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# Recent Advances in the α-Hydrazination (α-Amination) of Carbonyl Compounds

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The electrophilic α-hydrazination (generally referred to as α-amination) of carbonyl compounds with dialkyl azodicarboxylates is a powerful approach for the preparation of synthetically useful intermediates such as α-amino aldehydes and ketones, α-amino acids, and β-amino alcohols. Many methods for the enantioselective α-hydrazination have been published in the past and many new approaches have been disclosed in the last decade that deal with previously unresolved issues such as the direct enantioselective α-hydrazination of α-branched ketones. The enantioselective α-hydrazination is the field where most significant advances have been attained thanks to new approaches, catalysts and techniques. With this review we intend to cover the literature that appeared between 2015 and 2024. We will classify the various methods according to the strategies for the enantioselective formation of the new C–N bond, mainly based on the formation of chiral enamines, enols and enolates. Miscellaneous methods are grouped at the end of the review. Where relevant, the application of α-hydrazino carbonyl compounds to the synthesis of target molecules will also be illustrated.

## 1. Introduction – A General Overview

The electrophilic α-hydrazination of carbonyl compounds with dialkyl azodicarboxylates is one of the most exploited approaches to install a nitrogen functionality into aldehydes and ketones, which, after proper functional group manipulation, can be converted into synthetically useful α-amino aldehydes and ketones, α-amino acids, and β-amino alcohols.[1] As the usual fate of the hydrazine N–N bond is its cleavage to generate an amino group, the α-hydrazination of carbonyl compounds is referred to by most, if not all, authors as *α-amination* of carbonyl compounds, even when the N–N bond cleavage is either not possible at all (because of the presence of incompatible functionalities) or only after transformation of the carbonyl into another group tolerant the cleavage conditions.[2] For this reason, in this review we will preferentially use the term α-hydrazination to indicate the reaction between a carbonyl compound and a dialkyl azodicarboxylate, instead of α-amination, regardless of the subsequent transformations to which the products are subjected after their isolation.[3]

The enantioselective α-hydrazination of carbonyl compounds is especially important for two reasons: first, the products of such a reaction are key intermediates in the synthesis of a large and diverse array of natural and bioactive compounds (see Figure 1 for a selection of examples), including hydrazines themselves and other N–N bond-containing molecules.[4a–c]

A few cases will be illustrated in this review where relevant. Moreover, β-amino alcohols in particular, besides being present in a variety of natural products and pharmaceutical molecules, are also employed as chiral ligands and auxiliaries in asymmetric synthesis.[4d–g] Then, the α-hydrazination, and especially the direct enantioselective α-hydrazination of carbonyl compounds with dialkyl azodicarboxylates (Figure 2), represents a benchmark reaction to testing either unprecedented methodologies or new chiral catalysts, many of which have appeared in the last decade and will be discussed in this review.

In the 2015–2024 decade, the direct asymmetric α-hydrazination of carbonyl compounds promoted by a variety of chiral (organo)catalysts has been the most studied approach to provide α-amino carbonyl compounds, and it will be dealt with first herein. This is the field where the most significant results have been achieved, among which noteworthy are the synthesis of α-tertiary amines by the direct enantioselective α-hydrazination of α-branched ketones by both chiral Brønsted and Lewis acid catalysis, and the deployment of novel chiral catalysts (e.g., rotaxanes, planar chiral catalysts, chiral covalent organic frameworks) and techniques (e.g., catalyst immobilization for batch and flow chemistry) to achieve higher performance in terms of final yield and enantioselectivity in standard α-hydrazination. A smaller number of methods based on other and more diversified approaches, not necessarily leading to enantioenriched compounds, based on, e.g., radical or metal-mediated rearrangements, will be collected and discussed at the end of this review. Since there is some confusion on azodicarboxylate acronyms, in the schemes we will call di-*t*-butyl azodicarboxylate as DtBAD and dibenzyl azodicarboxylate as DBeAD.

As shown in Figure 2, the direct α-hydrazination of carbonyl compounds with dialkyl azodicarboxylates requires the generation of a nucleophilic C atom at the proper position (i.e., α to the carbonyl group) capable of reacting with one of the N atoms of the electrophile. This can be accomplished through

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the formation of enamines, enols and enolates. Asymmetry (facial selectivity) in the new C–N bond formation is imparted differently, depending on the nucleophile. Chiral enamines are generally obtained in situ by using proline, or one of its derivatives, as well as chiral primary amines. This organocatalytic approach is fruitfully used with aldehydes and, with α-branched aldehydes, gives access to chiral α-tertiary amines. "Chiral" enols are instead generated by using chiral Brønsted acid organocatalysts, such as chiral phosphoric acids, which promote the formation of an enol tightly coordinated by an H-bonding network. Chiral Brønsted acid catalysis has been successfully exploited by Toste[5] and List[6] for the enantioselective hydrazination of cyclic α-branched ketones in 2015 and, more recently, by Yang[7] for the electrophilic α-hydrazination of acyclic α-branched ynones. "Chiral" enolates can be formed in two different ways, i.e. either in the presence of a chiral metal-ion based Lewis acid catalyst (e.g., chiral complexes of $Zn^{2+}$, $Li^{+}$, $Ca^{2+}$, $Sn^{2+}$) to which coordination of the electrophile is possible or with H-bond donor catalysts, usually bifunctional organocatalysts bearing a Brønsted base group capable to perform the α-deprotonation of the carbonyl compound. With the latter, a dense network of H-bonds between catalyst, enolate and electrophile accounts for the high enantioselectivity generally observed. As the major achievements with chiral enolates, Trost has recently described the enantioselective hydrazination of cyclic α-branched ketones[2] and, later, of acyclic α-branched enones[8] for the synthesis of α-tertiary amine derivatives by using dinuclear Zn-ProPhenol catalysts.

Accordingly, the review is organized by commenting first all the papers issued in the last decade which deal with enamine organocatalysis, with a section devoted to proline and its derivatives, and a second one to other chiral amines. Then the papers describing chiral Brønsted acid catalysis will be reviewed. Next chapter is on papers about chiral enolates, in turn divided in two sections, one treating metal-ion based Lewis acid catalysis and the other H-bond donor/Brønsted base catalysts. In a final chapter miscellaneous approaches to α-hydrazino carbonyl compounds will be discussed before a concluding chapter.

## 2. α-Hydrazination of Carbonyl Compounds via Chiral Enamine Intermediates

### 2.1. Organocatalytic α-Hydrazination with Proline and its Derivatives

Asymmetric organocatalysis exerted by small organic molecules is currently one of the most important approaches to the enantioselective synthesis.[9] The formation of an intermediate enamine is one of the activation modes of the substrate which allows for the enantioselective α-functionalization of carbonyl compounds. Proline (**1**), a small organic compound, and its derivatives are amongst the most used chiral organocatalysts, reacting with aldehydes to form transient enamine intermediates which can react with an array of electrophiles, among which dialkyl azodicarboxylates,[10] to deliver a diverse range of enantioenriched α-functionalized carbonyl compounds.[11,12] Three different mechanistic pathways were proposed to explain the formation of a key enamine intermediate (Scheme 1), i.e., of an *anti*-enamine carboxylic acid (**3**), either directly *via* iminium ion **2** (Houk-List)[13] or *via* an oxazolidinone intermediate **4** (Gschwind);[14] and of a *syn*-enamine carboxylate **5** from the same oxazolidinone (Seebach-Eschenmoser).[15] Another picture of the mechanism has been recently disclosed by Vetticatt

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Samuele Visi graduated in Chemical Science at the University of Florence (Italy) in 2024, majoring in Organic Chemistry with an experimental thesis on gold(I)-catalysed cascade processes in the group of Prof. Occhiato. He has currently a research contract at the University of Florence under the supervision of Prof. Occhiato, working on gold-catalysed methodologies for the synthesis of hetero- and carbocyclic structures.

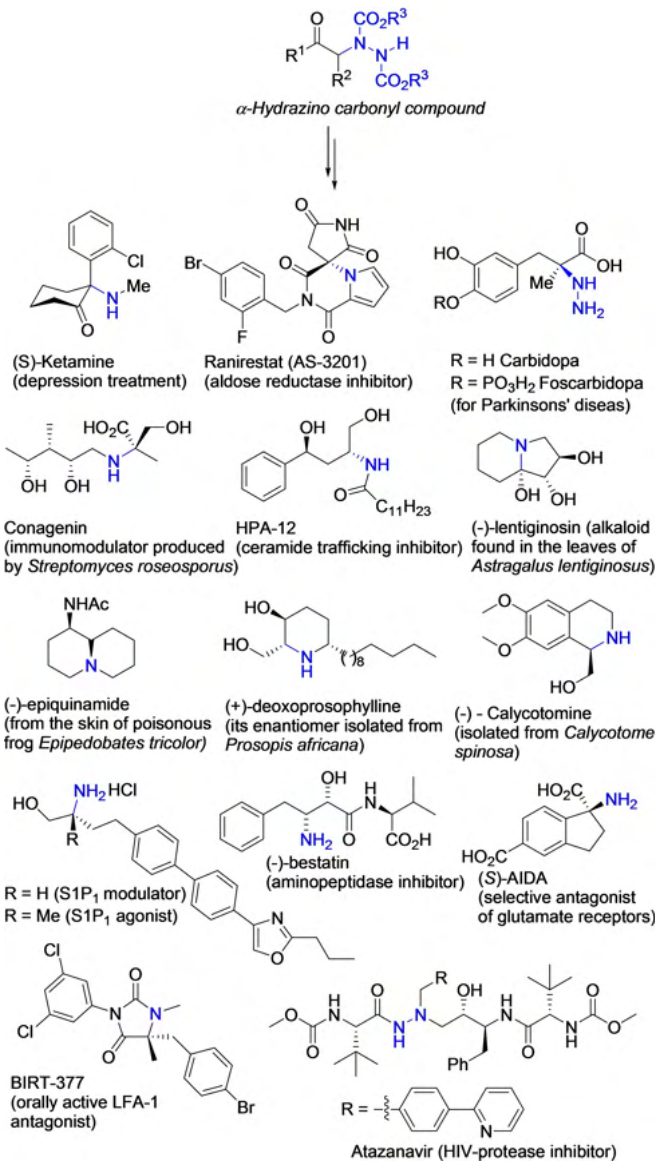



**Figure 1.** Examples of natural and bioactive compounds prepared from α-hydrazino carbonyl compounds.

thanks to a study realized using a combination of experimental kinetic isotope effects (KIEs) and theoretical calculations.[12b] That enamine formation is the rate-determining step of the process is supported by a significant carbonyl $^{13}C$ KIE and a large primary α-deuterium KIE. However, the study shows also that a protonated enamine species **6** is first formed by an E2 elimination mechanism from oxazolidinone intermediate **4**, which then generates *anti*-enamine carboxylic acid **3**, thus supporting the nonparasitic role of oxazolidinone **4** in proline catalysis.

Since the concurrent reports by the research groups of Jorgensen[16] and List,[17] and then Zhong[18] on the use of proline as a catalyst in the enantioselective, direct α-hydrazination of aldehydes using azodicarboxylate esters as electrophiles, there was an explosive growth of studies aimed both at developing better-performing proline-derived catalysts for such

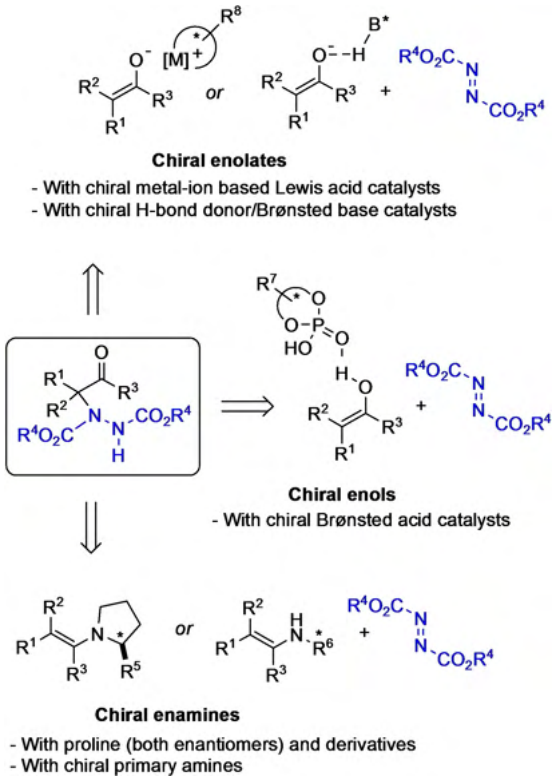
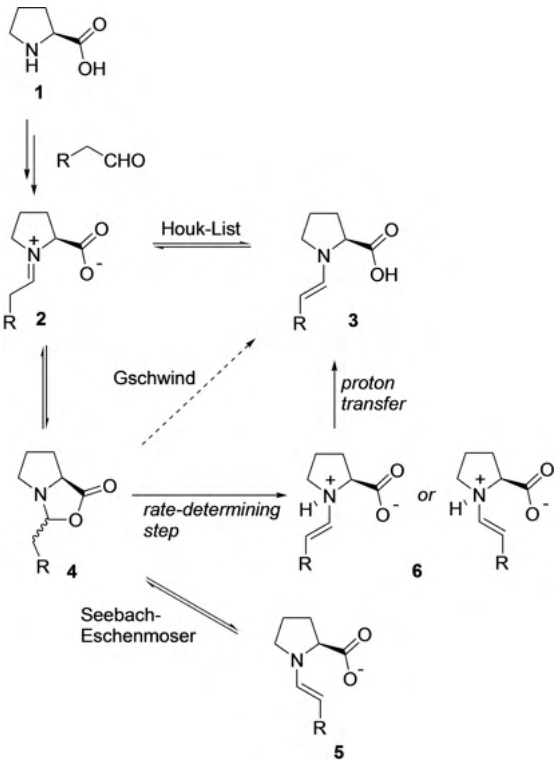



**Figure 2.** General approaches for the direct enantioselective α-hydrazination of carbonyl compounds with dialkyl azodicarboxylates.




**Scheme 1.** Proposed mechanisms for the formation of the enamine intermediate with proline.

a process and exploiting its generally high enantioselectivity for the synthesis of natural and biologically active compounds or intermediates.[1]

With enantiopure fluoro alcohols **7** (Scheme 2), obtained by organocatalytic fluorination of suitable aldehydes followed by Horner-Wadsworth-Emmons (HWE) reaction, Khonde et al. proceeded with the proline-catalyzed diastereoselective α-hydrazination of the corresponding aldehydes (not isolated) prepared by the Dess-Martin Periodinane (DMP) oxidation of the alcohol functionality and using commercially available DBeAD as a nitrogen source.[19] With L-proline as the catalyst, after *in situ* reductions with sodium borohydride, the reaction led to the *anti*-1,3-fluoro hydrazines **8** in good yield and high diastereomeric ratio (anti/syn > 90:1) as determined by chiral HPLC. The reaction sequence had a broad substrate scope, resulting compatible with functionalities including alkyl, phenyl, substituted phenyl, and naphthyl groups.

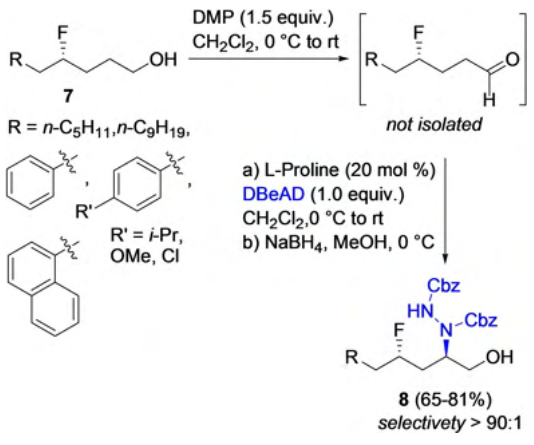
Interestingly, with D-proline, albeit yields were always very good, the *anti*/*syn* selectivity was impaired by the stereochemistry of the substrate in a mismatched case as it was much lower or almost none (0.75–2.2:1) with the same fluoro alcohols. Unfortunately, the cleavage of the N–N bond in **8**, attempted using Raney Nickel under standard hydrogenation conditions, was unsuccessful, presumably due to strong intramolecular hydrogen bonding with fluorine.

The synthesis of foscarbidopa (Scheme 3), identified as a phosphate prodrug of carbidopa with greater aqueous solubility for the treatment of Parkinson's disease, was realized through the key enantioselective α-hydrazination of racemic aldehyde **9** which allowed Huters et al. to install the desired quaternary stereocenter.[20a] After screening four different catalysts and different reaction conditions, the authors found that the aldehyde was converted preferentially to the desired (*S*)-enantiomer of hydrazine **10** when the reaction was catalyzed by (*R*)-(5-(pyrrolidin-2-yl)-1*H*-tetrazole **11**[20b] in acetonitrile in the presence of dibenzyl azodicarboxylate and trifluoroacetic acid (TFA) as an additive. Under such conditions, (*S*)-hydrazine **10** was obtained in high yield and with 60% ee, which was increased to > 99% after crystallization.

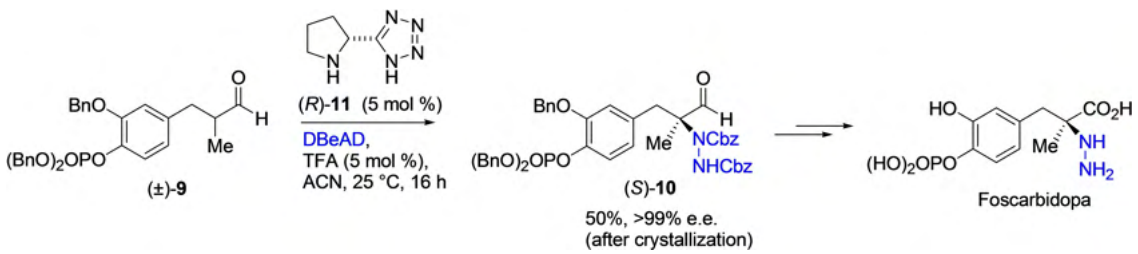
In the quest of new natural product-derived bioactive compounds, Calderón-Rangel et al. realized the first electrophilic α-hydrazination reaction of the labdane-type diterpenes cativic acid **12** and 13-*epi*-labdanolic acid, the latter isolated from aerial parts of *Ageratina jocotepecana* (Scheme 4).[21] After conversion of cativic acid into the corresponding aldehyde, in the presence of 1.1 equiv. of dibenzyl azodicarboxylate and L-proline (40 mol %) as the organocatalyst in $CHCl_3$, followed by an in situ reduction, β-hydrazino alcohol (*R*)-**13** was obtained in 76% yield and 52% de.[22] Interestingly, while the diterpene moiety of cavitic acid had no influence on the diastereoselectivity, that was determined by the absolute configuration of the proline, the opposite occurred with the aldehyde deriving from 13-*epi*-labdanolic acid in which the hydroxyl group at position C-8 biased the face selectivity by hydrogen binding with DBeAD.

