1,3-Dipolar cycloadditions of azomethine imines

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Azomethine imines are considered 1,3-dipoles of the aza-allyl type which are transient intermediates and should be generated in situ but can also be stable and isolable compounds. They react with electron-rich and electron-poor olefins as well as with acetylenic compounds and allenoates mainly by a [3 + 2] cycloaddition but they can also take part in [3 + 3], [4 + 3], [3 + 2 + 2] and [5 + 3] with different dipolarophiles. These 1,3-dipolar cycloadditions (1,3-DC) can be performed not only under thermal or microwave conditions but also using metallo- and organocatalytic systems. In recent years enantiocatalyzed 1,3-dipolar cycloadditions have been widely considered and applied to the synthesis of a variety of dinitrogenated heterocycles with biological activity. Acyclic azomethine imines derived from mono and disubstituted hydrazones could be generated by prototropy under heating or by using Lewis or Brønsted acids to give, after [3 + 2] cycloadditions, pyrazolidines and pyrazolines. Cyclic azomethine imines, incorporating a C=N bond in a ring, such as isoquinolinium imides are the most widely used dipoles in normal and inverse-electron demand 1,3-DC allowing the synthesis of tetrahydro-, dihydro- and unsaturated pyrazolo[1,5-a]isoquinolines in racemic and enantioenriched forms with interesting biological activity. Pyridinium and quinolinium imides give the corresponding pyrazolopyridines and indazolo[3,2-a]isoquinolines, respectively. In the case of cyclic azomethine imines with an N=N bond incorporated into a ring, N-alkylidene-3-oxo-pyrazolidinium ylides are the most popular stable and isolated dipoles able to form dinitrogen-fused saturated and unsaturated pyrazolopyrazolones as racemic or enantioenriched compounds present in many pharmaceuticals, agrochemicals and other useful chemicals.

1 General introduction

Azomethine imines are 1,3-dipoles of the allyl type, which present two types of resonance structures, iminium imide and diazonium ylide.1–4 They are readily accessible as stable compounds or as intermediates for the synthesis of diverse dinitrogenated heterocycles by 1,3-dipolar cycloadditions (1,3-DC) under thermal or catalyzed conditions.2–12 Numerous types of pharmaceuticals, agrochemicals and other biologically active compounds can be prepared by different types of [3 + 2] cycloadditions, mainly with alkenes and alkynes, but also higher order cycloadditions, such as [3 + 3], [4 + 3] and [3 + 2 + 2], have been recently developed. The asymmetric processes have been performed using chiral substrates, chiral metal complexes or organocatalysts.13–15 In this review we have summarized the diverse types of azomethine imines (Scheme 1) which have been used as 1,3-dipoles in the last ten years, not only in racemic, but also in asymmetric processes. They have been classified according to Schantl’s review10 covering the literature until 2003.

2 Acyclic azomethine imines

These types of dipoles have been postulated as intermediates in [3 + 2] cycloaddition reactions and are derived from hydrazones and carbazates (Scheme 1) leading to pyrazolines and pyrazolidines, and their derivatives. The corresponding precursors can be prepared from monosubstituted and 1,2-disubstituted hydrazines.

2.1 Monosubstituted hydrazines

Azomethine imines derived from acyclic hydrazones are generated easily upon 1,2-protonation either under heating by Lewis acid catalysis or by protonation, and can be trapped with different dipolarophiles to afford five-membered dinitrogenated heterocycles through inter- and intramolecular cycloadditions.16–19 Normally, electron-deficient dipolarophiles are used, but also simple alkenes in the case of intramolecular processes.10 A recent intramolecular process has been applied to the synthesis of androstenoarylpyrazolines using BF3·OEt2 as a Lewis acid, previously used for intermolecular cycloadditions (Scheme 2).20 The reaction takes place stereoselectively at 0 °C in high yields from the corresponding hydrazones 1 by a BF3-promoted formation of intermediate azomethine imines 2.
Three-component or consecutive intermolecular 1,3-DC of azomethine imines with α-oxoketenes 5 has been performed under thermal conditions. Both hydrazones and dipolarophiles are generated in situ, affording the corresponding pyrazolidinones 6 in a stereoselective manner (Scheme 3). Intermediate dipolarophiles 5 are generated from 2-diazo-1,3-diones 4 under microwave heating. When isatins are used as a carbonyl precursor the corresponding spirooxindoles 7 are obtained in a stereoselective manner (Scheme 3).

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Recently, a microwave-assisted intramolecular 1,3-DC of azomethine imines, \textit{in situ} generated from indole-2-carboxaldehydes and phenylhydrazine, has been described. This process takes place in the presence of HCl as an additive in ethanol, providing \( \alpha \)-annelated pyrazolopyrroloindoles in a regio- and stereoselective manner (Scheme 4).\(^{21b}\) The reaction in the presence of other additives such as AcOH, BF\(_3\)·OEt\(_2\) or iodine gave either lower yields or no reaction.

The stereocontrolled synthesis of \textit{cis}-cyclopentanopyrazolidines has been carried out from the \( \alpha \)-methoxy-\( \alpha \),\( \beta \)-unsaturated ester bearing an \( \alpha \)-keto ester at the end of the chain (Scheme 5).\(^{22}\) In the case when thiosemicarbazide is used, the intermediate azomethine imine is generated under heating, giving the tricyclic thiohydantoin. \( N \)-Acyl or \( N \)-alkoxycarbonyl hydrazines gave, under thermal conditions, the corresponding cycloadducts in good yields (Scheme 5). This approach was previously described by the same group to prepare potential precursors of palau’amine (Scheme 6).\(^{23}\)

The high stereoselectivity observed in these cycloadditions can be explained by the formation of a chair-like transition state, which favors the overlap between the \( \pi \)-orbitals of the dipole and dipolarophile (Scheme 7).

Alternatively, it was possible to prepare the corresponding hydrazones from using a catalytic amount of HCl in

\[ \text{Scheme 3} \quad \text{1,3-DC of hydrazones with \( \alpha \)-oxoketenes.} \]

\[ \text{Miguel Yus was born in Saragossa in 1947 and received his BSc (1969), MSc (1971) and PhD (1973) from the University of Saragossa. After spending two years as a postdoctoral fellow at the Max Planck Institut in Mülheim he became Associate Professor (1977) and Professor (1987) at the University of Oviedo. In 1988 he moved to his current position at the University of Alicante. He has been an invited professor at ETH-Zürich, Oxford, Harvard, Uppsala, Tucson, Okayama, Paris, Strasbourg, Bologna, Sassari, Tokyo and Kyoto. Dr Yus has authored more than 500 papers and five patents, has delivered around 200 lectures abroad and has supervised more than 60 PhD students. Among others he has received the Spanish-French Prize (1999), twice the Japan Society for the Promotion of Science Prize (2000, 2007), the Stiefvater Memorial Lectureship Award (2001), the Conference Lawrence-Madina-watia (1912), the Serratusa Lectureship (2010) and the Medalla Felix Serratusa (2012), as well as Academician of the European Academy of Sciences and Arts (2012). He has been in the Advisory Board of about 20 international journals and he founded ten years ago the company MEDALCHEMY for the commercialization of fine chemicals.} \]

\[ \text{Scheme 4} \quad \text{Synthesis of pyrazolopyrroloindoles by intramolecular 1,3-DC.} \]

\[ \text{Scheme 5} \quad \text{Synthesis of \textit{cis}-cyclopentanopyrazolidines by intramolecular 1,3-DC.} \]
ethanol at room temperature, and then the 1,3-DC takes place at ambient temperature in the presence of one equivalent of FeCl₃ in dichloromethane, giving products 12 in good yields (Scheme 8).

The first example of a catalytic asymmetric intramolecular [3 + 2] cycloaddition of hydrazones with olefins was performed in the presence of a chiral zirconium catalyst. Different 4-nitrobenzoylhydrazones 17 gave trans-pyrazolidines 18 with high diastereo- and enantioselectivity in the presence of Zr(Oi-Pr)₄ (10 mol%) and the Binol derivative 19 at room temperature in dichloromethane (Scheme 9).

The same chiral catalyst formed by Zr(Oi-Pr)₄ and Binol 19 has been used in the intermolecular [3 + 2] cycloaddition of benzoylhydrazones 20 and electron-rich alkenes like the ketene dimethyl dithioacetal 21. The corresponding 3,5-disubstituted pyrazolidines 22 were obtained in good yields and enantioselectivities (Scheme 10). In the case of vinyl ethers or thioethers 23, compounds 24 were obtained in low to moderate diastereoselectivity and high enantioselectivity. Samarium diiodide reduction of 24 afforded the corresponding 1,3-diamines, whereas LiAlH₄ gave pyrazolidines.

