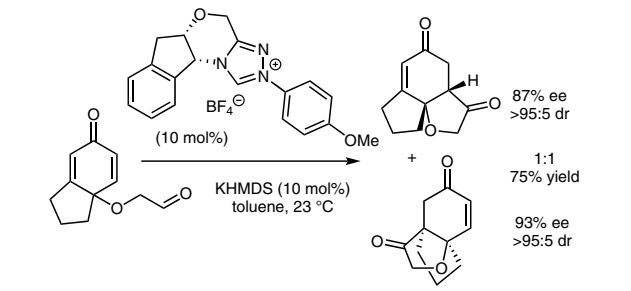


Scheme 30 Asymmetric desymmetrization of cyclohexadienones and 1,4-dienes via NHC-mediated intramolecular Stetter reactions

Chiral aminoindanol triazolium salts were found to be optimal NHC precatalysts for desymmetrizing both cyclohexadienones and 1,4-dienes,[59,60,62,64] with cyclohexadiones also being effectively desymmetrized in the presence of a D-camphor-derived NHC.[61,63]

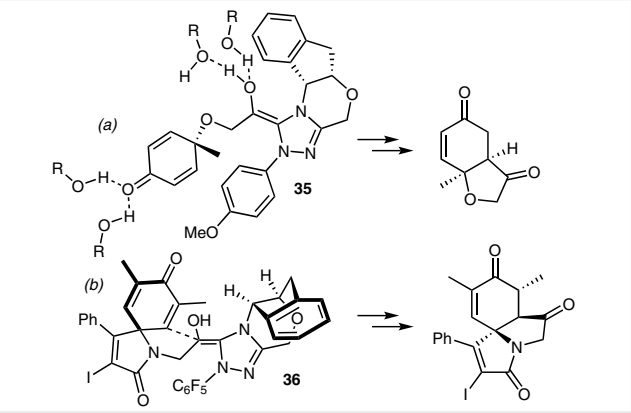
These processes afforded, respectively, bicyclic (Scheme 30, a and b)[59,60] and tricyclic products (Scheme 30, c–e)[61–63] with two or more stereogenic centers, as well as cyclic ketone derivatives containing two contiguous tertiary/quaternary stereocenters (Scheme 30, f).[64] In each case, high yields and stereoselectivities were generally found. Interestingly, both the tricyclic and the cyclohexanone adducts could be used for useful synthetic transformations, including Pd-mediated cross-couplings[61] and α-allylation reactions.[64]

When it comes to the desymmetrization of cyclohexadienones, detailed analyses have borne some remarkable achievements. Firstly, PKR was provided with cyclopentane-fused cyclohexadienones producing two structural isomers (1:1 ratio) with high enantioselectivity (Scheme 31).[60]



Scheme 31 PKR of cyclopentane-fused cyclohexadienones via Stetter reaction

Second, it has been possible to propose a rationale for the stereochemical outcome of the reactions promoted by the aminoindanol catalysts (Scheme 32).



Scheme 32 Proposed transition-state models for the asymmetric desymmetrization of cyclohexadienones

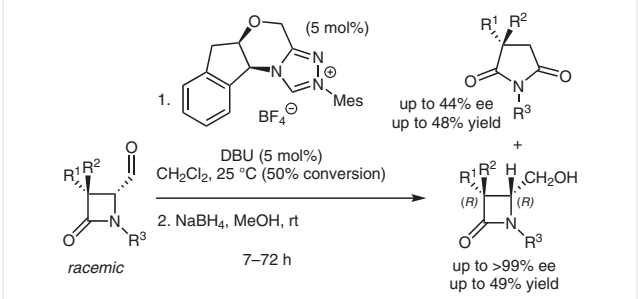
Surprisingly, hydrobenzofuranone formation in an alcohol solvent produced the opposite enantiomers to those obtained in toluene without exception, particularly due to hydrogen-bonding interactions that alter the chiral environment, as shown in the transition state model **35** (Scheme 32, a).[60] Besides, the highly enantioselective formation of the tricyclic adducts has been assumed to pass through a favored transition state (e.g., **36**), minimizing steric interactions between neighboring cyclohexadienone and aminoindanol backbones (Scheme 32, b).[62]

6 Miscellaneous Approaches

Chiral NHCs have also been reported to catalyze a series of KR, DKR and asymmetric desymmetrization transformations based on a variety of reaction types other than those discussed so far.

