Organic & Biomolecular Chemistry

REVIEW

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Cite this: *Org. Biomol. Chem.*, 2015, **13**, 8596

1,3-Dipolar cycloadditions of azomethine imines

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Received 29th May 2015,
Accepted 24th June 2015

DOI: 10.1039/c5ob01086a

www.rsc.org/obc

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 extensively considered and applied to the synthesis of a great 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 enantiomerically enriched compounds present in many pharmaceuticals, agrochemicals and other useful chemicals.

1 General introduction

Azomethine imines are 1,3-dipoles of the allylic 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 high order cycloadditions, such as [3 + 3], [4 + 3] and [3 + 2 + 3], 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 review[10] covering the literature until 2003.

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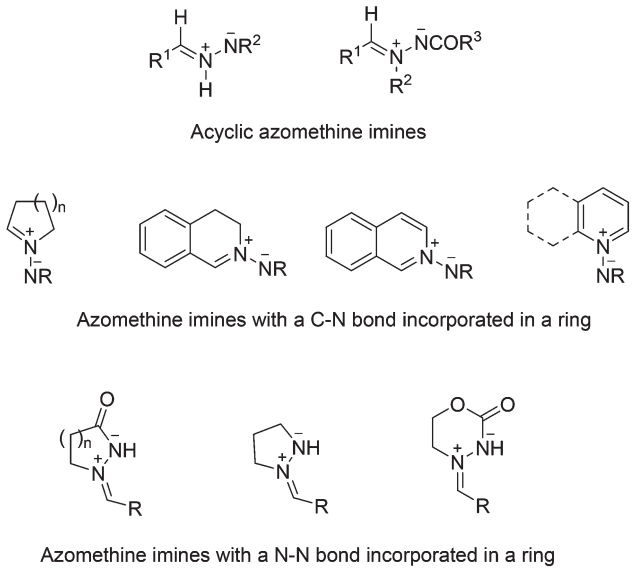
2 Acyclic azomethine imines

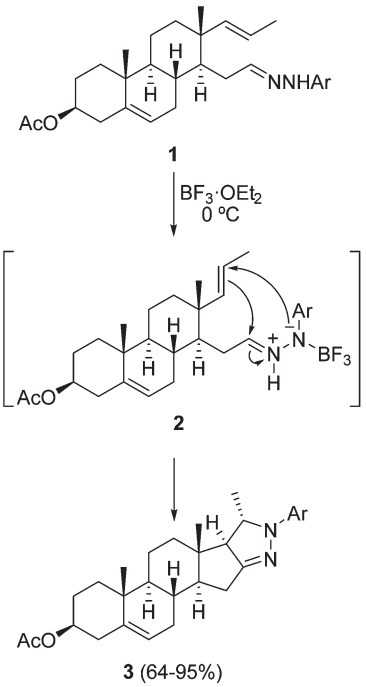
These types of dipoles have been postulated as intermediates in [3 + 2] cycloaddition reactions and are derived from hydrazones and carbazates (Scheme 1) leading to pyrazolines and pyrazolidines, and their derivatives. The corresponding precursors can be prepared from monosubstituted and 1,2-disubstituted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

2.1 Monosubstituted hydrazines

Azomethine imines derived from acyclic hydrazones are generated easily upon 1,2-prototropy 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 **3** using $BF_3{\cdot}OEt_2$ 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 BF_3-promoted formation of intermediate azomethine imines **2**.



Scheme 1 Typical azomethine imines.



Scheme 2 Intramolecular BF_3-catalyzed [3 + 2]-cycloaddition of hydrazones with alkenes.

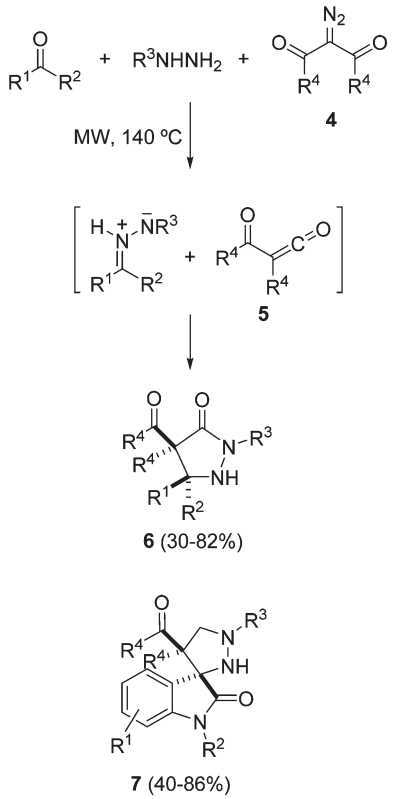
Three-component or consecutive intermolecular 1,3-DC of azomethine imines with α-oxoketenes **5** has been performed under thermal conditions. Both hydrazones and dipolarophiles are generated *in situ*, affording the corresponding pyrazolidinones **6** in a stereoselective manner (Scheme 3).[21a] Intermediate 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).

Carmen Nájera

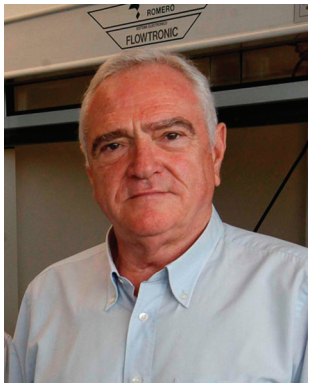
Carmen Nájera was born in Nájera (La Rioja) and graduated from the University of Zaragoza in 1973, obtaining her doctorate in chemistry from the University of Oviedo in 1979. She spent postdoctoral stays at the ETH (Zurich), the Dyson Perrins Laboratory (Oxford), Harvard University, and Uppsala University. She became Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. She is coauthor of more than 300 papers and book chapters and has supervised more than 40 PhD students. She has been awarded with the 2006 Organic Chemistry Prize from the Spanish Royal Chemical Society of Chemistry, the 2006 Rosalind Franklin International Lectureship from the English Royal Society, the SCF 2010 French-Spanish Prize from the Société Chimique de France and the IUPAC 2015 Distinguished Women in Chemistry or Chemical Engineering Award. In 2012 she was named Full Member of the Royal Spanish Academy of Sciences and was appointed as Active Member of the European Academy of Sciences and Arts.

José Miguel Sansano

José Miguel Sansano studied chemistry at the University of Alicante, where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. His Thesis was supervised by Prof. C. Nájera and dealt with sulfone chemistry. After spending a two-year postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. In 2010 he was promoted to Professor in the same University.

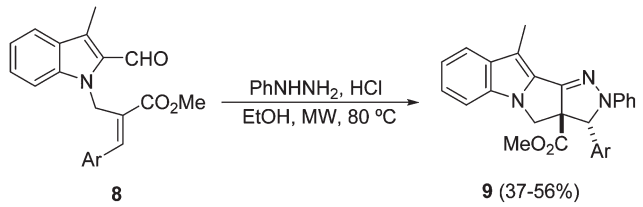


Scheme 3 1,3-DC of hydrazones with α-oxoketenes.



Miguel Yus

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 Lourenco-Madinaveitia (1912), the Serratosa Lectureship (2010) and the Medalla Felix Serratosa (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.



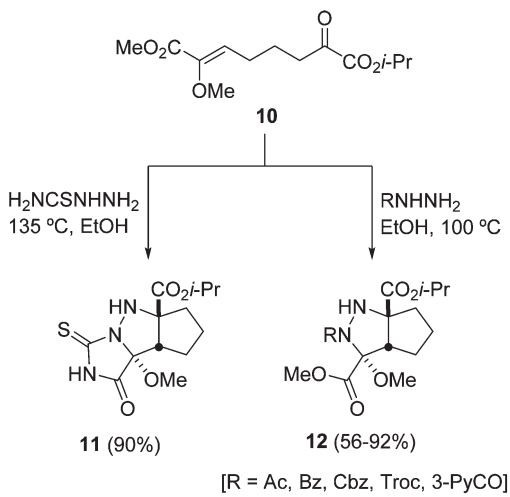
Scheme 4 Synthesis of pyrazolopyrroloindoles by intramolecular 1,3-DC.

Recently, a microwave-assisted intramolecular 1,3-DC of azomethine imines, *in situ* generated from indole-2-carboxaldehydes **8** and phenylhydrazine, has been described. This process takes place in the presence of HCl as an additive in ethanol, providing [*a*]-annelated pyrazolopyrroloindoles **9** in a regio- and stereoselective manner (Scheme 4).[21b] The reaction in the presence of other additives such as AcOH, $BF_3{\cdot}OEt_2$ or iodine gave either lower yields or no reaction.

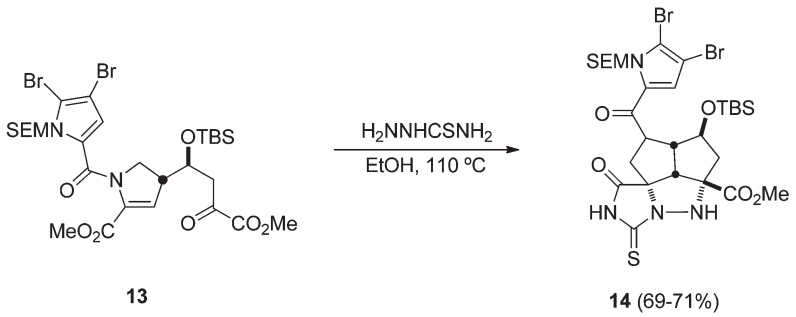
The stereocontrolled synthesis of *cis*-cyclopentanopyrazolidines has been carried out from the α-methoxy-α,β-unsaturated ester **10** bearing an α-keto ester at the end of the chain (Scheme 5).[22] In the case when thiosemicarbazide is used, the intermediate azomethine imine is generated under heating, giving the tricyclic thiohydantoin **11**. *N*-Acyl or *N*-alkoxycarbonyl hydrazines gave, under thermal conditions, the corresponding cycloadducts **12** 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 **15**, which favors the overlap between the π-orbitals of the dipole and dipolarophile (Scheme 7).