A chiral silicon Lewis acid has been used in the intermolecular 1,3-DC of benzoylhydrazones 20 with vinyl ethers 23 (Scheme 11). The process needs 1.5 equivalents of compound 25, derived from pseudoephedrine, to take place, giving the corresponding pyrazolidines 24 at room temperature in...
high trans-diastereoselectivity and excellent ee. The intermediacy of complex 26, isolated and characterized by X-ray crystallography, explains the approach of the ether by the Si face of the hydrazone (27). Samarium diiodide reduction of pyrazolidines 22 gave the corresponding anti-1,3-diamines.

Hydrazones derived from ethyl glyoxylate and aliphatic or aromatic aldehydes react with cyclopentadiene (28) at room temperature in the presence of TMSOTf (10 mol%) as a catalyst. The enantioselective process was next assayed with an in situ generated Binol-phosphate derived silicon Lewis acid from 30 and Ph₂SiCl₂ (Scheme 12). Cycloadduct 29 was obtained in a high syn/anti diastereomeric ratio (95 : 5) and up to 89% ee, but in a low yield (13%).

The asymmetric Bronsted acid catalyzed 1,3-DC of benzoylhydrazones 20 could be efficiently performed with cyclopentadiene (28) and α-methylstyrenes 31 as dipolarophiles (Scheme 13). Different Binol-derived phosphoric acids (pKa 13–14 in acetonitrile) were initially assayed as organocatalysts giving very low yields. However, the more acidic [H8]-Binol-based N-trifluorophosphoramides 33 (pKa 6–7 in acetonitrile) gave pyrazolidines 29 and 32, respectively, in high yields and enantioselectivities. Cycloadducts 29 were isolated mainly as cis-diastereomers, whereas α-methylstyrene adducts 32 were obtained as single diastereomers. The cycloaddition product 29 with R = t-Bu was transformed by SmI₂ reduction into a 1,3-diamine with a core structure similar to that of the influenza drug peramivir. By the oxidation of cycloadduct 32 (R = t-Bu) with copper(II) chloride the corresponding pyrazoline was obtained maintaining the ee value.

However, for the [3 + 2] cycloaddition of N-benzylohydrazones 20 with ethyl vinyl ether 23 (R² = Et) the [H8]-Binol derived N-triflylphosphoramide 34 was the optimized catalyst. The corresponding cis-pyrazolidines 24 (XR² = OEt) were obtained in good yields and enantioselectivities (Scheme 14). However, for the cycloaddition with ethyl vinyl thiether 23 (XR² = SEt) the Spinol-derived N-triflylphosphoramide 35 was the best organocatalyst affording pyrazolidines 24 (XR² = SEt) in good yields, diastereo- and enantioselectivities.

The mechanism of N-triflylphosphoramide-catalyzed asymmetric [3 + 2] cycloadditions was explored using DFT (MO6-2X) calculations. Protonation of hydrazones 20 by these Bronsted acids produces ion-pair complexes, which are more reactive than those formed from azomethine imines by 1,2-prototropy of the hydrazone through the transition state I (Scheme 15). These ion-pair hydrazonium–phosphoramide anions are reactive in [3⁺ + 2] cycloadditions and only small distortions of them are required in the transition state II giving in this case the cis-pyrazolidines 24. The origin of enantioselectivities was also explained.
2.2 1,2-Disubstituted hydrazines

The condensation of 1,2-disubstituted hydrazines and N-substituted carbazates or hydrazides with carbonyl compounds generates in situ directly the corresponding acyclic azomethine imines,\(^3\) which can be trapped in situ by dipolarophiles through an inter- or intramolecular [3 + 2] cycloaddition.\(^1\) In this case, they react preferentially with electron-deficient dipolarophiles under thermal conditions.

Intermolecular 1,3-DC of azomethine imines 37, generated in situ from aldehydes and \(N^1\)-alkyl-\(N^2\)-acyl hydrazines 36, takes place with electron-deficient dipolarophiles under refluxing toluene using a Dean–Stark trap (Scheme 16).\(^3\) The corresponding 3,4-disubstituted pyrazolidines 38–40, derived from

Scheme 12 First catalytic asymmetric 1,3-DC of hydrazones 20 with cyclopentadiene.

Scheme 13 Chiral N-tritylphosphoramidate-catalyzed 1,3-DC of \(N\)-benzoylhydrazones 20.
benzaldehyde, were obtained as a mixture of cis/trans diastereomers in low yields.

The first and only example of an enantiocatalytic three-component 1,3-DC of aldehydes, hydrazides and alkynes was performed using a PyBox 45/Cu(I) complex as a catalyst and a chiral binaphthyl dicarboxylic acid 46 as a cocatalyst (Scheme 17).35 N1-Benzylbenzoylhydrazide 41 was used for the generation of the corresponding azomethine imine intermediates 42, which react with terminal alkynes affording pyrazolines 43 in a chemoselective manner (>95 : 5); only small amounts of compounds 44 resulting from the nucleophilic addition of copper acetylide to 42 were also obtained. Aromatic and aliphatic aldehydes can be used in the presence of 4 Å MS to eliminate the water formed during the condensation step. Moreover, aromatic and aliphatic alkynes can be used as well, affording the corresponding pyrazolines 43 in high enantioselectivities (Scheme 17).

A representative 3,4-disubstituted pyrazoline 43a (with R1 = R2 = Ph) was further transformed into different heterocyclic compounds 47 and 48, as well as the diamine 49 by reduction of the last one with samarium diiodide (Scheme 18).
3 Cyclic azomethine imines incorporating C–N in the ring

Several types of heterocyclic systems with the C–N double bond incorporated into a ring constitute a subclass of azomethine imines (Scheme 1). These types of dipoles have been extensively studied for the synthesis of different ring-fused pyrazolidines, pyrazolines, and pyrazoles.

3.1 Heterocyclic hydrazone derived azomethine imines

Few examples have been described of using heterocyclic azomethine imines mainly in intramolecular processes. Hetero-
cyclic azomethine imines of the type 51 can be prepared from the corresponding aldehydes 50 bearing a halogen atom at the γ- or δ-position. A cascade of cyclization and 1,3-DC gave all-cis tricyclic compounds 52 in high yields (Scheme 19).16

Azomethine imines 54 can be prepared by MW heating of benzoylhydrazides 53 bearing an alkyne in the chain through an intramolecular hydroamination reaction (Scheme 20).17 The reactivity of one example 54a with methyl acetylenedicarboxylate gave the fused pyrazoline 55 in a moderate yield.

### 3.2 Isoquinolinium-N-aryl imides

N-Iminoisooquinolin-2-ium ylides 57 are the most recently used cyclic azomethine imines bearing a C–N bond in the ring.10 They have been mainly used in metal-catalyzed [3 + 2] cycloadditions not only with electron-deficient dipolarophiles but also with electron-rich alkenes. In addition, organocatalyzed processes, including asymmetric ones, have also been studied. A direct method to access this type of intermediate is the cascade cyclization reaction of the aldehyde 56 with hydrazines to afford azomethine imines 57,38 which can be trapped in situ with N-phenylmaleimide (NPM) (Scheme 21).36 Cycloadducts 58 were obtained as mixtures of endo:exo diastereomers (2 : 1–3 : 1). The reaction of the aldehyde 56 with benzylhydrazine in the presence of dimethyl maleate gave the cycloadduct 59 with all-cis relative configuration. The same 3 : 1 mixture of cycloadducts 60 was obtained by a reaction of the aldehyde 56 with hydrazine hydrate in the presence of dimethyl maleate or fumarate. In the case of dimethyl acetylenedicarboxylate a 5 : 1 mixture of diastereomeric fused pyrazolines 61 was isolated under toluene reflux (Scheme 21).

Already prepared C,N-cyclic azomethine imines 57 (with R = Bz) were used for the first time as dipoles in enantiocatalyzed [3 + 2] cycloadditions using enals 62 as dipolarophiles and titanium binate complexes as catalysts (Scheme 22).38 The 2 : 1 (S)-Binol/Ti(Oi-Pr)₄ complex gave at 0 °C the corresponding exo-cycloadducts 63 in high yields, diastereo-, and enantioselectivities. Structurally related C,N-cyclic azomethine imines 65 were prepared in situ from 64 under basic conditions using 2,6-di-tert-butyl-4-methylpyridine (DTMP) as a base compatible with the Lewis acid as a catalyst. The resulting cycloadducts 66 were obtained mainly as exo-adducts with β-substituted enals (62, R₂ = H), whereas β-unsubstituted enals (62, R₃ = H) gave mainly endo-cycloadducts 67 (Scheme 22).

