Hydrazones as singular reagents in asymmetric organocatalysis

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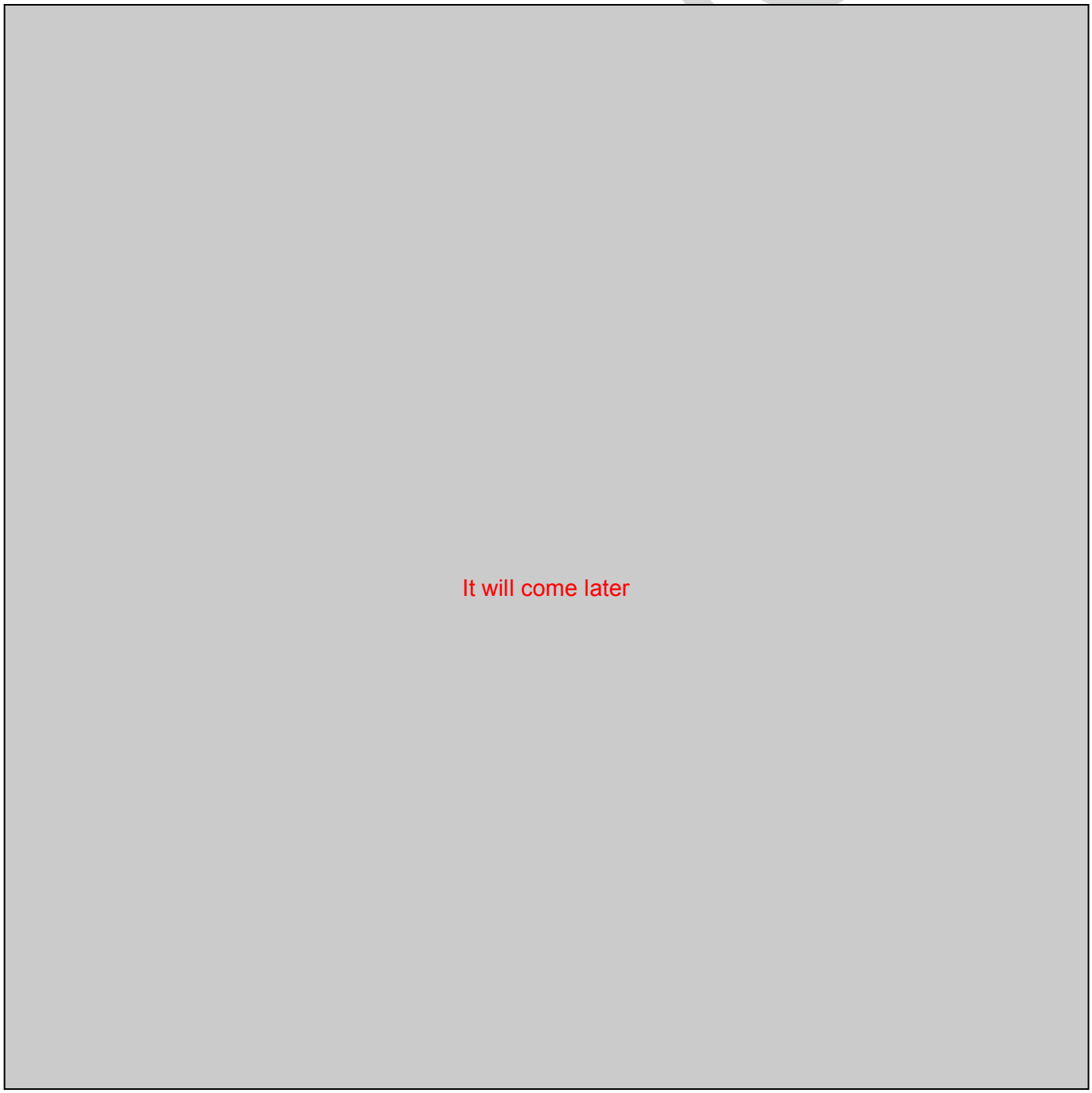

Abstract: This Minireview summarizes strategies and developments regarding the use of hydrazones as reagents in asymmetric organocatalysis, their distinct roles in nucleophile-electrophile reactions, cycloadditions and cyclizations. The key structural elements governing the reactivity of these reagents in a preferred pathway will be discussed, as well as their different interactions with organocatalysts, leading to diverse activation modes. Along these studies, the synthetic equivalence of *N*-monoalkyl-, *N*,*N*-dialkyl- and *N*-acyl hydrazones with several synthons is also highlighted. Emphasis is also put on the mechanistic studies performed to understand the observed reactivities. Finally, the functional group transformations performed from the available products has also been analysed, highlighting the synthetic value of these methodologies, which served to access numerous families of valuable multifunctional compounds and nitrogen-containing heterocycles.

1. Introduction

Hydrazones have emerged in recent years as a versatile family of reagents with multiple applications in organic synthesis.[1] They are usually stable compounds, readily accessible from the condensation between hydrazines or hydrazides and carbonyl compounds, among other methods. Their core skeleton (N-N=C) provides these nitrogen reagents with multiple reactivity patterns (Figure 1), depending on the substitution pattern (R^1-R^3), the nature of the reaction partners (nucleophiles, electrophiles and others), the mode of activation by different catalysts and the reaction conditions. Consequently, several types of hydrazones have been investigated in C-N and C-C bond forming processes. *N*-Monosubstituted hydrazones (*type* A), and eventually *N*-sulfonyl hydrazones (*type* C, X = S) have been employed as *N*-centered nucleophiles. Moreover, pioneering work by Baldwin and co-workers showed that metallated aldehyde *N*-monosubstituted hydrazones might disclose an ambident nucleophilic reactivity (*N* vs *C*-selectivity) which was strongly influenced by the substitution patterns (R^1, R^2).[2] A proper design of bulky hydrazones (*type A*, R^2 = ^{t}Bu or Tr) as anionic aza-enolate precursors enhanced the *C*-selectivity that, together with subsequent release of the masked carbonyl group allowed their use as acyl anion equivalents. *N*,*N*-Dialkylhydrazones (*type* B) are characterized by an ambiphilic behavior at the azomethine carbon, expressed in reactions with nucleophiles (imine-like reactivity) and electrophiles (aza-enamine reactivity).[1] These reactions afford hydrazone or hydrazine adducts which are valuable precursors for the synthesis of multifunctional compounds and nitrogen-containing heterocycles. Additionally, the utility of *N*-acyl hydrazones (*type C*, X = C) as stable imine surrogates has been widely demonstrated.[3]

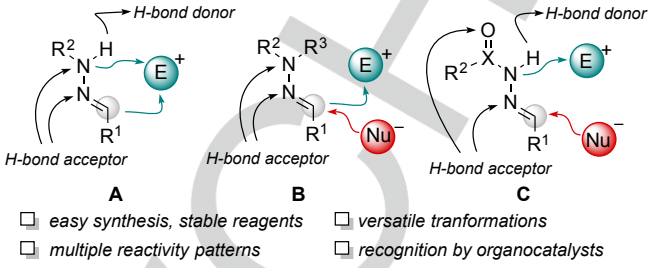

Figure 1. Hydrazones as ambiphilic reagents in asymmetric organocatalysis.

During years, the role of hydrazones in asymmetric synthesis had been associated with the efficiency of (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) and related proline-derived auxiliaries.[4] Nowadays, though, hydrazones are emerging as versatile entities in the field of asymmetric catalysis, able to play different roles depending on the scenario. On the one hand, chiral N-ligands based on *N*,*N*-dialkylhydrazones have met an increasing number of useful applications[5] but, on the other hand, the use of this type of hydrazones as reagents in catalytic, enantioselective procedures has been hampered by the high affinity or sensitivity of these nitrogen-containing reagents towards most Lewis acids, that often led to undesired side reactions (decomposition, dimerization, or catalyst deactivation).[6] Alternatively, the milder nature of the interactions involved in organocatalytic activation[7] have recently been shown to be particularly appropriated for the characteristics of hydrazones. Engagement of the appropriate hydrazone type, interacting through basic sites (amine and imine like nitrogens), H-bond donor (NH in *N*-monosubstituted hydrazones) or H-bond acceptor (X=O, in *N*-acyl hydrazones) functionalities with different organocatalysts has emerged as a promissing strategy for the development of new reactivity patterns. In this Minireview, we aim to outline the currently available methodologies that use hydrazones as key reagents in asymmetric organocatalysis. The structural elements which modulate the different reactivities, the plausible activation modes, as well as the mechanistic aspects that explain the observed reactivities and stereoselectivities will be discussed, aiming to offer a timely and clear overview of this growing topic and its key concepts.

2. Hydrazones as nucleophiles

From a structural viewpoint, hydrazones can be considered as 2-azaenamines and, consequently, behave as ambident nucleophiles that react with electrophiles either at the amine sp^3 nitrogen or at the azomethine carbon by virtue of the $n\rightarrow\pi$ conjugation (Scheme 1). In general, the nitrogen atom is the most nucleophilic center and monosubstituted hydrazones (R^3 = H) usually yield products **E** after reaction with electrophilic

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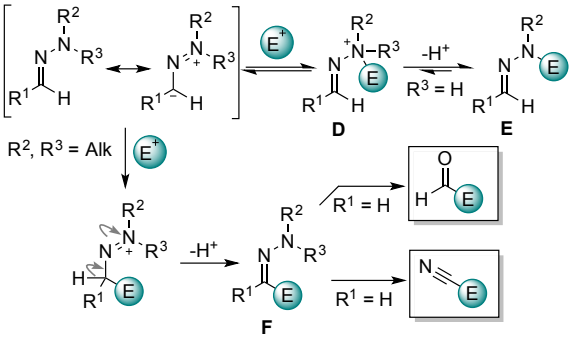
species E^+. However, hydrazonium species **D** formed from *N*,*N*-dialkylhydrazones (R^2, $R^3 \neq H$) cannot evolve in the same way and, eventually, the irreversible *C*-attack can proceed to afford products **F** via diazenium intermediates. In the particular case of formaldehyde *N*,*N*-dialkylhydrazones (FDAHs; $R^1 = H$, R^2, $R^3 \neq H$), the minimum steric hindrance around the azomethine carbon dramatically enhances the nucleophilic reactivity at this center and allows formation of products **F** through an essentially irreversible C–C bond forming process.



Scheme 1. Nucleophilic reactivity profile of hydrazones.

Maji and Mayr have recently reported on the *C*-nucleophilicity quantification of representative FDAHs, **1a** (*N* = 6.98) and **1b** (*N* = 7.94). As expected, these values are lower than those of common enamines and comparable to those of enamides (Figure 2).[8] The nucleophilicity can be modulated by tuning the structure of the dialkylamino fragment, being the pyrrolidine ring more effective than *N*,*N*-dimethylamino group in the $n \rightarrow \pi$ conjugation and, therefore, 1-methyleneaminopyrrolidine **1b** has been one of the most used FDAHs.

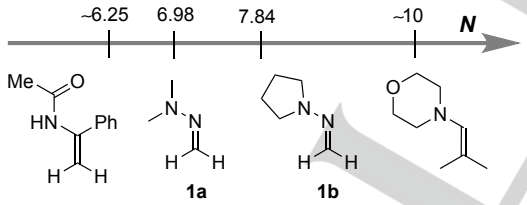
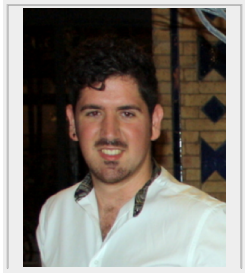


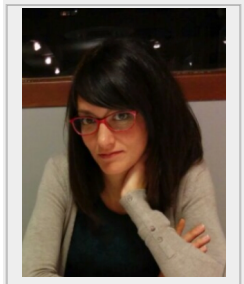
Figure 2. Comparison of nucleophilicity parameters *N* of the *N*,*N*-FDAH **1a**,**b** with those of enamines and enamides.