Alternatively, it was possible to prepare the corresponding hydrazones **16** from **10** using a catalytic amount of HCl in

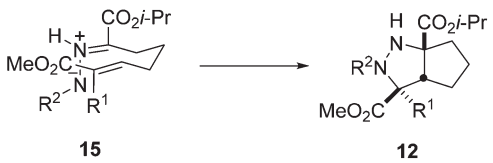


Scheme 5 Synthesis of *cis*-cyclopentanopyrazolidines by intramolecular 1,3-DC.



13 14 (69-71%)

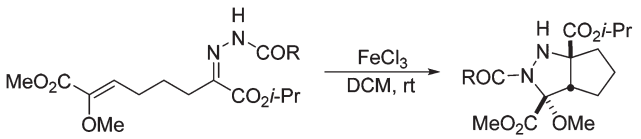
Scheme 6 Synthesis of a precursor of palau'amine.



15 12

Scheme 7 Proposed mechanism for the formation of cycloadducts **12**.

ethanol at room temperature, and then the 1,3-DC takes place at ambient temperature in the presence of one equivalent of $FeCl_3$ in dichloromethane, giving products **12** in good yields (Scheme 8).[22]



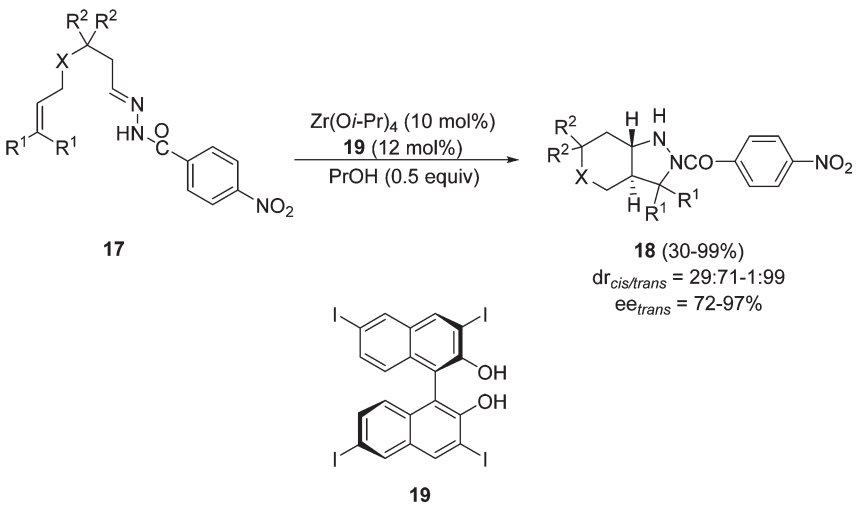
16 12

Scheme 8 $FeCl_3$-promoted 1,3-DC of hydrazones **16**.

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.[24] Different 4-nitrobenzoylhydrazones **17** gave *trans*-pyrazolidines **18** with high diastereo- and enantioselectivity in the presence of $Zr(Oi\text{-}Pr)_4$ (10 mol%) and the Binol derivative **19** at room temperature in dichloromethane (Scheme 9).

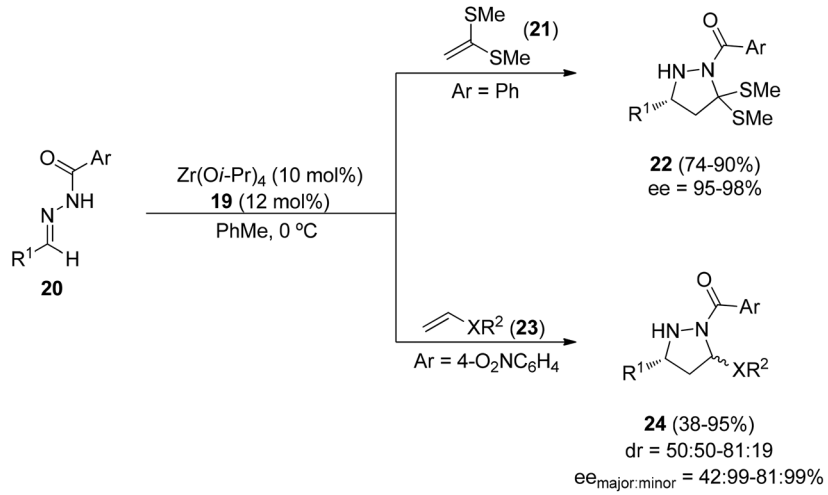
The same chiral catalyst formed by $Zr(Oi\text{-}Pr)_4$ and Binol **19** has been used in the intermolecular [3 + 2] cycloaddition of benzoylhydrazones **20** and electron-rich alkenes like the ketene dimethyl dithioacetal **21**. The corresponding 3,5-disubstituted pyrazolidines **22** were obtained in good yields and enantioselectivities (Scheme 10).[25] 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 $LiAlH_4$ 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).[26] The process needs 1.5 equivalents of compound **25**, derived from pseudoephedrine, to take place, giving the corresponding pyrazolidines **24** at room temperature in

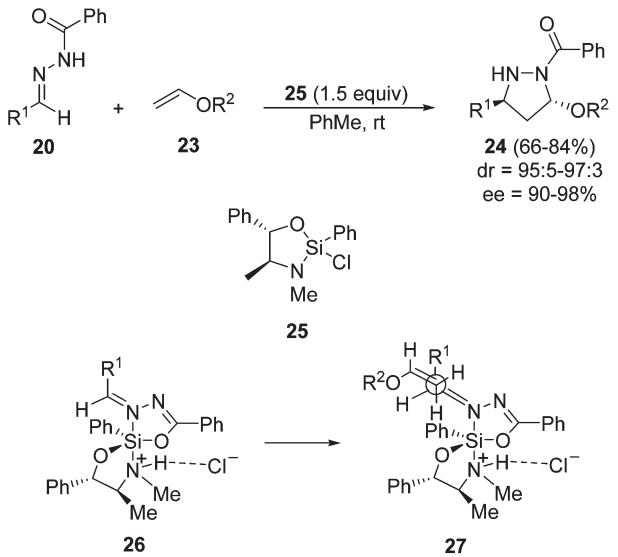


17 18 (30-99%)
$dr_{cis/trans}$ = 29:71-1:99
ee_{trans} = 72-97%
19

Scheme 9 Asymmetric intramolecular 1,3-DC of hydrazones **17** using a chiral Zr-Binol catalyst.



Scheme 10 Asymmetric intermolecular 1,3-DC of benzoylhydrazones **20**.



Scheme 11 Chiral silicon Lewis acid mediated 1,3-DC of benzoylhydrazones **20**.

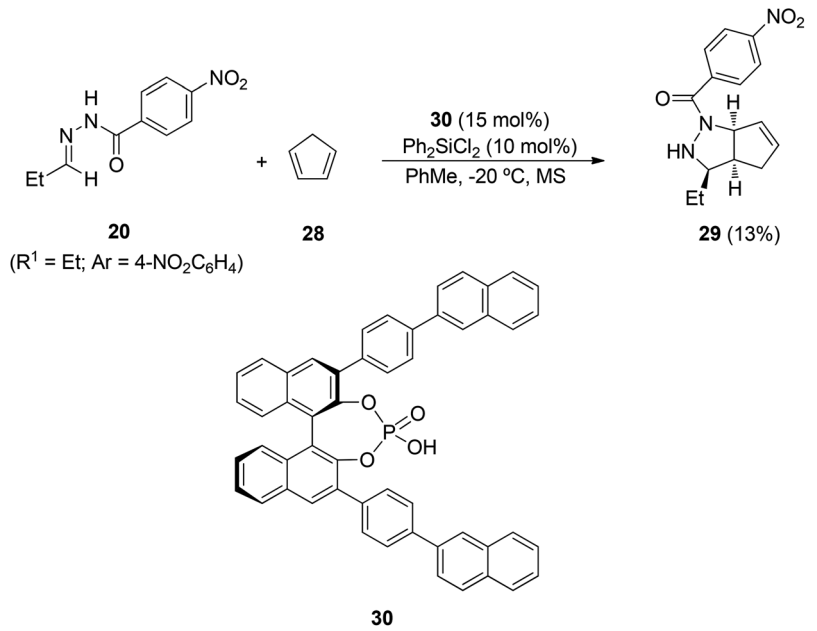
high *trans*-diastereoselectivity and excellent ee. The intermediacy of complex **26**, isolated and characterized by X-ray crystallography,[27] explains the approach of the ether by the Si face of the hydrazone (**27**). Samarium diiodide reduction of pyrazolidines **22** gave the corresponding *anti*-1,3-diamines.

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 enantiocatalytic process was next assayed with an *in situ* generated Binol-phosphate derived silicon Lewis acid from **30** and Ph_2SiCl_2 (Scheme 12).[28] Cycloadduct **29** was obtained in a high *syn*/*anti* diastereomeric ratio (95 : 5) and up to 89% ee, but in a low yield (13%).