Samarium diiodide-mediated N–N cleavage of the adduct 66a (with R² = R₃ = H, R₁ = Me) gave the tetrahydroisoquinoline 68 (Scheme 23).38 The same type of metal-catalyzed 1,3-DC of the azomethine imine 57 with unsaturated nitriles 69 was performed using a dicationic nickel(II) complex containing bis[(R)-1-[(Sₚ)-2-(di-phenylphosphino)ferrocenyl]ethyl]cyclohexylphosphine [(R,Rₚ)-Pigiphos] 71 as the catalyst (Scheme 24).39 The [3 + 2] cycloaddition gave compounds 70 mainly as the endo-diastereomer in good yields and enantioselectivities.
Asymmetric inverse-electron-demand 1,3-DC of C,N-cyclic azomethine imines 57 with tert-butyl vinyl ether could be performed firstly with the chiral dicarboxylic acid 74 as a Bronsted acid (Scheme 25).\(^{40}\) The corresponding adducts 72 were obtained with different regioselectivities by interaction of the LUMO of the dipole with the HOMO of the alkene. Moreover, \textit{exo}-cycloaducts 72 were obtained in high yields and enantioselectivities. Vinylogous aza-enamines gave mainly \textit{exo}-cycloaducts 73 in high yields and good enantioselectivities. The hydrazone unit of compound 73 (with \(R^1 = \text{Br}, R^2 = \text{H}\)) was

Scheme 21 Cascade cyclization 1,3-DC of hydrazines derived from 56.

Scheme 22 Enantiocatalyzed 1,3-DC of C,N-cyclic azomethine imines with enals.

Scheme 23 Reductive N–N bond cleavage of compound 66a.

Scheme 24 Ni-Pigiphos-catalyzed 1,3-DC of C,N-cyclic azomethine imines 57 with unsaturated nitriles.
transformed into the corresponding cyano group by magnesium monoperoxyphthalate in 80% yield.

The thermal [3 + 2] cycloaddition reaction of azomethine imines 57 with α-substituted allenoates 75 occurs under mild reaction conditions to provide adducts 76 as a mixture of diastereomers in a highly regioselective manner (Scheme 26).41 The major endo-diastereomer could be separated and isolated by flash chromatography or recrystallization. In the case of γ-substituted allenoates 77 the 1,3-DC takes place in lower yields giving mainly exo-cycloadducts 78.

When the same 1,3-DC was carried out in the presence of a trialkyl phosphine as a catalyst (20 mol%) two different reaction pathways, [3 + 2] and [4 + 3] cyclizations depending on the phosphine and the allenoate were observed. In the case of α-alkyl substituted allenoates, only [3 + 2] cycloaddition products 79 were obtained independently of the phosphine used (Scheme 27).42 However, α-benzyl substituted allenoates gave mainly the diazepine derivatives 80 through a [4 + 3] cycloaddition.

Scheme 25 Organocatalyzed asymmetric 1,3-DC of cyclic azomethine imine 57 with electron-rich alkenes.

Scheme 26 Thermal [3 + 2] cycloaddition of azomethine imines 57 with allenoates.
However, when \( \gamma \)-substituted allenates 77 were used as dipolarophiles the phosphine-catalyzed 1,3-DC with azomethine imines 57 gave the \([3 + 2]\) cycloaddition. This process has been carried out with the ferrocenyl diphosphine 82 as a chiral catalyst affording tetrahydroisoquinoline derivatives 81 in good yields, high \( \text{exo} \)-diastereoselectivities and moderate to high enantioselectivities (Scheme 28).43

Based on previous experiments about the formation of phosphonium-inner salts by reaction of allenoates with phosphines,44–46 the zwitterionic intermediates 83 and 84 were proposed. Intermediate 84 underwent \( \delta \)-addition to the azomethine imine 57 to give 85 (Scheme 29).43 Intramolecular Michael addition gave 86, which after [1,2] proton transfer afforded intermediate 87. Final elimination of the phosphine catalyst yielded the cycloadduct 81.

Triflyl alkynes 88 gave 1,3-DC by a reaction with azomethine imines 57 at room temperature, and after oxidative aromatization, pyrazolosiquinoline triflones 89 were regioselectively obtained (Scheme 30).47

A \([4 + 3]\) cycloaddition has been observed when 1,2-diaza-1,3-dienes 91, generated \textit{in situ} from the corresponding \( \alpha \)-halo hydrazones 90, are allowed to react with C,N-cyclic azomethine imines 57 (Scheme 31).48 These 1,2-diaza-1,3-dienes 91 behave differently compared to azaenamines, which gave \([3 + 2]\) cycloaddition with 57 (Scheme 25).46 In this case, an unprecedented \([4 + 3]\) cycloaddition afforded highly functionalized 1,2,4,5-tetrazepine derivatives 92, which were obtained under mild reaction conditions.

In the case of isocyanides 93 these azomethine imines 57 experimented a \([5 + 1]\) cycloaddition at room temperature leading to the corresponding imino-1,3,4-oxadiazin-6-one derivatives 94 in high yields (Scheme 32).49 Related C,N-cyclic azomethine imine 64 not fused to the aromatic ring also gave this \([5 + 1]\) cycloaddition with tert-butyl isocyanide in the presence of DTBMP as a base, affording product 95 (Scheme 32).

Amine-catalyzed enantioselective \([3 + 2]\) cycloadditions of aldehydes with azomethine imines 57 led to the formation of adducts 97 (Scheme 33).50 Intermediate enamines formed with the chiral prolinol silyl ether 99 gave intermediate products 96, which after water attack afforded compounds 97. These hemiaminals were reduced \textit{in situ} with sodium borohydride to 1-substituted tetrahydroisoquinolines 98 in high diastereo- and enantioselectivities.

The same group performed an enantioselective 1,3-DC using an intermediate dienamine 57 and enals (\( R_2 = \text{aryl} \)) and a silylated prolinol 102 as an organocatalyst. By the subsequent reduction of the aldehyde functionality the corresponding alcohols 100 were isolated in good yields, diastreo- and enantioselectivities (Scheme 34).51 However, when aliphatic enals (\( R_2 = \text{alkyl} \)) were used, regioisomeric derivatives 101 were obtained according to the formation of \( \alpha,\beta \)-unsaturated

![Scheme 27](organic-biomolecular-chemistry.org/10.1039/c5ob00261d/schemes/12.png)

**Scheme 27** Phosphine-catalyzed \([3 + 2]\) versus \([4 + 3]\) cycloadditions of azomethine imines 57 with allenoates 75.

![Scheme 28](organic-biomolecular-chemistry.org/10.1039/c5ob00261d/schemes/13.png)

**Scheme 28** Enantiocatalyzed \([3 + 2]\) cycloaddition of azomethine imines 57 with \( \gamma \)-substituted allenates 77 by the chiral phosphine 82.
iminium ions as intermediates. Similar iminium–dienamine reactivity has been reported independently with prolinols\(^99\) and\(^102\) by Alemán and Fraile.\(^{52}\)

A new type of 1,3-DC has been recently performed with azo-methine imines\(^{57}\) and \(N\)-acyliminium ions\(^{105}\) affording cycloadducts\(^103\) (Scheme 35).\(^{53}\) The chiral Lewis base\(^{104}\) acted as an organocatalyst forming the corresponding activated intermediates\(^{105}\) by reaction with mixed anhydrides.

Another family of isoquinolinium ylides are the corresponding unsaturated systems which should be prepared \textit{in situ} in two- or three-component reactions. Thus, \(N\)-\{2-alkynylbenzylidene\}hydrazides\(^{106}\) react with bromine and \(\alpha,\beta\)-unsaturated ketones \textit{via} a three-component reaction to afford either 6-bromo-4\(H\)-pyrazolo[5,1-\(a\)]isoquinolines\(^{108}\) in NMP at 70 °C in the presence of DABCO as a base, or 6-bromo-1,2,3-10b-tetrahydropyrazolo[5,1-\(a\)]isoquinolines\(^{109}\) in DMAC at room temperature in the presence of potassium phosphate as a base (Scheme 36).\(^{54}\) These processes took place by a bromine-pro-
moted 6-endo-cyclization to give the isoquinolinium-2-yl amide 107 followed by a [3 + 2] cycloaddition with the α,β-unsaturated carbonyl compound followed by aromatization. The same group has shown that H-pyrazolo[5,1-a]isoquinolines present promising activity as protein tyrosine phosphatase inhibitors.

When the former process was carried out with 2-alkynyl benzaldehydes 110, p-toluenesulfonyl hydrazide and unsaturated carbonyl compounds in the presence of bromine or iodine, the multicomponent reaction afforded isoquinolines 108 with alkyl groups at the 1 and 5 positions. A similar process has been performed using AgOTf as a catalyst, which after a 6-endo-dig cyclization produced the isoquinolinium-2-yl imide 111. The three-component reaction between 2-alkynyl

Scheme 33  [3 + 2] Cycloaddition of azomethine imines 57 and aldehydes organocatalyzed by the chiral silylated prolinol 99.