The marked aza-enamine character of FDAHs and their equivalences with formyl and cyanide anions have been exploited for the functionalization of a wide palette of electrophiles. Moreover, 1-methyleneamino-2-(1-methoxymethyl) pyrrolidine and related proline-derived formaldehyde hydrazones have been used as chiral analogues of **1b** for the synthesis of enantiomerically enriched formylated and/or cyanated derivatives.[9]

David Monge received his PhD in 2007 at University of Sevilla under the supervision of Prof. Rosario Fernández and José M. Lassaletta. After he worked as postdoctoral researcher at CSIC (Sevilla) for BayerCropScience GmbH (2007-2008) and he joined the group of Prof. Karl Anker Jørgensen at Center for Catalysis at the University of Aarhus (Denmark, 2009-2010). In 2011 he returned to University of Sevilla, where he was a postdoctoral "Juan de la cierva" fellow and was promoted to Associate researcher in 2015. His current research interests include green chemistry and asymmetric metal catalysis and organocatalysis, with emphasis on hydrazones as reagents or ligands.



Esteban Matador received his B. S. degree from University of Sevilla in 2014. A year later, he finished his M.S. and he is now pursuing his Ph.D. degree in R. Fernández and J. M. Lassaletta group at the same University. His research interest focuses on the use of hydrazones as reagents or ligands in asymmetric catalysis.



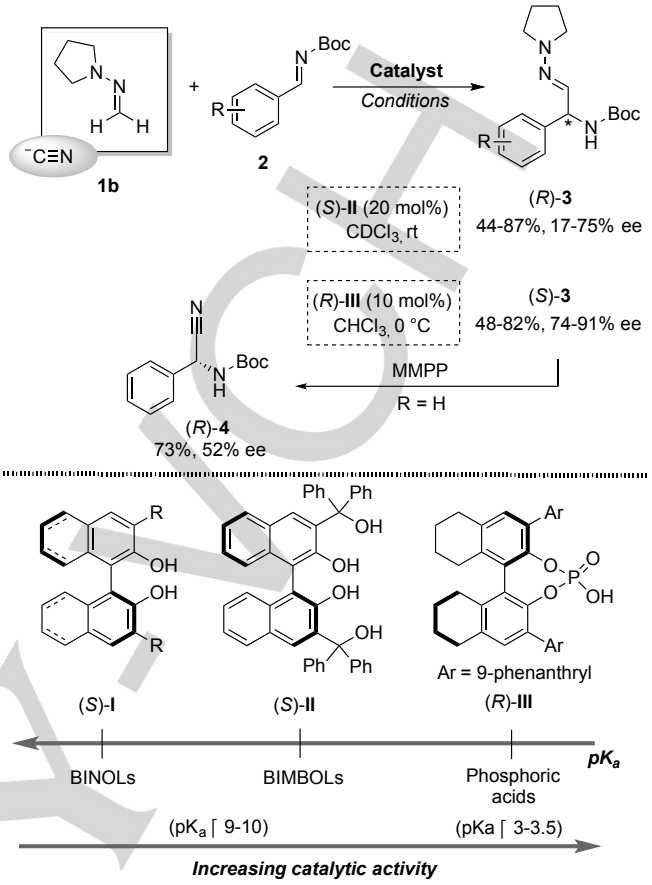
Mª de Gracia Retamosa received her PhD in 2008 at University of Alicante under the guidance of Prof. Carmen Nájera and José Miguel Sansano. After she did several postdoctoral stages [Prof. Michael Greaney at University of Edimburgh (2009), Prof. Jesús M. Sanz at University Miguel Hernández (Elche, 2009-2011) and Prof. Fernando P. Cossío at the University of the Basque Country and Donostia International Physics Center (2012-2016)]. Recently, she has joined R. Fernández and J. M. Lassaletta group as postdoctoral researcher [CSIC (Sevilla)]. Her current resarch interests include asymmetric metal and organocatalysis and synthesis of compound with pharmacological interest.

Rosario Fernández studied chemistry at the University of Sevilla and received both her BS degree (1980) and her PhD degree (1985) under the supervision of Prof. Antonio Gómez Sánchez. She was a NATO postdoctoral fellow at the University of Paris-Sud (Orsay, France) in the laboratory of Prof. Serge David from 1986 to 1987. In 1987 she returned to the University of Sevilla, where she was promoted to Associate Professor. In 2008 she became a Full Prof. at the same University. Her current research interests include asymmetric synthesis and enantioselective catalysis, in both aspects, asymmetric metal catalysis and organocatalysis.

José María Lassaletta received his PhD in 1990 from the University of Seville. After a postdoctoral stage in the 'Instituto de la Grasa y sus Derivados' (CSIC, Seville) he joined the group of Professor Richard R. Schmidt (U. Konstanz, Germany). In 1995 he moved to the Instituto de Investigaciones Químicas (CSIC, Seville), where he was promoted to Tenured Scientist in 1996, Research Scientist in 2005 and Research Professor in 2009. He is currently interested in the development of synthetic methodologies, cross-coupling and C–H activation strategies, and ligand design with emphasis on hydrazones and N-heterocyclic carbenes, and asymmetric organocatalysis.

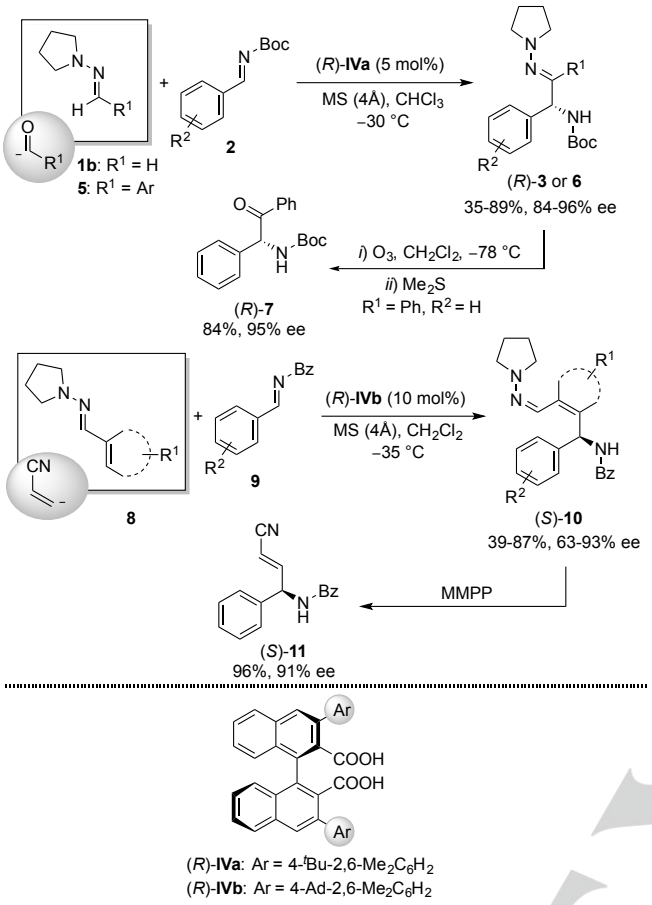
2.1. Addition of aldehyde *N*,*N*-dialkylhydrazones to imines

The first example using FDAHs in asymmetric organocatalysis was reported by Dixon in 2005.[10] 1-Methyleneaminopirrolidine **1b** readily added to *N*-Boc aryl imines **2** in the presence of binaphtol-type catalysts, of which Ph_2-BIMBOL (*S*)-**II** was found to be the most efficient one (Scheme 2). Application of this system afforded the corresponding α-aminohydrazones (*R*)-**3** in fair to good yields and moderate enantioselectivities. These adducts could be directly transformed into Strecker–type products, such as (*R*)-**4**, by oxidative cleavage (N-oxidation/ aza-Cope elimination) of the hydrazone moiety using magnesium monoperoxy phthalate (MMPP) as the oxidant.[11] Later, Rueping and co-workers reported improved catalytic efficiency of BINOL-derived chiral phosphoric acid (*R*)-**III** in the same reaction.[12] The results achieved by using these catalytic systems indicate a direct correlation between acidity and catalytic activity,[13] while other factors like the establishment of additional H-bond cooperative networks, steric hindrance around reaction site or π–π stacking interactions might have an essential impact in the selectivity.



Scheme 2. First organocatalysts employed in reaction of 1-methyleneaminopyrrolidine **1b** with *N*-Boc protected imines **2**.

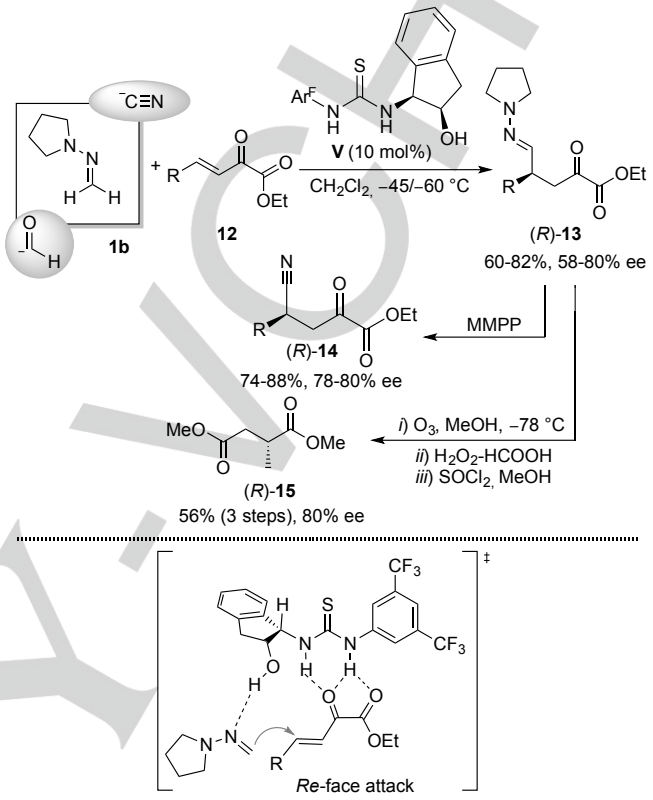
In 2008, Maruoka and co-workers went a step further to achieve reactivity with arylaldehyde *N*,*N*-dialkylhydrazones. Thus, the catalytic efficiency of axially chiral dicarboxylic acids **IV** overcame that of by BIMBOL **II** or phosphoric acid catalyst **III** and, using a lower catalyst loading of only 5 mol%, hydrazones **5** could also be used as acyl anion equivalents to afford α-aminohydrazones (*R*)-**6** in moderate to good yields and high enantioselectivities (Scheme 3).[14] The versatility of the hydrazone functionality was demonstrated with the synthesis of α-aminoketone (*R*)-**7** by ozonolysis. This activation strategy was successfully extended to vinylogous imino aza-enamine reactions (addition at C3-position) between α,β-unsaturated aldehyde hydrazones **8** and *N*-benzoyl protected imines **9**.[15] The synthetic potential of the 1,2-addition products (*S*)-**10** was highlighted by their direct transformation into alkenyl amines, exemplified by (*S*)-**11**. To the best of our knowledge, axially chiral dicarboxylic acids **IV** represent the only catalysts able to facilitate nucleophilic asymmetric additions of *N*,*N*-dialkylhydrazones of aldehydes different from formaldehyde.