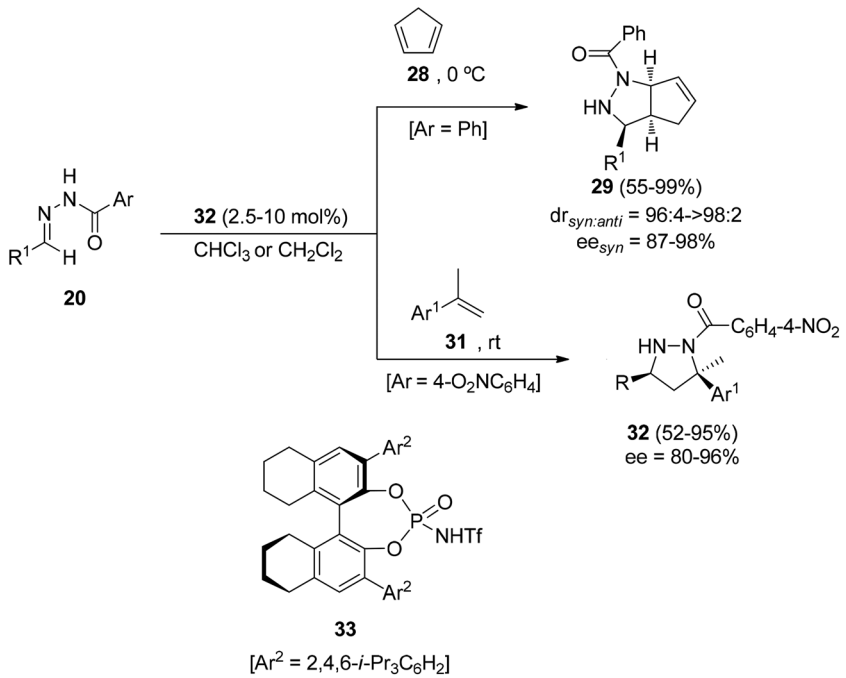
The asymmetric Brønsted acid catalyzed 1,3-DC of benzoylhydrazones **20** could be efficiently performed with cyclopentadiene (**28**) and α-methylstyrenes **31** as dipolarophiles (Scheme 13).[29] Different Binol-derived phosphoric acids (pK_a 13–14 in acetonitrile) were initially assayed as organocatalysts giving very low yields. However, the more acidic [H8]-Binol-based *N*-trifluorophosphoramides **33** (pK_a 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 SmI_2 reduction into a 1,3-diamine with a core structure similar to that of the influenza drug peramivir.[30] 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*-benzoylhydrazones **20** with ethyl vinyl ether **23** (R^2 = Et) the [H8]-Binol derived *N*-triflylphosphoramide **34** was the optimized catalyst. The corresponding *cis*-pyrazolidines **24** (XR^2 = OEt) were obtained in good yields and enantioselectivities (Scheme 14).[31] However, for the cycloaddition with ethyl vinyl thioether **23** (XR^2 = SEt) the Spinol-derived *N*-triflylphosphoramide **35** was the best organocatalyst affording pyrazolidines **24** (XR^2 = SEt) in good yields, diastereo- and enantioselectivities.

The mechanism of *N*-triflylphosphoramide-catalyzed asymmetric [3 + 2] cycloadditions was explored using DFT (MO6-2X) calculations.[31] Protonation of hydrazones **20** by these Brønsted 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[32] of them are required in the transition state **II** giving in this case the *cis*-pyrazolidines **24**. The origin of enantioselectivities was also explained.



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

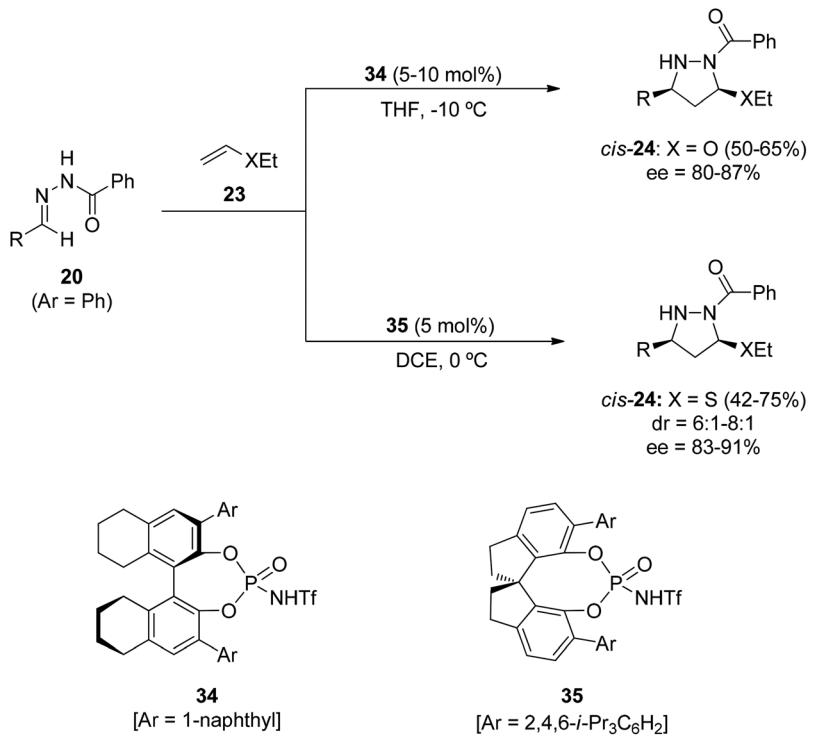


Scheme 13 Chiral *N*-triflylphosphoramide-catalyzed 1,3-DC of *N*-benzoylhydrazones **20**.

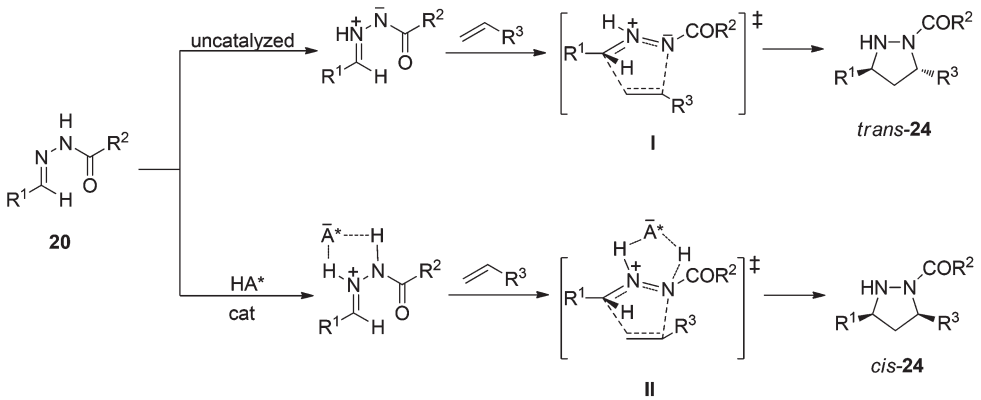
2.2 1,2-Disubstituted hydrazines

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,[33] which can be trapped *in situ* by dipolarophiles through an inter- or intramolecular [3 + 2] cycloaddition.[10] 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).[34] The corresponding 3,4-disubstituted pyrazolidines **38–40**, derived from



Scheme 14 *N*-Triflylphosphoramides as chiral organocatalysts in the intermolecular 1,3-DC of benzoylhydrazones **20**.

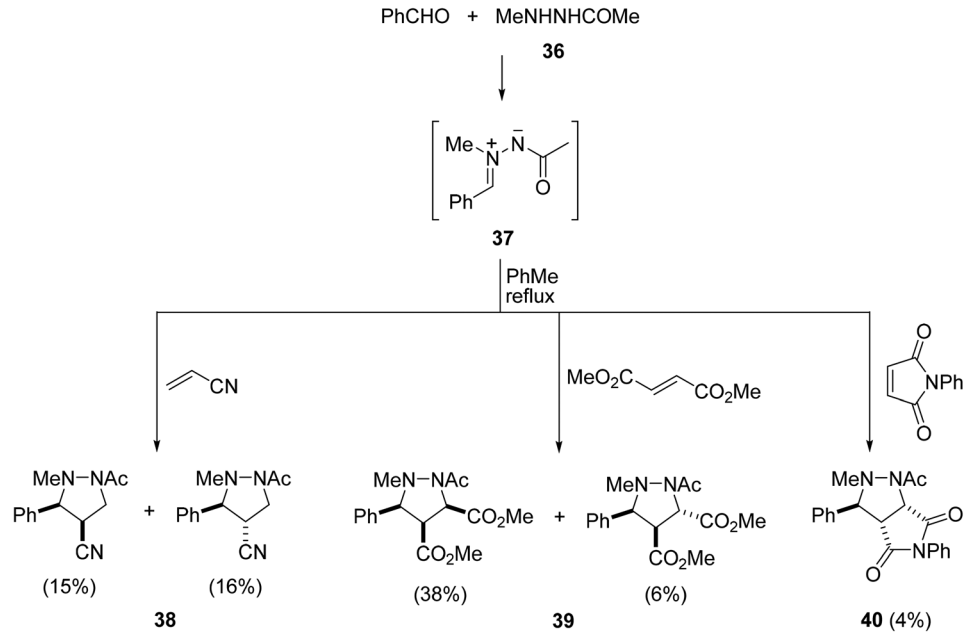


Scheme 15 Uncatalyzed and catalyzed 1,3-DC of hydrazones and olefins.