L-Proline was used by Tien et al. as organocatalyst for the successful α-hydrazination of α-borylacetaldehyde **14** with DtBAD to provide a new class of MIDA boronates **15** after Pinnick oxidation of the carbonyl group directly on the crude reaction mixture (enantiomeric excesses undisclosed).[23] The α-carboxy MIDA boronates so obtained were then used for the synthesis of a variety of heterocyclic compounds by exploiting the α-hydrazino group. Unfortunately, no attempts at cleaving the N–N bond to obtain α-amino boronic acids were reported by the authors (Scheme 5).

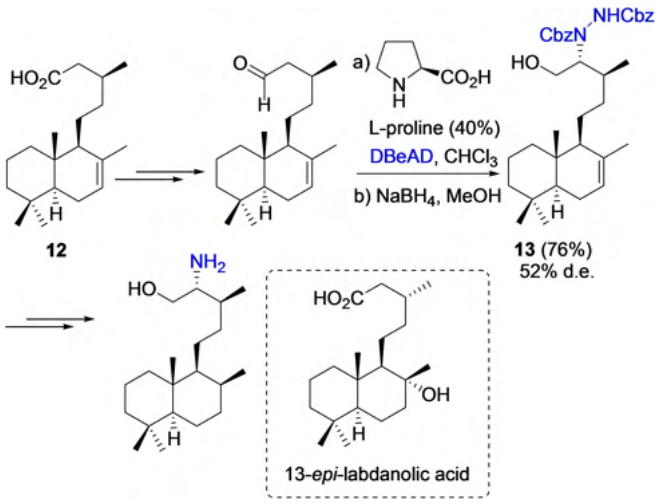
In their successful enantioselective synthesis of (+)-lycoperdic acid, a natural product isolated from the mushroom *Lycoperdon perlatum* which shares structural similarities with some ionotropic glutamate receptor binders, Kortet et al.[24] realized a diastereoselective α-hydrazination of enantioenriched (er 94:6) substrate **16** with DBeAD in dichloromethane and D-proline as the catalyst according to List's protocol.[17] After oxidation to the corresponding carboxylic acid **17**, unfortunately the subsequent N–N bond cleavage failed and this route



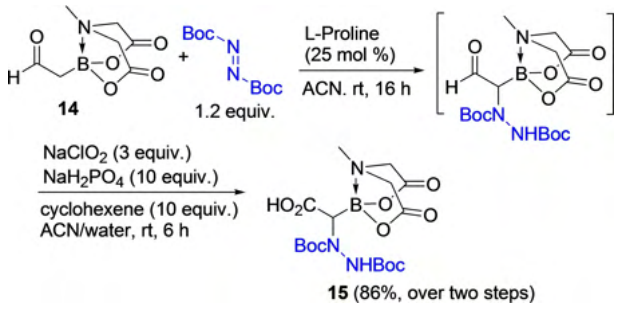

**Scheme 2.** Proline-catalyzed diastereoselective α-hydrazination of aldehydes from alcohols **7**.




**Scheme 3.** Synthesis of foscarbidopa.



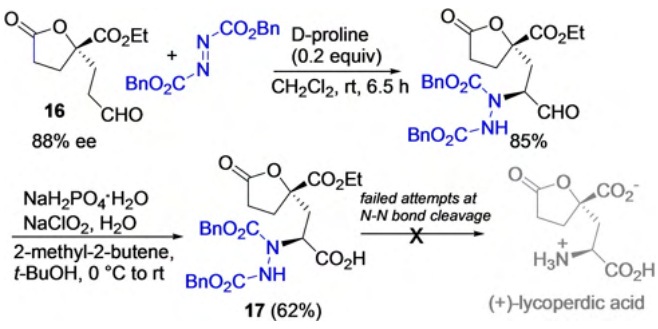

**Scheme 4.** α-Hydrazination of labdane-type diterpene cativic acid **12**.




**Scheme 5.** α-Hydrazination of α-borylacetaldehyde **14** to provide MIDA boronate **15**.

had to be abandoned in favor of a sequence including a different α-amination strategy (Scheme 6).

For the synthesis and subsequent rearrangements of *N*-Boc-*N*-allyhydrazones **20** to furnish isoprenyl compounds, Heerdegen et al. needed α-hydrazino aldehydes **19** with orthogonally protected N atoms.[25] To this end, they prepared known *N*-Troc-*N*-Boc-protected diazene **18**[26] and subjected it to reaction with isobutyraldehyde in the presence of three different organocatalysts, i.e., L-proline, L-phenylalanine, and tetrazole (*S*)-**11**. The latter gave the best results in this α-hydrazination in terms

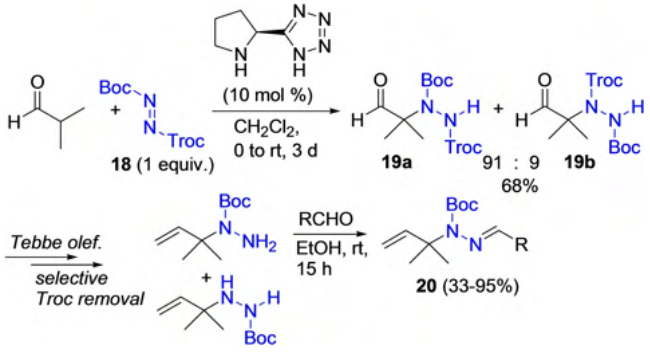



**Scheme 6.** Attempt at the enantioselective synthesis of (+)-lycoperdic acid by α-hydrazination.

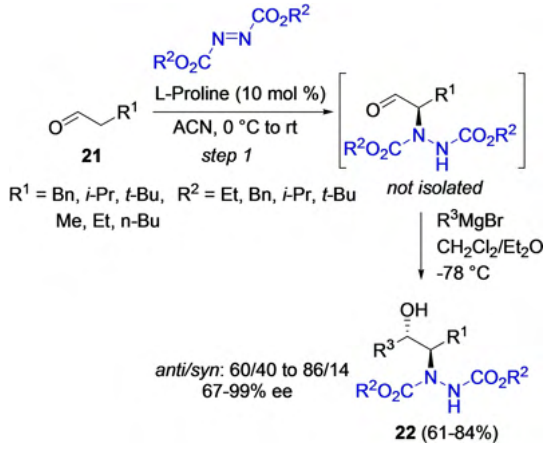
of yield (68%) and isomeric ratio in favor of **19a** which reached a 91:9 value (Scheme 7).

An efficient stereoselective synthetic approach to the vicinal amino alcohol motif was reported by Liu et al. via an organocatalytic cascade reaction which included direct asymmetric α-hydrazination of aldehydes **21** catalyzed by L-proline followed by nucleophilic attack to the carbonyl group by a Grignard reagent to generate both the amino and hydroxyl functionalities.[27] The challenges inherent in this process (possible racemization of the α-amino aldehyde formed in situ, compatibility of the solvent system for the α-hydrazination and subsequent Grignard addition, and the level of diastereoselectivity in the latter process) were all evaded by removing the solvent employed in the first step and using the Grignard reagent after diluting the crude reaction mixture in a $CH_2Cl_2$/$Et_2O$ mixture. Moderate to excellent levels of both enantio- and diasteroselectivity were attained by such a methodology. Conversion of final products **22** into the corresponding amino alcohols was demonstrated with a single example (Scheme 8).

Gurka et al. compared the organocatalytic activity of a series of substituted 4-hydroxyprolines in the α-hydrazination of propionaldehyde with diethyl azodicarboxylate (DEAD) in water and organic solvents.[28] While in organic media most of the catalysts behaved as L-proline and showed high activity and enantioselectivities, only low enantioselectivities were obtained




**Scheme 7.** Synthesis of *N*-Boc-*N*-allyhydrazones **20**.



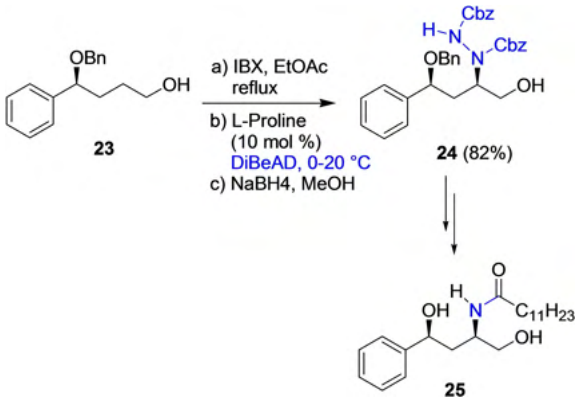

**Scheme 8.** Stereoselective synthetic approach to vicinal amino alcohols **22**.

in water as a solvent, primarily due to the racemization of the product under the reaction conditions.

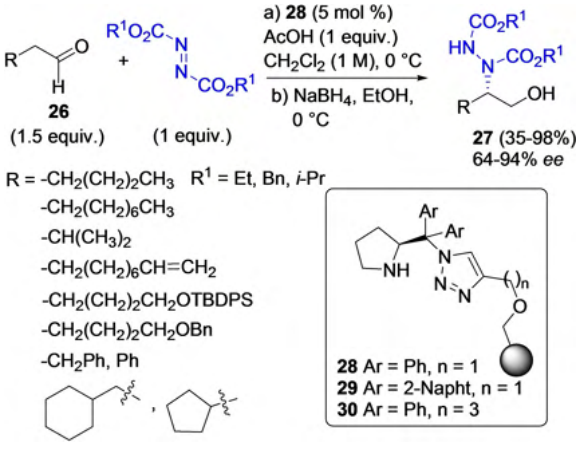
An organocatalytic route to enantioselective synthesis of ceramide trafficking inhibitor HPA-12[29] (Scheme 9), devised by Lalwani et al., was based on proline-catalyzed α-hydrazination reaction of a suitable aldehyde (obtained by in situ oxidation of the corresponding alcohol **23**) followed by reduction with $NaBH_4$, N–N bond cleavage and N-functionalization to obtain a revised structure of target product **25**.[30] Similarly, the formal synthesis of (−)-epiquinamide[31] was realized by Ahuja et al. with the L-proline-catalyzed one-pot sequential α-hydrazination/propargylation of an aldehyde as the key step.[32]

Kumar et al. (Scheme 10) envisaged the synthesis of polymer-supported, prolinol-derived catalysts **28**–**30** that could offer a better enantio-induction through the bulky solid-support and be reusable after their recovery, as well.[33] Other successful asymmetric α-aminations of aldehydes using polymer-supported catalysts derived from L-proline with a dipeptide (see next paragraph)[34a] and a tripeptide linker,[34b] and from a *trans*-4-hydroxy-proline derivative,[34c] were reported in the literature. Commercially available diaryl prolinols were anchored to the polystyrene support with a triazole linker in a three-step procedure which included conversion of the prolinol into the corresponding azide and the subsequent click chemistry with a polymer-supported alkynyl ether. The catalytic activity of **28**–**30** was first demonstrated with the asymmetric α-hydrazination of *n*-hexanal (1.5 equiv.) using dibenzyl azodicarboxylate (1 equiv.) as the electrophile, followed by reduction to alcohol using $NaBH_4$. The highest yield (85%) and ee (91%) were achieved in the presence of 5 mol % of **28** and acetic acid (1 equiv.) in $CH_2Cl_2$ (1 M) at 0 °C, after 1.5 h of reaction. The polystyrene-supported catalysts **29** (containing 2-naphthyl group) and **30** (containing a longer chain length) were also tested under the optimized reaction conditions affording similar results. The scope of the process was extended to a variety of substituted aldehydes **26** using **28** and DBeAD, DEAD and di-*i*-propyl azodicarboxylate (DIAD) as the electrophiles, obtaining products **27** in 70–98% yield and with ee values of 64–94%. The reusability of the aminocatalyst **28**, separated from the reaction mixture by filtration, was also demonstrated with two different aldehydes (R=Bn, *n*-Bu). After four cycles, with both aldehydes, the enantiopurity of the product measured after the first experiment (93 and 91%, respectively) remained unchanged, with just a slight decrease in the yield.

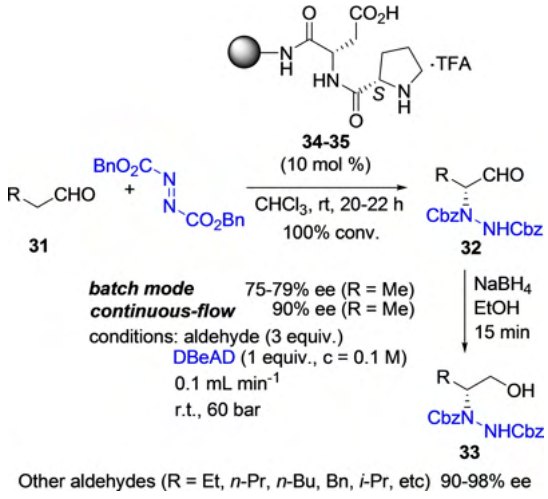
L-Proline was immobilized by Ötvös et al. on amino-functionalized, non-TFA-labile resins PS-MBHA and TentaGel by using both single amino acids (Asp, Glu) and dipeptides (Pro-Asp and Pro-Glu) as the linkers (Scheme 11).[34a] The catalysts so obtained were initially screened in the batch reaction of propanal with DBeAD in chloroform to evaluate their organocatalytic activity. Best catalysts were PS-MBHA supported H-Pro-Asp-NH-PSMBHA and TentaGel supported H-Pro-Asp-NH-TentaGel both with a single amino acid (Asp) as the linker. After 20–22 h, reduction of the α-hydrazino aldehydes **32** provided the corresponding β-hydrazino alcohols **33** in 75–79% ee and with *R* absolute configuration.After an extensive study of the reaction under continuous-flow conditions with the TentaGel-supported catalyst the strategic control of the residence time allowed the authors to achieve both high enantioselectivity (> 90% ee) and reaction rates with propanal and some other α-




**Scheme 9.** Asymmetric α-hydrazination for the synthesis of the revised structure of HPA-12 (**25**).




**Scheme 10.** Asymmetric α-hydrazination with polymer-supported prolinol-derived catalysts.

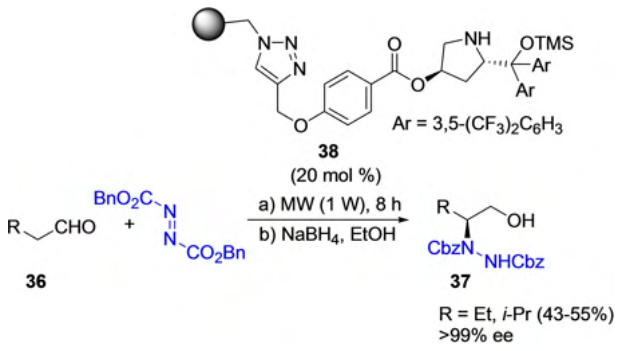



**Scheme 11.** Asymmetric α-hydrazination with proline immobilized on PS-MBHA and TentaGel resins.

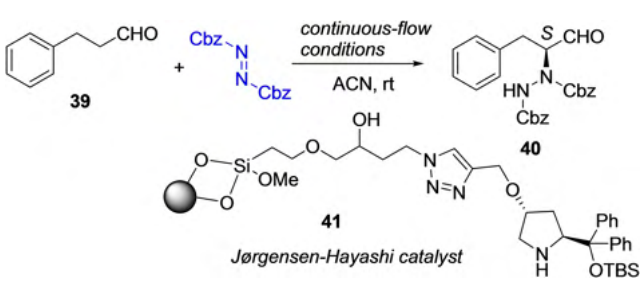
substituted aldehydes **31**, as well. No reaction was instead observed with isovaleraldehyde. No decrease in catalyst activity or selectivity was observed throughout 20 h of continuous-flow operation to prove the robustness of the catalyst.

A diarylprolinol catalyst was immobilized by Guryev et al. on Merrifield resin through the reliable click chemistry.[35] The catalytic activity of this catalyst was studied in the direct asymmetric α-hydrazination of some aldehydes **36** with dialkyl azodicarboxylates. Best results in terms enantiomeric excesses (>99%) were obtained using the less reactive dibenzyl azodicarboxylate, under MW irradiation (1 W, T<30 °C), although yields were not the highest. Recycling of the catalyst **38** was studied with isovaleraldehyde. Prolonging the reaction time in the first run, the yield of the product increased to 87% but ee's were lower (77%) because of partial racemization of the aldehyde. However, the optical purity was retained in the next cycles showing the efficiency of the catalyst upon several cycles (Scheme 12).

Flow chemistry and microreactors technologies are increasingly used in the production of fine chemicals and bioactive compounds,[36] so it is not surprising that α-hydrazination of carbonyl compounds has been studied under continuous-flow operation.[37] Westphal et al. reported on a new method for studying stereoselective catalyzed reactions at a small scale based on a microsized chemical reactor integrated with a chiral chromatographic column on a single microfluidic chip hyphenated to mass spectrometry (Scheme 13). On the grounds of their previous experience with Lab-on-a-Chip devices (LOCs) to couple miniaturized chiral high-performance liquid chromatography (HPLC) with synthesis in microflow in a direct manner, but operated in a stopped-flow manner, in the present work they report on heterogeneous catalyzed transformations in truly continuous flow operation. Sampling was done on small portions of reactor effluent, analyzing these by chiral HPLC/MS with an automized sampling protocol. They investigated the α-hydrazination of aldehyde **39** with dibenzyl azodicarboxylate in the presence of silica-supported Jørgensen-Hayashi catalyst **41**.[38] Not only was poor selectivity observed with the TMS-protected catalyst (racemic mixture after 30 min), but also a slight trend towards the opposite *R* enantiomer (25% ee at 200 min runtime) was observed.This could be accounted for by interactions between silanol groups on the silica surface and the catalyst, which would promote the OH deprotection by hydrolysis. Instead, with the sterically more demanding and stable *tert*-butyldimethylsilyl protecting group a much-improved enantioselectivity toward the *S* enantiomer was observed (74% ee) in the steady-state (at about 215 min runtime). After optimization of the conditions, to investigate the long-term performance of the immobilized catalyst, a continuous-flow experiment was evaluated over 3 days on-stream with automized injections every 25 min, showing that the immobilized catalyst proved to be highly enantio- and diastereoselective under the applied conditions for the whole experiment, with enantiomeric and diastereomeric ratio for product **40** higher than 95%.The product was instead obtained in a lower ee (50%) when the same OTMS-protected catalyst was immobilized on a Monolith-HJ support based on polystyrene divinylbenzene copolymer, generated inside the channels of microfluidic chips.[39]




**Scheme 12.** Asymmetric α-hydrazination with a diarylprolinol immobilized on Merrifield resin.




**Scheme 13.** α-Hydrazination of carbonyl compounds under continuous-flow operation.

## 2.2. Organocatalytic α-Hydrazination with Chiral Primary Amines

Besides proline and its derivatives, a variety of chiral primary amines have also been used as organocatalysts for the α-amination of aldehydes, some of which are shown in Figure 3.