On the subject of KR reactions, procedures based on ring expansion[65,66] and cycloaddition[67,68] have been reported.

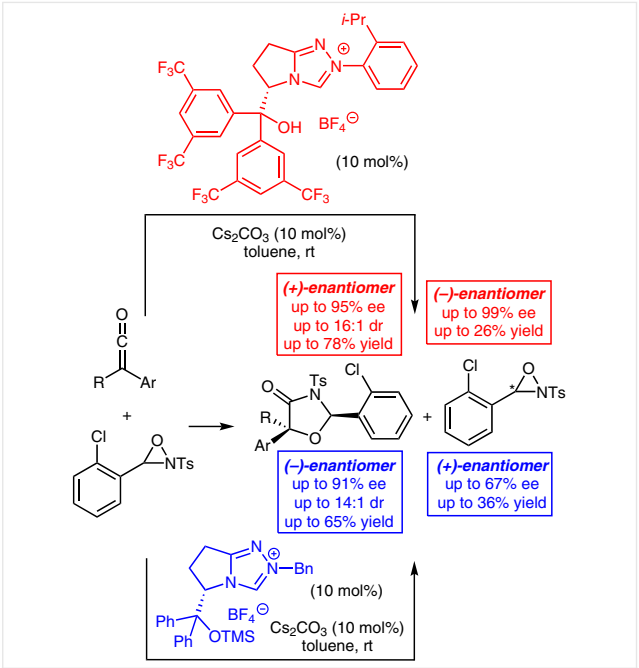
In the first case, racemic *cis*-4-formyl-β-lactams were transformed into enantioenriched *cis*-4-formyl-β-lactams and succinimide compounds containing quaternary carbon centers, with the best results being depicted in Scheme 33.[66]



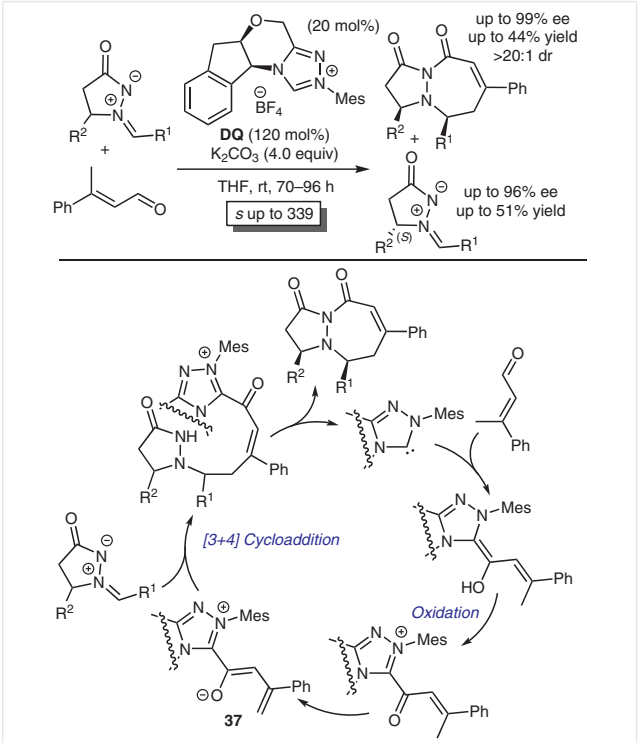
Scheme 33 KR of *cis*-4-formyl-β-lactams via NHC catalysis

Talking of the cycloaddition reaction mode, effective KR of racemic oxaziridines was achieved through formal [3+2] cycloaddition with ketenes (Scheme 34).[67] This approach furnished the enantiomers of oxazolin-4-one compounds together with the recovered optically active oxaziridine enantiomers.

Furthermore, Chi and co-workers reported the KR of azomethine imines by means of a [3+4] cycloaddition with enals (Scheme 35).[68] A possible mechanistic pathway calls for the formation of the vinyl enolate **37**. This represents the 1,4-dipolarophile species which reacts with the azomethine imine to form the cycloaddition product with concomitant release of the NHC catalyst. Most likely, the enantiomeric azomethine imines react at different rates with the chiral intermediate **37**, so giving rise to KR.