Scheme 34  [3 + 2] Cycloaddition of compound 57 with enals organocatalyzed by the chiral silylated prolinol 102.

Scheme 35  1,3-DC of compounds 57 with mixed anhydrides catalyzed by a chiral Lewis base 104.

Scheme 36  Three-component reaction of hydrazides 106 with bromine and enones.
benzaldehydes 110, tosyl hydrazide and α,β-unsaturated carboxyl compounds gave functionalized H-pyrazolo[5,1-a]isoquinoline-1-carboxylates 112 (Scheme 37).56

When an acetylenic dipolarophile is used, only a halogen or silver triflate promotes the [3 + 2] cycloaddition. Thus, N′-(2-alkynylbenzylidene)hydrazides 106 react with acetylenes either catalyzed by silver triflate or promoted by bromine or iodine in the presence of NaOAc. In the case of dimethyl acetylenedicarboxylate (DMAD) in the presence of either AgOTf or bromine the fused dihydroisoquinolines undergo a rearrangement involving an N–N homolysis to give compounds 113 or 114, respectively (Scheme 38).57 However, in the presence of iodine the fused 1,2-dihydroisoquinolines 115 are obtained.

The same process in the presence of terminal acetylenes gave the H-pyrazolo[5,1-a]isoquinolines 116 (X = H) in the case of AgOTf or 116 (X = Br, I) first by a bromine or iodine promoted cyclization followed by a silver-catalyzed nucleophilic addition of the acetylide to give the isoquinolinium-2-yl imide of the type 117 (Scheme 39). However, when this process is carried out in the presence of tosyl azide with silver triflate and copper(i) bromide as a cocatalyst, 5-sulfonylaminesubstituted isoquinolines 117 were obtained (Scheme 39).59

N- Allyl ynamides reacted with N′-(2-alkynylbenzylidene) hydrazides 106 in a process catalyzed by silver triflate and palladium acetate generating 2-amino-H-pyrazolo[5,1-a]isoquinolines 118 in good yields (Scheme 40).60 In this case, the [3 + 2] cycloaddition takes place after the silver-promoted cyclization to give azomethine imines 111, with ynamido-palladium π-allyl complexes 119 affording intermediates 120. Subsequently, an intramolecular [3,3]-sigmatropic rearrangement produces compound 121, which undergoes aromatization releasing a tosyl group.

An alternative route to pyrazoloisoquinolines 116 (X = H) used bromoalkynes as dipolarophiles. In this case, the alknylation of 111, formed by the silver-catalyzed cyclization of 106, takes place by a C–H activation. The bromoalkyne is activated via oxidative addition to CuI, which through a concerted metallation-deprotonation process would give intermediates 122. After reductive elimination, intermediates 123 undergo a 5-endo-dig-cyclization to give 124, followed by subsequent aromatization to form the final H-pyrazolo[5,1-a]isoquinolines 116 (Scheme 41).61

2-Trifluoromethylpyrazolo[5,1-a]isoquinolines 125 can be prepared from N′-(2-alkynylbenzylidene) hydrazides 106 and ethyl 4,4,4-trifluorobut-2-ynoate by means of the tandem silver triflate catalyzed cyclization and [3 + 2] cycloaddition of the

Scheme 37 Silver triflate-catalyzed three-component reaction of 2-alkynyl benzaldehydes 110, tosyl hydrazide and α,β-unsaturated esters.

Scheme 38 Reaction of hydrazones 106 with dimethyl acetylenedicarboxylate.
corresponding N-iminoisoquinolinium ylides 111 (Scheme 42).62

In the case of the silver triflate-catalyzed cyclization of compounds 106 in the presence of the in situ generated pyridyne 127 from 126, the corresponding regioisomeric H-pyrazolo[5,1-a]-isoquinolines 128 and 129 were prepared in modest yields (Scheme 43).63a Polyfluoroarenes react with N’-(2-alkynylbenzylidene) hydrazide 106 catalyzed by silver triflate in the presence of cesium carbonate leading to polyfluoroaryl-fused H-pyrazolo-[5,1-a]isoquinolines in good yields.63b Recently, the three-component reaction of aldehydes 110, sulfonyl hydrazide and benzyne, affording the corresponding H-pyrazolo[5,1-a]isoquinolines in very good yields (83–98%), has been described.63c

Propargyl amines afford [3 + 2] cycloadditions with N-iminoisoquinolinium ylides 111 generated in situ from hydrazides 106, to give the corresponding H-pyrazolo[5,1-a]isoquinolines 130 bearing an aminomethyl substituent at the 5-position (Scheme 44).64

Silyl enol ethers have been used as dipolarophiles with N-iminoisoquinolinium ylides 111, generated in situ from hydrazides 106. Thus, the tandem process affords the 5,6-disubstituted H-pyrazolo[5,1-a]isoquinolines 131 in good yields (Scheme 45).65

The multicomponent reaction of 2-alkynyl benzaldehydes 110, tosyl hydrazide, methanol and α,β-unsaturated aldehydes catalyzed by silver triflate gave H-pyrazolo[5,1-a]isoquinolines 132 with excellent regioselectivity (Scheme 46).66 Preliminary biological assays of these compounds show their promising activity as CDC25B, TC-PTP, and PTP1B inhibitors.
Scheme 41 Reaction of N-iminoisoquinolinium ylides 111 with bromoalkynes.

Scheme 42 Synthesis of compounds 125 by a [3 + 2] cycloaddition of N-iminoisoquinolinium ylides 111.

Scheme 43 Reaction of compound 106 with pyridyne 127.

Scheme 44 Synthesis of compounds 130 from propargyl amines.
Similarly, the bromine-promoted cyclization of hydrazides 106 afforded the brominated N-iminoisoquinolinium ylides 107, which also react with α,β-unsaturated aldehydes in the presence of methanol to give the fused brominated isoquino-
lines 133 (Scheme 47).

Based on the former methods for the in situ generation of isoquinolinium-2-yl imides 134, these azomethine imines have been recently prepared and isolated by the one-pot reaction of 2-alkynyl benzaldehydes 110, hydrazides and final silver triflate catalyzed cyclization (Scheme 48).

A silver-catalyzed process involving 2-alkynyl benzaldehydes 110, tosyl hydrazide and carbonyl compounds is a simple and direct strategy for the synthesis of H-pyrazolo[5,1-a]isoquinolines 135 (Scheme 49).

Alternatively, by using primary alcohols and hydrazides 106 instead of aldehydes 110, the presence of the Dess–Martin reagent (DMP) as an oxidant is compulsory to afford 6-monosubstituted H-pyrazolo[5,1-a]isoquinolines 135 (Scheme 50).

The same transformation can be performed by a silver triflate–palladium chloride cooperative catalysis. The presence of oxygen promotes the palladium-catalyzed oxidation of the alcohol to the corresponding aldehyde or ketone. The in situ generated enolate attacks the isoquinolinium-2-yl imide, followed by condensation and aromatization to afford products 135 in 47–90% yield.

Silver triflate–copper(II) acetate cooperative catalysis has been used for the cyclization/[3 + 2] cycloaddition of N’-(2-alkynylbenzylidene) hydrazides 106 with allenotes 77 in the presence of dioxygen to afford H-pyrazolo[5,1-a]isoquinolines 136 (Scheme 51). The proposed mechanism involves a peroxy-copper(III) intermediate 138, which evolves to 139 and, after elimination of Cu(II)–OH, generates a carbonyl compound 140. Final aromatization yielded products 136 in moderate to good yields. When this reaction was performed with Ph3P as a catalyst the corresponding isoquinolines 136 were obtained with an R3CH2 group instead of the ketone functionality.

Silver–rhodium(I) cooperative catalysis has been used for the reaction of hydrazides 106 with cycloprop-2-ene-1,1-dicarboxylate72 or with 2-vinyloxirane73 for the synthesis of the corresponding H-pyrazolo[5,1-a]isoquinolines 141 or 142, respectively (Scheme 52). The use of the Wilkinson catalyst is crucial for the [3 + 2] cycloaddition.

When silver triflate and copper(II) chloride are used as cooperative catalysts it is possible to prepare H-pyrazolo[5,1-a]-isoquinolines 135 through a three-component process. Thus, 2-alkynyl benzaldehydes, tosyl hydrazide and tertiary amines in air gave products 135 by a silver-catalyzed cyclization and

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**Scheme 45** Reaction of hydrazides with silyl enol ethers.