The introduction of an α-tertiary amino group into an α-branched aldehydes is of particular importance as the products can be transformed into quaternary α-amino acids useful for building peptidomimetics and various pharmaceuticals.[40] In fact, all examples of organocatalytic α-hydrazination with chiral primary amines reported in the last decade, and discussed

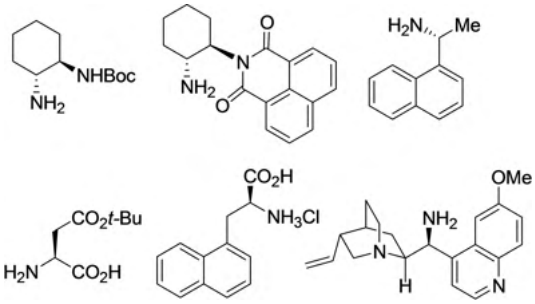
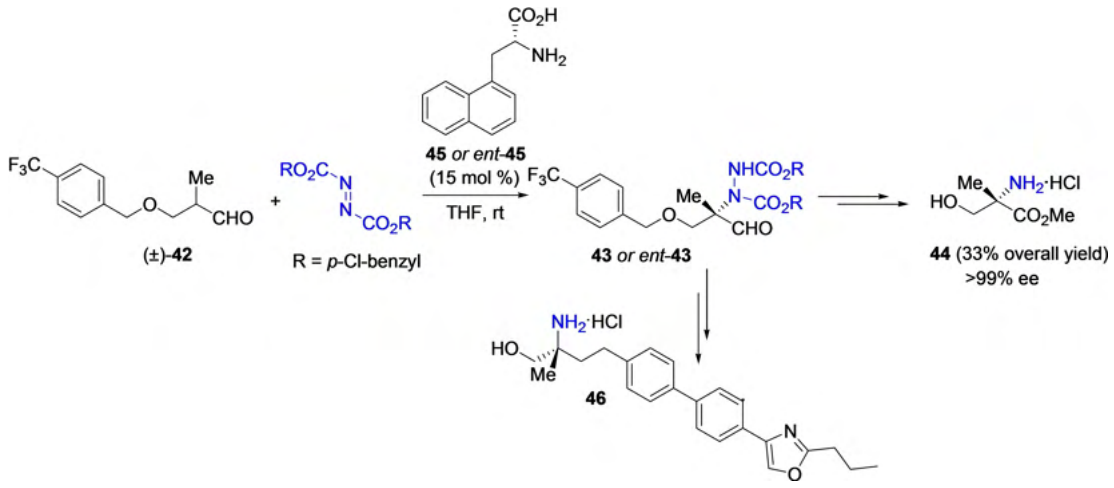


**Figure 3.** Examples of chiral primary amines used for the direct asymmetric α-hydrazination of carbonyl compounds.

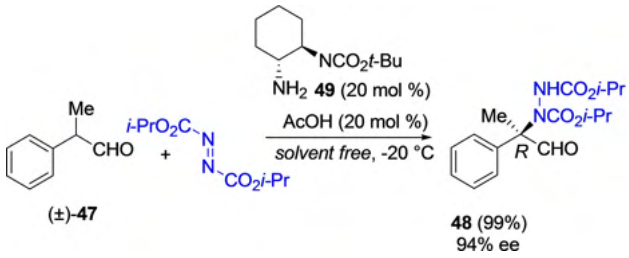



**Scheme 14.** 3-(1-Naphthyl)-alanine **45** as organocatalyst in the enantioselective α-hydrazination.

herein, concern the amination of α-branched aldehydes. Such a process is far less well-developed than with unbranched aldehydes. With few exceptions, because of the steric demands of the reacting partners, secondary amines are ineffective catalysts for reactions of α-branched aldehydes, while primary amines introduce problems such as unfavorable tautomer equilibria and poorer control of *E*/*Z* selectivity.[41]

For example, Xiao et al.[42] recently reported on the use of the *R* enantiomer of 3-(1-naphthyl)-alanine **45** as organocatalyst in the key enantioselective α-hydrazination of 2-methyl-3-[(4-trifluoromethylbenzyloxy]propanal **42** with *p*-chlorobenzyl azodicarboxylate to synthesize pure (*S*)-α-methyl-serine methyl ester hydrochloride **44** with >99% ee (Scheme 14). The same catalyst,[43] but with opposite absolute configuration, was used in the analogous reactions to obtain *ent*-**43** (with and without the *p*-$CF_3$ group) as an intermediate for the synthesis of sphingosine-1-phosphate receptor 1 agonist **46** which showed a high phosphorylation rate in human blood than known IMMH001 agonist.

To make the direct asymmetric α-hydrazination of α,α-disubstituted aldehydes more environmentally friendly, Torregrossa-Chinillach et al.[40] developed a highly efficient enantioselective solvent-free process using the simple mono-*N*-Boc-protected cyclohexa-1,2-diamine **49** as a chiral organocatalyst (20 mol %). Under the best conditions (acetic acid as additive and at −20 °C), the reaction, extended to a variety of disubstituted aldehydes, almost always provided products with *R* absolute configuration in high yield and enantiomeric excesses (Scheme 15).To understand the reason for the high enantioselectivity, extensive calculations of all possibilities with major enamine intermediate *E* resulted in the mode of attack **A** (Figure 4) as the one leading to the less energetic transition state. Despite in the alternate mode **B** there is lower steric congestion, calculations showed the stronger stabilizing effect of the H-bond in **A**, which outcompetes the steric destabilization, thus making the corresponding transition state as the lowest in energy and explaining the formation of the experimental *R* major enantiomer. Related transition states were




**Scheme 15.** Solvent-free α-hydrazination with mono-*N*-Boc-protected cyclohexa-1,2-diamine **49**.

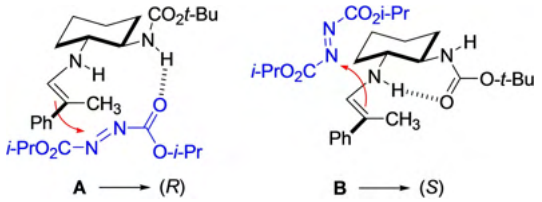
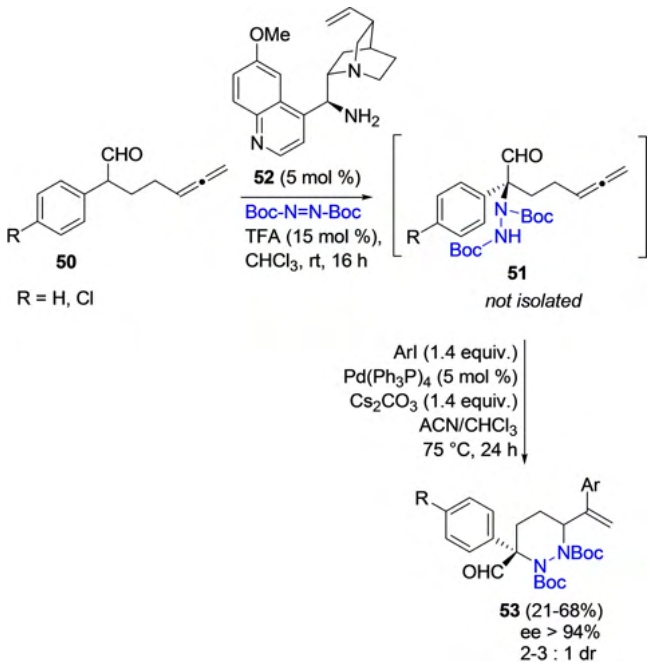


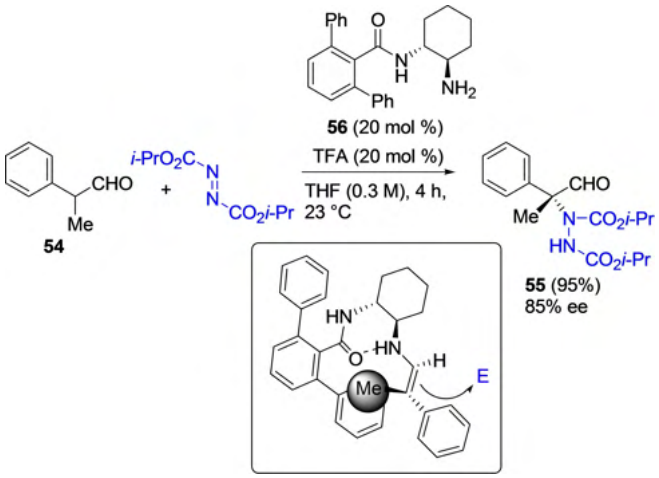

**Figure 4.** Modes of attack in the α-hydrazination with mono-*N*-Boc-protected cyclohexa-1,2-diamine **49**.

found for the minor *Z* enamine intermediate, but their activation energies were at least 2.0 kcal/mol higher, indicating that they do not participate in the reaction.

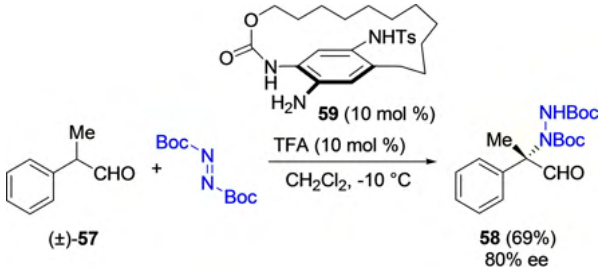
Marques et al.[44] reported on the synthesis of enantioenriched polysubstituted hexahydropyridazines via a sequential, multicatalytic process entailing organocatalysis and transition metal catalysis (Scheme 16).Cyclic hydrazines are an important class of molecules due to their presence in a variety of bioactive compounds,[4a–b,45] and consequently several syntheses of hydrazine-containing heterocycles have been reported in the literature.[46] In their work, the authors developed a one-pot, two-step protocol in which the amino catalyzed α-hydrazination of aldehydes **50**, in the presence of 5 mol % of catalyst **52** and 15 mol % of TFA, affords key intermediates **51** (with *S* absolute configuration) that then, after dilution with acetonitrile, undergo cyclization upon addition of the palladium catalyst and the




**Scheme 16.** Synthesis of enantioenriched polysubstituted hexahydropyridazines **53**.




**Scheme 17.** Highly enantioselective α-functionalization of α-branched aldehydes with primary amine catalyst **56**.




**Scheme 18.** Planar-chiral macrocycles as chiral aniline-type organocatalysts.

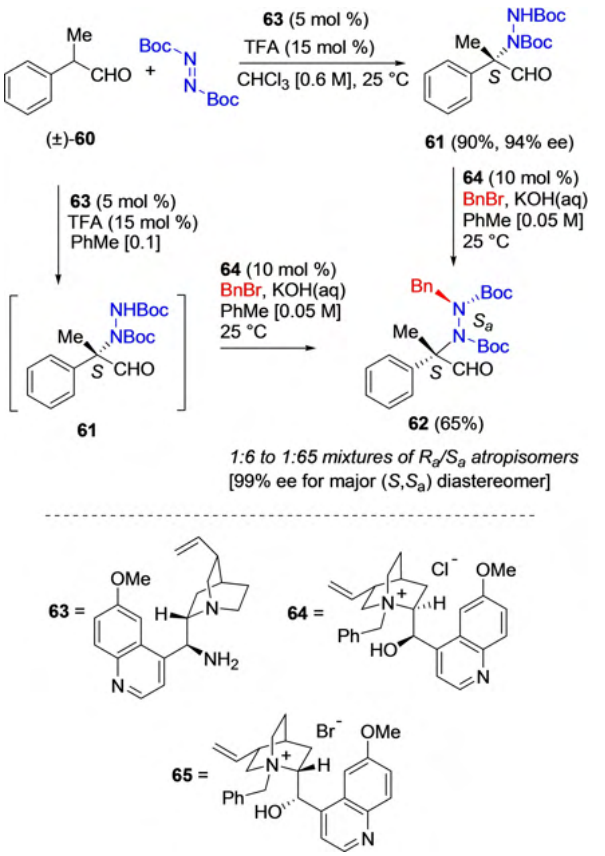
aryl iodide. The reaction provides a series of hexahydropyridazines **53** bearing different aryl rings with high enantiomeric excesses but low diastereomeric ratios (at best 3:1 ratio). In the second catalytic cycle the oxidative addition of aryl iodide to palladium(0) is followed by the insertion of the complex to the allene moiety of **51**. The next intramolecular reaction to form the target products takes place between the hydrazine and a π-allyl species in the presence of $Cs_2CO_3$.

Witten and Jacobsen[41] reported on a simple, new primary amine catalyst to promote highly enantioselective α-functionalization of α-branched aldehydes. Although mostly efficient in the α-hydroxylation and α-fluorination of branched aldehydes, the catalyst **56** developed by the authors showed promising organocatalytic activity (95% yield and 85% ee) in the α-hydrazination, too, as demonstrated with the single example reported in Scheme 17. The high general enantioselectivity attained with this catalyst was ascribed to a highest populated enamine intermediate configuration *E* stabilized by an intramolecular H-bond, making its upper face more available to the electrophile, correctly predicting the predominant *R* configuration of the α-hydrazination product **55**.

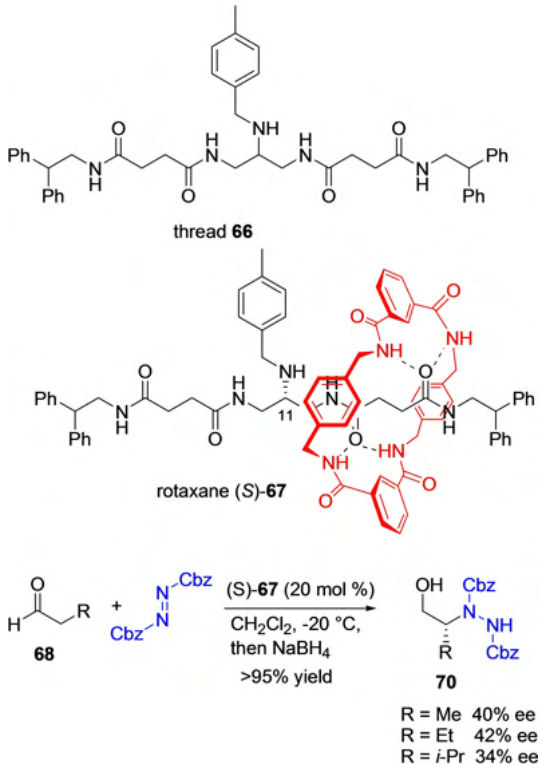
Planar-chiral cyclophanes have attracted much interest in the last decades not only for their structural features, but also because of their presence in natural products and applications in asymmetric catalysis, host-guest chemistry, and material science.[47] Wang et al. recently reported on the preliminary application of planar-chiral macrocycles (paracyclophanes) as chiral aniline-type organocatalysts in the asymmetric electrophilic hydrazination of aldehydes (Scheme 18).[48] These paracyclophanes, bearing different ring sizes (16–23-membered) and functional group-containing *ansa* chains, were in turn prepared by enantioselective electrophilic aromatic hydrazination of macrocyclic substrates with azodicarboxylates, in the presence of a chiral phosphoric acid catalysis with excellent yields and high enantioselectivities (up to 99% ee). As organocatalysis, two of these macrocycles were tested, with amine **59** (92% ee) providing the best results in terms of yield and ee when racemic aldehyde **57** was reacted with the di-*t*-butyl azodicarboxylate in $CH_2Cl_2$ in the presence of 10 mol% of TFA.

Atroposelective catalysis for the construction of rotationally constrained compounds around the N–N bond was recently disclosed by Portolani et al.[49] The catalytic strategy involved the use of azodicarboxylates for the initial direct asymmetric α-hydrazination of aldehydes, followed by alkylation of the distal N atom of the hydrazine appendage to increase the steric hindrance around the N–N single bond, thus leading to rotationally stable, chiral tetrasubstituted hydrazine derivatives.

Trisubstituted hydrazine **61** (Scheme 19) was prepared through the hydrazination of racemic 2-phenylpropanal (**60**) with di-*tert*-butyl azodicarboxylate in chloroform using 9-*epi*-9-amino-9-deoxy-quinine (**63**) as the organocatalyst and TFA as the co-catalyst. The hydrazine **61** was thus isolated in 90% yield and 94% ee and was used for alkylation optimization. A thorough screening of chiral phase transfer (PT) catalysts using benzyl bromide as the alkylating agent in toluene/water (aqueous KOH solution) resulted in *N*-benzyl-quininium chloride (**64**) as the best catalyst to produce atropisomeric hydrazine **62** in a 65% yield as a 1:6.3 mixture of diastereoisomers, and with




**Scheme 19.** Construction of atropisomers around the N–N bond by α-hydrazination of α-branched aldehydes.




**Scheme 20.** α-Hydrazination with chiral rotaxane (*S*)-**67** as organocatalyst.

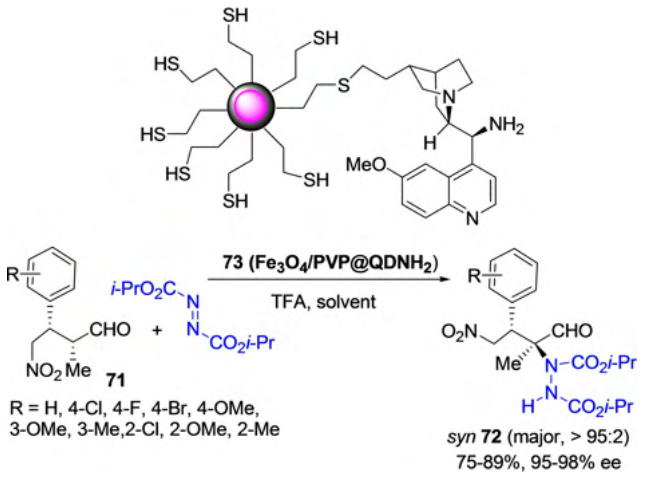
99% ee for the major (*S*, $S_a$) atropisomer. Similar results were obtained by a two-step, one-pot reaction in toluene as the solvent. When catalyst **65** was used for the alkylation step in toluene at −5 °C, the other atropisomer (*S*, $R_a$) was obtained in 73% yield, 80% de and with >99% ee. The authors demonstrated the applicability of the one-pot approach to a large series of differently substituted benzyl bromides and starting aldehydes, with high values of yield, enantioselectivity, and diastereocontrol obtained in most cases. A reaction mechanism was also proposed to explain the atroposelectivity in the last step of the sequence.