Scheme 34 NHC-catalyzed KR of racemic oxaziridines

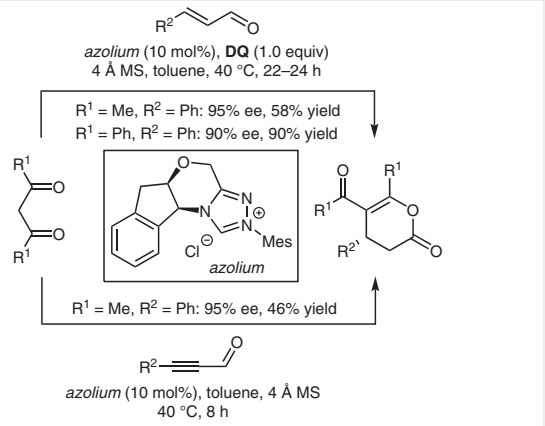


Scheme 35 NHC-promoted KR of azomethine imines

In this process the chiral NHC catalyst is far away from the substrate reactive sites. This is an important distinguishing feature compared to NHC-catalyzed KR of alcohols and amines by esterification and amidation, respectively.

NHC-promoted annulation reactions having a final lactonization step in common were performed in asymmetric desymmetrization and DKR processes.

Thus, enantioselective desymmetrization of 1,3-diketones was carried out through annulation with α,β-ynals and enals to supply functionalized dihydropyranone scaffolds (Scheme 36).[69] The reactions were run under similar conditions except for the use of a quinone oxidant (**DQ**) in the case of enals. Finally, but importantly, the molecular sieves are reported to play a key role in determining the yields and stereoselectivities.

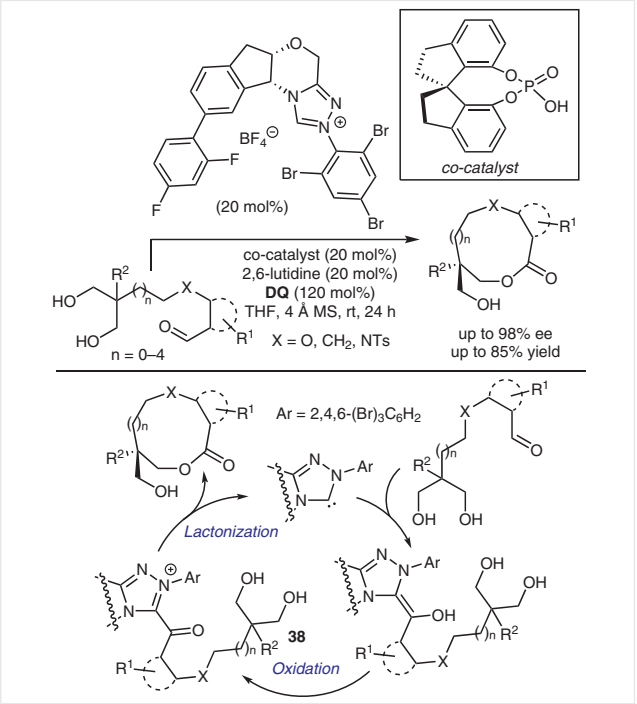


Scheme 36 NHC-catalyzed asymmetric desymmetrization of 1,3-diketones by annulation with ynals and enals

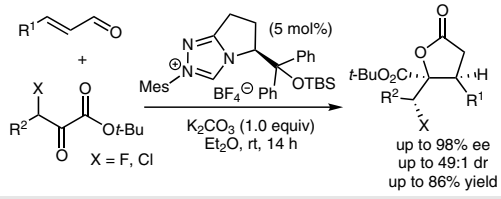
Recently, asymmetric desymmetrization of prochiral 1,3-diols has been achieved by synergistic catalysis using a chiral NHC and a Brønsted acid (Scheme 37).[70] Cooperative NHC/Brønsted acid catalysis promoted intramolecular annulation reactions leading to medium-sized (8–12 membered ring) lactones in moderate to good yields and high enantioselectivities.

The proposed mechanistic route calls for an intramolecular desymmetric lactonization of the acylazolium intermediate **38**. In all probability, the Brønsted acid is able to stabilize the transition state by means of hydrogen-bonding interactions with the hydroxy group and the carbonyl moiety of **38**.[71] A noticeable fact is that stereocontrol of the process is not affected by the absolute configuration of the acid cocatalyst.