**Scheme 46** Synthesis of compounds 132 from 2-alkynyl benzaldehydes 110.

**Scheme 47** Bromine promoted cyclization of hydrazides 106 and [3 + 2] cycloaddition with α,β-unsaturated aldehydes.

**Scheme 48** Synthesis of isoquinolinium-2-yl imides 134.
copper(II)-catalyzed oxidation of an aliphatic C–H bond of the tertiary amine in air (Scheme 53). A related process using palladium dibromide as a cocatalyst gave isoquinolines 131, which has been performed starting from the hydrazides 106 instead of aldehydes 110 (Scheme 53). The same transformation has been previously performed using Fe2(CO)9 as a co-catalyst (5 mol%) and tert-butyl hydroperoxide (3 equiv.) affording products 135 in 46–83% yields.

Methylene indolinones have been used as dipolarophiles for the diastereoselective construction of fused H-pyrazolo[3,2-a]isoquinolines 143 as a mixture of diastereomers (Scheme 54). In this case, the Wu et al. methodology was applied to a process starting from N′-(alkynylbenzylidene) hydrazides 106 under silver-catalyzed 6-endo cyclization to generate the N-iminoisoquinolinium ylide 111.

In general, these unsaturated isoquinolinium imides have been mainly used in [3 + 2] cycloaddition with acetylenic dipolarophiles. The only example of a [3 + 3] cycloaddition of azomethine imines 144 has been performed using cyclopropane diesters and a Ni(ClO4)2 complex with trisoxazoline derivatives 146 as a chiral ligand. This process allows the preparation of 6,6,6-tricyclic dihydroisoquinoline derivatives 145, in general with high diastereo- and enantioselectivities (Scheme 55). This reaction is based on the non-asymmetric example described previously by Charette et al. with N-benzoyliminoisoquinolinium ylide and methyl 2-phenylcyclopropane-1,1-dicarboxylate catalyzed by Ni(ClO4)2 in a modest yield (21%).

3.3 Pyridinium and quinolinium imides

Pyridinium imides 147, also called N-iminopyridinium ylides or pyridin-N-imines, are masked cyclic azomethine imines incorporating C–N into the ring, which react mainly with acetylenic dipolarophiles. They are unstable and have to be generated in situ from N-aminopyridinium halides and since the
The aromaticity of pyridine is broken after the cycloaddition, they have to be oxidized to give the desired product. A greater stability can be achieved by introducing an electron-withdrawing group such as acyl, alkoxycarbonyl, or sulfonyl to a ylide. N-Benzoyliminopyridinium ylides have been the most used imines of this family. They can be prepared by benzoylation of the corresponding N-aminopyridinium salts easily accessible by direct N-amination of pyridine using hydroxylamine-O-sulfonic acid. Alternatively, N-aminopyridinium salts can be prepared using different electrophilic amination reagents, especially efficient being O-(2,4-dinitrophenyl) hydroxylamine, which gave good yields with...
several types of substituted pyridines, quinolines and isoquinolines.82

By using alkynes as dipolarophiles pyrazolopyridines can be prepared83 which exhibit a wide range of biological activities including dopamine D3 receptor antagonist and partial agonist,84 dopamine D4 antagonist,85 as well as adenosine A1 receptor antagonist,86 and antihypernergic87 and antiherpetic88 properties. Consequently, they are applicable in the treatment of neurological disorders such as schizophrenia, attention-deficit disorder, and Parkinson’s disease.

Polystyrene-bound alkenes 152 have been used for the solid-phase synthesis of pyrazolopyridines 153 by a [3 + 2] cycloaddition of pyridinium imides with polymer-bound propiolates 152.

The thermal [3 + 2] cycloaddition of N-benzoylquinolinium imide 156 with allenoates 75 provides products 157 in good yields, albeit with poor diastereoselectivity (Scheme 59).91 This cycloaddition has been carried out with N-benzoylisoquinolinium imides with similar results concerning yield and diastereoselectivity.

A formal [3 + 2] cycloaddition catalyzed by a gold complex 159 between N-benzoyliminopyridinium imides 158 and N-alkynylsulfonamides gave 2,4,5-trisubstituted oxazoles 160 in high yields (Scheme 60).92

The benzocondensed azomethine imines 156 have been employed in [3 + 3] cycloadditions. Thus, the nickel-catalyzed [3 + 3] cycloaddition of N-benzoylquinolinium imide 156 with 1,1-cyclopropane diesters provided products 161 in modest to good yields and moderate diastereoselectivity (Scheme 61).78

An enantioselective formal [3 + 3] cycloaddition has been performed also with N-benzoyliminopyridinium ylides 158 and sily-
lated enol diazoacetates 162 using the rhodium catalysts 164. Bicyclic dearomatized 1,2,3,6-tetrahydropyridazine derivatives 163 were obtained in high yields and enantioselectivities (Scheme 62).93 The reaction is triggered by Rh(II)-catalyzed dinitrogen extrusion with formation of a rhodium carbenoid intermediate followed by addition of the pyridinium ylide.

4 Cyclic azomethine imines incorporating a N–N bond in a ring

The most studied cyclic azomethine imines incorporating a N–N bond in a ring are N-alkylidene-3-oxopyrazolidinium imides 166, which are stable and readily accessible. They have been employed as 1,3-dipoles in thermal and metallo- or organocatalyzed cycloadditions, not only [3 + 2] but also [3 + 3], [4 + 3] and [3 + 2 + 3] ones. These annulation reactions gave rise to dinitrogen-fused heterocycles including tetrahydropyrazolo-pyrazolones, -pyridazinones, -diazepinones, and -diazocinones, which are important products or intermediates for the preparation of useful chemicals and diverse bioactive molecules.

4.1 N-Alkylidene-3-oxopyrazolidin-1-ium-2-ides

Azomethine imines 166, derived from pyrazolidin-3-ones 165, are usually prepared by condensation with carbonyl compounds.10 They can be isolated, especially in the case of aromatic aldehydes, by heating in anhydrous methanol catalyzed by means of trifluoroacetic acid (Scheme 63).10,94

A new route to azomethine imines has recently been described using hydrazones derived from ketones and N-alkoxycarbonylhydrazines 167 and alkenes (Scheme 64).95 Under microwave assisted heating at 150 °C the intermediate
isocyanate is formed and through a concerted alkene aminocarbonylation pathway the corresponding azomethine imines 168 are produced in good yields. Several types of acyclic and cyclic alkenes can be used, including vinyl ethers and enamides. With terminal alkenes (R^4 = H) a total regioselectivity was observed.

### 4.1.1 Thermal cycloadditions.

A common reaction of azomethine imines 169 with dipolarophiles such as methyl propiolate or dimethyl acetylenedicarboxylate gave the corresponding cycloadducts 2,3-dihydro-1H,5H-pyrazolo[1,2-a]-pyrazol-1-ones 170 (Scheme 65).94

![Scheme 65](image)

Scheme 65 [3 + 2] Cycloaddition of azomethine imines 169 with alkynes.

Stereoselective synthesis of fused pyrazolones has been studied with racemic pyrazolidin-3-one 171, which after reaction with benzaldehydes, followed by [3 + 2] cycloadditions of the generated azomethine imines 172 with electron-deficient dipolarophiles such as methyl acrylate, dimethyl acetylene dicarboxylate and dimethyl maleate, gave pyrazolopyrazolone derivatives 173–175 with high stereocontrol (Scheme 66).96,97

The stereoselective cycloaddition of azomethine imines 172 with maleimides provided cycloadducts 176 when the aldehydes had no substituents at the ortho-position. However, with ortho-substituted aldehydes diastereomeric adducts 177 were formed.98,99 Similarly, butyraldehyde and acetone react with pyrazolidinone 171 under an acid-catalyzed process to afford the corresponding azomethine imines, which react under thermal conditions with dimethyl acetylenedicarboxylate, methyl acrylate, methyl maleate or fumarate and N-phenylmaleimide to give the corresponding cycloadducts.100

In the case of the Cu(I)-catalyzed [3 + 2] cycloaddition of azomethine imines 172 (Ar = Ph) it takes place at room temperature in acetonitrile using Hünig’s base with methyl propi-
late giving the product 178 (Scheme 67). When the chiral ynone 179 was allowed to react with 172 a mixture of diastereomeric cycloadducts 180 was obtained.

Azomethine imines 166 and 172 derived from unsubstituted 165 and substituted 171 pyrazolidin-3-ones, respectively, have been used as dipoles in the reaction with α-(trifluoromethyl)acrylates affording the corresponding adducts with a moderate diastereoselectivity. In the case of alkynyl Fischer carbene complexes a regioselective [3 + 2] cycloaddition takes place giving, after oxidative demetallation, the corresponding functionalized pyrazolopyrazolone derivatives 182 (Scheme 68).

Several pyrazolidin-3-ones bearing a chiral chain have been applied as precursors of chiral azomethine imines in diastereoselective [3 + 3] cycloadditions. Thus, 5-substituted pyrazolidin-3-ones 183 derived from 2,3-unsaturated sugar 1,5-lactones react at room temperature with acetone and then with dimethyl acetylenedicarboxylate (DMAD) to provide either the

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**Scheme 68**  [3 + 2] Cycloaddition of azomethine imines 166 with alkynyl Fischer carbene complexes.