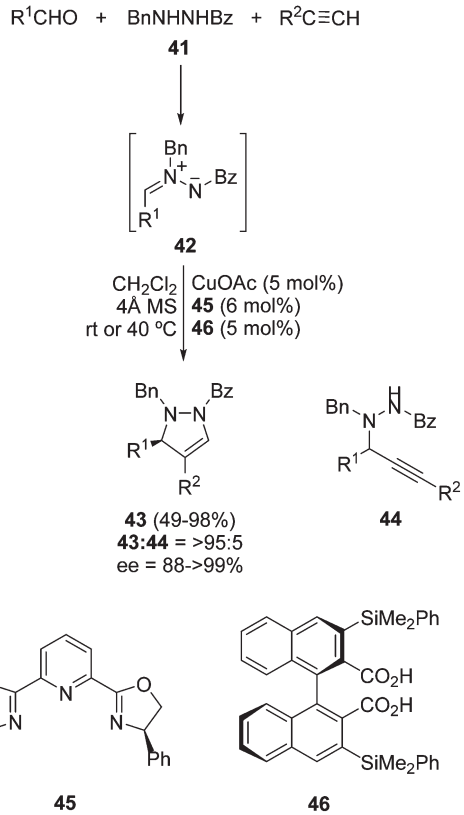
benzaldehyde, were obtained as a mixture of *cis*/*trans* diastereomers in low yields.

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] N^1-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).

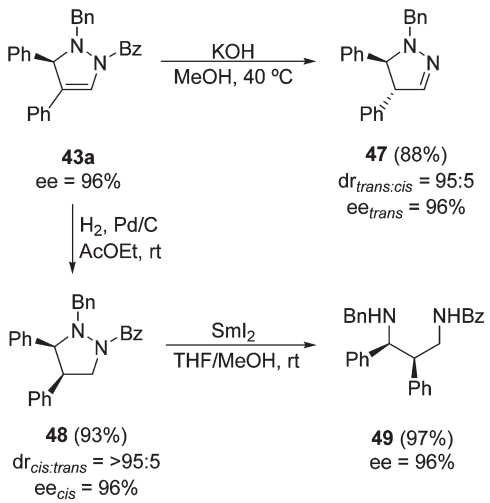
A representative 3,4-disubstituted pyrazoline **43a** (with R^1 = R^2 = Ph) was further transformed into different heterocyclic compounds **47** and **48**, as well as the diamine **49** by reduction of the last one with samarium diiodide (Scheme 18).



Scheme 16 Thermal intramolecular 1,3-DC of azomethine imines derived from hydrazine **36**.



Scheme 17 Three-component enantiocatalytic 1,3-DC of hydrazide **41** with aldehydes and acetylenes.



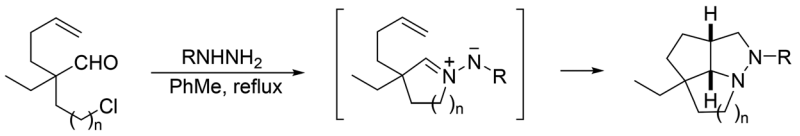
Scheme 18 Synthetic applications of pyrazoline **43a**.

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).[10] 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-



50 [n = 1,2] **51** **52** (75-98%)

Scheme 19 Cascade cyclization and 1,3-DC of hydrazones derived from **50**.

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).[36]

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).[37] The reactivity of one example **54a** with methyl acetylenedicarboxylate gave the fused pyrazoline **55** in a moderate yield.

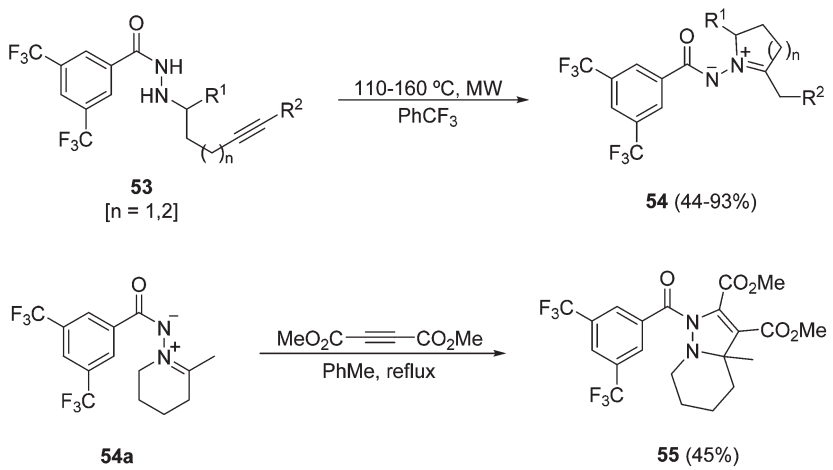
3.2 Isoquinolinium-*N*-aryl imides

N-Iminoisoquinolin-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 binolate 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**, R^2 = H), whereas β-unsubstituted enals (**62**, R^3 = H) gave mainly *endo*-cycloadducts **67** (Scheme 22).

Samarium diiodide-mediated N–N cleavage of the adduct **66a** (with R^1 = R^2 = H, R^3 = Me) gave the tetrahydroisoquinoline **68** (Scheme 23).[38]

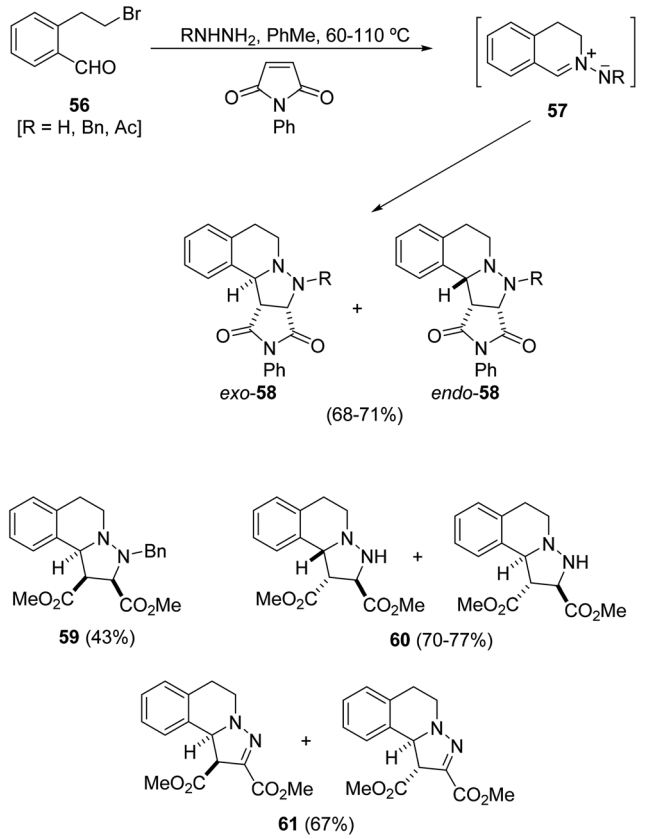
The same type of metal-catalyzed 1,3-DC of the azomethine imine **57** with unsaturated nitriles **69** was performed using a dicationic nickel(II) complex containing bis{(*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyl}cyclohexylphosphine [(*R*,S_P)-Pigiphos] **71** as the catalyst (Scheme 24).[39] The [3 + 2] cycloaddition gave compounds **70** mainly as the *endo*-diastereomer in good yields and enantioselectivities.



53 [n = 1,2] **54** (44-93%)

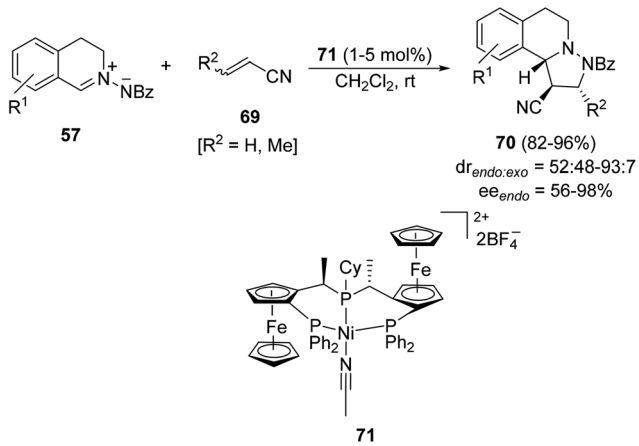
54a **55** (45%)

Scheme 20 Synthesis of azomethine imines by intramolecular hydroamination.



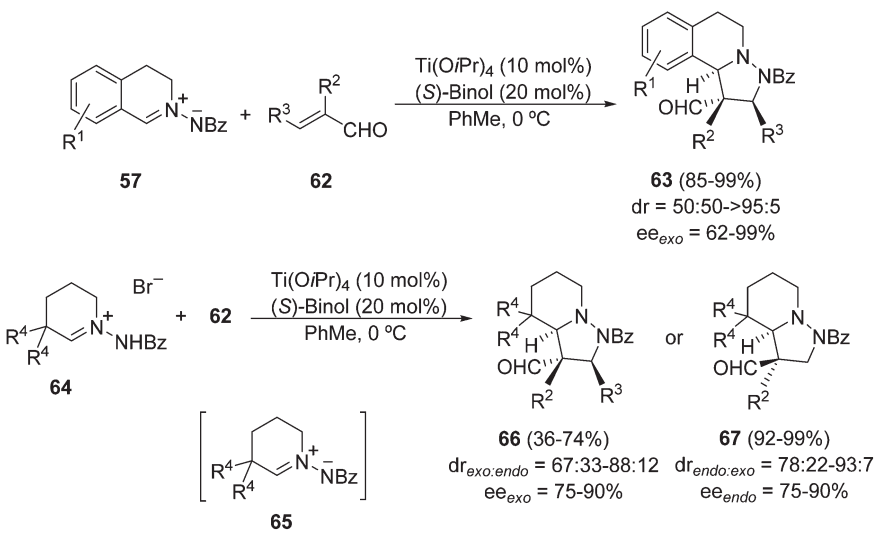
Scheme 21 Cascade cyclization 1,3-DC of hydrazines derived from **56**.