An asymmetric homoenolate annulation approach has made possible the DKR of β-halo α-ketoesters by reaction with α,β-unsaturated aldehydes. The process yields γ-butyrolactones with three adjacent stereogenic centers in generally excellent diastereo- and enantioselectivities (Scheme 38).[72] The stereochemistry of the obtained compounds may be explained in analogy with previous work[53] due to the presence of the polar β-halogen group.



Scheme 37 NHC/Brønsted acid catalyzed asymmetric desymmetrization of prochiral 1,3-diols

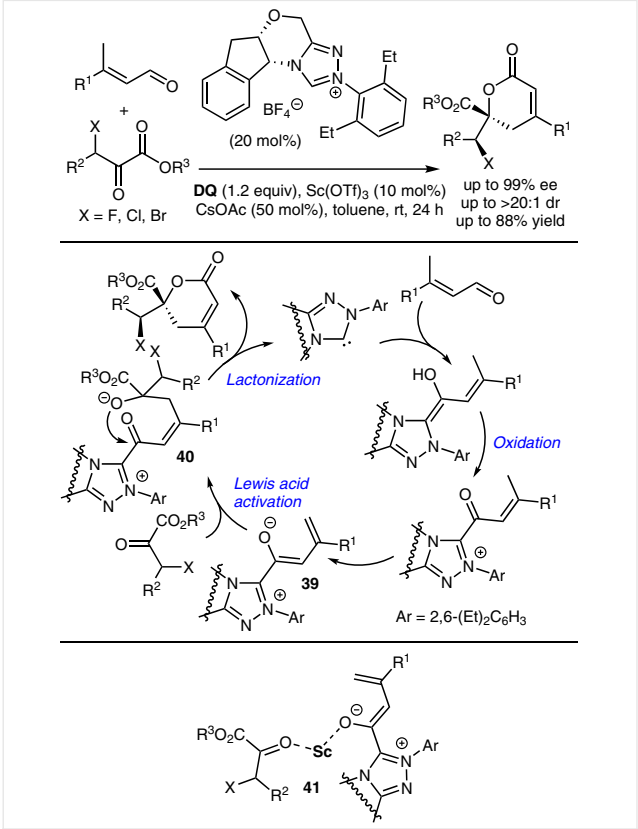


Scheme 38 DKR of β-halo α-ketoesters through asymmetric homoenolate annulation with α,β-unsaturated aldehydes

Chiral NHC/Lewis acid catalysis has provided the DKR of β-halo α-ketoesters through oxidation–lactonization sequences in the presence of α,β-enals (Scheme 39).[73] This method resulted in good to high yields of δ-lactones with excellent diastereo- and enantioselectivities.

A postulated mechanistic path for this transformation involves the vinyl enolate species **39**. Lewis acid mediated addition of the latter to the α-ketoester substrate likely produces alkoxide **40**, which is finally converted into the target compound by intramolecular lactonization. However, a concerted route for this transformation has not been totally ruled out.

With regard to the Lewis acid, it has been suggested that it probably operates through a multisite coordination bringing the ketone group and the enolate **39** into close proximity, as shown in species■■*change OK?*■■ **41**.[74] This



Scheme 39 Cooperative NHC/Lewis acid catalysis for the DKR of β-halo α-ketoesters

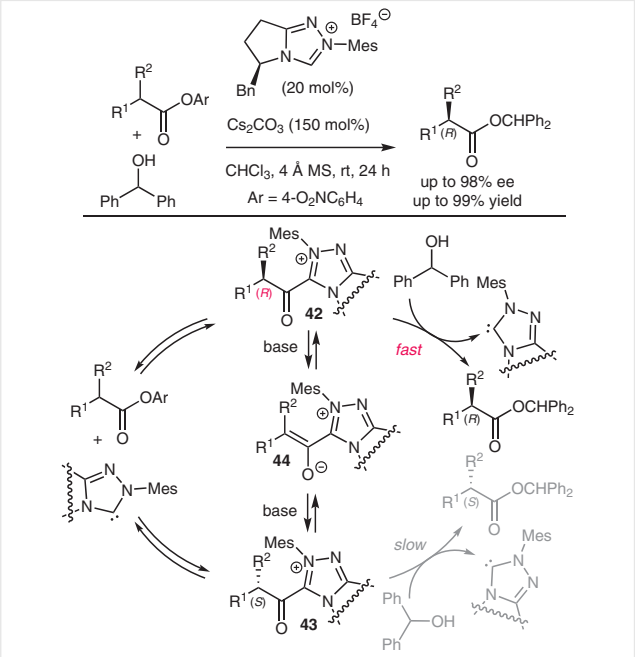
effect is thought to have a key role in determining chiral induction, as demonstrated by control experiments in the absence of the Lewis acid.