Amongst chiral amines deployed to catalyze asymmetric direct α-hydrazination of carbonyl compounds, surely that reported by Cakmak et al.[50] stands out for its originality and structural complexity, the catalytically active amino group being installed on the thread of a rotaxane structure **67** in which chirality is due to the 4-tolylamine group itself that blocks shuttling of the macrocycle to the other side of the prochiral thread **66** (Scheme 20). This generates a configurationally stable enantiomer with a stereocenter at C11, in the specific case with *S* absolute configuration. This exotic chiral amine was tested in the reaction of some aldehydes with a dialkyl azodicarboxylate, but although yields in **70** were very high, in all cases ee's were quite low (34–42%). In any case, these results show that point chirality induced by mechanical bonding between an achiral macrocycle and an achiral thread can be used to generate a chiral space suitable for asymmetric catalysis.

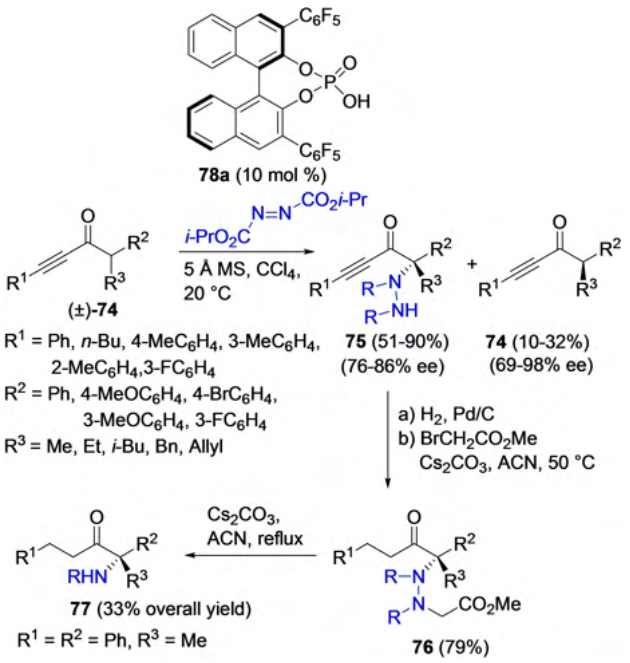
Magnetic nanoparticles (MNP) have also been used to support a chiral amine as organocatalyst for the direct asymmetric α-hydrazination of aldehydes.[51] Chiral amine 9-amino(9-deoxy)*epi*-quinidine was supported on $Fe_3O_4$ magnetic nanoparticles to give an heterogeneous catalyst ($Fe_3O_4$/PVP@QDNH$_2$) **73** capable to provide products **72** in excellent yields (75–89%), diastereoselectivities (*syn*/*anti* > 95:5) and enantioselectivities (95–98% ee for the *syn diastereomer*) with (2*R*,3*S*)-2-methyl-3-nitro-4-phenylbutyraldehyde and some of its derivatives (**71**) as the substrates and DIAD as the electrophile. By recycling the catalysts, both diastereoselectivity (*syn*/*anti* = 88/12) and enantioselectivity (95% ee *syn*) could be maintained up to the fifth run (Scheme 21).

## 3. α-Hydrazination of Carbonyl Compounds via Chiral Enols - Chiral Brønsted Acid Organocatalysis

Access to chiral α-tertiary amines is possible through the enantioselective α-hydrazination of α-branched carbonyl compounds followed by N–N bond cleavage. However, while enamine catalysis exerted by chiral amines allows for the asymmetric amination of α-branched aldehydes, as shown in the previous chapter, the same is not true for α-branched ketones because of issues related to steric hindrance in the




**Scheme 21.** Magnetic nanoparticles (MNP)-supported chiral amines as organocatalysts.



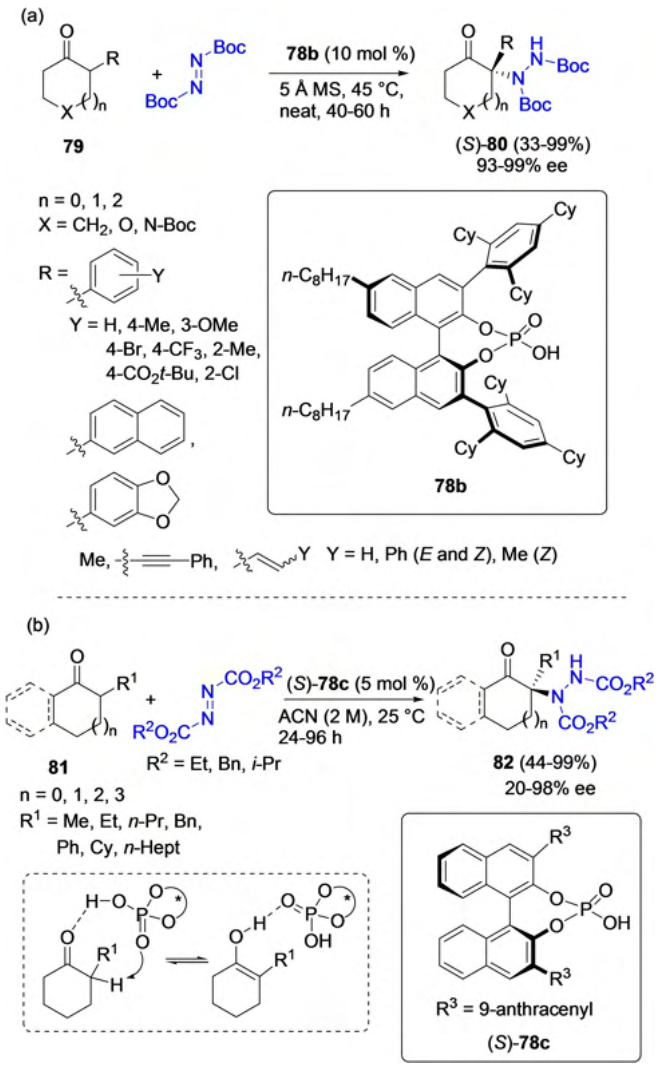

**Scheme 22.** Synthesis of acyclic α-tertiary amines by the enantioselective α-hydrazination of α-branched ynones **74**.

enamine intermediate and regioselectivity in the formation of the latter (amino catalysis preferentially forms the kinetic enamine). Thus, developing efficient approaches for the asymmetric electrophilic α-hydrazination of α-branched ketones would be of paramount importance for the synthesis of α-branched α-amino ketones. Substantial progresses have been reached in the last ten years in the direct asymmetric amination of cyclic α-branched ketones, from which stereodefined and configurationally stable enols/enolates can be generated, which have successfully been used as substrates for the enantioselective α-hydrazination with azodicarboxylates by using chiral Brønsted acid catalysis[5,6] and chiral Lewis acid catalysis.[2,52]

Instead, the asymmetric electrophilic amination of acyclic α-branched ketones has the extra requirement of controlling the *E*/*Z* geometry of the enol/enolate intermediate and thus only acyclic ketones with particular features could successfully be used as substrates in Lewis acid[8] and Brønsted acid catalysis.[7]

Chiral Phosphoric Acids (CPAs) are a class of Brønsted acid organocatalysts that, because of their high versatility, have found increasing applications in academia and industry in the asymmetric synthesis of organic compounds.[53a] In Trost 's first asymmetric electrophilic hydrazination of α-branched, conjugated enones for the synthesis of α-tertiary amines (with a dinuclear zinc-ProPhenol catalysis, see next chapter), the ketone unsaturation was crucial for the observed reactivity and regioselectivity.[8] Racemic α-branched ynones **74** where instead used by He et al.[7] for the asymmetric synthesis of acyclic, α-tertiary amine derivatives through the enantioselective α-hydrazination with DIAD in the presence of chiral phosphoric acid catalyst **78a** (the best amongst those tested) (Scheme 22). The process provided the α-hydrazination products (**75**) in high yield and in 76–86% ee with a wide range of α-aryl and α-alkyl substituted ynones. Moreover, kinetic resolution of racemic starting material was realized under these conditions, to provide valuable enantioenriched α-substituted ketones **74**. The authors demonstrated that the conjugated alkynyl group in the α-branched ketones not only modulates the reactivity of the latter in the α-hydrazination but also plays an important role in controlling the stereoselectivity, especially in the kinetic resolutions. One example was converted into the tertiary amine derivative **77** according to standard conditions, but prior reduction of the triple bond was required.

Yang and Toste reported on the first direct asymmetric hydrazination of α-branched cyclic ketones **79** with di-*t*-butyl azodicarboxylate catalysed by chiral phosphoric acids to generate compounds **80** with a N-containing quaternary stereocenter (Scheme 23, a).[5] Catalyst **78b** proved superior to other similar CPAs under optimized conditions, i.e. when running the reactions under "neat" conditions at 45 °C and with 10 mol % of the catalyst (almost complete conversions after 40–60 h, with enantiomeric excesses generally higher than 95%). Although the stereogenic center of the starting ketone is destroyed in the keto/enol tautomerization, and thus the reaction can be thought as a simple dynamic kinetic transformation in which the phosphoric acid mediates the enantioselective hydrazination of the enol form, very interestingly the authors observed kinetic resolution of the starting material with some substrates under milder conditions, which provided enantioenriched α-branched ketones. The authors therefore proposed that, in addition to mediating the enantioselective hydrazination, the phosphoric acid can also catalyse the enantioselective enolization of chiral ketones, a process which has been rarely taken into consideration before. As for the scope of the asymmetric hydrazination of α-substituted cyclic ketones, the reaction tolerates a range of aryl, alkenyl, alkynyl, and alkyl substitutions at the α-position, different ring sizes, and modifications of the cyclohexanone ring. The efficiency of this approach was demonstrated with a short synthetic route to enantioenriched




**Scheme 23.** Direct asymmetric hydrazination of α-branched cyclic ketones catalysed by CPAs.

(*S*)-ketamine (Figure 1) starting with the α-hydrazination of the proper cyclic ketone.

In the same year, List independently reported on the direct asymmetric hydrazination of α-branched, cyclic ketones through the same enol catalysis exerted by chiral phosphoric acids.[6] After screening several phosphoric acids bearing different substituents in the 3,3′-positions, catalyst **78c** with a 9-anthracenyl moiety in those positions proved to be superior, in terms of both reactivity (40–99% yield) and selectivity (20–98% ee), in the α-hydrazination of a series of α-branched cyclic ketones **81** using three different dialkyl azodicarboxylates as the electrophiles in acetonitrile at room temperature (Scheme 23, b). Best results were obtained with five- and six-membered cycloalkanones, whereas with both larger cycles and benzo-fused cycloalkanones the enantioselectivity was lower. In the catalytic cycle, protonation of the carbonyl compound and concomitant α-H abstraction by the organocatalyst generate a chiral enol which then undergoes facial selective electrophilic attack by the azodicarboxylate.

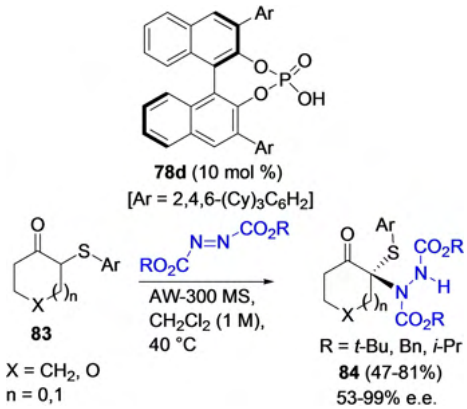
The asymmetric α-hydrazination of α-sulfanyl cyclic ketones **83** was enabled by chiral phosphoric acid catalysis, which generated a series of chiral cyclic ketone derivatives **84** possessing a sulfur-containing tetrasubstituted stereocenter (Scheme 24).[54] Among various chiral phosphoric acids, only **78d** was tested with dialkyl azodicarboxylates as the electrophiles to generate the target compounds in 47–81% yield and moderate to excellent optical purity. The observed stereochemical outcome of these reactions could be accounted for by the activation of both the electrophile and the enol form of the α-sulfanyl cyclic ketones through dual H-bonding interactions, with the CPA catalyst acting therefore as a bifunctional catalyst, under the guidance of which the enol preferentially reacts with one face of the dialkyl azodicarboxylate.

A single example of chiral enol generation through a thiourea organocatayst[53b] for the direct α-hydrazination appeared in the last decade.[55] The involvement of the 3,5-bis(trifluoromethyl)phenyl motif in the formation of an H-bond in which an aromatic ortho C–H bond participates, has been exploited by Jovanovic et al. to devise a novel proline-derived thiourea organocatalyst **87** rationally designed to modify the typical H-bonding pattern of thiourea derivatives. This catalyst was tried in the direct asymmetric α-hydrazination of a number of aldehydes **85**, affording products **86** (in excellent yields and with a high level of stereoselectivity) only when a carboxylic acid (10 mol %) was present in the reaction mixture (Scheme 25). Unfortunately, NMR experiments carried out to shed light on the reasons of the observed stereoselectivity with this new catalyst were not conclusive.

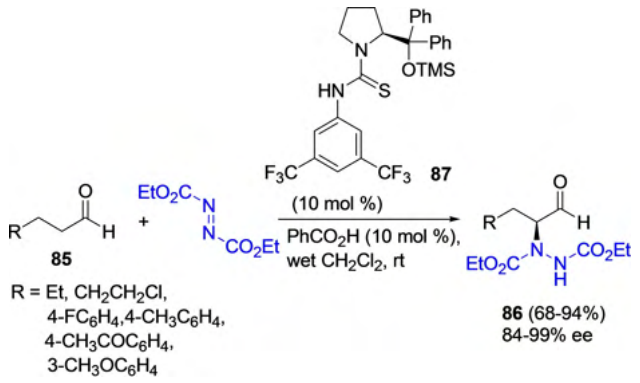
## 4. α-Hydrazination of Carbonyl Compounds via Chiral Enolates

### 4.1. Chiral Metal-Ion Based Lewis Acid Catalysis

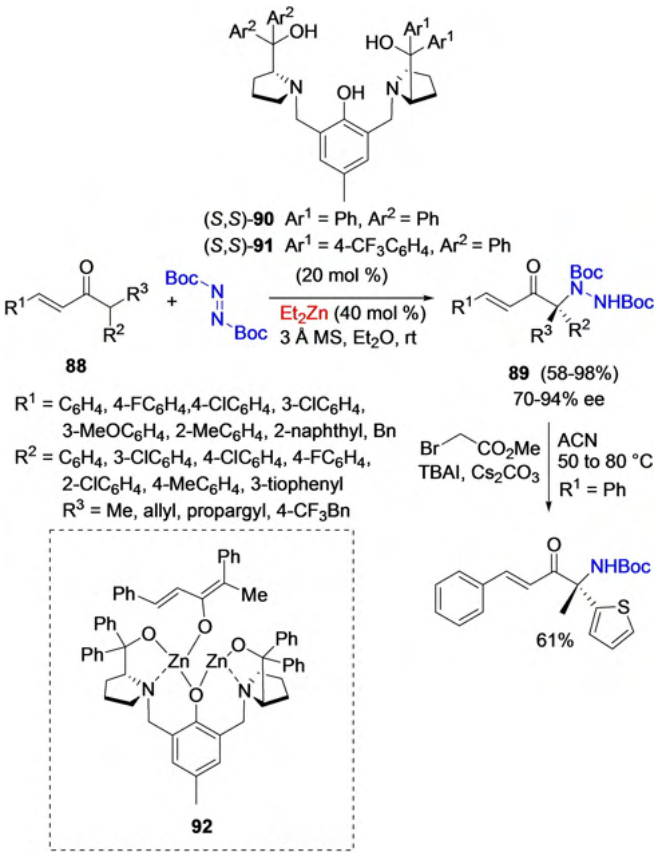
As shown before, cyclic α-branched ketones, with which stereodefined and configurationally stable enols/enolates can be generated, have successfully been used as substrates for the




**Scheme 24.** Asymmetric α-hydrazination of α-sulfanyl cyclic ketones with CPAs.




**Scheme 25.** Asymmetric α-hydrazination with the proline-derived thiourea organocatalyst **87**.



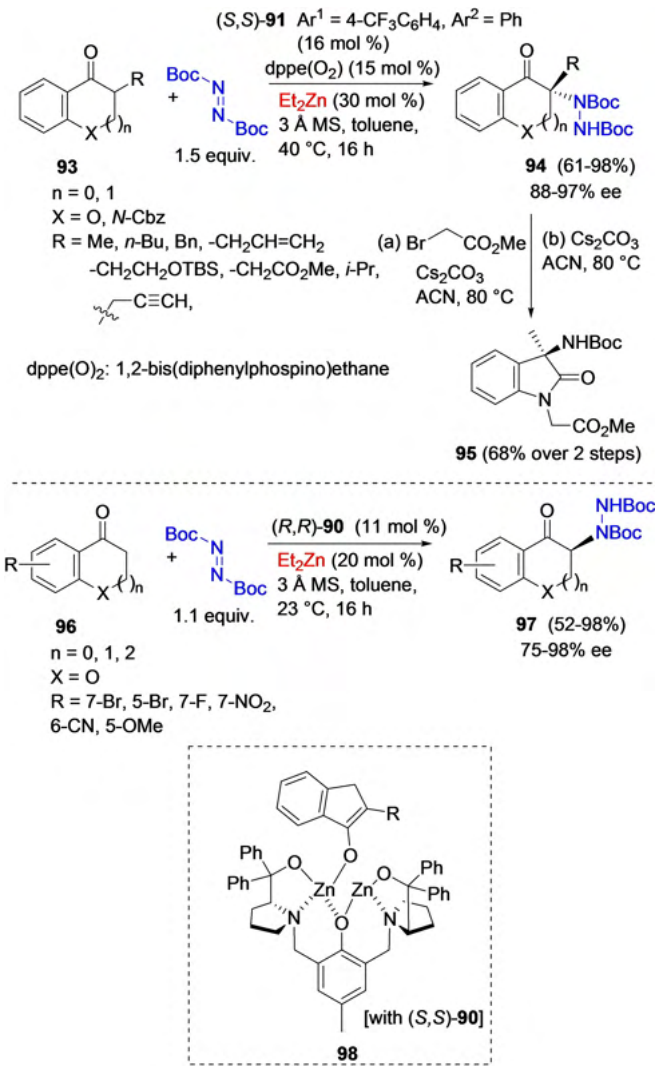

**Scheme 26.** Direct electrophilic α-hydrazination of acyclic α-branched ketones catalysed by dinuclear zinc-ProPhenol complexes.

enantioselective α-hydrazination with azodicarboxylates. In 2018, Trost reported on the use of chiral metal-ion based Lewis acid catalysis for the direct asymmetric hydrazination of both α-branched and unbranched cyclic ketones[2] and then, in 2019, of acyclic ketones[8] using di-*t*-butyl azodicarboxylate as the electrophile. In the decade covered by this review, chiral Zn(II)-, Li(I)-, Ca(II)-, B(III)-, and Sn(II)-enolates were all successfully used for the direct α-hydrazination of carbonyl compounds.