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

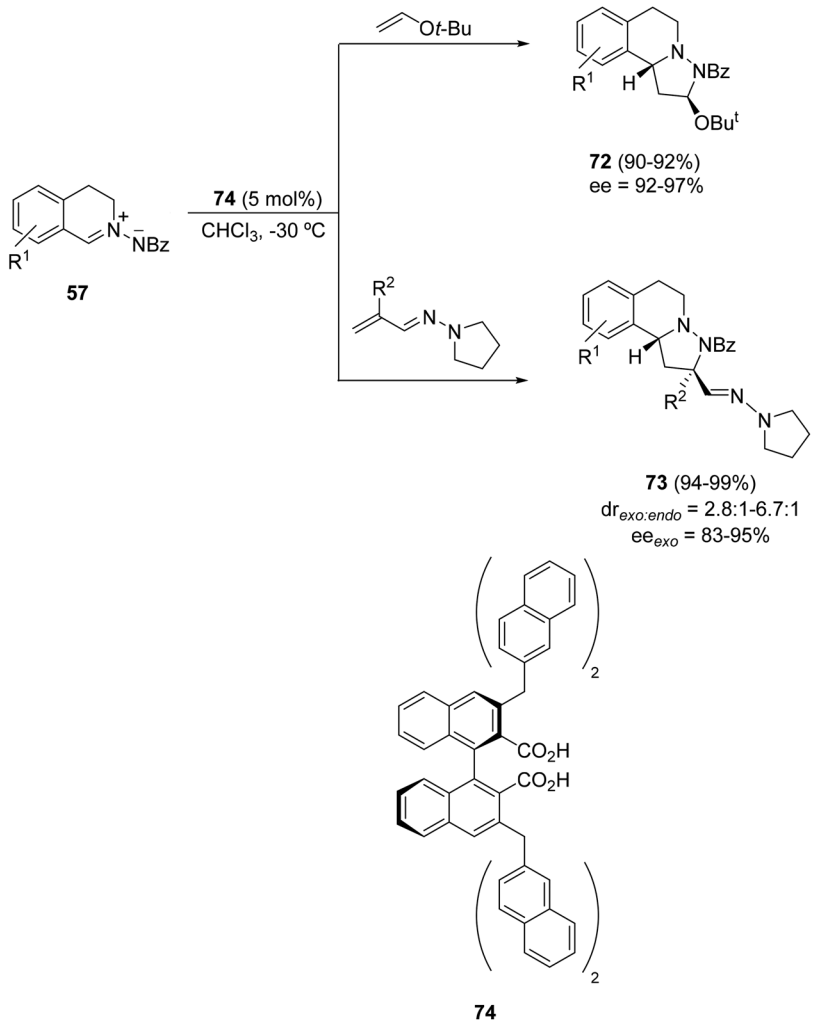


Scheme 24 Ni-Pigiphos-catalyzed 1,3-DC of C,N-cyclic azomethine imines **57** with unsaturated nitriles.

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 Brønsted 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, *exo*-cycloadducts **72** were obtained in high yields and enantioselectivities. Vinylogous aza-enamines gave mainly *exo*-cycloadducts **73** in high yields and good enantioselectivities. The hydrazone unit of compound **73** (with R^1 = Br, R^2 = H) was



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

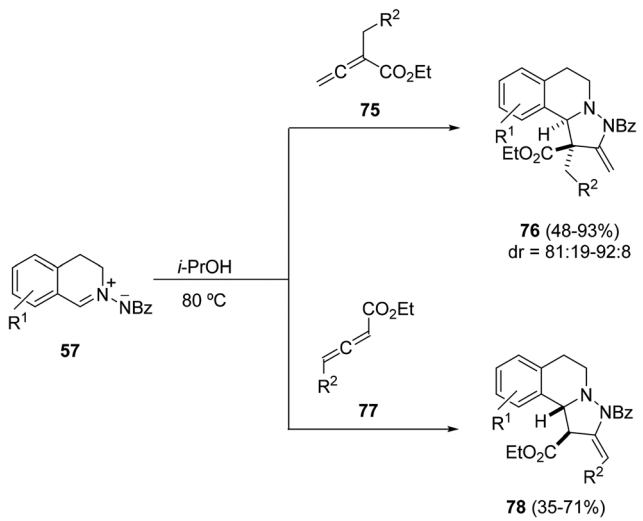


Scheme 25 Organocatalyzed asymmetric 1,3-DC of cyclic azomethine imine **57** with electron-rich alkenes.

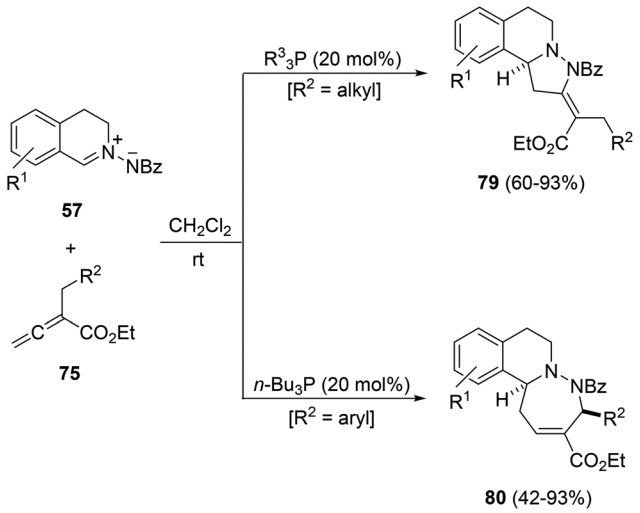
transformed into the corresponding cyano group by magnesium monoperoxyphthalate in 80% yield.

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 26 Thermal [3 + 2] cycloaddition of azomethine imines **57** with allenoates.



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

However, when γ-substituted allenoates **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 *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 δ-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**.

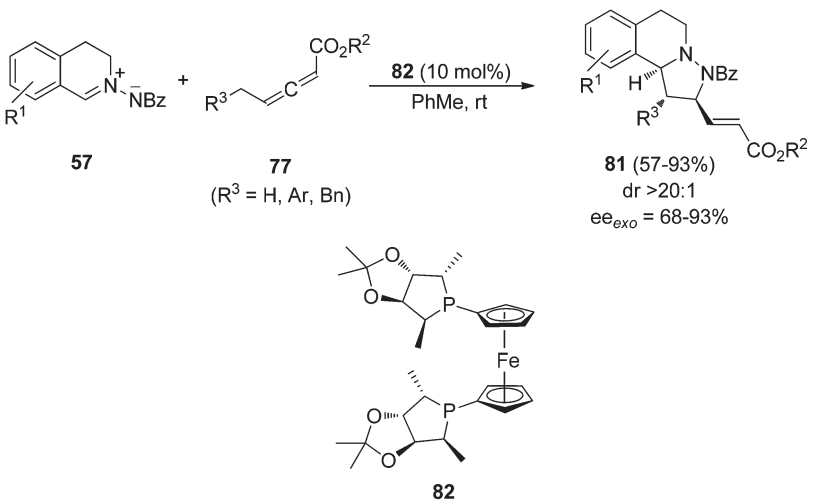
Triflyl alkynes **88** gave 1,3-DC by a reaction with azomethine imines **57** at room temperature, and after oxidative aromatization, pyrazoleisoquinoline triflones **89** were regioselectively obtained (Scheme 30).[47]

A [4 + 3] cycloaddition has been observed when 1,2-diaza-1,3-dienes **91**, generated *in situ* from the corresponding α-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).[40] 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.

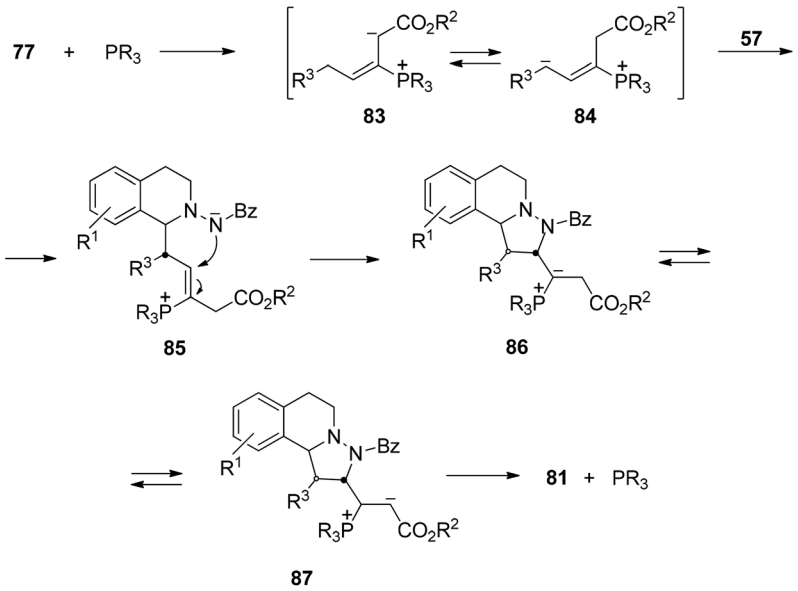
In the case of isocyanides **93** these azomethine imines **57** experimented a [5 + 1] cycloaddition at room temperature leading to the corresponding imino-1,3,4-oxadiazin-6-one derivatives **94** in high yields (Scheme 32).[49] Related C,N-cyclic azomethine imine **64** not fused to the aromatic ring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

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 *in situ* with sodium borohydride to 1-substituted tetrahydroisoquinolines **98** in high diastereo- and enantioselectivities.