Scheme 3. Asymmetric dicarboxylic acid-catalysed additions of formaldehyde, aryl- and alkenyl- aldehyde hydrazones to imines.

2.2. Conjugate addition of formaldehyde *N,N*-dialkyl hydrazones to enoates

Our research group considered hydrogen-bonding organocatalysts as an alternative to Brønsted acid catalysts for developing reactions involving formaldehyde *N,N*-dialkylhydrazones and enoate surrogates.[16] It was found that the 1,4-addition of 1-methyleneaminopyrrolidine **1b** to β,γ-unsaturated α-ketoesters **12** was strongly accelerated by catalytic amounts of multiple H-bond donors such as thioureas. Thiourea **V** [Ar^F = 3,5-$(CF_3)_2C_6H_3$] derived from (1*S*,2*R*)-aminoindan-2-ol allowed the preparation of adducts (*R*)-**13** in good yields and moderate to good enantioselectivities (Scheme 4).[17] The versatility of these masked 1,4-dicarbonyl compounds was illustrated by their transformation into α-keto γ-cyano esters (*R*)-**14** promoted by MMPP and the synthesis of succinate derivate (*R*)-**15** following an ozonolysis/oxidative decarboxylation sequence. The presence of the hydroxyl group in the aminoindanol scaffold proved to be essential for both reactivity and selectivity, supporting a bifunctional mode of action by the catalyst **V**. Accordingly, the acidic hydrogen atoms of the thiourea would activate the substrate while the approach of the hydrazone to the ester might be driven by an OH–N hydrogen bond, resulting in the addition of the azomethine carbon to the *Re* face of the C=C bond.



Scheme 4. Enantioselective addition of 1-methyleneaminopyrrolidine **1b** to β,γ-unsaturated α-ketoesters **12** and proposed stereochemical model.

2.3. Addition of formaldehyde *N*-*tert*-butylhydrazone to carbonyl compounds

The asymmetric 1,2-addition of acyl anion equivalents to carbonyl compounds is a powerful synthetic tool that provides direct access to densely functionalized carbinols.[18] As discussed above, the marked aza-enamine character of 1-methyleneaminopyrrolidine **1b** had been exploited in enantioselective organocatalytic additions to imines[10,12,14,15] and Michael acceptors.[17] This approach, however, failed to afford high enantioselectivities in 1,2-addition to carbonyl compounds. We envisaged that replacement of the pyrrolidino group of **1b** by a *N*-*tert*-butylamino group in **16** should still favor reactivity at the azomethine carbon for steric reasons, while providing additional interaction opportunities with bifunctional organocatalysts (Figure 3).

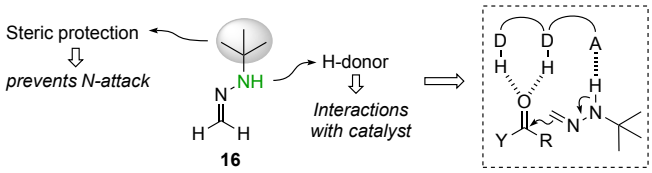
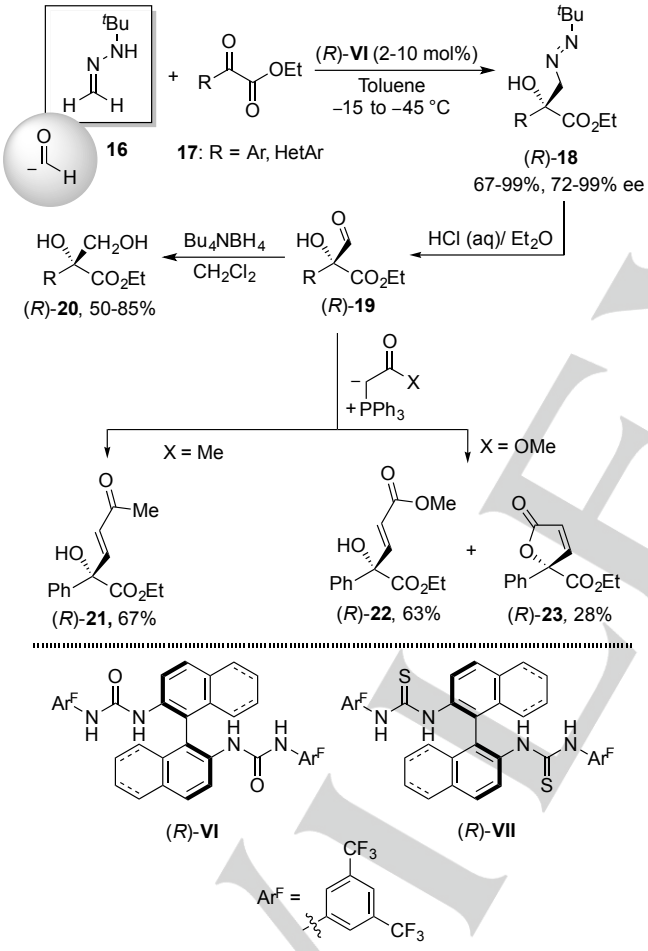


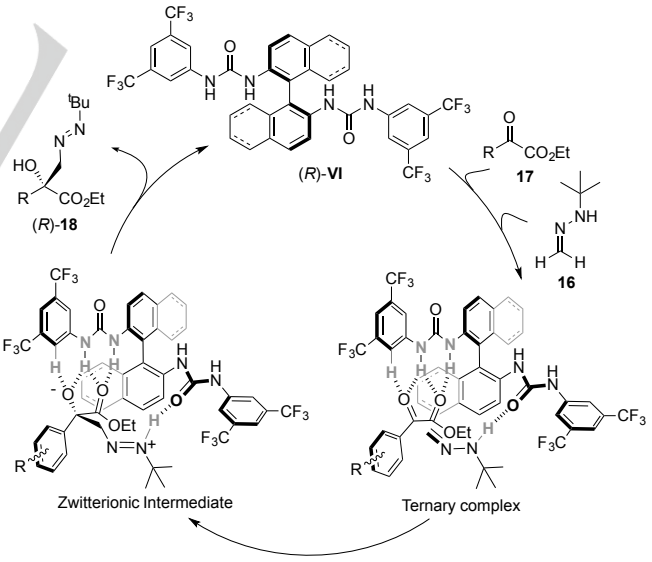
Figure 3. Dual activation strategy with formaldehyde *N-tert*-butyl hydrazone **16**. D-H: H-bond donor, A: H-bond acceptor.

This strategy was successfully applied to perform highly enantioselective additions (formally hetero-carbonyl-ene reactions) to α-keto esters, that reached very high enantioselectivities by using BINAM-derived bis-ureas **VI** (Scheme 5).[19]



Scheme 5. Enantioselective addition of formaldehyde *tert*-butylhydrazone **16** to α-ketoesters **17** and further derivatizations.

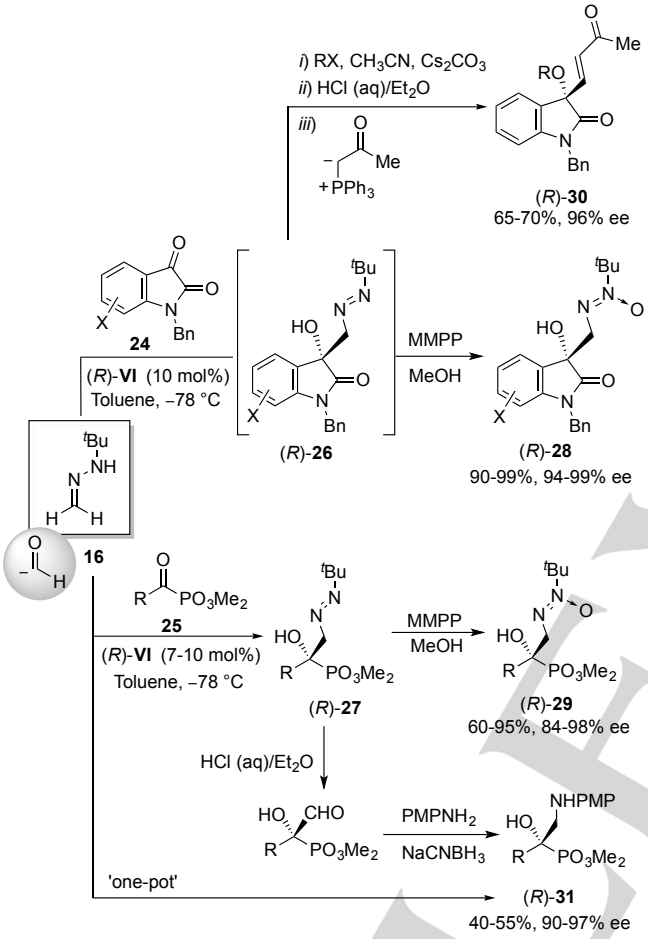
The key racemization–free diazene to aldehyde transformation (**18→19**), which serves to demonstrate the synthetic equivalence of **16** with the formyl anion, could be efficiently performed via 'one pot' tautomerization/hydrolysis promoted by HCl in a byphasic H_2O/Et_2O medium. Aldehydes **19** showed a limited stability and did not resist chromatographic purification, but the crude products could be reduced with Bu_4NBH_4 to afford diols **20** or used in Wittig reactions to yield enones **21** or unsaturated esters **22** and lactones **23** in good overall yields and without racemization. Unexpectedly, bis-urea catalysts (*R*)-**VI** showed a better catalytic activity than the bis-thiourea analogs (*R*)-**VII**, and both types of catalysts afforded opposite major enantiomers, suggesting that different activation modes operate in each case. Considering the higher H-bond acceptor capability of the urea carbonyl group, a key interaction with the NH group of **16** was considered. Accordingly, ^{1}H-NMR spectra recorded for **16** in the presence of increasing amounts of (*R*)-**VI** showed a progressive upfield shift of the azomethine protons, as expected from a higher electron density at the azomethine carbon. As observed also in ^{1}H-NMR experiments, a second urea moiety activates the keto ester by means of an H–bond network with participation of one of the acidic ortho CH bonds of the $(CF_3)_2C_6H_3$ groups. All the collected experimental evidences, as well as the observed absolute configuration, are consistent with the mechanism and stereochemical model shown in Scheme 6. As envisaged in the original design (Figure 3), bis-urea **VI** behaves as a bifunctional catalysts, performing a dual activation of both reactants. In the ternary complex formed, the relatively bulky aromatic group of the substrate avoids the more hindered inner region of the catalyst, thus facilitating the attack of the activated (H–bonded) hydrazone reagent from the *Re* face.



Scheme 6. Proposed mechanism and stereochemical model.