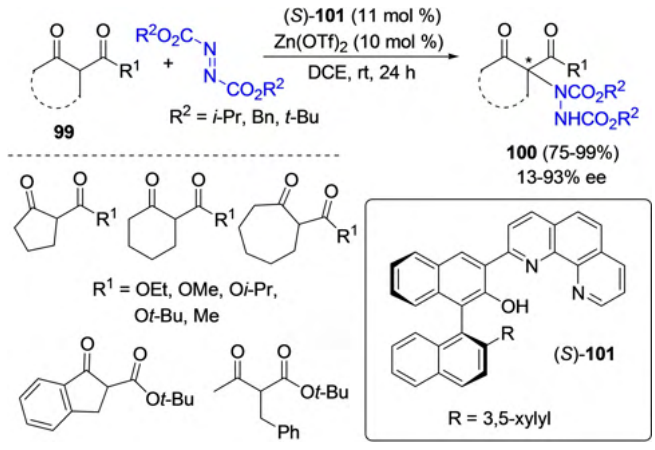
The first direct electrophilic α-hydrazination of acyclic α-branched ketones, aimed at the synthesis of chiral α-tertiary amines, was carried out on α,β-unsaturated ketones **88** as the substrates by using chiral metal-ion based Lewis acid catalysts (Scheme 26).[8] The process was in fact catalysed by the dinuclear zinc-ProPhenol complexes previously used by Trost in the hydrazination of cyclic ketones, and proceeded under mild reaction conditions affording a diverse array of vinyl ketones **89**. A model for the stereochemical outcome is shown with the $C_2$ symmetric ligand (*S,S*)-**90**. Upon formation of the initial dinuclear zinc catalyst, deprotonation of the ketone results in formation of complex **92** (a chiral Zn-enolate) to which coordination of the azodicarboxylate via two-point binding across the two zinc centers takes place before undergoing stereocontrolled nucleophilic attack. The authors suggest that a bidentate chelation of the electrophile is important to both reactivity and selectivity. The final products can eventually undergo chemoselective N–N bond cleavage without reduction of the α,β-unsaturated ketone to form chiral α-amino ketones (one example reported).

As mentioned above, these dinuclear zinc-ProPhenol complexes were previously used by Trost to promote the direct catalytic α-hydrazination of both α-branched and unbranched cyclic ketones, without observing, or with limited racemization in the final products when using the latter as substates.[2] For α-branched ketones (mainly indanones), the reactions were carried out in toluene at 40 °C with a large variety of substrates **93** in the presence of a Lewis basic additive to significantly increase both catalyst turnover and enantioselectivity, the best of which being 1,2-bis(diphenylphospino)ethane [dppe(O)$_2$] (Scheme 27). Of the two ligands used, non-$C_2$ symmetric (*S,S*)-**91** provided the highest enantioselectivity (88–97% ee for α-branched cyclic ketones) although it required a slight increase of catalyst loading (to 15 mol %) to improve the yields (up to 98% depending on the substrate). For unbranched ketones (mainly tetralones) the enantiomer of the $C_2$-symmetric catalyst was used [i.e. (*R,R*)-**90**] with which the hydrazination provided products with 75–98% ee. With these substrates the addition of a Lewis-basic additive was unnecessary, and the reaction took place at lower temperature in diethyl ether. Analogously to the mechanism with α,β-unsaturated ketones, the initially formed dinuclear Zn–ProPhenol catalyst enters the catalytic cycle through a deprotonation of the ketone to form a complex **98** which by bi-dentate coordination of the electrophile produces a complex in which the electrophile is spatially arranged for the face-selective attack by the enolate. With both types of substrates, the authors demonstrated how it was possible to effectively transform the α-hydrazino into an amino group, too, to form synthetically interesting amino products (e.g., **95**).

In the course of their evaluation of 1,10-phenanthroline (phen) – a N,N-bidentate ligand with a strong affinity for a wide range of transition metals – for the preparation of new class of chiral ligands, Naganawa et al.[56] designed, amongst others, chiral phen ligand (*S*)-**101** which would enable N,N,O-tridentate coordination through the phen moiety and an additional phenolic hydroxy group (Scheme 28). The authors studied this chiral ligand as organocatalyst in the Lewis acid-catalyzed electrophilic hydrazination of β-keto carbonyl compounds **99**



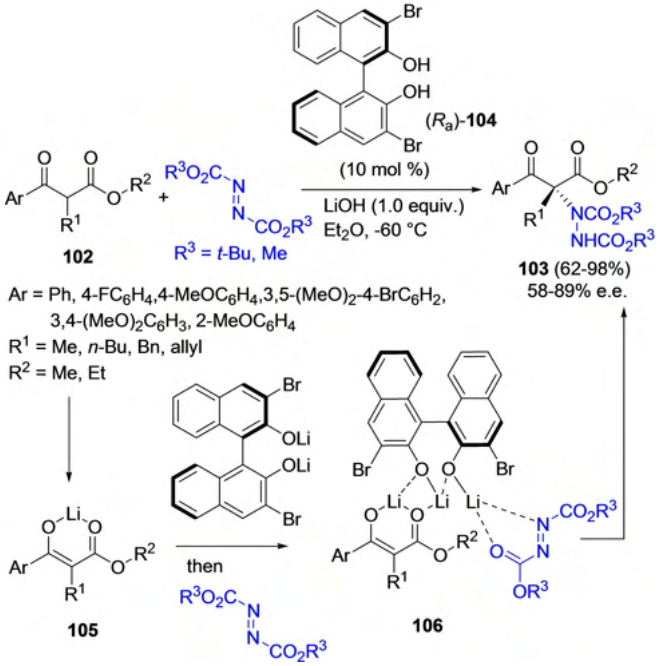

**Scheme 27.** Direct electrophilic α-hydrazination of cyclic α-branched ketones catalysed by dinuclear zinc-ProPhenol complexes.




**Scheme 28.** Lewis acid-catalyzed electrophilic hydrazination of β-ketocarbonyl compounds with chiral phen ligand (*S*)-**101**.

with azodicarboxylates. The complex with $Zn(OTf)_2$ of this axially chiral phenanthroline ligand was the most efficient catalysts for this transformation, providing α-hydrazino-β-ketocarbonyl compounds **100** in excellent yield and generally high (up to 91 %) ee. Based on control experiments, the authors found that the free OH group of the binaphthyl moiety seems to have not much influence on the asymmetric induction, which implies that ligand (*S*)-**101** is a neutral ligand toward $Zn(OTf)_2$ in this reaction. However, it is difficult to determine whether the coordination of (*S*)-**101** occurs as an *N,N*-bidentate or *N,N,O*-tridentate ligand.

Among the number of asymmetric processes aimed at optically active compounds such as α,α-disubstituted α-amino acids, Jørgensen et al. were the first to demonstrate in 2003 that a chiral Ph-bis(oxazoline)copper complex could be used to catalyze the enantioselective α-hydrazination of α-alkyl-β-keto esters with azodicarboxylates to produce optically active α,α-disubstituted α-amino acids with high enantioselectivity.[57] Following this line, Asano et al.[58] reported on the enantioselective hydrazination of acyclic α-alkyl β-keto esters catalyzed by a chiral lithium binaphtholate (Scheme 29). The formation of trinuclear Li complexes **106** (embedding a chiral lithium-enolate) between lithium enolate **105** generated from α-substituted β-ketoesters **102** and chiral naphthol ($R_a$)-**104** has been invoked by the authors to explain the enantioselectivity (58–89 % e.e.) observed in the α-hydrazination of **102** using dialkyl azodicarboxylates. It was in fact found that in this reaction the use of a stoichiometric amount of LiOH brings about an increase of the enantioselectivity of the process, in which the chirality of the naphthol determines the face of the enolate attacking the electrophile. A concise, asymmetric syn-



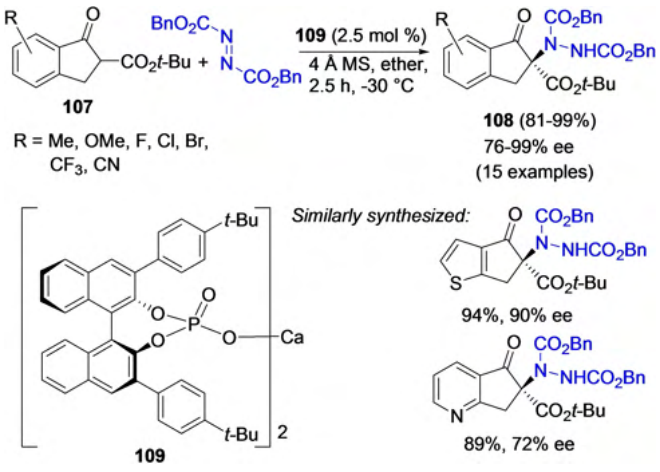

**Scheme 29.** Enantioselective hydrazination of acyclic α-alkyl β-keto esters catalyzed by chiral lithium binaphtholate **104**.

thesis of L-carbidopa (Figure 1) was thus possible using this enantioselective hydrazination as a key step.

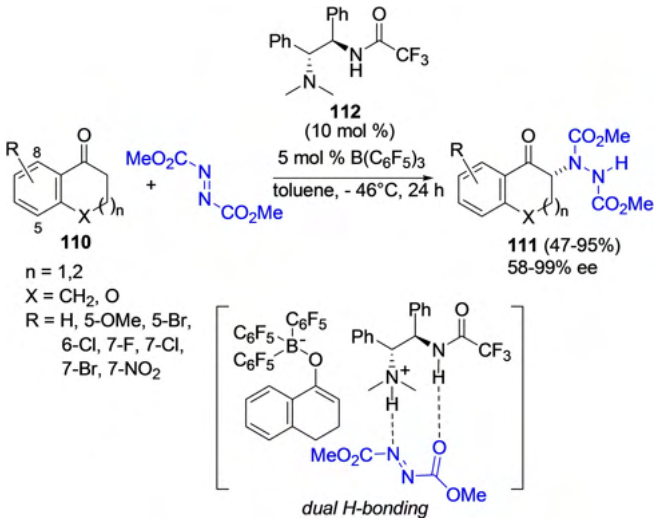
Chiral Ca-enolates were exploited by Wu et al.[59] for the synthesis of α-hydrazino indanone derivatives **108** from 1-oxo-indanecarboxylates **107** in high yield (81–99%) and optical purity (76–99% ee) (Scheme 30). This catalytic enantioselective hydrazination of β-keto esters was realized by using (*S*)-BINOL calcium phosphate **109** bearing the bulky *t*-butyl group at the para position of the phenyl rings, which was chosen for the evaluation of the scope after a screening of several BINOL ligands. Dibenzyl azodicarboxylate was used as the electrophile, whose involvement in the amination of 1,3-dicarbonyl compounds is less frequent. The chiral calcium phosphate could successfully be recovered at the end of the reaction and reused for a few runs, without losing its activity in terms of yields and asymmetric induction.

Shang et al. reported on the enantioselective direct α-hydrazination of cyclic ketones **110** by the catalysis exerted by a sterically "frustrated" Lewis acid/Brønsted base complex.[60] Using boron-based Lewis acid $(C_6F_5)_3B$ to enhance the acidity of an α-C–H bond by binding to the carbonyl group of the substrate, deprotonation by the amine results in the formation of a tightly bound ionic pair consisting of a boron enolate and an ammonium cation (Scheme 31). The latter functions as a Brønsted acid to activate the dialkyl azodicarboxylate, which is at the same time precisely located for reaction with the enolate component to provide products **111** with generally good to high enantioselectivity (58–99% ee). A series of chiral amines were tested and those providing dual H-bonding such as **112** were superior to proline-derived or other amines capable of a single H-bonding.

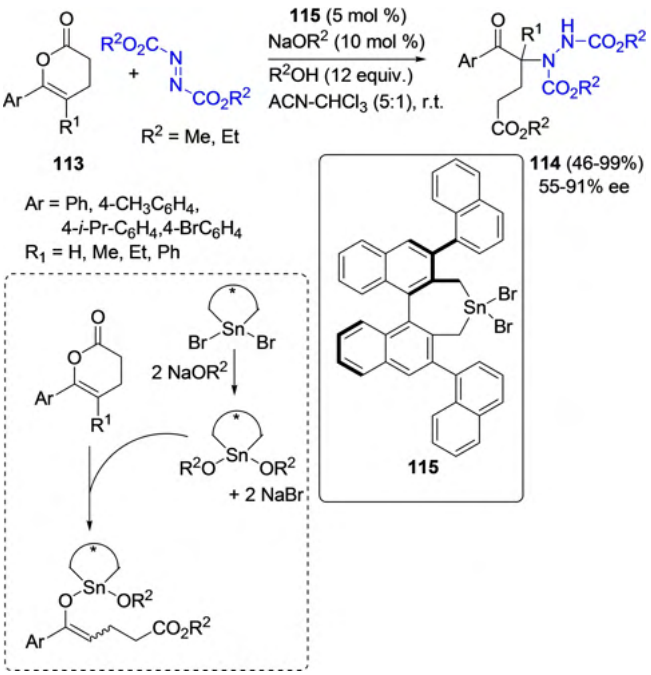
The α-hydrazination of cyclic alkenoate esters **113** bearing various alkyl and aryl groups was achieved by using a 3,3′-di(1-naphthyl)-substituted (*R*)-BINOL–dibromostannane complex **115** as a chiral precatalyst in the presence of a sodium alkoxide and an alcohol.[61] α-Hydrazino ketones were obtained in moderate to excellent yields and with up to 91% ee in the presence of the chiral tin alkoxide generated in situ in an acetonitrile-chloroform (5:1) mixed solvent (Scheme 32). In the catalytic cycle, the chiral tin dibromide **115** reacts first with two equivalents of sodium alkoxide ($NaOR^2$) to form the chiral tin dialkoxide which then attacks the alkenoate cyclic ester **113** with the participation of the alkoxide present in situ to generate a chiral tin enolate. This then will react with the dialkyl azodicarboxylate to provide the final product.




**Scheme 30.** Chiral Ca-enolates in the synthesis of α-hydrazino indanone derivatives.




**Scheme 31.** Direct α-hydrazination of cyclic ketones through sterically "frustrated" Lewis acid/Brønsted base complexes.

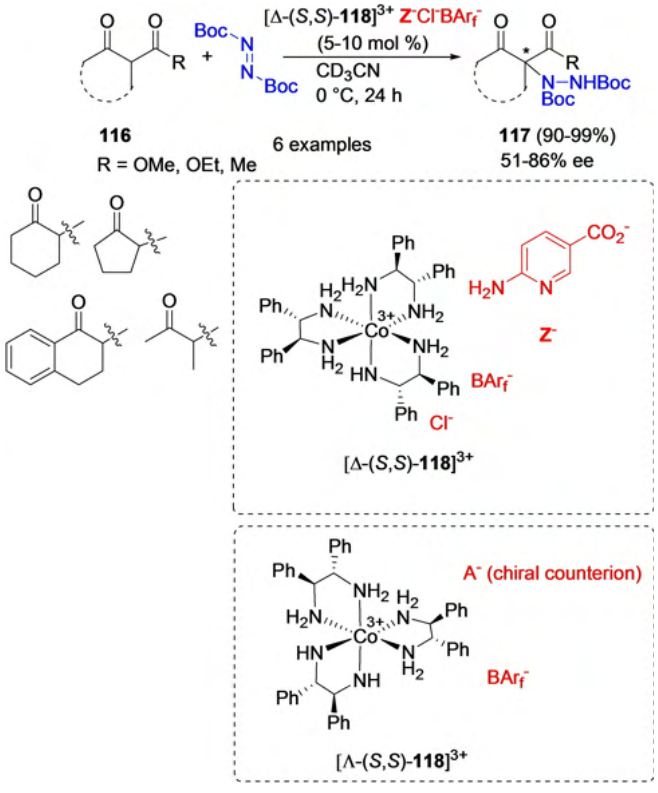



**Scheme 32.** α-Hydrazination of cyclic alkenoate esters with (*R*)-BINOL-dibromostannane complex **115**.

### 4.2. Lewis-Acidic H-Bond Donor/Brønsted Base Bifunctional Catalysts

One of the activation strategies in the field of organocatalys is the noncovalent catalysis, in which no covalent bonding is established between the catalyst and the reactant molecule. An advantage compared to enamine-based organocatalysis is that degradative pathways of enamine intermediates are completely suppressed when organocatalysts activating substrates through H-bonding are used.[62] In the electrophilic amination of carbonyl compounds a Brønsted base is necessary to generate the requisite enolate. Bifunctional organocatalysts are those which embed the base in their structure.