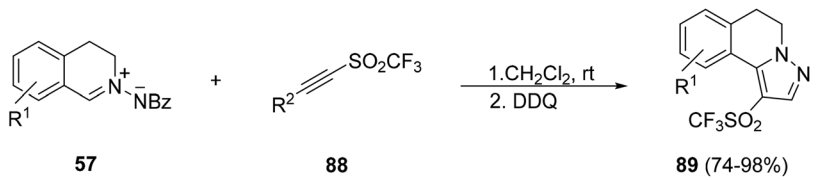
The same group performed an enantioselective 1,3-DC using an intermediate dienamine **57** and enals (R^2 = aryl), and a silylated prolinol **102** as an organocatalyst. By the subsequent reduction of the aldehyde functionality the corresponding alcohols **100** were isolated in good yields, diastereo- and enantioselectivities (Scheme 34).[51] However, when aliphatic enals (R^2 = alkyl) were used, regioisomeric derivatives **101** were obtained according to the formation of α,β-unsaturated



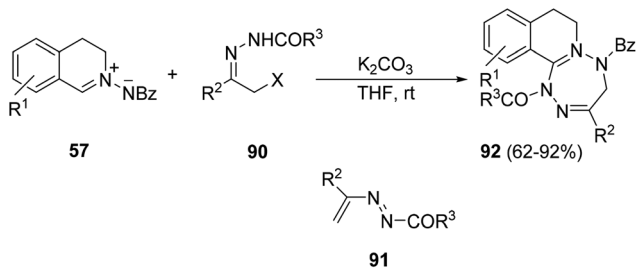
Scheme 28 Enantiocatalyzed [3 + 2] cycloaddition of azomethine imines **57** with γ-substituted allenoates **77** by the chiral phosphine **82**.



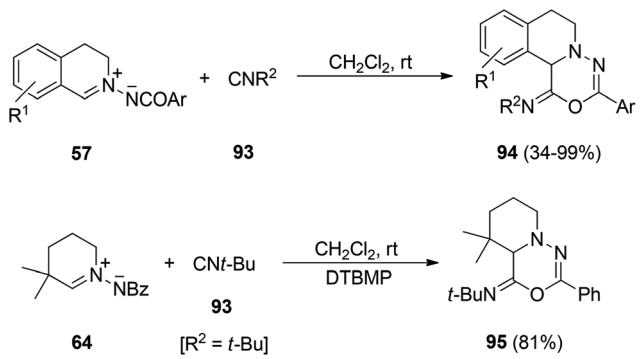
Scheme 29 Mechanism of the phosphine-catalyzed [3 + 2] cycloaddition of **57** with **77**.



Scheme 30 [3 + 2] Cycloaddition of **57** with triflyl alkynes **88**.



Scheme 31 [4 + 3] Cycloaddition of azomethine imines **57** with diazadienes **91**.

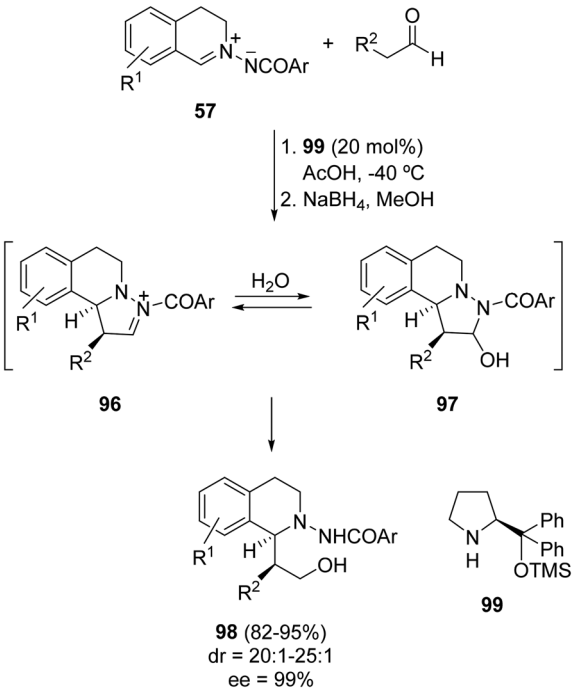


Scheme 32 [5 + 1] Cycloaddition of compounds **57** with isocyanides.

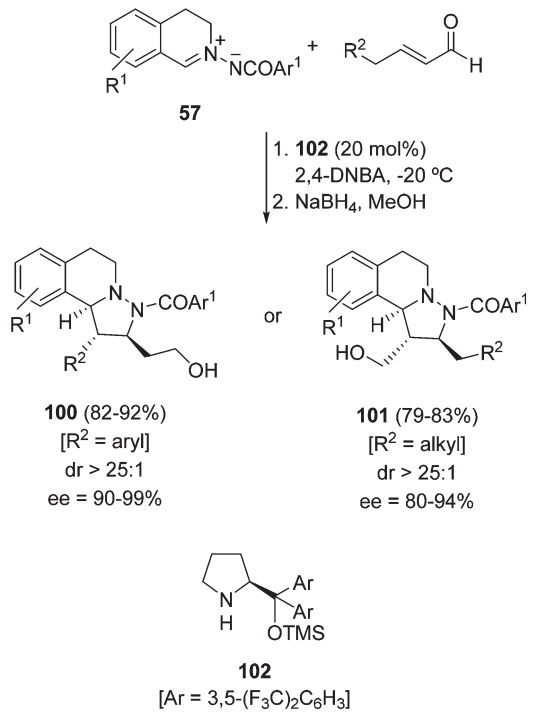
iminium ions as intermediates. Similar iminium–dienamine reactivity has been reported independently with prolinols **99** and **102** by Alemán and Fraile.[52]

A new type of 1,3-DC has been recently performed with azomethine 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.

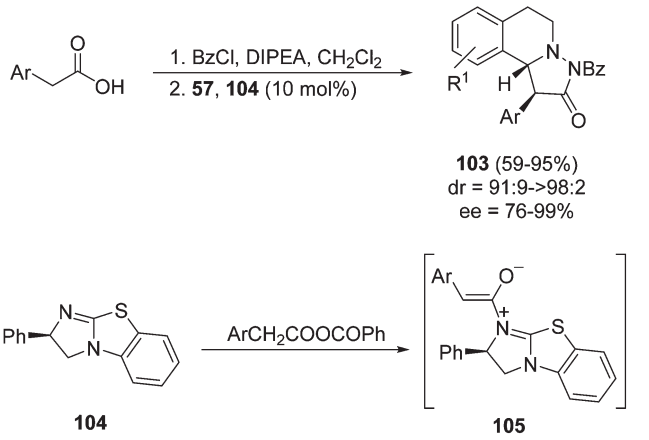
Another family of isoquinolinium ylides are the corresponding unsaturated systems which should be prepared *in situ* in two- or three-component reactions. Thus, *N*′-(2-alkynylbenzylidene)hydrazides **106** react with bromine and α,β-unsaturated ketones *via* a three-component reaction to afford either 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-



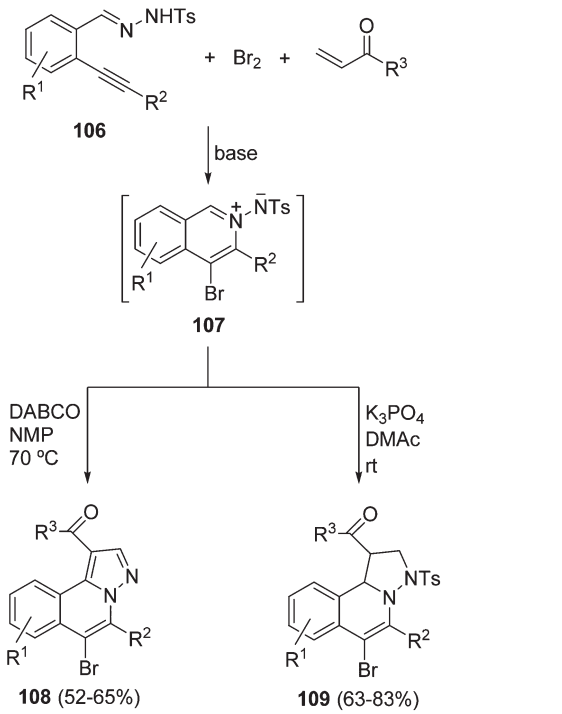
Scheme 33 [3 + 2] Cycloaddition of azomethine imines **57** and aldehydes organocatalyzed by the chiral silylated prolinol **99**.



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.