Aiming to expand the scope of this dual activation strategy, we reported later on the enantioselective reactions of FTBH (**16**) with isatins **24**[20] and α-keto phosphonates **25**,[21] leading to highly functionalized diazenes **26** and **27** in good yields and

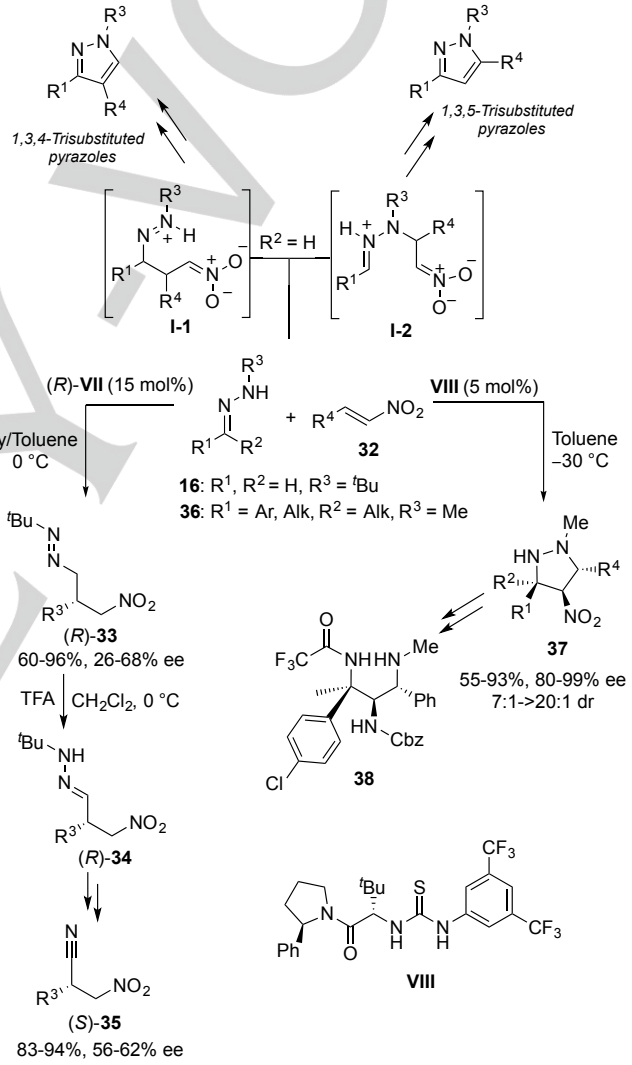
enantioselectivities (Scheme 7). Subsequent high-yielding and racemization-free transformations provide direct access to relevant azoxy compounds **28** and **29**, enones **30** bearing an oxindole scaffold, and *N*-PMP protected phosphaisoserines **31**. Remarkably, most of these transformations can be performed in a 'one pot' fashion without isolation of diazene or aldehyde intermediates.



Scheme 7. Enantioselective addition of FTBH **16** to isatins **24** and acyl phosphonates **25**.

2.4. Conjugate addition of *N*-monoalkylhydrazones to nitroalkenes

Preliminary investigations had shown that simple formaldehyde *N*,*N*-dialkylhydrazones **1a**,**b** readily add to nitroalkenes, spontaneously or promoted by thiourea catalysts,[22] but the enantioselective organocatalytic version could not be successfully developed for these reagents. Previously, aldehyde *N*-substituted hydrazones were reported to react with nitroalkenes to afford pyrazoles through a formal 1,3-cycloaddition/oxidation sequence under basic, acid or thermal conditions.[23] In these reactions, the regioselectivity is assumed to be controlled by the first nucleophilic attack (C *vs* N) driven by hydrazone structure or reaction conditions *via* hydrazonium-nitronate intermediates **I-1** or **I-2** (Scheme 8, left). Interestingly, FTBH (**16**) allowed *C*-selective conjugate addition to nitroalkenes **32** under mild conditions. This unprecedented diaza-ene reaction could be catalyzed by (*R*)-BINAM-derived bis-thiourea (*R*)-**VII** to afford the corresponding diazenes (*R*)-**33** in good yields and moderate enantioselectivities.[24] These products were transformed into β-nitro-nitriles (*S*)-**35** employing a two-step alkylation/oxidative cleavage protocol from the tautomeric hydrazones (*R*)-**34**.



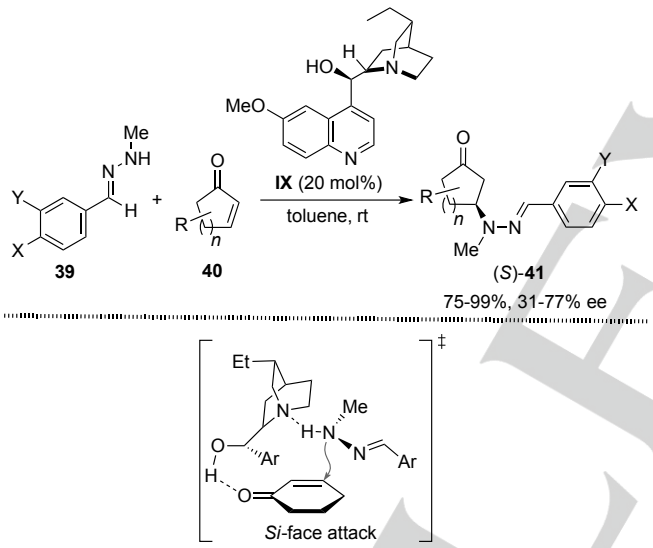
Scheme 8. Enantioselective reactions of *N*-monoalkylhydrazones with nitroalkenes.

On the other hand, Jørgensen and co-workers described a new reaction pathway exerted by ketone-derived *N*-methylhydrazones **36** (Scheme 7, right). Asymmetric H-bonding activation of nitro-olefins by Jacobsen-type thiourea **VIII**

facilitated the formal 1,3-dipolar cycloaddition with hydrazones **36**, acting as *N*-nucleophiles in the first bond formation.[25] Subsequent cyclization afforded 4-nitropirazolidines **37**, in which oxidative formation of pyrazoles would be blocked due to the presence of a quaternary stereogenic center (R^1 and $R^2 \neq H$). These products **37**, obtained in good to excellent yields with high to excellent stereocontrol (enantio- and diastereoselectivity), were also used as precursors of 1,2,3-triamines, exemplified by the synthesis of **38**.

2.5. Conjugate addition of *N*-monosubstituted hydrazones to α,β-unsaturated ketones/aldehydes

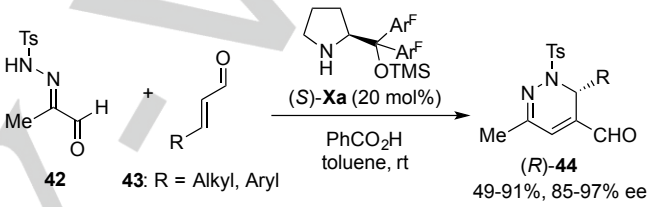
The aza-Michael reaction[26] involving hydrazones as N-centered nucleophiles had been scarcely investigated. In 2007, Jørgensen and co-workers reported on the first enantioselective organocatalytic 1,4-addition of aryl-substituted *N*-methyl hydrazones **39** to cyclic enones **40**. The expected adducts **41** were isolated with moderate enantioselectivities using cinchona alkaloid **IX** as the catalyst (Scheme 9).[27]



Scheme 9. Enantioselective addition of *N*-methy hydrazones **39** to cyclic enones **40**.

As observed in other related thia-Michael additions,[28] the hydroxyl group in **IX** was found to be essential to induce enantioselectivity. The interaction between the catalyst and hydrazone was observed by ^{1}H-NMR in some cases and, accordingly, the postulated working model includes an H-bond between the hydroxyl group and the enone carbonyl, accounting for its activation, while the quinuclidine moiety drives the approach of the hydrazone through a second (NH–N) H-bond interaction. A minimum steric repulsion between the aromatic ring in the catalyst and the enone led to a preferred orientation, in agreement with the observed (*S*) absolute configuration.

The use of aminocatalysis[29] as an obvious strategy for the activation of α,β-unsaturated carbonyl compounds in this context remained elusive until 2012, when Vicario's group described the first example of an aza-Michael reaction involving an *N*-tosyl hydrazone under iminium activation.[30] The choice of pyruvaldehyde 2-tosyl hydrazone **42** as a bifunctional reagent bearing a strategically installed formyl group was essential for completing a cyclization process, thereby avoiding reversibility issues frequently observed in aza-Michael reactions. Thus, diarylprolinol (*S*)-**Xa** in the presence of benzoic acid as co-catalyst promotes the reaction of **42** with alkyl- and aryl-substituted enals **43** to afford 2,3-dihydropyridazines (*R*)-**44** in good yields and with excellent stereocontrol (Scheme 10). The overall process might be described as a three-step aza-Michael/aldol reaction/dehydration cascade through iminium/enamine catalysis.



Scheme 10. Enantioselective aza-Michael/aldol condensation cascade between pyruvaldehyde *N*-tosyl hydrazone **42** and cyclic enones **43**.

In 2012, the same group introduced a new push-pull monosubstituted hydrazone design to switch from *N*- to *C*-selectivity for an acylation strategy of α,β-unsaturated aldehydes[31] (Figure 4).

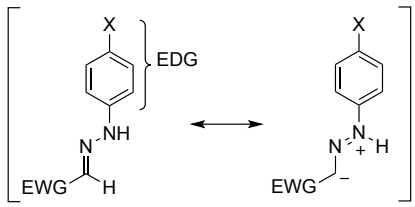
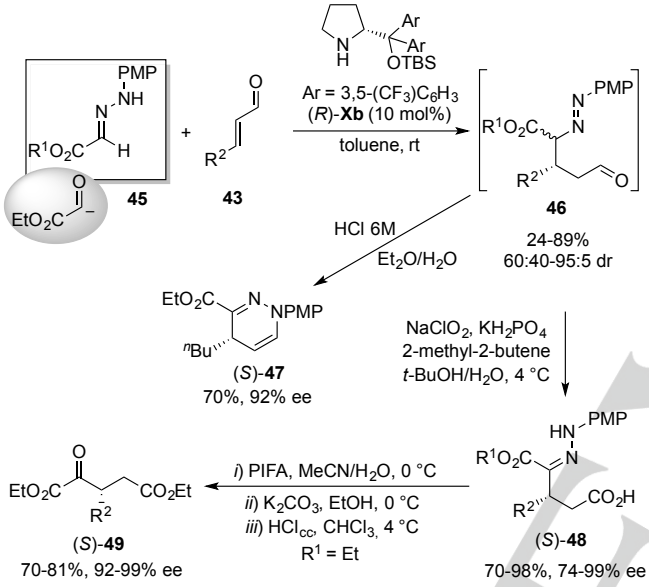


Figure 4. Push-pull monosubstituted hydrazone design for nucleophilic acylation strategies.

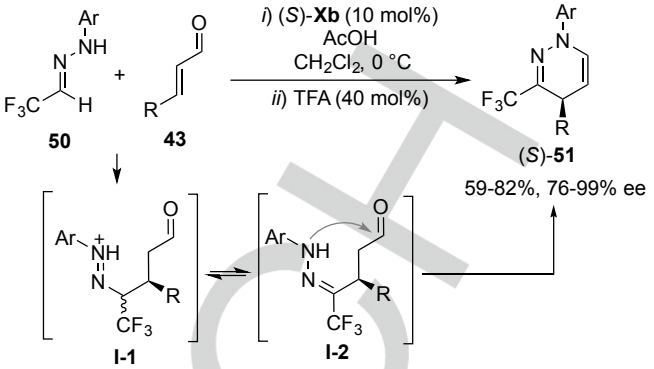
The optimized hydrazone structure incorporated an electron-donating group (EDG) at nitrogen, typically *p*-methoxyphenyl (X = OMe) and an electron–withdrawing group (EWG) as the azomethine carbon substituent (α-anion stabilizing), hence resulting in an increased reactivity of the azomethine carbon. Under iminium catalysis provided by the silylprolinol ether (*R*)-**Xb**, the projected 1,4-additon of hydrazones **45** to α,β-unsaturated aldehydes **43** afforded diazenes **46** as a mixture of diasteroisomers (Scheme 11). These highly functionalized

adducts showed high tendency to decompose and, therefore, subsequent tranformations were required. Treatment of **46** with HCl in a biphasic Et_2O/H_2O medium gave cyclic 1,4-dihydropyridazine derivative (*S*)-**47**. Moreover, aldehyde oxidation in **46** employing Pinnick conditions afforded the corresponding γ-hydrazonocarboxylic acids (*S*)-**48** in excellent yields and high enantioselectivities. To complete the indirect β-glyoxylation of enals from hydrazones **45**, representative γ-hydrazonocarboxylic acids (*S*)-**48** were transformed into diesters (*S*)-**49** by a three-step reaction sequence including oxidation of the azomethine carbon, esterification and hydrolytic cleavage, without erosion of enantiomeric purity.