Following their work on the use of chiral $Co^{3+}$ complexes Λ-(*S*,*S*)-**118**$^{3+}$ and Δ-(S,S)-**118**$^{3+}$ (related to helically chiral Werner complexes, with a $D_3$ symmetric trication $[Co(en)_3)]^{3+}$]),[63] having either achiral[64] or one or two chiral counterions,[65] as bifunctional hydrogen bond donor – Brønsted base catalysts in the highly enantioselective, asymmetric direct α-hydrazination of β-ketoesters of type **116**, Gladysz's research group next reported on the use of the same type of complexes possessing achiral counterions deriving from nicotinic acid, besides $BAr_f^-$ and $Cl^-$ (Scheme 33).[66] After a screening of various counterions, which replaced one of the two chloride anions originally present in the complex, the best complex (with a nicotinate counterion) was used to catalyse the addition of a series of dicarbonyl compounds **116** to di-*t*-butyl azodicarboxylate. Compared to the use of the same $Co^{3+}$ complexes having chiral



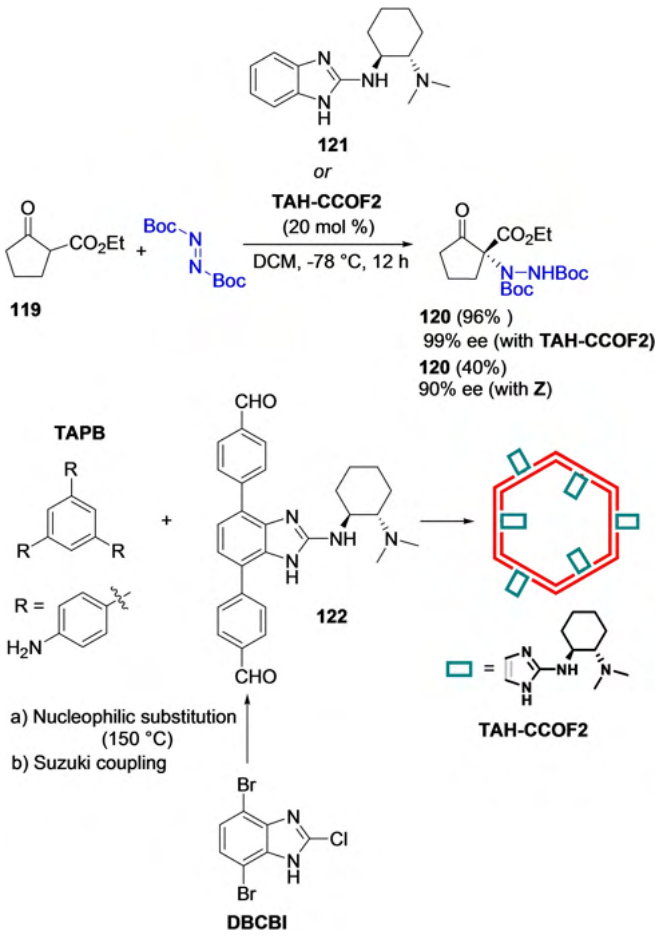

**Scheme 33.** Chiral $Co^{3+}$ complexes as bifunctional hydrogen bond donor-Brønsted base catalysts.

counterions, the enantiomeric excesses were in the present case lower, ranging from 51–81 % ee. Although the nicotinate anion almost certainly deprotonates the substrate to form the corresponding enolate which reacts with the electrophile, a more detailed picture of the mechanism is not possible for two reasons: the first is that the most productive assembly between the tricationic Co(III) complex and the counterions can be only guessed; the second is that many NH donor groups might participate at any stage of the process so that up to four or five simultaneous interactions can take places.

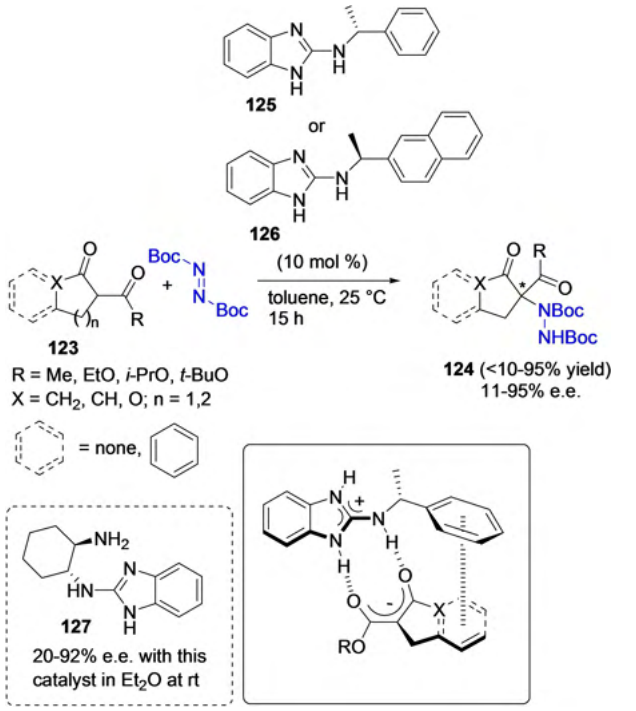
Other chiral enantiopure, $CH_2Cl_2$ soluble, octahedral cobalt(III) salts from the same group with aliphatic hexaamine ligands were less effective in the enantioselective α-hydrazination of carbonyl compounds in terms of optical purity (6–40 % ee). Possessing amino groups as ligands, the catalysts were originally thought as bifunctional catalysts, however this was not the case as the reactions occurred in the presence of $Et_3N$ as a base only.[67]

Covalent Organic Frameworks (COFs) are crystalline and porous macromolecules organized by a covalent assembly.[68] Due to their potential in asymmetric catalysis and enantioselective recognition, a few chiral COFs (CCOFs) have been successfully synthesized so far. Wang et al.[68] developed a divergent strategy from a common building block which, in three steps only, produced several CCOFs to be tested as catalysts in the direct asymmetric α-hydrazination of β-keto esters (Scheme 34). Each of these CCOF catalysts possesses hydrogen-bond donor and Brønsted-basic sites according to a catalytic model which mimics that of (thio)urea and squaramide bifunctional catalysts frequently used in homogeneous organocatalysis.[69] The starting platform of the divergent synthesis of these CCOFs was 4,7-dibromo-2-chloro-1*H*-benzo[d]imidazole (**DBCBI**) which first underwent nucleophilic substitution by reaction with a chiral amine in DIPEA at 150 °C, and then coupled with 4-formylphenylboronic acid under Suzuki-Miyaura conditions [$(Pd(Ph_3P)_4$, $K_2CO_3$, in dioxane/water) to form dialdehyde **122** ready to be reacted with 1,3,5-tris(4-aminophenyl)-benzene (**TAPB**). Crystallization at 120 °C in ethanol/mesitylene (1 : 1 v/v) as mixed solvents and with aqueous acetic acid as the catalyst provided the final CCOFs. Among those synthesised, **TAH-CCOF2** provided the best yield (96 %) and the highest ee (99 %) in the reaction of β-keto ester **119** with di-*t*-butyl diazocarboxylate, performing better than simple amine **121** having the same chiral moiety. Interestingly, the **TAH-CCOF2** catalyst could be recovered by centrifugation and reused at least for seven times without substantial erosion of activity and enantioselectivity. The substrate generality was further demonstrated by the α-hydrazination reactions of other β-keto esters.

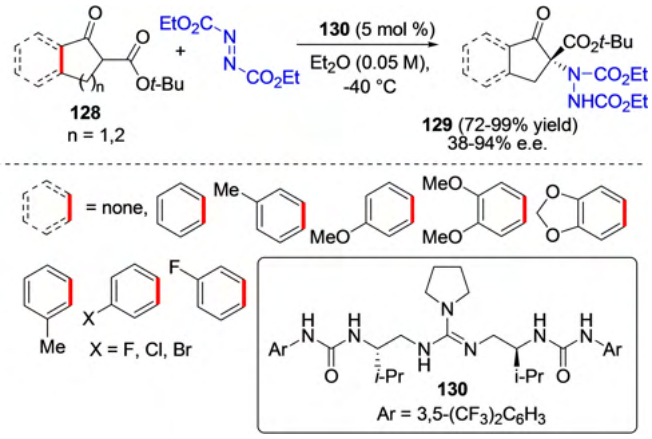
Following Baeza's work on the use of *trans*-cyclohexanediamine benzimidazole **127** derivatives as bifunctional H-bond donor/Brønsted base organocatalysts for the electrophilic amination of cyclic 1,3-dicarbonyl compounds,[70] his group reported on the enantioselective α-hydrazination of the same type of substrates with di-*t*-butyl azodicarboxylate as electrophile using organocatalysts based on new chiral guanidines derived from bennzimidazoles (Scheme 35).[71] These catalysts




**Scheme 34.** CCOFs tested as catalysts in the direct asymmetric α-hydrazination of β-keto esters.




**Scheme 35.** Enantioselective α-hydrazination using chiral benzimidazole-derived guanidines.



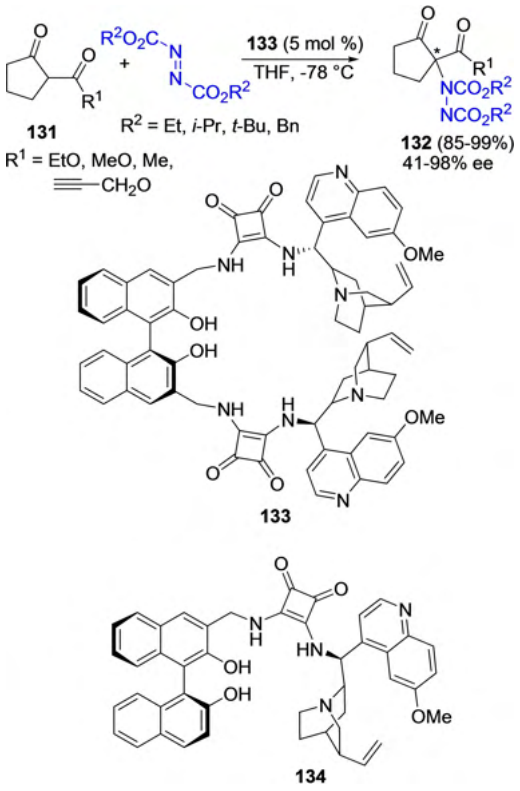

**Scheme 36.** α-Hydrazination with guanidine-bisurea catalyst **130**.

were easily synthesized by reacting 2-chlorobezimidazole with a chiral amine. Out of ten organocatalysts tested with ethyl 2-oxocyclopentanecarboxylate as the substrate, those derived from (*R*)-1-phenylethan-1-amine (**125**) and (*S*)-1-(2-naphthyl)ethan-1-amine (**126**) resulted the most efficient for such asymmetric transformation (90–91% ee), although in the next evaluation of the scope the enantioselectivities observed were rarely so high. The authors suggest that these guanidine benzimidazole-derived compounds could act as a bifunctional organocatalysts, acting initially as bases to form the 1,3-dicarbonyl compound enolate which could be coordinated with the organocatalyst through hydrogen bonding. The good results observed in the benzocondensed β-keto esters could be explained by invoking a π–π stacking interaction as illustrated. Next, the protonated guanidine group activates the azodicarboxylate thus promoting the enantioselective attack of the enolate to the electrophile.

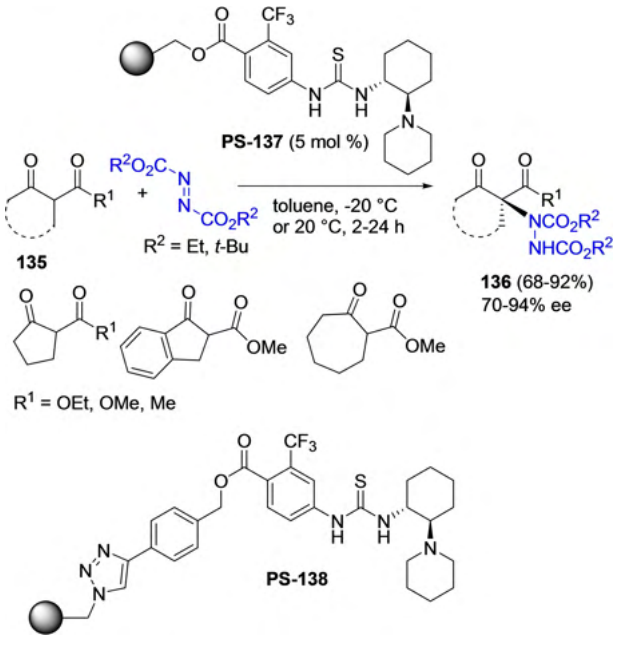
Bifunctional H-bond donor/Brønsted base organocatalysts based on guanidine-bisurea were investigated by Odagi et al.[72] essentially on the same type of substrates. Such catalysts, especially **130** bearing the pyrrolidine moiety, proved excellent organocatalysts as they provided α-hydrazineyl β-keto esters with generally high yields and enantiopurity (Scheme 36). The authors demonstrated that the guanidine and urea moieties in their catalysts are mandatory for obtaining high enantioselectivity, presumably interacting the former with the enolate and the second with the electrophile, through a H-bond network.

Chiral squaramides and their derivatives were introduced by Rawal et al. as highly efficient organocatalysts in the asymmetric Michael addition reactions, which were next investigated in a number of asymmetric transformations.[73] As part of their efforts to develop novel chiral squaramide organocatalysts Dong's group became interested in applying the chiral BINOL-squaramide derivatives as H-bond donor/Brønsted base organocatalysts in asymmetric α-hydrazination reaction of 1,3-dicarbonyl with dialkyl azodicarboxylates.[74a] Following their

work on a recyclable BINOL-quinine-squaramide organocatalyst **134** in the enantioselective hydrazination of 1,3-dicarbonyl compounds with azodicarboxylates,[74b] the authors reported, among others, on a $C_2$-symmetric BINOL-squaramide-cinchonine organocatalyst **133** which provided **132** in high yields and excellent enantioselectivities (up to 98% ee) (Scheme 37). The squaramide organocatalyst was assumed to create multiple hydrogen-bonding sites in which squaramide and cinchonine moieties simultaneously interact through hydrogen bonding with the diketone, while the two OH groups of binaphthyl moiety provide hydrogen bonding to azodicarboxylate. The tertiary amine of cinchonine moiety plays the role of the Brønsted base by deprotonating the α-carbon of **131** to generate the required enolate.




**Scheme 37.** Chiral BINOL-squaramide **133** as organocatalysts in asymmetric α-hydrazination of 1,3-dicarbonyl compounds.

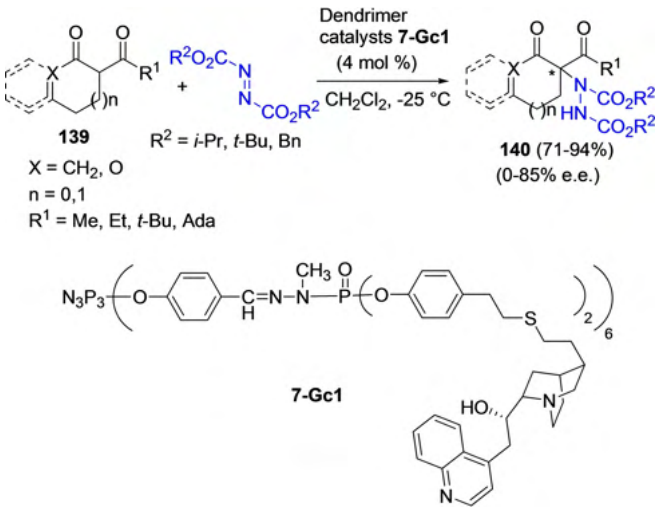



**Scheme 38.** Immobilized thiourea organocatalyst **PS-137** for the asymmetric α-hydrazination of 1,3-dicarbonyl compounds.

Immobilized thiourea organocatalysts as H-bond donor/Brønsted base organocatalysts for the asymmetric α-hydrazination reaction of 1,3-dicarbonyl with dialkyl azodicarboxylates were prepared by Kasaplar et al.[75] The first polystyrene-supported organocatalyst prepared had a triazole linker (**PS-138**), but probably due to the uncontrolled presence in the catalytic resin of copper traces deriving from the CuAAC reaction, inconsistent results were obtained in the α-hydrazination. On the other hand, by changing strategy for the immobilization, i.e. relying on a simple ester linkage, all batches of the polystyrene-supported catalyst **137** gave reproducible results in the same reaction, which provided products **136** in good yields and enantiomeric excesses (Scheme 38). Interestingly, in sharp contrast with immobilized squaramides previously reported by the same authors,[76] the use of dichloromethane as a solvent was not necessary to attain optimal results which were instead achieved with toluene, rendering the process more benign. As this catalyst was designed to work in flow, experiments in continuous were carried out. The authors found that to maintain over extended periods of time the catalytic activity of the catalyst, periodically washing of the resin with $Et_3N$ was necessary. In this way, the desired product could be obtained in 93% ee (71% isolated yield) with a productivity of 4.88 mmol $mmol_{cat}^{-1}$ $h^{-1}$ and a TON of 37, with a 21 minute residence time.

Phosphorus dendrimers are robust molecules that can been decorated on their surface (generally with organometallic and organic compounds, as well) and used as recoverable catalysts for different organic reactions.[77] Rull et al. reported on the preparation of organocatalysts for the enantioselective α-hydrazination of β-dicarbonyl compounds by grafting (+)-cinchonine on the surface of phosphorus dendrimers of the first- and fourth-generation.[78] The authors studied the activity of these catalysts, the possible dendritic effect and the recyclability in this α-hydrazination reaction as a tool to prepare quaternary α-amino acids. The first-generation dendrite **7-Gc1** showed the highest activity and enantioselectivity in the α-hydrazination of different β-dicarbonyl compounds **139**, although with many substrates enantiomeric excesses were very low. Its recovery and reuse over 10 cycles in the reaction of a model β-keto ester was also demonstrated to occur without substantial loss of activity (Scheme 39).