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.[55] 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

benzaldehydes **110**, tosyl hydrazide and α,β-unsaturated carbonyl compounds gave functionalized *H*-pyrazolo[5,1-*a*]isoquinoline-1-carboxylates **112** (Scheme 37).[56]

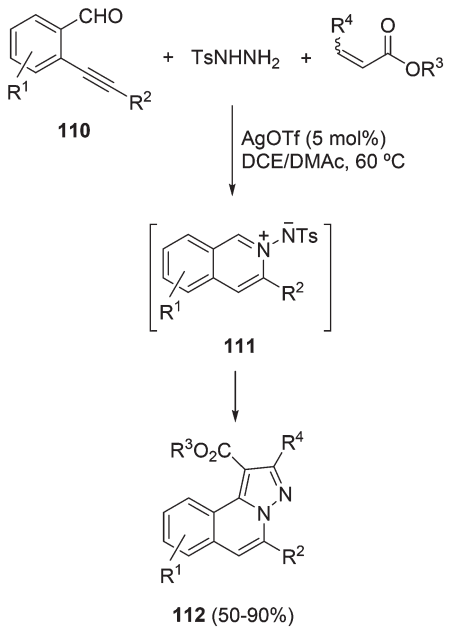
When an acetylenic dipolarophile is used, only a halogen or silver triflate promotes the [3 + 2] cycloaddition. Thus, *N*′-(2-alkynylbenzylidene)hydrazides **106** react with acetylenes either catalyzed by silver triflate or promoted by bromine or iodine in the presence of NaOAc. In the case of dimethyl 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)[58a] in the case of AgOTf or **116** (X = Br, I)[58b] 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-sulfonylamine-substituted isoquinolines **117** were obtained (Scheme 39).[59]

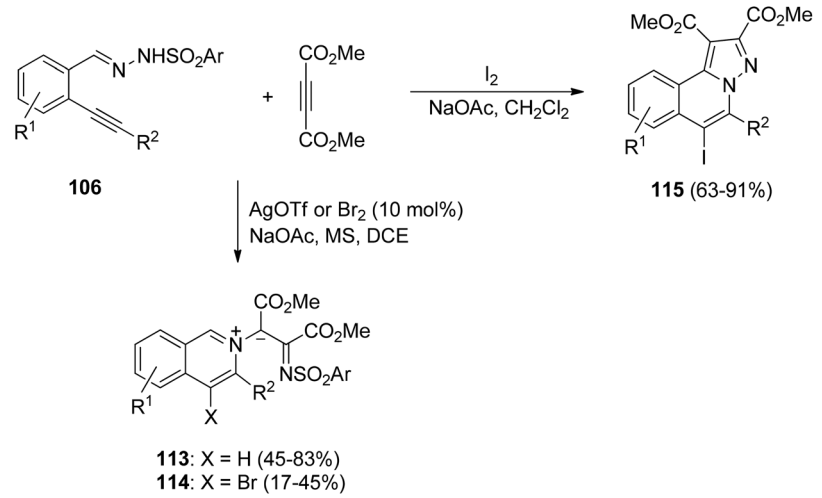
N-Allyl ynamides reacted with *N*′-(2-alkynylbenzylidene) hydrazides **106** in a process catalyzed by silver triflate and palladium acetate generating 2-amino-*H*-pyrazolo[5,1-*a*]isoquinolines **118** in good yields (Scheme 40).[60] In this case, the [3 + 2] cycloaddition takes place after the silver-promoted 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 alkynylation 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]

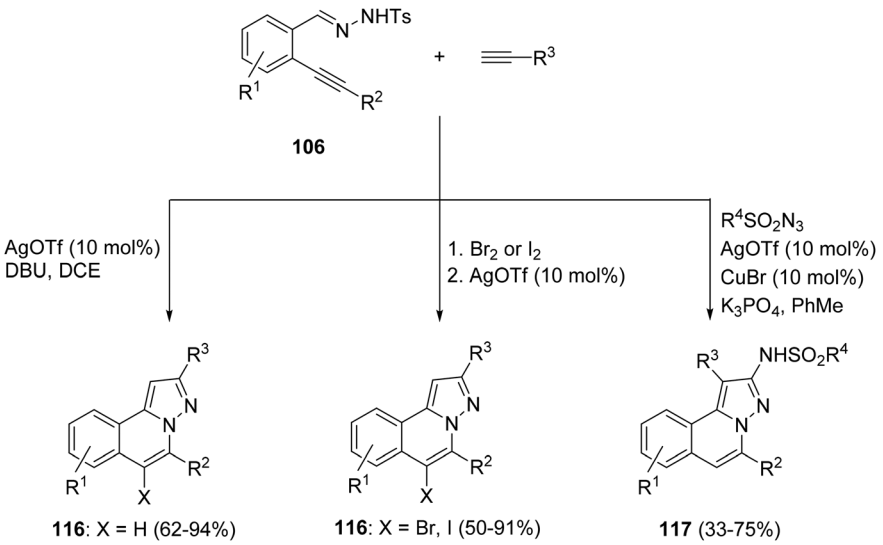
2-Trifluoromethylpyrazolo[5,1-*a*]isoquinolines **125** can be prepared from *N*′-(2-alkynylbenzylidene)hydrazides **106** and ethyl 4,4,4-trifluorobut-2-ynoate by means of the tandem silver triflate catalyzed cyclization and [3 + 2] cycloaddition of the



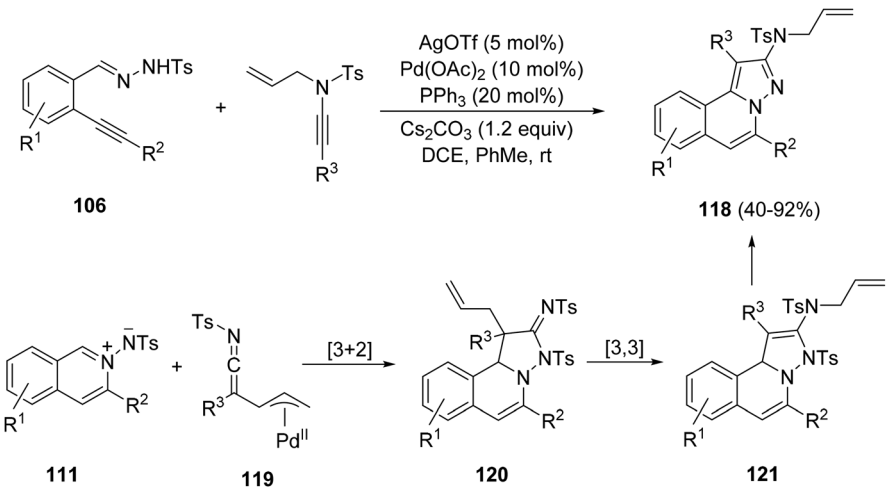
Scheme 37 Silver triflate-catalyzed three-component reaction of 2-alkynyl benzaldehydes **110**, tosyl hydrazide and α,β-unsaturated esters.



Scheme 38 Reaction of hydrazones **106** with dimethyl acetylenedicarboxylate.



Scheme 39 Reaction of hydrazides **106** with alkynes.



Scheme 40 Synthesis of compounds **118** by AgOTf and $Pd(OAc)_2$ catalyzed cascade reactions of hydrazides **106** with *N*-allyl ynamides.

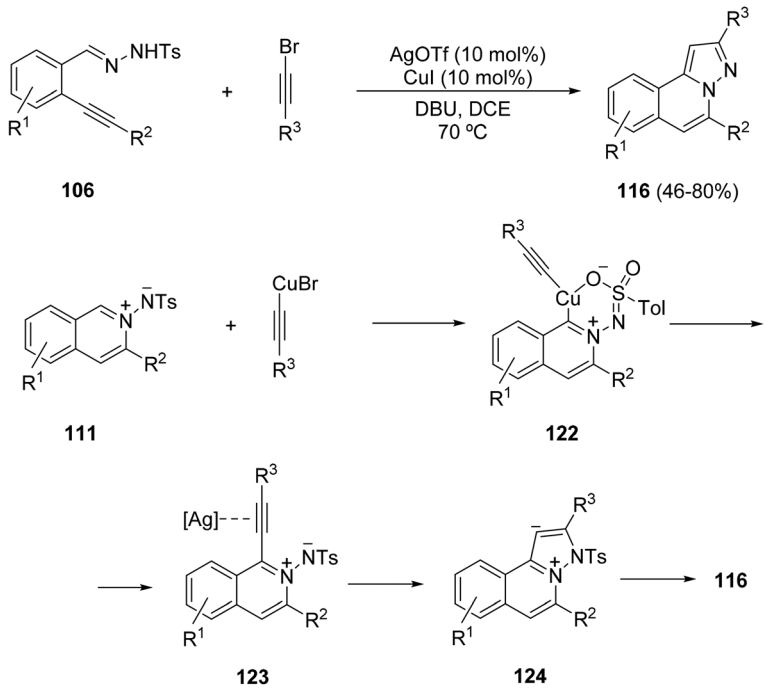
corresponding *N*-iminoisoquinolinium ylides **111** (Scheme 42).[62]

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-alkynylbenzylidine) 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]

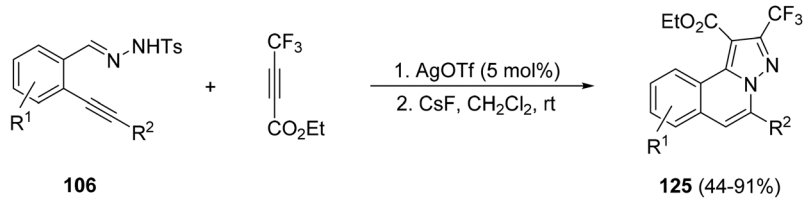
Propargyl amines afford [3 + 2] cycloadditions with *N*-iminoisoquinolinium ylides **111** generated *in situ* from hydrazides **106**, to give the corresponding *H*-pyrazolo[5,1-*a*]isoquinolines **130** bearing an aminomethyl substituent at the 5-position (Scheme 44).[64]

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]

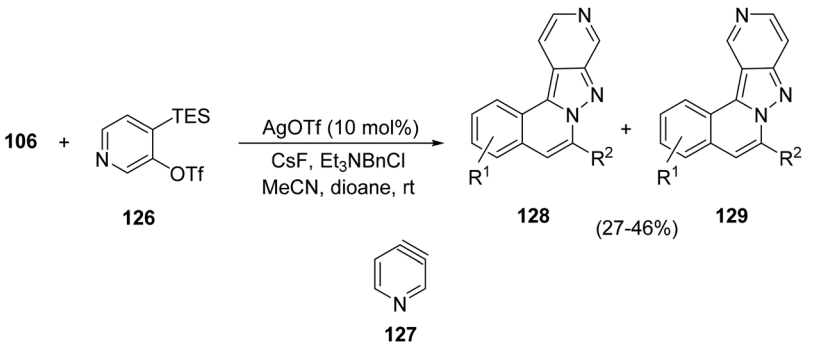
The multicomponent reaction of 2-alkynyl benzaldehydes **110**, tosyl hydrazide, methanol and α,β-unsaturated aldehydes catalyzed by silver triflate gave *H*-pyrazolo[5,1-*a*]isoquinolines **132** with excellent regioselectivity (Scheme 46).[66] Preliminary biological assays of these compounds show their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



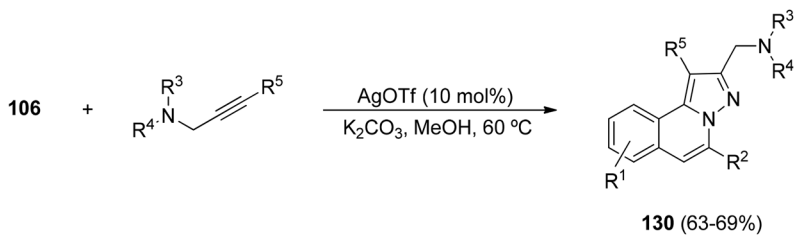
Scheme 41 Reaction of *N*-iminoisoquinolinium ylides **111** with bromoalkynes.