Finally, transesterification has been used in the chiral NHC-catalyzed DKR of racemic α,α-disubstituted 4-nitrophenyl esters with diphenylmethanol (Scheme 40).[75]

In-depth experiments and DFT calculations have allowed for a possible mechanistic pathway. Thus, reaction of the racemic ester compound with the chiral NHC produces the diastereomeric acyl azolium species **42** and **43**, which are interconverted through the achiral enol species **44**. Intermediates **42** and **43** react with the alcohol at different rates, with the (*R*)-configured transesterified derivative being preferentially formed.

7 Conclusion

Over the last 15 years, chiral NHCs have proven to be effective as stereoselective organocatalysts for KR, DKR and asymmetric desymmetrization processes. These asymmetry-inducing transformations have been successfully realized making use of various reactions, with acylation being primarily used (Figure 2).



Scheme 40 NHC-catalyzed DKR of α,α-disubstituted carboxylic esters

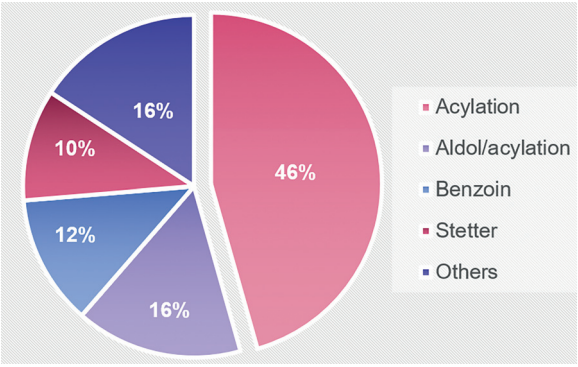


Figure 2 Pie chart of NHC-catalyzed reactions involving KR, DKR and asymmetric desymmetrization

As depicted in Figure 3, acylation has been mostly implicated in KR and asymmetric desymmetrization reactions, while both aldol–acylation and benzoin reactions have resulted in DKR and asymmetric desymmetrization. On the other hand, Stetter reactions were applied to asymmetric desymmetrizations only. As far as other methods are concerned, they could find application in KR, DKR and asymmetric desymmetrization processes, with preference for the KR.

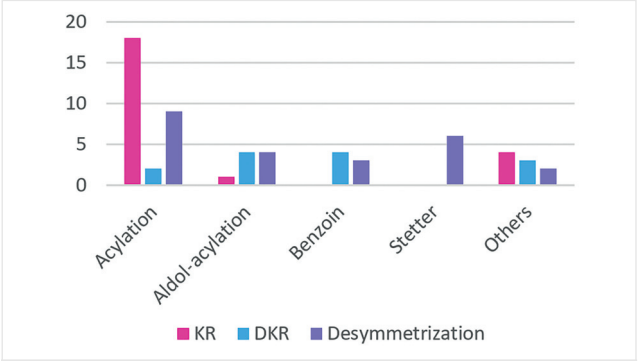


Figure 3 Distribution of the asymmetry-inducing transformations for each NHC-promoted reaction type

For the most part, the NHC-catalyzed KR, DKR and asymmetric desymmetrization reactions have provided enantioenriched final products with C-stereocenters, but P- and S-stereogenic compounds were also obtained giving rise to further molecular diversity. According to the current state of the art, we must not overlook the fact that both substrates and reactions (activation modes) seem to be relatively limited. Future developments in NHC-catalyzed KR, DKR and asymmetric desymmetrization strategies are expected to take place to access new chiral (complex) molecules, and in addition through reactions proceeding via non-conventional NHC-bound intermediates.

■■*any Acknowledgment?*■■

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