A new type of chiral $C_2$-symmetric *N*-heterocyclic olefins (NHOs) were developed by Wang et al. and were employed as efficient chiral bifunctional organocatalysts in the asymmetric α-hydrazination of β-keto esters **141** with di-*t*-butyl azodicarboxylate.[79] These *N*-heterocyclic olefins possess an




**Scheme 39.** α-Hydrazination of β-dicarbonyl compounds by (+)-cinchonine grafted on a phosphorus dendrimer.

electron-rich and highly polarized exocyclic C=C double bond due to the donating property of the nitrogen atoms, which imparts the exocyclic carbon atom of NHOs with strong basicity and high nucleophilicity. NHOs were prepared by the reaction of free NHCs with organic halides, which afforded the NHO salts in >65% yield, followed by the deprotonation of the latter by using t-BuOK to furnish the corresponding free NHOs. Of these, NHO **143** was particularly efficient as with as low as 0.1 mol % of catalyst loading the desired products were obtained in good yields and enantioselectivities (both up to 99% depending on the substrate) in MTBE (methyl *t*-butyl ether) (Scheme 40).

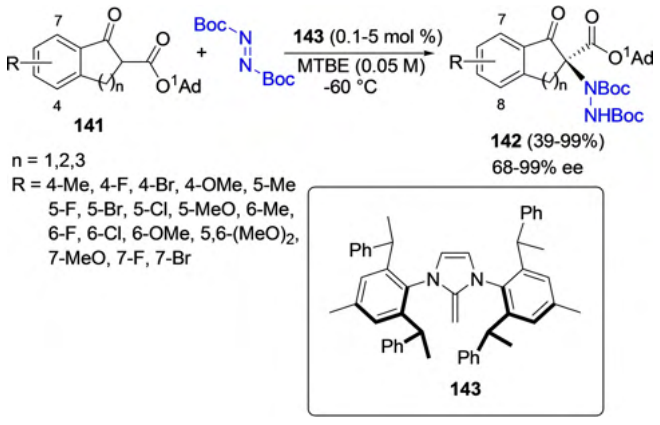
However, a much lower enantioselectivity was obtained (34% ee) when a simple methyl ester was used instead of the bulky adamantyl ester moiety. Based on experimental studies and theoretical calculation the authors suggest that, due to the strong basicity of NHOs, the deprotonation of 1-adamantyl substituted β-keto ester substrate occurs upon mixing it with the NHO. This gives rise to an ion-pair complex in which a dual hydrogen bonding interaction between the two hydrogens of the NHO imidazole ring and the oxygen atoms of enolized substrate takes places. These hydrogen-bonding interactions as well other weak interactions between substrate and the catalyst are thus crucial for the high enantiocontrol observed.

In the field of bifunctional H-bond donor/Brønsted base organocatalysts, Ogawa et al.[80] studied the substituent effects on the aromatic rings in the diarylmethylamine unit (which the authors have named 'butterfly'-type amine unit) of an amino-thiourea catalyst (Scheme 41). This study resulted in the discovery of compound **146** having a 3,5-bis(trifluoromethyl)phenyl group as the best catalyst for as series of reactions, among which the direct α-hydrazination of a cyclic β-keto ester. The involvement of additional interactions between the substrate and the catalyst, such as a C–H–π/π–π interactions, were assumed to improve the catalytic performance of the catalyst. The ability as a chiral catalyst of **146** was found to be superior to that of the well-known Takemoto's aminothiourea,[81] but unfortunately, only one example of reaction (on **144**) was reported, and no scope evaluation was carried out.

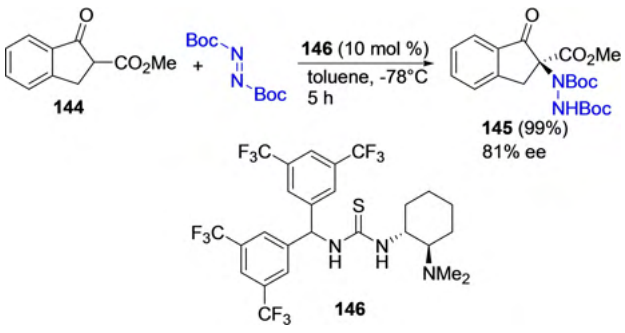
1,2,3-Thiadiazole derivatives are known to exhibit broad pharmacological properties and are also useful intermediates in the synthesis of various sulfur-containing acyclic, alicyclic, and heterocyclic compounds.[82]

Zeng and Xie[82] reported on the efficient, enantioselective synthesis of 1,2,3-thiadiazole-containing compounds **149** by a direct organocatalytic α-hydrazination of substituted tetralones bearing an α-thioamide moiety (Scheme 42). The product intermediates **148** so obtained then underwent cyclization upon treatment with $K_2CO_3$ to provide target compounds **149** in good yields and enantiomeric excesses. The organocatalytic α-hydrazination was best carried out with cinchona alkaloids such as **150** bearing a 6′-hydroxyquinoline ring. This acted as bifunctional catalyst by activating both the thioamide and azodicarboxylate substrates through a hydrogen bond network, followed by the facial selective nucleophilic attack of the thioenol intermediate to the azodicarboxylate.

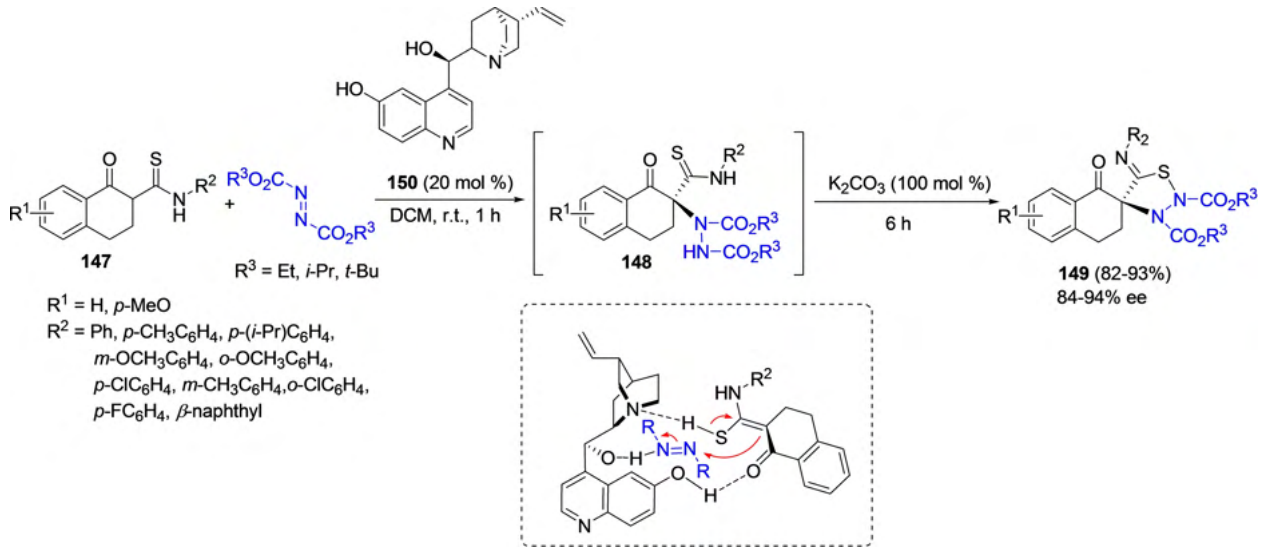
β-Keto acids **151** capable to generate highly reactive ketone enolate equivalents via decarboxylation, have been used by Wei et al.[83] to perform an organocatalytic asymmetric α-hydrazination with dialkyl azodicarboxylates in the presence of various commercially available cinchona alkaloids as organo-catalysts, of which **154** gave the best results (Scheme 43). Under



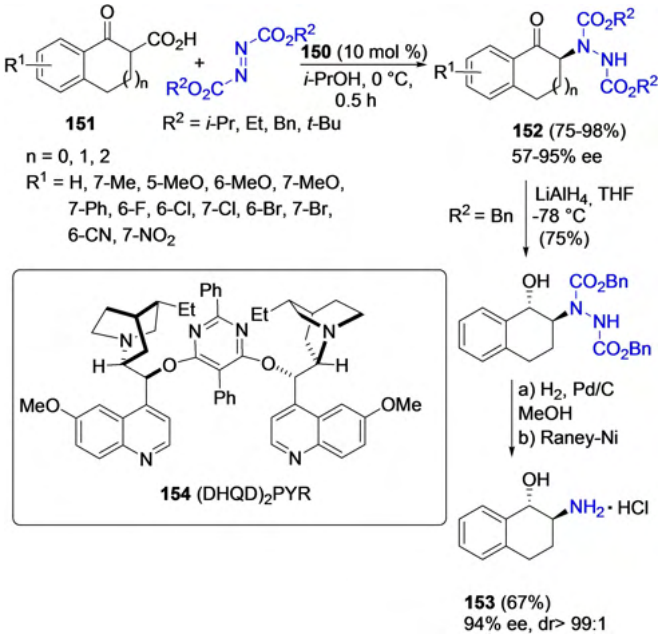

**Scheme 40.** Chiral $C_2$-symmetric N-heterocyclic olefins (NHOs) as bifunctional organocatalysts for the α-hydrazination of β-keto esters.




**Scheme 41.** Aminothiourea catalyst **146** for the α-hydrazination of β-keto esters.




**Scheme 42.** Enantioselective synthesis of 1,2,3-thiadiazole-containing compounds **149**.



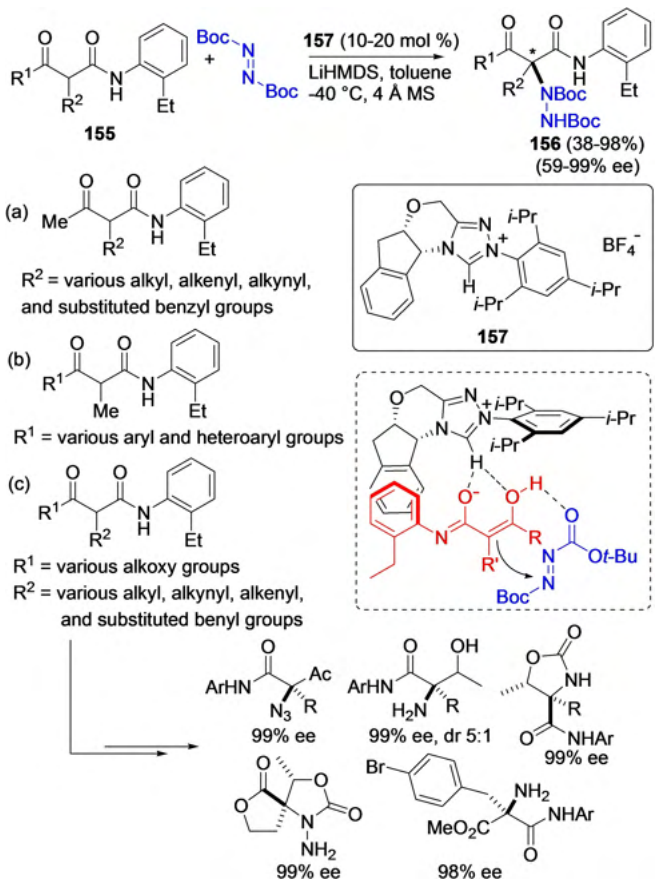

**Scheme 43.** α-Hydrazination of β-keto acids catalyzed by commercially available cinchona alkaloids as organocatalysts.

very mild reaction conditions (i-PrOH as the solvent at 0 °C), a series of chiral α-hydrazino ketones **152** were obtained in good to high yields (up to 98%) and enantioselectivities (up to 95% ee). To demonstrate the potential of the approach in the synthesis of optically active amino alcohols, the reaction was scaled up to 3 mmoles of substrates with the simplest substrate ($R^1 = H$, $n = 1$) which was converted into the corresponding amino alcohol **153** through reductive N–N bond cleavage.

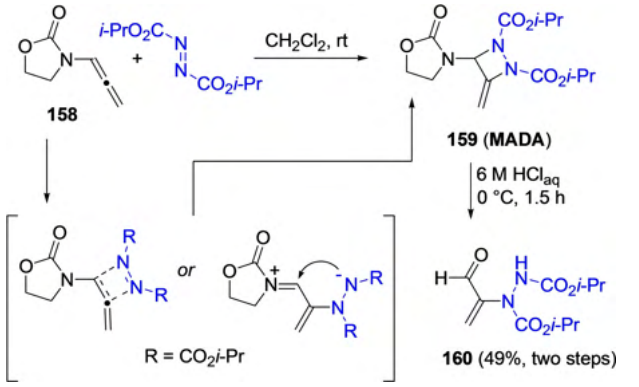
Enantioselective organocatalysis based on N-heterocyclic carbenes (NHCs) relies in most cases on covalent interactions with the substrate,[84] whereas the potential of asymmetric NHC catalysis via noncovalent interactions has just begun to be realized. Santra et al.[85] reported on a general method for the highly enantioselective α-hydrazination of conformationally flexible α-substituted secondary 1,3-ketoamides and 1,3-amidoesters using a NHC (from salt **157**) as the Brønsted base. The reaction (Scheme 44) has been carried out on three different types of substrates **155** (a–c) and most likely proceeds through deprotonation of the acidic N–H present in the substrate by the chiral NHC to form a chiral ion pair constituted by the enolate and the azolium ion.To this, the electrophile is coordinated by a possible H-bond interaction as shown in Scheme 44 and the activated chiral enolate internally transfers to the azodicarboxylate allowing for a wide range of open-chain 1,3-dicarbonyl compounds containing an N-substituted quaternary stereocenter to be obtained with excellent enantioselectivity (up to 99%) and yields. The synthetic usefulness of this method was demonstrated with the preparation of enantioenriched and densely substituted α-amino ketones and oxazolidinone derivatives, a few of which are shown in Scheme 44.

## 5. Miscellaneous Methods

Allenamides are synthetically very useful as their reactions with electrophiles at the β-carbon of the allene, having moderate nucleophilic properties, can be anticipated. Okitsu et al.[86] tried the preparation of 3-methylene-4-amido-1,2-diazetidine **159** (MADA) via formal [2 + 2] cycloaddition of allenamide **158** with diisopropyl azodicarboxylate in $CH_2Cl_2$ at room temperature (Scheme 45). Besides MADA, a small amount of enal **160** was present in the crude reaction mixture. Although the conversion of MADA into **160** was not the objective of their work, the authors treated MADA with 6 M HCl without isolating it, to obtain the α-hydrazino-α,β-unsaturated aldehyde **160** in 49% over two steps. No other such examples were, however, reported.

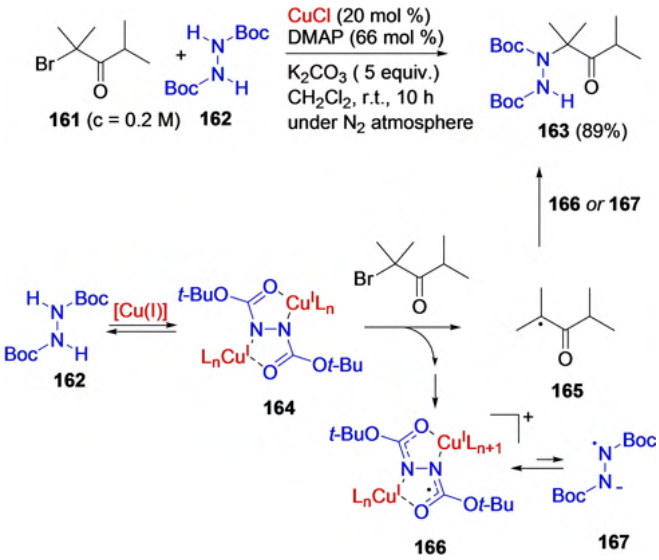



**Scheme 44.** Enantioselective α-hydrazination of 1,3-ketoamides and 1,3-amidoesters using NHC **157**.




**Scheme 45.** Preparation of α-hydrazino enal **160**.

Lu et al.[87] reported on a novel radical reaction-based approach to hindered α-hydrazines exploiting Cu-catalysis (Scheme 46). The electron transfer between an activated alkyl halide and a hydrazodiformate under mild thermal conditions generates radical species that could undergo cross-coupling to afford hindered hydrazines, products which are not easy to be prepared by current methods. In fact, the nucleophilic substitution of sterically hindered alkyl bromides, especially those with electron-withdrawing groups such as **161**, is difficult to attain through either $S_N1$ or $S_N2$ processes. The authors reported



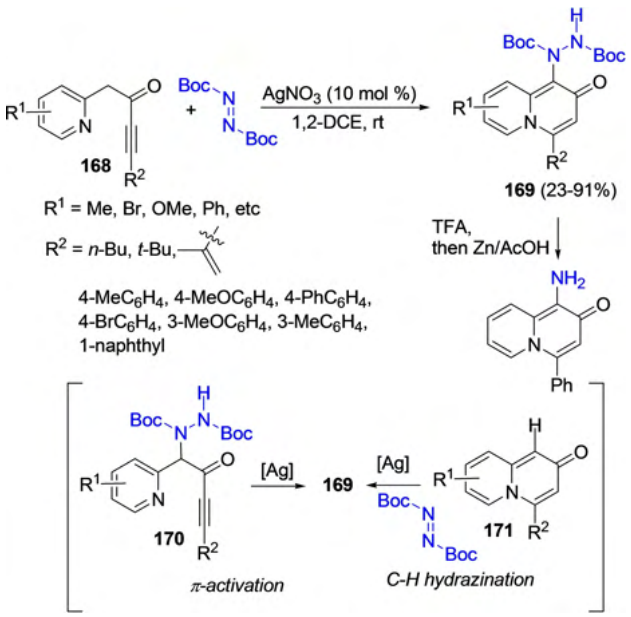

**Scheme 46.** A radical reaction-based approach to hindered α-hydrazines with Cu-catalysis.

one example only with α-bromoketones (many with other activated alkyl halides), in which substrate **161** was reacted with di-*t*-butyl hydrazodiformate **162** at room temperature under Cu catalysis to afford α-hydrazinoketone **163** in excellent yield. Mechanistic studies suggest that the hydrazodiformate forms a reducing dinuclear complex **164** with Cu and a ligand which, upon 1e-oxidation, turns into an open-shell species **166** with the major spin density on N atoms. With the assistance of a ligand, this species can selectively deliver the hydrazine moiety onto alkyl radical **165** leading to the formation of **163**.