**Scheme 69**  Diastereoselective [3 + 2] cycloaddition of 183 with DMAD.
cycloadduct 184 or two equivalents of DMAD, under camphor-sulfonic acid (CSA) catalysis, to give mainly the cycloadduct 185 (Scheme 69).104

The intramolecular [3 + 2] cycloaddition of azomethine imine 187 derived from pyrazolidin-3-one 165 \((R^1 = R^2 = R^3 = R^4 = H)\) and the glucose-derived aldehyde 186 gave the diazatriquinane 188 (Scheme 70).105 This methodology has been studied with different sugar-derived hexen-5-als giving the corresponding diazatriquinanes in high yields and total stereocontrol, which were used for biological screening.

Different types of dipolarophiles have been investigated under thermal conditions with azomethine imines 166 derived from unsubstituted 165, for example, acetylenic sulfones,106 arynes,107 \(\beta\)-nitrostyrenes,108 cyclic vinyl sulfones,109 and trifluoroethylidene malonates.110 In the case when azlactones 189 are used as dipolarophiles, a [3 + 2] cycloaddition, followed by a rearrangement at room temperature, gave the pyrazolopyrazolone derivatives 190 (Scheme 71).111 The cycloadduct intermediates 191 are unstable and undergo a rearrangement affording 190 with high diastereoselectivity (>20 : 1).

4.1.2 Copper-catalyzed cycloadditions. In 2003 Fu et al. described for the first time that CuI (5 mol%) catalyzed the cycloaddition of the azomethine imine 166 \((R^1 = \text{Ph})\) with ethyl acrylate at room temperature in the presence of 0.5 equivalent of Cy2NMe in dichloromethane, giving regioselectively the corresponding cycloadduct in 88% yield. After establishing these reaction conditions, different chiral ligands were assayed, the phosphaferrrocene oxazoline 193 giving the highest enantioselectivity for cycloadducts 192 in the reaction with terminal alkynes (Scheme 72).112 The same reaction conditions have been applied to the kinetic resolution of racemic substituted azomethine imines 166 (Scheme 73).113

The [3 + 2] cycloaddition of azomethine imines 169 with the \(N\)-acyrlylpyrazolidinone 194 catalyzed by the chiral complex Cu(OTf)2·bisoxazoline 196 gave regio- and diastereoselectively exo-cycloadducts 195 in good yields (Scheme 74).114 These processes have been performed only with pyrazolidinone 194, which is able to be chelated by the copper complex and different C5-substituted azomethine imines.

The chiral bis(imidazolidine) 198 CuOAc complex has been used as a catalyst for the [3 + 2] cycloaddition of the azomethine imine 169 with propiolates affording cycloadducts 197 with modest enantioselectivities (Scheme 75).115 The same group developed a better ligand PyBodine (L-Ala) 199, which is able to perform this cycloaddition with Cu(OAc)2 as a metallic salt in better yields and enantioselectivities (Scheme 76).116
Group 11 metal amides, copper(i) and silver bis(trimethylsilyl)amides (HMDS) in THF catalyzed the same \([3 + 2]\) cycloaddition of 166 with terminal alkynes with opposite regioselectivity. This process has been performed in an enantioselective manner when \((S)\)-DIP-BINAP ligand 201 was used with CuHMDS. Thus, the corresponding 5,7-disubstituted cycloadducts 200 were obtained in good yields and enantioselectivities (Scheme 77). 117,118 This regioselectivity is explained by 1,2-addition of the copper acetylide to the iminium moiety followed by intramolecular cyclization.

Scheme 73 Kinetic resolution of azomethine imines via a copper-catalyzed \([3 + 2]\) cycloaddition.

Scheme 74 Enantioselective copper-catalyzed \([3 + 2]\) exo-cycloaddition of azomethine imines 169 with the pyrazolidinone 194.

Scheme 75 Enantioselective copper-catalyzed \([3 + 2]\) cycloaddition of azomethine imines 169 with propiolates using ligand 198.

Scheme 76 Enantioselective copper-catalyzed \([3 + 2]\) cycloaddition of 169 with propiolates using ligand 199.
In the [3 + 2] cycloaddition of azomethine imines 166 catalyzed by a chiral π-cation catalyst 204 (Scheme 78), the main difference of this type of copper catalyst compared to the previous ones is that the copper(I) acetylide-mediated cycloaddition of azomethine imines with terminal alkynes is not operating (Method A). Instead, a Lewis acid-catalyzed cycloaddition by coordination with the carbonyl group (Method B) takes place (Scheme 79).

The racemic copper-catalyzed [3 + 2] cycloaddition has been performed not only with CuI but also with Cu(i) zeolites as the heterogeneous ligand-free catalysts. They are easy to be removed by simple filtration and can be recycled up to six times without decreasing the efficiency. Heterogeneous supported copper hydroxide Cu(OH)₂/Al₂O₃ has also been used as an efficient reusable catalyst.

The catalytic asymmetric cross-1,3-DC of two different dipoles, azomethine ylides generated from iminoesters 205 and imines 166, gave highly substituted 1,2,4-triazinanes with total diastereo- and enantioselectivity. (S, S)-t-Bu-Phosferrox 207 as a ligand and AgOAc or Cu(MeCN)BF₄ salts have been assayed as chiral catalysts for this [3 + 3] cycloaddition. The best results were obtained with the Cu complex giving the cycloadducts 206 in high yields, diastereo- (>20 : 1) and enantioselectivities (Scheme 80).

Independently, a similar [3 + 3] cycloaddition has been performed using the ferrocenyl P,N-chiral ligand 208 and the Cu(MeCN)₄ClO₄ salt as a catalyst. This process takes place giving products 206 with good yields (71–89%), diastereo- (>20 : 1) and enantioselectivities (50–96%).

Scheme 77 Enantioselective copper-catalyzed [3 + 2] cycloaddition of azomethine imines 166 with terminal alkynes.

Scheme 78 Enantioselective copper-catalyzed [3 + 2] cycloaddition of 166 with propiolyldiazirinones catalyzed by the chiral complex 202.

Scheme 79 Strategies for the copper-catalyzed [3 + 2] cycloaddition of azomethine imines 166 with alkynes.
Isocyanides 209 and azomethine imines 169 gave a [3 + 3] cycloaddition to give pyrazole[1,2-a]triazin-8(4H)-ones 210 (Scheme 81). The process takes place with high stereocontrol using CuI as a catalyst and DBU as a base at room temperature. Silver salts and other copper salts provided lower yield than CuI. The proposed mechanism involves the formation of the α-cuprioiocyanide followed by nucleophilic addition to the imine and final insertion of the isonitrile into the N–Cu bond to give the imidoyl-copper intermediate and final protonation.

4.1.3 Other metal-catalyzed cycloadditions. Enantioselective nickel-catalyzed 1,3-DC between azomethine imines 169 and 3-acryloyl-2-oxazolidinone 213 takes place using (R)-binaphthyldiimine 215 as a chiral ligand to provide cycloaducts trans- and cis-214 (Scheme 82). The process gave mainly the trans-diastereomers with a high level of enantioinduction, the metal complex acting as a chiral Lewis acid coordinating the Ni(n) atom of the acryloyloxazolidinone. A dipole–HOMO/dipolarophile–LUMO controlled asymmetric 1,3-DC is proposed.

Recently, a Ni(n)-catalyzed enantioselective [3 + 2] cycloaddition of azomethine imine 166 and alkylidene malonates as dipolarophiles has been described. In this case trans-pyrazolone derivatives 216 have been obtained with total diastereoselectivity and good enantioselectivities by using a chiral N,N'-dioxide 217 as the chiral ligand (Scheme 83). The reaction also proceeds by a dipole–HOMO/dipolarophile–LUMO inter-
action, the Ni-complex acting as a chiral Lewis acid coordinat-
ing the two carbonyl groups of the alkylidene malonate.

The palladium-catalyzed \([3 + 3]\) cycloaddition of trimethyl-
enemethane (TMM) with azomethine imines \(166\) led to the for-
mation of six-membered cycloadducts \(219\).\(^{128}\) Starting from \([2-
(acetoxymethyl)-2-propenyl]trimethylsilane \(218\), the Pd–TMM
complex reported by Trost,\(^{129}\) generated from Pd(PPh\(_3\))\(_4\) in
DCM, gave the best results (Scheme 84). Azomethine imines
bearing substituents on the pyrazolidinone ring can also be
used in this \([3 + 3]\) cycloaddition giving the hexahydropyrida-
zines in high diastereoselectivity. However, using substituted
TMM different products are formed.