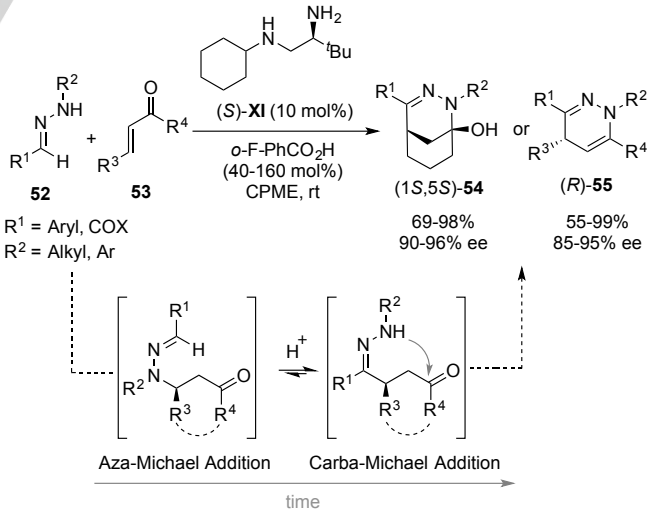
Scheme 11. Enantioselective reactions of push-pull hydrazones **45** with α,β-unsaturated aldehydes **43** and subsequent derivatizations.

The above-mentioned combination of push-pull hydrazone and iminium activation was also exploited by Rueping and co-workers to perform the reaction between trifluoromethylated *N*-arylhydrazones **50** and various aliphatic, aromatic and heteroaromatic α,β-unsaturated aldehydes **43** for the synthesis of 1,4-dihydropyridazines (*S*)-**51** (Scheme 12).[32] The strong inductive effect of the CF_3 group combined with the effect of acetic acid as an additive promoted a rapid formation of γ-hydrazonoaldehydes **I-2** (acid–catalyzed diazene-to-hydrazone isomerization from **I-1**). Intramolecular hemiaminal formation and dehydration assisted by TFA led to the desired trifluorometylated heterocycles (*S*)-**51** in good yields and high enantioselectivities.



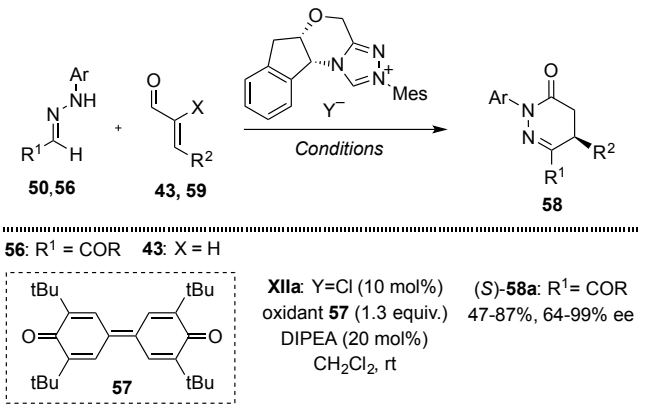
Scheme 12. Enantioselective cascade reactions of push-pull hydrazone **50** with α,β-unsaturated aldehydes **43**.

Recently, Ye and co-workers re-investigated the reaction of *N*-monosubstituted hydrazones with enones.[33] Preliminary results employing aryl-substituted *N*-methyl hydrazones **39** and 2-cyclohexenone in the presence of several amines as catalysts confirmed the aza-Michael reaction as the initial step in this process, in concordance with the previous results by Jørgensen.[27] However, prolonged reaction times and acid additives favored the formation of carba-Michael adducts which, upon subsequent intramolecular cyclization, lead to hemiaminal-type products **54** (Scheme 13). The reaction of *N*-monosubstituted hydrazones **52** (R^2 = Alkyl and Aryl) and different enones **53** (cyclic and acyclics) catalyzed by primary-secondary diamine **XI** in the presence of variable ammounts of *o*-fluorobenzoic acid afforded enantioenriched bicyclic products **54** or 1,4-dihydropyridazines (*R*)-**55** depending on the substitution patterns in both substrates.



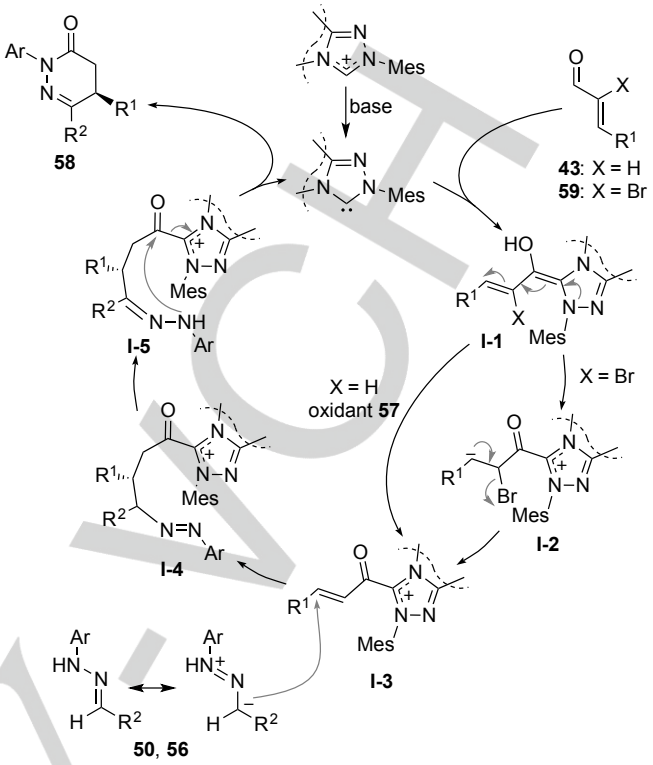
Scheme 13. Enantioselective reactions of *N*-monosubstituted hydrazones **52** with α,β-unsaturated ketones **53** and subsequent cyclizations.

Push-pull *N*-monoaryl hydrazones (**50**,**56**) have been also engaged in reactions with α,β-unsaturated aldehydes catalysed by N-heterocyclic carbenes.[34] Employing aminoindanol-derived triazolium salts **XIIa** as carbene precursor, DIPEA as the base and simple enals **43** in the presence of quinone **57** as oxidant, led the isolation of the corresponding 4,5-dihydropyridazones (*S*)-**58a** in good yields and high enantioselectivities (Scheme 14).[35] Comparable results were obtained performing the reaction with α-bromoenals **59** under similar conditions and without the need of oxidant.[36]



Scheme 14. Enantioselective reactions of push-pull *N*-monoaryl hydrazones with enals employing NHC catalysis.

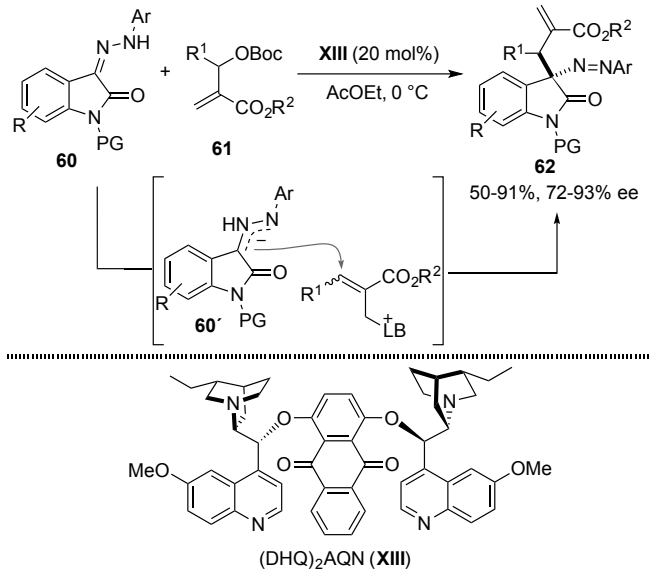
A plausible mechanism for these processes is depicted in Scheme 15. The catalytic cycle starts with the formation of homoenolate intermediate **I-1**. Then, either oxidation (X = H) or tautomerization/bromide elimination (X = Br) events provide a common α,β-unsaturated azolium intermediate **I-3**. Next, the hydrazone behaving as a *C*-nucleophile attacks the β position to generate diazene intermediate **I-4**, from which an intramolecular cyclization *via* tautomerization/*N*-nucleophilic acylic substitution yields the 4,5-dihydropyridazone product **58** (*S* enantiomer depicted) with concomitant regeneration of the NHC catalyst.



Scheme 15. Proposed mechanism for reactions of push-pull *N*-monoaryl hydrazones with enals employing NHC catalysis.

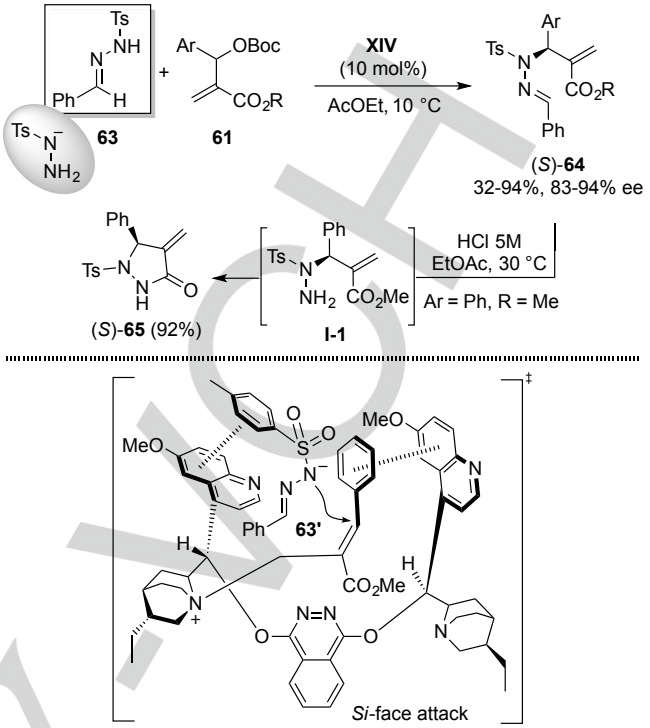
2.6. S_N2'-S_N2'-type reaction of *N*-tosyl and *N*-aryl hydrazones with Morita-Baylis-Hillman carbonates

The asymmetric allylic alkylation of Morita-Baylis-Hillman (MBH) adducts (S_N2'- S_N2'-type reaction) represents a powerful tool for the construction of chiral building blocks. The group of Shi first described the use of hydrazones as versatile nucleophiles for this reaction. Thus, the alkylation of isatin–derived *N*-monoaryl hydrazones **60** with MBH carbonates **61** catalysed by Cinchona alkaloid dimer $(DHQ)_2AQN$ (**XIII**), afforded diazenes **62** bearing an oxindole scaffold in good yields and enantioselectivities (Scheme 16).[37] It was assumed that the *tert*-butoxide ion, generated *in situ* from the reaction of the catalyst **XIII** with MBH adduct **61**, abstracts the NH proton of hydrazone **60** to give aza-enolate **60´**, which performed then as a *C*-centered nucleophile.