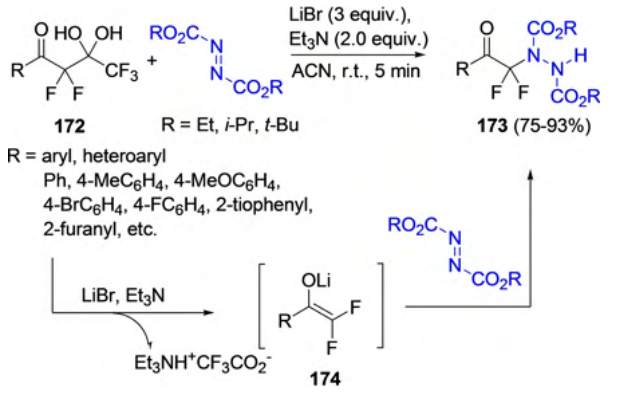
Min et al.[88] reported on the synthesis of differently substituted 1-hydrazino-2H-quinolizin-2-ones **169** by a tandem cycloisomerization/hydrazination process catalysed by a silver salt (Scheme 47). Preliminary mechanistic studies indicated two possible pathways of the reaction: the silver-promoted α-hydrazination of the propargyl ketone **168** to give intermediate **170** that, upon π-activation by Ag(I) undergoes cycloisomerization. Alternatively, or concurrently, after cycloisomerization to **171**, silver-catalyzed C–H hydrazination affords the target product. One example ($R^2$ = Ph) was converted into the corresponding amine by N–N bond cleavage.

The synthesis of a series of difluorosubstituted α-hydrazino ketones has been reported by Reddy et al.[89] by exploiting *gem*-difluoro-enolates **174**, generated in situ from the readily available difluorinated *gem*-diols **172** in the presence of LiBr and $Et_3N$, which readily react (5 min at room temperature) with various azodicarboxylates as the electrophiles (Scheme 48). The reaction displays a broad substrate scope although most of the substrates are either aryl or heteroaryl ketones.

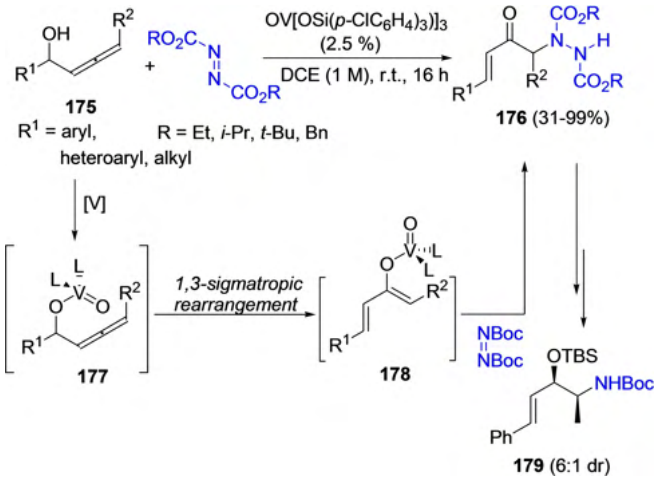
Trost and Tracy[90] reported on a chemo- and regioselective method for the catalytic in situ generation of vanadium enolates **178** through a 1,3-sigmatropic rearrangement of vanadium-allenol complex **177** generated from allenols **175**, in turn easily accessed from commercially available alkynes and aldehyde (Scheme 49).If the rearrangement is carried out in the




**Scheme 47.** Synthesis of 1-hydrazino-2H-quinolizin-2-ones **169** by a tandem cycloisomerization/hydrazination process catalysed by a silver salt.




**Scheme 48.** Synthesis of difluorosubstituted α-hydrazino ketones **173**.



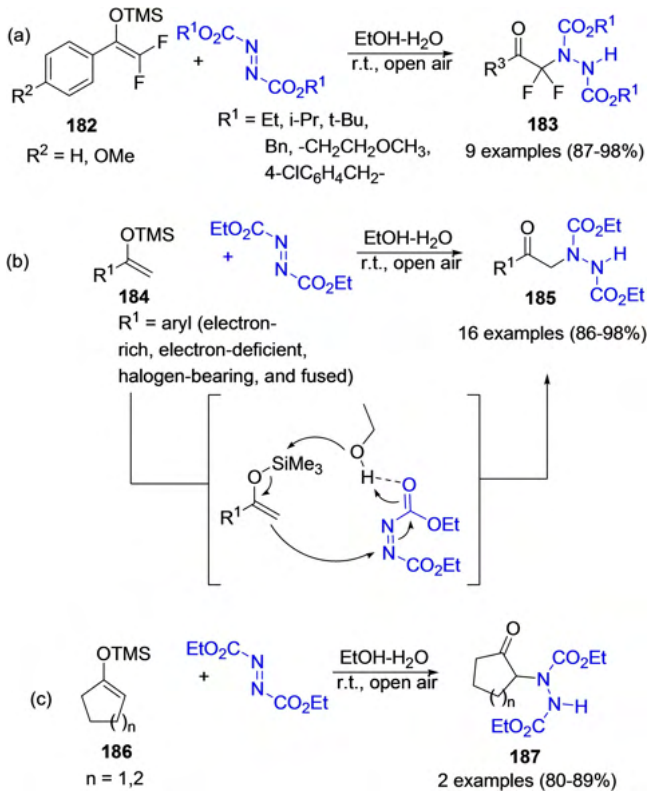

**Scheme 49.** 1,3-Sigmatropic rearrangement of vanadium-allenol complex **177** in the presence of an alkyl azodicarboxylate.

presence of an alkyl azodicarboxylate, the process continues with the nucleophilic attack by the transient enolate to the electrophile, with the consequent formation of a new C–N bond. In one case, product **176** was converted into the corresponding protected amino alcohol **179**, but of course this required prior reduction of the carbonyl and protection as TBS ether before subjecting the protected alcohol to Magnus's two-step alkylation E1cB elimination to yield the desired β-hydroxy amine.

The development of new methods to embody fluorinated groups into molecules is of great importance in pharmaceutical, material, and polymer sciences.[91] The installation of fluorinated groups on nitrogen atom to form $NCF_3$, $NCF_2H$, and $NCF_2R$ moieties is poorly studied. For this reason, Mamone et al.[91] evaluated the addition of phenyl-difluoroenoxysilane **180** on dialkyl azodicarboxylate to form α-hydrazino ketones bearing a $–CF_2–N$ group (Scheme 50). After several attempts, the authors found that with the use of silver triflate (10 mol %) in dichloromethane at −78 °C it was possible to obtain the corresponding difluorohydrazide derivative **181** in 85% yield, with a complete chemoselectivity on the nitrogen atom. A variety of products were obtained starting from differently substituted difluoroenoxysilanes. The authors studied also the regioselective addition to azodicarboxylates bearing different $R^2$ group, which occurred, but not exclusively, on the less hindered N atom, allowing consequent selective N deprotection and further functionalization.

Later, Polimera et al.[92] reported on an alternative approach to fluorinated α-hydrazino ketones **183** to avoid the use of silver triflate and the halogenated solvent, which was based on the nucleophilic addition of electron-rich silyl enol ethers **182** to azodicarboxylates in the presence of a safer solvent system like EtOH–$H_2O$ or, alternatively, under solvent-free conditions (Scheme 51). Moreover, the reactions could be performed at room temperature and under open air atmosphere. This alternative protocol includes key green chemistry principles like reducing or eliminating hazardous substances, use of a safe solvent and optimization of energy utility. The reaction could also be extended to other silyl enol ethers **184** with electron-rich, electron-deficient, halogen-bearing, and fused aryl systems, as well as to cyclic silyl enol ethers **186**, in all cases with excellent yields. A mechanistic proposal (b) entails the protic solvent-assisted metal-free Michael-type addition of the silyl enol ethers to azodicarboxylates in the presence of the EtOH–$H_2O$ system.


**Scheme 50.** Addition of phenyl-difluoroenoxysilane **180** on dialkyl azodicarboxylates.

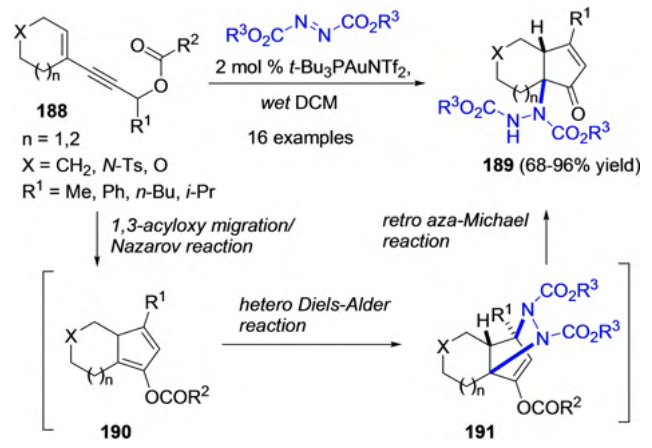



**Scheme 51.** Synthesis of fluorinated α-hydrazino ketones **183**.

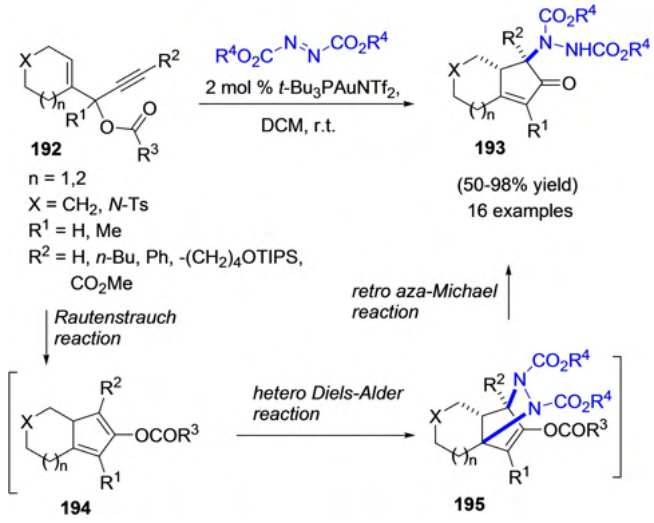
Following a preceding work by the same authors on the synthesis of α-tertiary hydrazine derivatives by gold catalysis,[93] an efficient method for the synthesis of α-hydrazino-2-cyclopentenones **189** was established by Scarpi et al.[94] By trapping with a dialkyl azodicarboxylate ($R^3 = Et$, i-Pr, Bn) the dienyl ester intermediate **190** which is formed in the gold(I)-catalyzed cycloisomerization of propargyl acetates (and pivalates), a highly tensioned cycloadduct **191** is formed (Scheme 52). The formation of this hetero-Diels-Alder product occurs with complete facial selectivity. The next spontaneous, highly regioselective ring opening of this HDA cycloadduct takes place in the presence of water, which is essential not only to promote the latter step, which occurs via a retro aza-Michael reaction, but also to avoid the formation of *N*-acylated byproducts. This cascade, one-pot process, includes a sequence of four reactions (1,3-acyloxy migration, Nazarov cyclization, hetero-Diels-Alder, and retro aza-Michael addition), and provides in high yields (68–96%) unprecedented 5-hydrazino-2-cyclopentenone derivatives **189** bearing an α-tertiary hydrazine moiety.

By a similar approach, exploiting the 1,2-acyloxy migration of propargyl esters **192**, Scarpi et al.[95] reported on the synthesis of regioisomeric products **193** in 50–98% yield (Scheme 53). In this case the dialkyl azodicarboxylate presents in situ traps the cyclopentadienyl ester intermediate **194** which is formed in the gold(I)-catalyzed Rautenstrauch reaction of ester **192**. As before, the next highly regioselective ring opening of the hetero-Diels – Alder cycloadducts to form α-hydrazino-2-cyclopentenones **193** takes places, with the presence of the right amount of water, as well as of the gold(I) catalyst, being both essential to promote the latter step which occurs via a retro aza-Michael reaction.

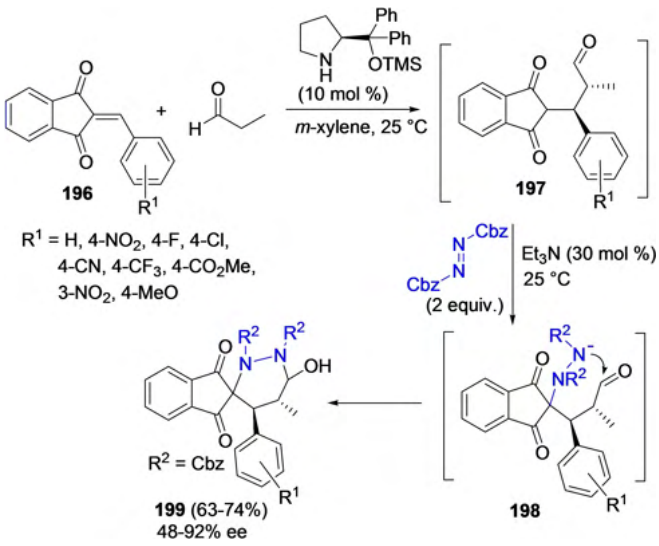
The hexahydropyridazine moiety is present in natural and biologically active products such as chloptosin, (−)-canglifehrin A, himastatin, luzopeptins and quinoxapeptins.[96] The chiral base-promoted formation of chiral Michael addition products **197** was exploited for the synthesis of hexahydropyridazines **199** in good yields and enantiomeric excesses (Scheme 54).This one-pot, cascade reaction entailed an asymmetric organocatalytic Michael addition of the enamine generated from propionaldehyde in the presence of α,α-L-diphenylprolinol trimethylsilyl ether to 2-phenylidene-1,3-indandiones **196** in *m*-xylene to form **197**, followed by the addition of $Et_3N$ and the dibenzyl azodicarboxylate to attain α-hydrazination of the enolate intermediate. Ensuing cyclization generated the target products **199**.




**Scheme 52.** Gold(I)-catalyzed cycloisomerization of propargyl esters **188** in the presence of a dialkyl azodicarboxylate.

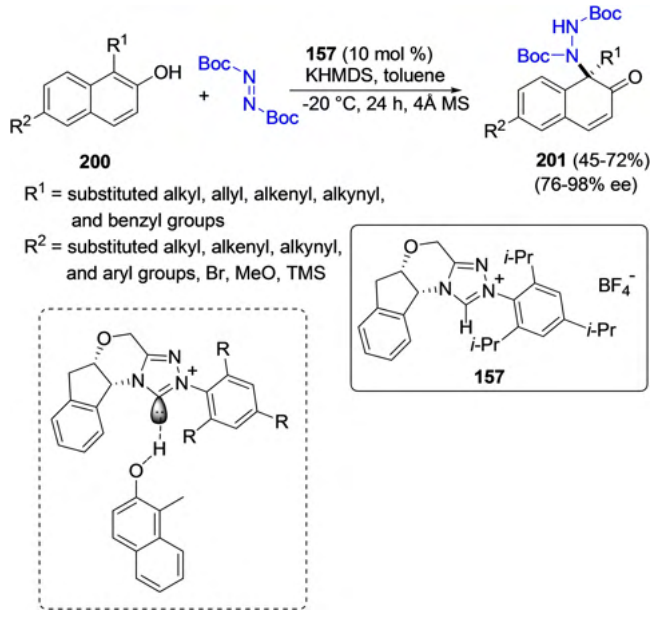



**Scheme 53.** Gold(I)-catalyzed cycloisomerization of propargyl esters **192** in the presence of a dialkyl azodicarboxylate.




**Scheme 54.** Chiral base-promoted formation of a chiral Michael addition product for the synthesis of hexahydropyridazines **199**.

The same NHC organocatalyst **157** developed by Guin, which was successfully used in the enantioselective α-hydrazination of acyclic 1,3-dicarbonyl compounds,[85] was likewise efficient in the unprecedented NHC-catalyzed asymmetric aminative dearomatization of β-naphthols, too.[97] The reaction (Scheme 55) was carried on a huge variety of substrates **200** providing in most cases functionalyzed α-hydrazino enones **201** in good yields and enantiomeric excesses. Besides the 6-substituted β-naphthols shown in Scheme 55, also other substitution patterns were tolerated. Low yields and enantioselectivities were instead obtained when DEAD was used as the electrophile. Mechanistic NMR studies indicate that substrate




**Scheme 55.** NHC-catalyzed asymmetric aminative dearomatization of β-naphthols.

activation occurs via non-covalent interaction with the NHC, i.e. through an O–H···NHC hydrogen-bonding interaction, whereas the formation of an ion-pair comprising azolium and phenolate ions is less likely in this process.

## 6. Summary and Outlook

In this review we have collected and discussed all procedures for the synthesis of α-amino carbonyl compounds, published in recent years (2015–2024), which were mainly based on the electrophilic enantioselective α-hydrazination with dialkyl azodicarboxylates. Other miscellaneous methods, not necessarily leading to enantioenriched products, have been assembled and reviewed at end. Considerable progress has been attained in the last ten years in the α-hydrazination of carbonyl compounds. Various methodologies and novel catalysts have been developed to overcome the difficulties especially encountered in the direct enantioselective α-hydrazination of carbonyl compounds. Particularly noteworthy is the synthesis of α-tertiary amines by the direct enantioselective α-hydrazination of α-branched ketones by both chiral Brønsted and Lewis acid catalysis reported initially for cyclic ketones and later extended to acyclic ones. Moreover, the introduction of novel chiral catalysts (e.g., rotaxanes, planar chiral catalysts, chiral covalent organic frameworks) and the use of techniques (e.g., catalyst immobilization for batch and flow chemistry) allowed chemists to achieve higher performance in terms of final yield and enantioselectivity in standard α-hydrazination, as well as the potential for large-scale and industrial applications. Clearly, there could be an atom economy issue when a hydrazine is not the final target as half of the electrophile has to be reductively removed from the product to generate an amino group. And about this, a difficulty often encountered after a successful α-hydrazination of a carbonyl compound is the conversion of the hydrazino group into a "true" α-amino group by the N–N bond cleavage. This process, which depends on the azodicarboxylate ester used, often requires prior manipulation of the product and not always is possible. According to Trost's words "a requirement for any useful amination technique utilizing dialkyl azodicarboxylate electrophiles is to show that the resulting hydrazines can be readily transformed into synthetically desirable amino products", so it would be desirable that this will push synthetic chemists to always accompany the preparation of new α-hydrazination products with a study on their conversion into amino derivatives to make them real useful intermediates in the synthesis of more complex natural and bioactive compounds.

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**Keywords:** Amination · Hydrazination · Amino aldehydes · Amino alcohols · Amino ketones

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