Gold-catalyzed \([3 + 3]\) cycloadditions of azomethine imines
\(166\) and propargyl esters have been observed to proceed by a
stepwise mechanism with a gold(III) carbenoid \(221\) as an in-
termediate. The reaction takes place in the presence of 5 mol% of
picolinate–gold dichloride \((159)\) as a catalyst affording adducts
\(220\) with moderate to high diastereoselectivity (Scheme 85).\(^{130}\)

\(\text{N-Allenyl amides } 222\) underwent 1,3-DC of azomethine
imines \(166\) under gold(I) catalysis to provide \([3 + 2]\) cyclo-
adducts \(223\) (Scheme 86).\(^{131}\) This process can occur through a
gold allene intermediate, which can give another intermediate
\(224\) by an outer-sphere nucleophilic addition. Subsequent
intramolecular cycloaddition of \(224\) yielded the iminium inter-
mediate \(225\), which after deauration gave the final cycloadduct
\(226\).

The asymmetric 1,3-DC of azomethine imines \(166\) to allyl
alcohol was possible using stoichiometric amounts of a strong
Lewis acid formed by diisopropyl \((R,R)\)-tartrate (DIPT) and an
excess (3 equiv.) of butylmagnesium bromide necessary for the
deprotonation of allyl alcohol to form the intermediate \(228\).
The reaction proceeds at 80 °C in acetonitrile affording only the
corresponding trans-pyrazolinonepyrazolidines \(227\) (Scheme 87).\(^{132,133}\)

Under similar reaction conditions homoallylic alcohols
have been used for this type of \([3 + 2]\) cycloaddition. In this
case only 20 mol% of DIPT, one equivalent of MgBr2 and 1.5 equivalents of n-BuMgCl were used providing also the
trans-cycloadducts 230 in 23–93% yield and 63–93% ee.133,134 In the proposed transition state 229, the azomethine imine is co-
ordinated to magnesium by the nitrogen and the carbonyl
group to afford pyrazolidinones 230 (Scheme 88). The same
group has developed a desymmetrization of 1,4-pentadien-3-ol by the asymmetric 1,3-DC of azomethine imines using
magnesium diisopropyl tartrate as a chiral Lewis acid in up to
98% ee.135

Doyle et al. have studied enol diazoacetate 162 as a dipolar-
ophile for the [3 + 2] cycloaddition with azomethine imines
166 catalyzed by Sc(OTf)3 or In(OTf)3 as Lewis acids.136 The
corresponding cycloadducts 232 are obtained diastereoselec-
tively in good yields. Selective 1,2-C→C and N→C migrations
catalyzed by rhodium(II) salts or CuPF6 were observed to give
six membered rings. However, using rhodium(II) acetate the
corresponding [3 + 3] annulation products cis-231 were regio-
and diastereoselectively obtained (Scheme 89). 137 The azo-
methine imine attacks the vinylogous position of the Rh(II)-
vinylic carbine 232 to give the intermediate 233, which after sub-
sequent ring formation followed by extrusion of the catalyst
gives the fused bicyclic pyrazolidinones 231.

When a diazoketone 234 was used as a dipolarophile a
formal [3 + 2 + 1] annulation with azomethine imines
166 was observed (Scheme 90).138 In this case, a similar intermediate
metal carbine 232 (Scheme 89) is trapped by another molecule
of the diazoketone 234 to give diastereoselectively products
235 by means of the chiral dirhodium(II) carboxamidate
236.

4.1.4 Metal-free-catalyzed cycloadditions. Different types of
Lewis bases such as amines, phosphines and Lewis and
Brønsted acids have been used for the racemic and enantio-
selective 1,3-DC of azomethine imines with dipolarophiles.

For electron-rich alkenes, such as vinyl ethers 23, the highly
reactive nitrosonium hexafluorophosphate must be used as a
catalyst for the [3 + 2] cycloaddition of azomethine imines
166 (Scheme 91). The corresponding fused pyridazinones 237 were
obtained with low to good cis/trans diastereoselectivity.139

The first organocatalyzed asymmetric [3 + 2] cycloaddition
of α,β-unsaturated aldehydes to azomethine imines 116 was
carried out using the α,α-diarylprolinol salt 239. The enal activa-
tion takes place by iminium formation giving the corres-
Rh-catalyzed [3 + 3] cyclization of enol diazoacetate 162 with azomethine imines 166 (Scheme 89).

Rh(II)-catalyzed formal [3 + 2 + 1] annulations of azomethine imines 166 and diazoketone 234 (Scheme 90).

Organocatalyzed enantioselective [3 + 2] cycloaddition of azomethine imines 166 with enals (Scheme 92).

Organocatalyzed enantioselective [3 + 2] cycloaddition of azomethine imines 166 with vinyl ethers (Scheme 91).
both transition states A and B with s-cis and s-trans conformations, respectively, would afford the exo-cycloadducts.

When this reaction is catalyzed by N-heterocyclic carbenes, a highly stereoselective formal [3 + 3] cycloaddition takes place to provide pyridazinones 240 (Scheme 93). The addition of the N-mesitylbenzimidazolyl carbene, generated from the benzimidazolium iodide 242, by an addition/acylation sequence with 166 affords the final bicyclic heterocycles 240.

The enantioselective [3 + 2] cycloaddition of cyclic enones and azomethine imines 166 has been performed in the presence of the chiral primary amine 9-amino-9-deoxyepiquinine 244 and 2,4,6-trisopropylbenzenesulfonic acid (TIPBA) as a catalyst (Scheme 94). The corresponding tricyclic pyrazolidinones 243 were obtained in good yields, diastereo- and enantioselectivities. The Cinchona derived catalyst activates the enone forming a ketiminium cation and an additional hydrogen bonding between the OH and the C=O groups to produce the endo and Re-face selectivities in the final cycloadducts.

The base-catalyzed diastereoselective [3 + 3] annulations of 3-isothiocyanatoxindoles 245 to azomethine imines 166 gave 3,3′-triazinyl spirooxindoles 246 (Scheme 95). Using 1 mol% of triethylamine the reaction takes place in only five minutes at room temperature with high yields and diastereoselectivities.

Another example of a base-catalyzed [3 + 3] cycloaddition of azomethine imines 166 takes place with 1,4-dithiane-2,5-diol 247. DABCO catalyzes this process (Scheme 96) in methanol.
giving products 248 resulting from the attack of the base to mercaptoacetaldehyde followed by addition to the azomethine imine and subsequent intramolecular cyclization, the diastereoselectivity being controlled by the anomeric effect.\textsuperscript{144} 5-Methyl and 5-phenyl substituted azomethines 166 gave the all cis-cycloadducts 248.

The multicomponent synthesis of pyrazolidinones 249 has been performed starting from 165, the aldehyde and Meldrum’s acid. This process was organocatalyzed by (DHQ)\textsubscript{2}PHAL 250 acting as a chiral base. A domino Knoevenagel-aza-Michael-cyclocondensation reaction gave the resulting cycloadducts 249 in good yields and enantioselectivities (Scheme 97).\textsuperscript{145}

Nucleophilic phosphine catalysis has been used for different types of $[3 + n]$ cycloadditions of azomethine imines 166 with allenoates 77 (Scheme 98). These reactions take place by the formation of various zwitterionic intermediates by the addition of a phosphine as a Lewis base to the $\beta$-carbon of the $\alpha$-allenic ester, affording five-, six-, seven-, and eight-membered dinitrogen containing heterocycles. These types of cycloadditions have also been studied with C,N-cyclic azomethine imines 57 (Scheme 27).\textsuperscript{42}

Ethyl 2-methylbuta-2,3-dienoate 75 reacted with azomethine imines 166 under tri-$n$-butylphosphine-catalyzed $[3 + 2]$ cycloaddition to afford the exocyclic alkylidene adducts 251 as single isomers (Scheme 99).\textsuperscript{146} By using a chiral phosphine 253, the product 251 (with $R^1 = \text{Ph}$) was obtained in 56\% yield and 89\% ee. When azomethine imine 166 [with $R = 4\{\text{O}_2\text{N}\}\text{C}_6\text{H}_4$] was allowed to react with other $\alpha$-alkyl allenoates 75, trimethylphosphine was the catalyst of choice to prepare products 252. These 1,3-DC take place by the formation of the corresponding 1,3-zwitterionic intermediate 254.

The reaction involving diethyl 2-vinylidene succinate 255 was more complicated giving mixtures of five-, six-, and seven-membered rings either with tri-$n$-butyl- or trimethylphosphine (Scheme 100).\textsuperscript{146} It has been proposed that zwitterionic intermediates A and B gave the five- and the six- or seven-membered ring, respectively.