Scheme 16. Enantioselective organocatalytic reaction between isatin-derived hydrazones **60** and MBH-adducts **61.**

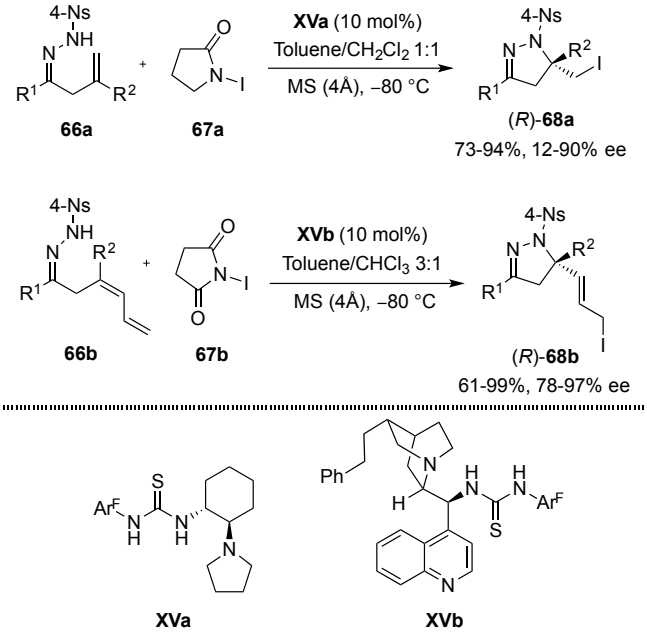
Recently, Wang and co–workers described the alternative asymmetric *N*-allylic alkylation variant of MBH adducts employing benzaldehyde derived *N*-tosyl hydrazone **63**.[38] This reagent, acting as a N-nucleophile, readily reacted with MBH carbonates **61** catalysed by modified Cinchona alkaloid $(DHQD)_2PHAL$ (**XIV**), affording the corresponding *N*,*N*´-disubstituted hydrazones (*S*)-**64** in moderate to good yields, complete regioselectivities and high enantioselectivities (Scheme 17). Subsequent hydrolysis of adducts **64** released alkylated hydrazines such as **I-1**, which were smoothly transformed into synthetically useful pyrazolidinones (*S*)-**65**, without loss of enantiomeric excess. In this reaction, the catalyst $(DHQD)_2PHAL$ (**XIV**) is believed to activate the MBH carbonate via $S_N2´$ reaction at the quinuclidine nitrogen, affording *tert*-butoxide ion and a cationic enoate intermediate which might be oriented by π-π interactions with one quinoline ring of the dimeric catalyst. Concurrently, aza enolate **63´**, formed by deprotonation of hydrazone **63** by *tert*-butoxide, would approach this intermediate to the most accessible *Si*-face. A subsequent $S_N2´$ reaction would yield the product **64** with the observed (*S*) absolute configuration.



Scheme 17. Enantioselective organocatalytic reaction between *N*-tosyl hydrazone **63** and MBH-adducts.

2.7. Iodoaminocyclization of β,γ-unsaturated hydrazones

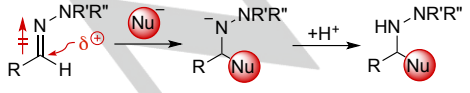
Mukherjee and co–workers described the first examples of the use of *N*-arenesulfonyl hydrazones as nucleophiles in olefin halofunctionalization reactions. Iodoaminocyclizations of unsaturated 4-nitrobenzenesulfonyl (4-Ns) hydrazones **66** were developed employing *N*-iodopyrrolidinones **67a** or *N*-iodosuccinimide **67b** as electrophilic iodine sources and amino-thioureas **XVa,b** as bifunctional catalysts (Scheme 18).[39] Intramolecular nucleophilic attack by the sp^3 nitrogen to cationic iodonium species, engaged in ion pair interactions with thiourea moieties, provided a direct access to 4,5-dihydropyrazole derivatives (*R*)-**68** in high yields and good enantioselectivities



Scheme 18. Enantioselective organocatalytic iodoaminocyclization of *N*-arenesulfonyl hydrazones **66**.

3. Hydrazones as electrophiles

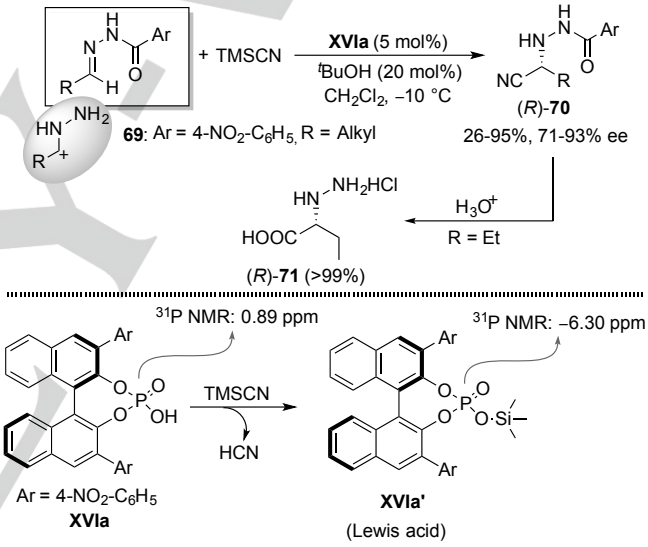
Concerning the imine-type electrophilic reactivity, hydrazones have been also employed as targets for the attack of diverse nucleophiles (Scheme 19).[1,3] Although their slightly polarized C=N bond normally exhibit a diminished reactivity compared with that of analogous imines, their higher stability and lower tendency to tautomerize (in the case of hydrazones derived from enolizable aldehydes) were found to be key for a better performance in several applications. Interestingly, the electrophilic character of the azomethine carbon can be increased by inhibition of $n \rightarrow \pi$ conjugation that in turn might be modulated by changing the structure of the attached amino group. Thus, maximum levels of electrophilicity are reached in *N*-acyl hydrazones and related derivatives, while, eventually, certain conformational restricted or bulky *N*,*N*-dialkyl hydrazones do also exhibit a marked imine-like character. Additionally, the *N*,*N*-dialkylamino or *N*-acylamino group offer opportunities to be involved in activation/fixation by organocatalysts.



Scheme 19. Electrophilic reactivity of hydrazones.

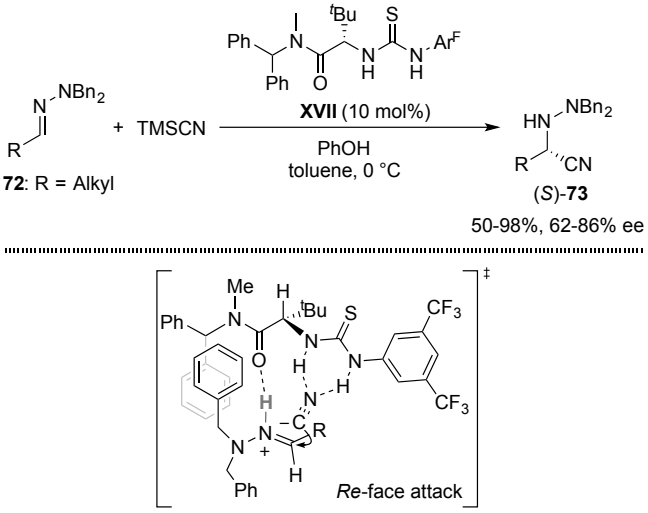
3.1. Strecker-type reactions of *N*-acyl and *N*,*N*-dialkyl hydrazones

In 2010, Tsogoeva and co–workers reported an enantioselective organocatalytic hydrocyanation of aliphatic *N*-benzoyl hydrazones **69** employing trimethylsilyl cyanide (TMSCN) as the cyanide source and BINOL-phosphoric acid **XVIa** in combination with ^{t}BuOH as the catalytic system (Scheme 20).[40] As supported by ^{31}P NMR studies, the active catalytic species was proposed to be an *in situ* generated *O*-silylated BINOL-phosphate **XVIa´**, acting as Lewis acid. The interaction of hydrazones **69**, presumably through the acyl group, with the silicon center in **XVIa´** was key to obtain α-hydrazinonitriles (*R*)-**70** in good to high yields and enantioselectivities. This methodology provides a direct route to biologically relevant α-hydrazinoacids, as (*R*)-**71**.



Scheme 20. Enantioselective Strecker-type reaction of *N*-acylhydrazones **69**.

Considering the higher basicity of *N*,*N*-dialkylhydrazones over *N*-acyl hydrazones, we described an alternative Strecker-type reaction based on thiourea organocatalysts.[41] Using again TMSCN as the reagent, the reaction with aliphatic *N*,*N*-dibenzylhydrazones **72** could be efficiently catalysed by *tert*-leucine-derived bifunctional thiourea **XVII** to afford the corresponding α-hydrazinonitriles (*S*)-**73** in good to excellent yields and moderate to good enantioselectivities (Scheme 21).

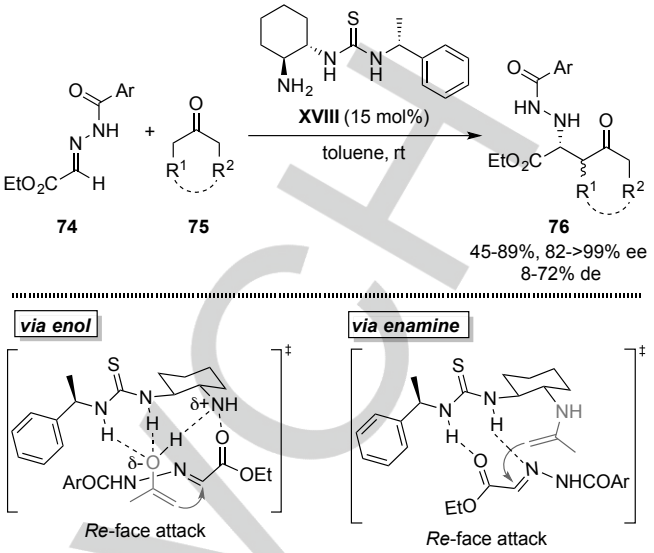


Scheme 21. Asymmetric Strecker-type reaction of *N*,*N*-dibenzylhydrazones **72** and proposed activation and stereochemical model.

The transformation is believed to proceed via anion-binding catalysis.[42] In the proposed reaction pathway, experimental data are consistent with an initial hydrazone protonation by HCN, formed from reaction of PhOH (or the dialkylamino group) with TMSCN, to generate a catalyst-bound hydrazonium-cyanide ion pair. In this intermediate the hydrazonium cation might be additionally stabilized and preferred orientated by π-π interactions between the benzhydryl moiety of catalyst and one of the benzyl groups of hydrazone **72**. Collapse of this ion pair and selective C-C bond formation lead to the observed (*S*) absolute configuration.

3.2. Mannich-type reaction of pyruvate derived *N*-acylhydrazones

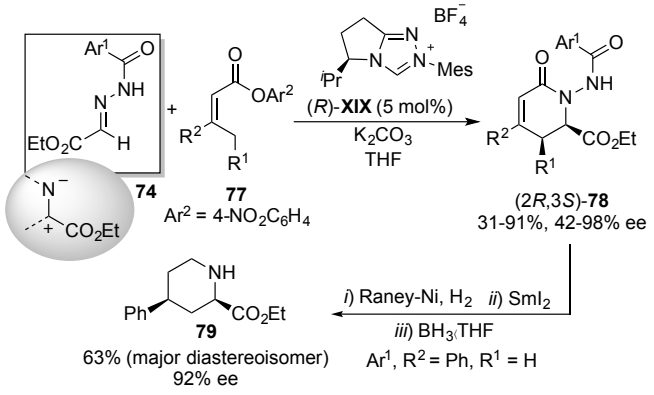
In 2008, Tsogoeva and co-workers reported an unprecedented Mannich-type reaction of α-hydrazono esters **74** with ketones **75** catalized by bifunctional chiral primary amine-thiourea **XVIII** (Scheme 22).[43] The reaction provided the corresponding α-hydrazino esters **76** in high enantioselectivities and moderate-to-good (for acyclic ketones) or good yields (for cyclic ketones). The use of unsymmetrical ketones as substrates afforded a mixture of products with moderate to good regioselectivities. Moreover, while acyclic ketones preferently provided *anti*-Mannich products **76**, cyclic ketones gave *syn* diastereomers, albeit in low to moderate diastereoselectivities. O^{18} incorporation studies in combination with ESI-MS analytic methods indicated that, employing primary amine-thiourea **XVIII** as the catalysts, there are stereo-convergent mechanisms *via* enol and enamine, where the hydrazone might be tightly approached by H-bonding in distinct coordination ways. DFT calculations indicated higher preference for the enol mechanism.



Scheme 22. Enantioselective Mannich-type reaction of pyruvate derived *N*-acylhydrazones **74**.

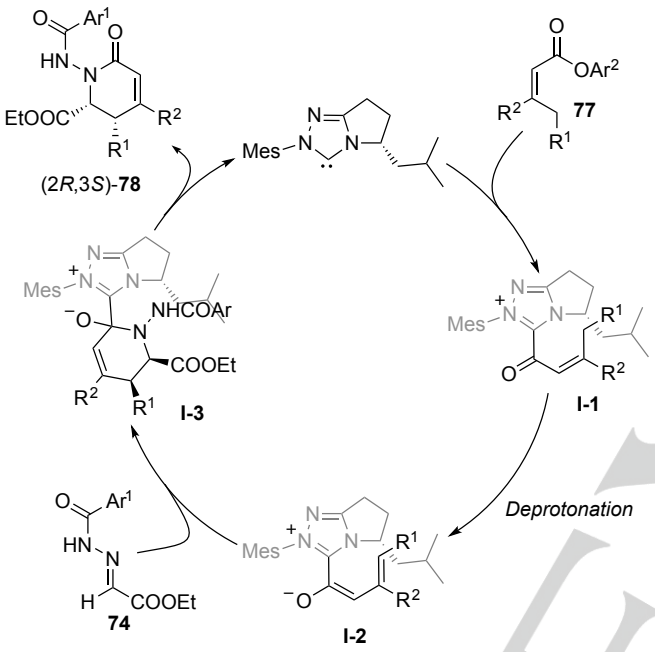
3.3. γ-Aminoalkylation of unsaturated esters with pyruvate derived *N*-acylhydrazones

In 2013, Chi and co-workers described a direct γ-aminoalkylation of α,β-unsaturated esters employing pyruvate derived *N*-benzoylhydrazones **74** as stable imine surrogates.[44] NHC-activation of α,β-unsaturated esters **77** (β-aryl/alkyl and β'-methyl substituted) employing triazolium salt (*R*)-**XIX** as carbene precursor generated a nucleophilic γ-carbon wich underwent addition to electrophilic *N*-benzoylhydrazones **74**, affording δ-lactams **78** in high yields and enantioselectivities (Scheme 23). These lactams could be transformed into optically enriched pipecolic acid derivatives, such as **79**, applying standard protocols which include a SmI_2-promoted N-N cleavage.



Scheme 23. Enantioselective γ-aminoalkylation of unsaturated esters **77** with pyruvate derived *N*-benzoylhydrazones **74**.

As outlined in the postulated catalytic cycle shown in Scheme 24, the reaction starts with the addition of the free NHC catalyst to the ester **77**, thus generating the active enoate intermediate **I-1**. Then, deprotonation follows to form vinyl enolate intermediate **I-2** which reacts with hydrazone **74** through a nucleophilic addition/intramolecular acylic substitution sequence (formally an aza-Diels Alder cycloaddition) to afford zwitterionic intermediate **I-3** which, finally, releases the δ-lactam product **78** with simultaneous regeneration of the NHC catalyst.



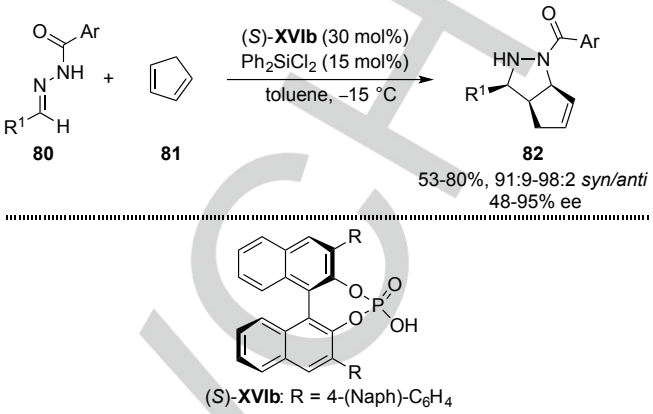
Scheme 24. Postulated catalytic cycle for the γ-aminoalkylation of unsaturated esters **77** with pyruvate derived *N*-benzoylhydrazones **74**.

4. Hydrazones in cycloadditions and other cyclizations

N-Acyl and *N*-aryl hydrazones have also been engaged in cycloadditions and other pericyclic reactions where the polarized C=N bonds are targeted by unsaturated molecules (inter or intramolecularly) to yield interesting diaza heterocycles.

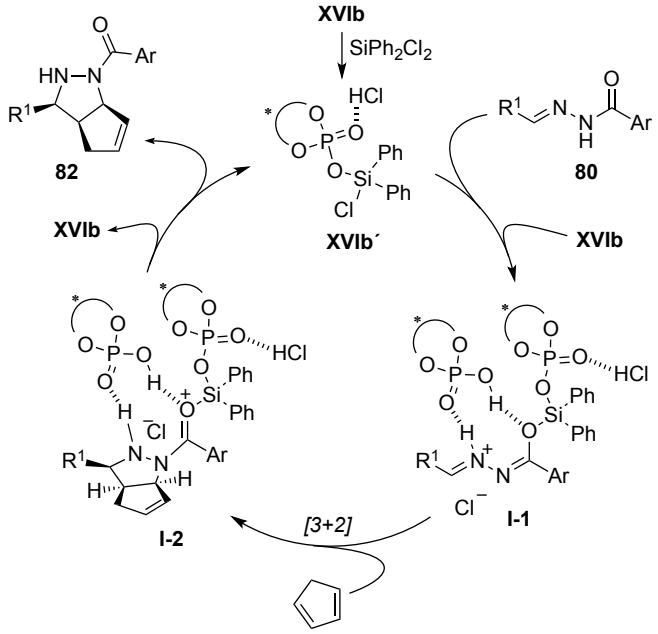
4.1. [3+2]-Cycloadditions of *N*-acylhydrazones

The Lewis-acid catalyzed 1,3-dipolar cycloadditions (1,3-DCs) between *N*-acylhydrazones and alkenes provide an atom and step–economic access to pyrazolidines.[3] In 2005, Leighton discovered that chiral pseudoephedrine-derived silane Lewis acids are efficient promoters (1.5 eq. required) for the 1,3-DCs between *N*-acylhydrazones and enol ethers.[45] Following this metal-free activation concept, Tsogoeva and co-workers reported in 2012 an alternative organocatalytic system for similar reactions between *N*-acylhydrazones **80** and cyclopentadiene **81** (Scheme 25).[46] The use of phosphoric acid (*S*)-**XVIb** as the catalyst and Ph_2SiCl_2 as the Lewis acid led to pyrazolidines **82** in moderate to good yields and, in general, good stereocontrol.



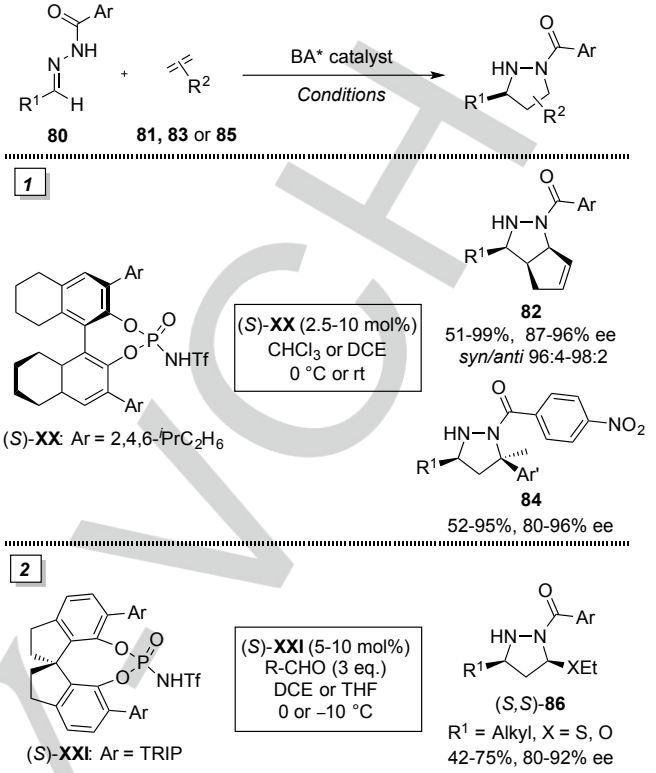
Scheme 25. Organocatalytic enantioselective synthesis of pyrazolidines via 1,3-DC between *N*-benzoylhydrazones **80** and cyclopentadiene.

A mechanism based in cooperative silicon Lewis acid/ Brønsted acid catalysis can be proposed on the basis of the observed experimental results, along with NMR studies (^{31}P and ^{29}Si) and DFT calculations (Scheme 26). Accordingly, the combination of phosphoric acid (*S*)-**XVIb** with Ph_2SiCl_2 *in situ* generates *O*-silylated BINOL-phosphate species (*S*)-**XVIb´** (as previously discussed in section 3.1). This silicon Lewis acid activates hydrazone **80** which might initially coordinate in mono- or bidentate fashion (in analogy to the original report of Leighton[45]). Additionally, a second BINOL-phosphate molecule (*S*)-**XVIb** is proposed to participate in the intermediate **I-1** with a dual role: the P=O moiety acting as a Lewis base and the P-OH group as a Brønsted acid. This intermediate undergoes 1,3-DC to form a second intermediate **I-2**, which finally releases the pyrazolidine product **82,** with regeneration of the catalysts (*S*)-**XVIb** and (*S*)-**XVIb´**.



Scheme 26. Mechanism proposed for the [3+2]-DC between *N*-acylhydrazones **80** and cyclopentadiene.

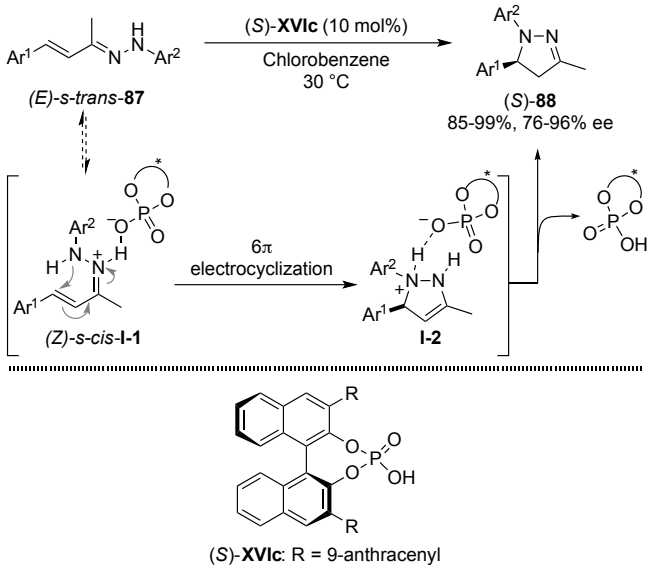
Alternatively, Rueping and co-workers exploited the superior Brønsted acidity and catalytic performance of *N*-triflylphosphoramides[47] to develop a more general and highly enantioselective 1,3-DC between various alkenes and *N*-benzoylhydrazones **80**. Under optimized conditions, *N*-triflylphosphoramide (*S*)-**XX** catalysed cycloadditions of **80** with cyclopentadiene **81** and α-methyl stirenes **83** to afford optically active pyrazolidine derivatives **82** and **84**, respectively (Scheme 27, example 1).[48] Later, the same group expanded the scope of this activation strategy and reported 1,3-DCs between aliphatic *N*-benzoylhydrazones **80** and vinyl (thio)ethers **85**, employing SPINOL-derived *N*-triflylphosphoramide (*S*)-**XXI** as the catalyst, to afford the pyrazolidine products **86** (Scheme 27, example 2).[49] Mechanistic studies suggest a plausible protonation of the hydrazone to form an hydrazonium-phosphoramide ion-pair complex which might act as a 'monopole' instead of a classical 1,3-dipole.