For unsubstituted ethyl 2,3-butadienoate 260, a mixture of $[3 + 2]$ and $[3 + 3]$ cycloadditions 261 and 262 is formed in different proportions depending on the phosphine used as a catalyst. Trimethylphosphine favors the formation of the tetrahydropyrazoloazatolone 261 and tri-$n$-butylphosphine the tetrahydropyrazolopyridazinone 262 by the addition of the

Scheme 97  Multicomponent enantioselective $[3 + 2]$ cycloaddition of pyrazolidinones 165 with aldehydes and Meldrum’s acid.

Scheme 98  Phosphine-catalyzed $[3 + n]$ cyclization of azomethine imines 166 with allenoates.
When γ-substituted allenoates 77 are allowed to react with azomethine imine 166 [Ar = 4-(O₂N)C₆H₄], only the tetrahydro-pyrazolopyridazines 263 were obtained in modest yields and with total diastereoselectivity, among other non-isolated products (Scheme 102).¹⁴⁶

The reaction of ethyl 2,3-butadienoate 260 with different azomethine imines 166 was studied in more detail in order to determine the structure of secondary products. It was found that the formation of [3 + 2 + 3] products, such as 1-oxo-2,3,5,6-tetrahydro-1H-pyrazolo[1,2-a][1,2]diazines 264 and 265, took place mainly when tricyclohexylphosphine was used as a catalyst (Scheme 103).¹⁴⁶ In this case, experimental and theoretical studies support the participation of 1,5-zwitterionic intermediates 266, in order to explain the formation of the eight- and seven-membered rings through [5 + 3] and [5 + 2] cycloadditions, respectively.¹⁴⁷
However, under thermal conditions, only the [3 + 2] cycloaddition products 267 were formed in high yields (Scheme 104), whereas with α- and γ-substituted allenates a complex mixture of products was obtained. When ethyl 2-butynoate was used instead of ethyl 2,3-butadienoate (260), the tri-n-butylphosphine-promoted cyclization with azomethine imines 166 also afforded a mixture of products 261 and 262 by intermediacy of the same 1,3-zwitterionic intermediate 254.

Electron-deficient alkenes such as the (Z)-1,2-bis(phenyl-sulfonyl)ethylene 268 gave, under Ph₃PMe-catalysis at room
temperature, the corresponding \([3 + 2]\) cycloaddition products \(269\) in the reaction with azomethine imines \(166\) (Scheme 105).\(^{149}\)

Products \(269\) were obtained with high diastereoselectivity and the relative configuration was the same when using \((E)-268\). In this case, the participation of the zwitterionic intermediate \(270\) has been proposed, which attacks the azomethine imine followed by intramolecular cyclization regenerating the phosphine. The same \([3 + 2]\) cycloaddition has been observed with C,N-cyclic azomethine imines \(57\), as well as with \(144\) and \(156\).

Chiral bis-phosphoric acid \(272\) has been used as the Bronsted acid catalyst for the 1,3-DC of alkylideindolinones \(271\) with azomethine imines \(166\) to afford spiro spiro pyrazolidin-3,3'-oxindoles \(273\) (Scheme 106).\(^{150}\) By MS and DFT calculation experiments the best transition state has been established in which both the alkylideneindolines and the azomethine imines are hydrogen bound with the OH group of both phosphoric acid moieties.

The phosphoric acid \(30\) (Ar = 9-anthracenyl) has shown good diastereo- and moderate enantioselectivities in the organocatalyzed enantioselective inverse-electron-demanding 1,3-DC of azomethine imines \(166\) with \(\alpha\)-hydroxy-\(\alpha\)-methylstyrene \(274\). Thus, \([3 + 2]\) cycloaddition takes place in 1,3-difluorobenzene giving mainly cycloadducts \(275\) through a two-step mechanism. The presence of the hydroxy group at the \(ortho\) position is crucial for the reaction to occur. A dual activation mode by hydrogen bonding interaction between the two substrates and the catalyst together with the conjugative effect initiated by the \(\alpha\)-hydroxy group played an essential role in the proposed transition state \(A\) (Scheme 107).\(^{151}\)

4.2 \(N\)-Alkylidenepyrazolidin-1-ium-2-ides

Azomethine imines \(277\) can be generated from the opening of the diaziridine ring in 1,5-diazabicyclo[3.1.0]hexane \(276\) either by thermolysis\(^{152-154}\) or by means of scandium triflate and trapped by dipolarophiles to give products \(278\) (Scheme 108).\(^{155,156}\) This ring opening can be performed in ionic liquids (ILs) in the presence of BF\(_3\)·EtO and the resulting unstable azomethine imines can be trapped by nitrostyrenes or chalcone to give the corresponding \([3 + 2]\) cycloadducts \(278\) and \(280\), respectively (Scheme 109).\(^{157}\)

When acrylonitrile or 4-nitrophenyl vinyl sulfone was used as dipolarophiles the corresponding cycloadducts \(281\) or \(282\) were obtained with modest diastereoselectivity and with opposite regioselectivity in the first case (Scheme 110).\(^{158,159}\)
Scheme 109  [3 + 2] Cycloaddition of azomethine imines 277 with nitrostyrenes and chalcone.

Scheme 110  [3 + 2] Cycloaddition of azomethine imines 276 with acrylonitrile and 4-nitrophenyl vinyl sulfone.

Scheme 111  Diastereoselective [3 + 2] cycloadditions of chiral glyoxylic azomethine imine.
4.3 N-Alkylidene 3-oxodiazolimid-1-ium-2-ides

These types of azomethine imines have been less studied than the pyrazolidinium imides. Only glyoxylic azomethine imines derived from 283 have been investigated. These chiral six-membered hydrazides 283 react with aliphatic and aromatic aldehydes to give the corresponding azomethine imines, which react with diethyl acetylene dicarboxylate and olefinic dipolarophiles to provide pyrazolo[1,2-a]pyridazin-5(6H)-ones.10,160,161 When ethyl glyoxylate is used as a carbonyl component in the presence of an excess of magnesium bromide etherate, the corresponding oxadiazolidine 284 is formed, which undergoes cycloreversion–cycloaddition in the presence of various electron-poor dipolarophiles such as styrenes giving cycloadducts 285 (Scheme 111).162 Methyl maleate, fumarate and crotonate as well as N-phenylmaleimide gave cycloadducts 286–289 with modest diastereoselectivities and good yields.

5. Conclusions

In the last 10 years, the chemistry of acyclic and especially cyclic azomethine imines has experienced a renaissance in synthesis of heterocycles of wide structural diversity, such as pyrazolidines, pyrazoloisoquinolines and pyrazolopyrazolones, among others. Their reactivity in 1,3-dipolar cycloadditions (1,3-DC) with a great variety of dipolarophiles in a highly regio- and diastereoselective manner has found many applications in the synthesis of dinitrogen heterocycles. Depending on the dipolarophile partially or totally saturated heterocycles can be prepared generally by a [3 + 2] cycloaddition but also by higher order cycloadditions. Most of the methodologies recently studied are in the field of asymmetric synthesis using chiral Lewis bases and Bronsted acids as organocatalysts depending on the dipolarophile and metal complexes bearing chiral ligands. The study of asymmetric catalytic methods has just started and further synthetic applications to be developed in this field would be important in the near future.

Abbreviations

Ac  Acetyl  DMAD  Dimethyl acetylenedicarboxylate
Bn  Benzyl  DMF  N,N-Dimethylformamide
Bz  Benzoyl  DMP  Dess–Martin reagent
Cbz  Benzoyloxycarbonyl  2,4-DNB  2,6-Dinitrobenzoic acid
CSA  Camphorsulfonic acid  DTBMP  2,6-Di-t-tert-butyl-4-methylpyridine
DABCO  Diazip bicyclo[2.2.2]octane  HDMDS  Hexamethyldisilazane
DBU  1,8-Diazabicyclo[5.4.0]jundec-7-ene  ILs  Ionic liquids
1,3-DC  1,3-Dipolar cycloaddition  MS  Mass spectrometry
DBQ  1,3-Dichloro-5,6-dicyano-1,4-benzoquinone  NMP  N-Methylpyrrolidone
DCE  1,2-Dichloroethane  NPM  N-Phenylmaleimide
DCM  Dichloromethane  Py  Pyridine
DDQ  1,3-Dichloro-5,6-dicyano-1,4-benzoquinone  rt  Room temperature
DFT  Density functional theory  SEM  Scanning electron microscopy
DIPEA  Diisopropyl ethyl amine  TIPS  Triisopropylsilyl
DIPT  Diisopropyl t artarate  TIPBA  2,4,6-Triisopropylbenzenesulfonic acid
DMAc  N,N-Dimethylacetamide  TIPSOFf  Trimethylsilyl triflate
Troc  2,2,2-Trichloroethoxycarbonyl  TBS  tert-Butyldimethylsilyl
Ts  p-Toluenesulfonyl

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