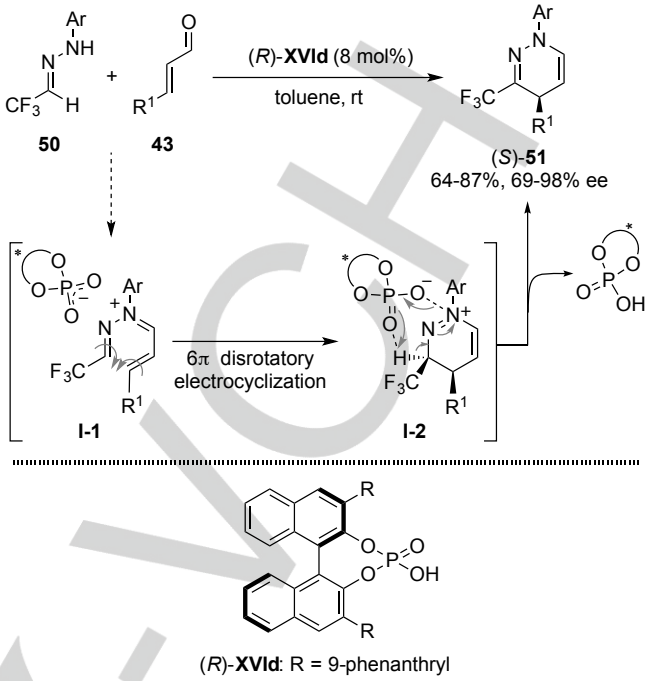
Scheme 27. Brønsted acid catalysed 1,3-DC between *N*-benzoylhydrazones **80** and alkenes.

4.2. Electrocyclizations of *N*-aryl hydrazones

Electrocyclizations are valuable tools for the synthesis of complex organic molecules. In such reactions, *N*-aryl hydrazones appear as useful substrates. In 2009, List and co-workers described a cycloisomerization process of α,β-unsaturated hydrazones.[50] Phosphoric acid (*S*)-**XVIc** efficiently catalysed the intramolecular cyclization of benzylideneacetone–derived *N*-arylhydrazones **87** to provide 2-pyrazoline products (*S*)-**88** in high yields and good enantioselectivities (Scheme 28). According to LC-MS experiments, a plausible mechanism starts with a phosphoric acid–catalysed *E/Z* isomerization of the α,β-unsaturated hydrazone leading to (*Z*)-**87** which, after adopting a *s*-cis conformation, is engaged in a chiral H-bond ion pair with the catalyst leading to intermediate **I-1**. This species undergo then a 6π electrocyclization to give a 3-pyrazoline intermediate **I-2**.[51] Subsequent isomerization and deprotonation yields the thermodynamically more stable 2-pyrazoline (*S*)-**88** with regeneration of the catalyst.



Scheme 28. Enantioselective synthesis of 2-pyrazolines (*S*)-**88** by 6π electrocyclizations of α,β-unsaturated hydrazones (*E*)-**87**.

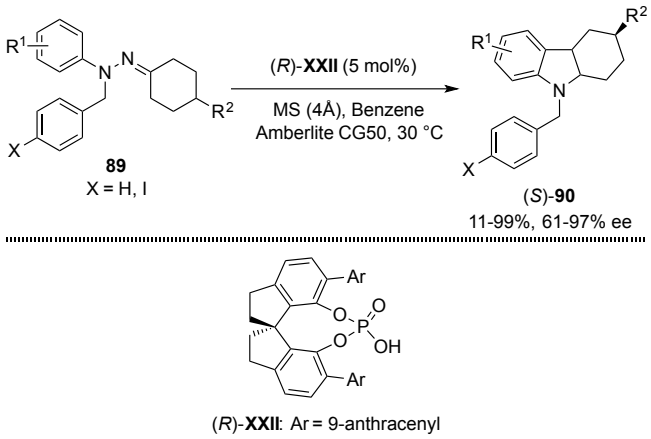


Scheme 29. Enantioselective synthesis of 1,4-dihydropyridazines (*S*)-**51** by 6π electrocyclizations involving trifluoromethylated *N*-aryl hydrazones **50** and enals.

Based on the reactions between trifluoromethylated *N*-arylhydrazones **50** and α,β-unsaturated aldehydes **43** (previously developed under aminocatalytic activation, section 2.5), Rueping and co-workers, performed a related phosphoric acid catalyzed strategy for the synthesis of 3-trifluoromethyl-1,4-dihydropyridazines (*S*)-**51** (Scheme 29).[52] For this system, a plausible mechanism based on NMR spectroscopy and ESI-MS measurements was proposed. First, a condensation between the *N*-arylhydrazone and the α,β-unsaturated aldehyde provides the chiral ion pair **I-1**, from which a 6π disrotatory electrocyclization results in the formation of a second intermediate **I-2**. The catalytic cycle is completed with a proton abstraction by the phosphate anion to release the heterocycle (*S*)-**51**, along with the phosphoric acid **XVId**.

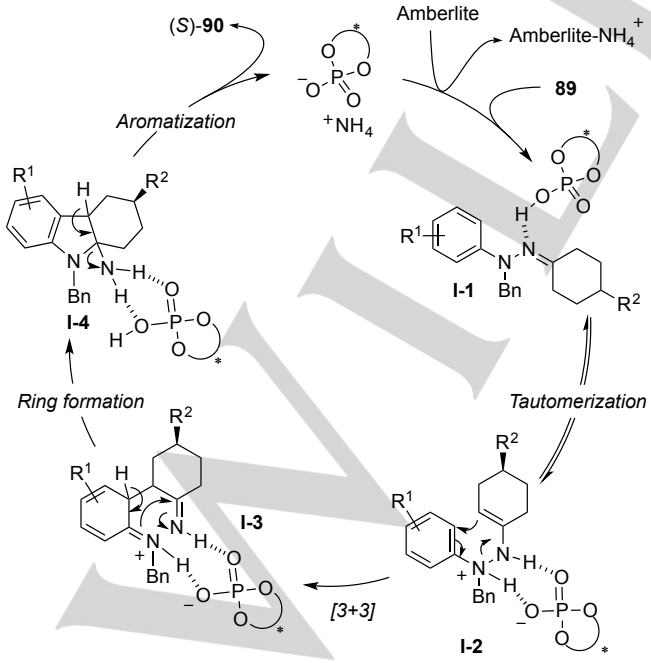
4.3. Fischer Indolization of cyclohexanone hydrazones

The Fischer indolization of phenylhydrazones, first reported over 125 years ago, is probably the most widely used procedure for the construction of indoles.[53] The development of the first catalytic enantioselective version of this reaction was a difficult task, due to the inherent poisoning of Brønsted acid catalysts by the ammonia formed during reaction, among other reasons. Remarkably, in 2011 List and co-workers identified a cation exchange resin for the efficient removal of ammonia from the reaction media, thereby increasing the turnover of phosphoric acid catalyst. Thus, the combination of a chiral (*R*)-SPINOL phosphoric acid (*R*)-**XXII** with Amberlite® CG50 resin was used to achieve highly enantioselective indolizations from 4-substituted cyclohexanone derived *N*-aryl *N*-benzyl hydrazones **89**, leading to 3-substituted tetrahydrocarbazoles (*S*)-**90** in moderate to good yields (Scheme 30).[54]



Scheme 30. First highly enantioselective Fischer Indolization catalysed by SPINOL-phosphate acid (*R*)-**XXII**.

In agreement with the accepted mechanism for Fischer indolization, the catalyst (*R*)-**XXII** is thought to facilitate a hydrazone-enehydrazine tautomerization (**I-1** to **I-2**, first step, Scheme 31). In this last intermediate **I-2**, different H-bond networks might be drawn. It´s proposed that one of the possible diastereomeric ion pairs undergoes the irreversible [3,3]-sigmatropic rearrangement faster (**I-2** to **I-3**), accounting for the observed asymmetric induction via a DKR process.[55] The intermediate **I-3** is a highly unstable double imine in which the aromaticity is immediately restored through a series of proton shifts and a C-N bond formation, yielding the product (*S*)-**90**, along with the ammonium salt of the catalyst. Finally, the active catalyst is regenerated by cation exchange by the resin.



Scheme 31. Proposed mechanism for the asymmetric phosphoric acid catalysed Fischer indolization of *N*-aryl *N*-benzyl hydrazones **89**.

Summary and Outlook

Hydrazones are ubiquitous reagents in organic synthesis that, according to the examples shown along this review, seem to be particularly well suited for organocatalytic activations which, in general, work under mild reaction conditions. Several well-designed types of hydrazones have been developed to discover new reaction profiles which include nucleophilic formylation/acylation or cyanation strategies, cascade reactions where hydrazones sequentially act as nucleophile and electrophile or cycloaddition/cyclization processes to access valuable multifunctional compounds and nitrogen-containing heterocycles thereof. In this Minireview article, successful examples employing hydrazone reagents in combination with diverse organocatalysts (H-bonding-, Brønsted acid-, secondary/primary amine-, NHC-catalysts, and others) have been summarized. Plausible interactions between reagents and (often multifunctional) organocatalysts, sometimes supported by experimental evidences, have been used to propose activation modes, mechanisms and stereochemical models constructed to explain the outcome of the analysed reactions. It can be anticipated that these discoveries will inspire the development of new organocatalysts and activation strategies resulting in new applications of hydrazone-based reagents showing their true potential in asymmetric synthesis.

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Keywords: Hydrazones • Asymmetric organocatalysis • H-bonding • Brønsted acid • Formylation/acylation • *N*-containing heterocycles

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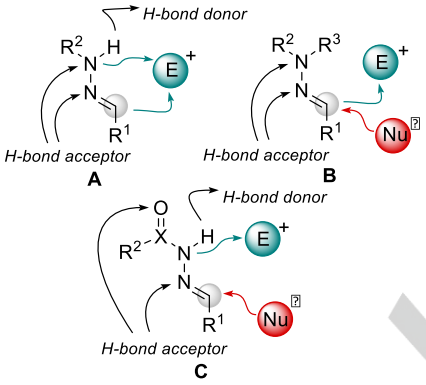
MINIREVIEW

This Minireview summarizes strategies and developments regarding the use of *N*-monoalkyl-, *N*,*N*-dialkyl- and *N*-acyl hydrazones as reagents in asymmetric organocatalysis. The key structural elements governing their reactivities, and their diverse activation modes with organocatalysts will be discussed. Finally, versatile tranformations to access numerous multifunctional compounds and nitrogen-containing heterocycles are shown.



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Hydrazones as singular reagents in asymmetric organocatalysis