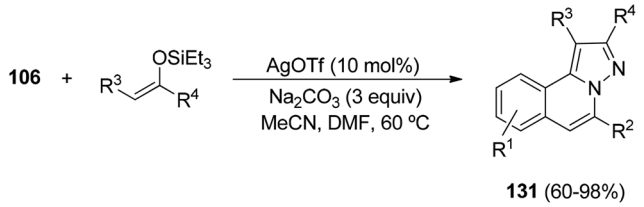
Scheme 42 Synthesis of compounds **125** by a [3 + 2] cycloaddition of *N*-iminoisoquinolinium ylides **111**.



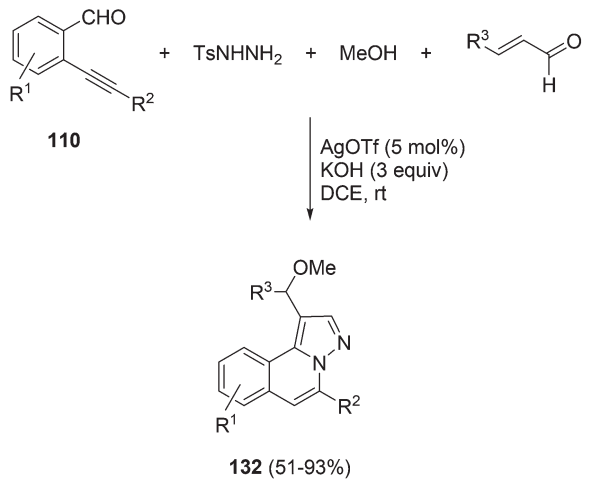
Scheme 43 Reaction of compound **106** with pyridyne **127**.



Scheme 44 Synthesis of compounds **130** from propargyl amines.

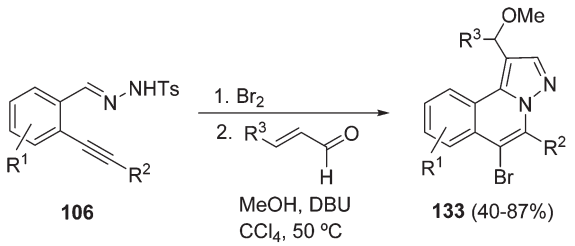


Scheme 45 Reaction of hydrazides with silyl enol ethers.



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

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 isoquinolines **133** (Scheme 47).[67]



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

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).[68]

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 **131** (Scheme 49).[69]

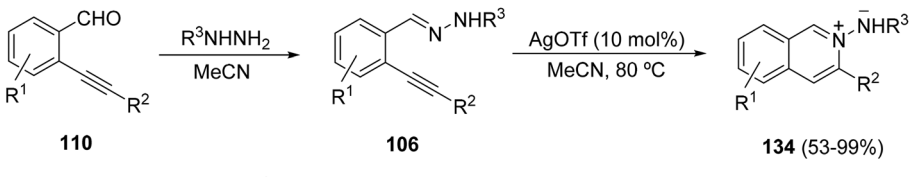
Alternatively, by using primary alcohols and hydrazides **106** instead of aldehydes **110**, the presence of the Dess–Martin reagent (DMP) as an oxidant is compulsory to afford 6-monosubstituted *H*-pyrazolo[5,1-*a*]isoquinolines **135** (Scheme 50).[70a,b]

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.[70c]

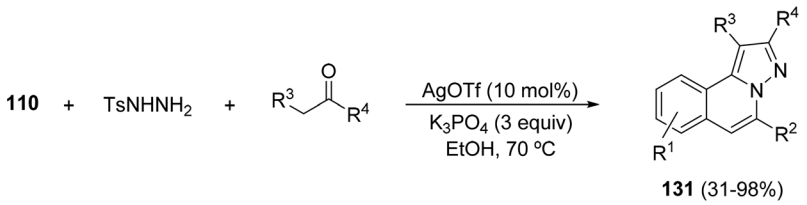
Silver triflate–copper(II) acetate cooperative catalysis has been used for the cyclization/[3 + 2] cycloaddition of *N*′-(2-alkynylbenzylidene) hydrazides **106** with allenoates **77** in the presence of dioxygen to afford *H*-pyrazolo[5,1-*a*]isoquinolines **136** (Scheme 51).[71a] The proposed mechanism involves a peroxycopper(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 Ph_3P as a catalyst the corresponding isoquinolines **136** were obtained with an R^3CH_2 group instead of the ketone functionality.[71b]

Silver–rhodium(I) cooperative catalysis has been used for the reaction of hydrazides **106** with cycloprop-2-ene-1,1-dicarboxylate[72] or with 2-vinyloxirane[73] 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.

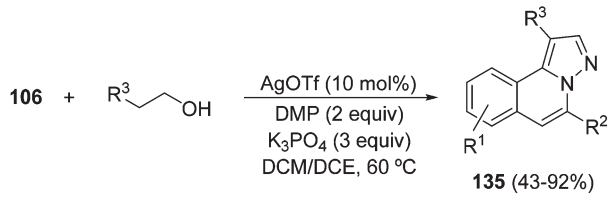
When silver triflate and copper(II) chloride are used as cooperative catalysts it is possible to prepare *H*-pyrazole[5,1-*a*]-isoquinolines **135** through a three-component process. Thus, 2-alkynyl benzaldehydes, tosyl hydrazide and tertiary amines in air gave products **135** by a silver-catalyzed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



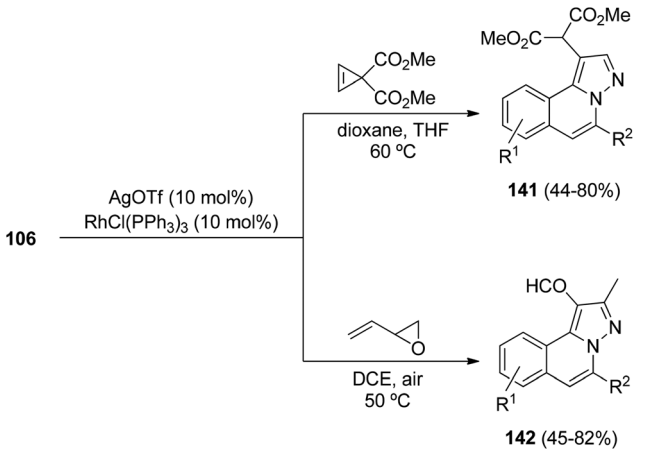
Scheme 48 Synthesis of isoquinolinium-2-yl imides **134**.



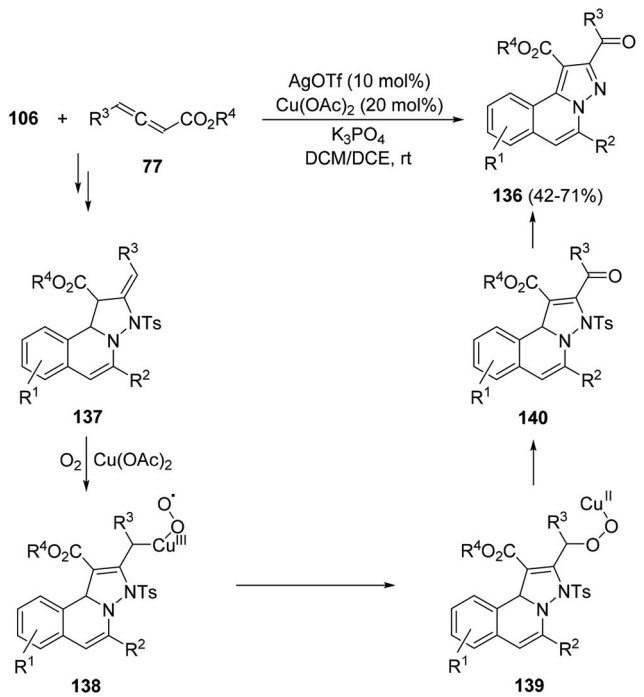
Scheme 49 One-pot tandem reaction of 2-alkynyl benzaldehydes, tosylhydrazide and carbonyl compounds.



Scheme 50 Tandem reaction of hydrazides **106** with alcohols.



Scheme 52 Silver–rhodium(I) cooperative catalysis in the reaction of **106** with cycloprop-ene-1,1-dicarboxylate or 2-vinyloxirane.



Scheme 51 Reaction of hydrazides **106** with allenoates **77** in the presence of dioxygen cocatalyzed by silver triflate and copper(II) acetate.

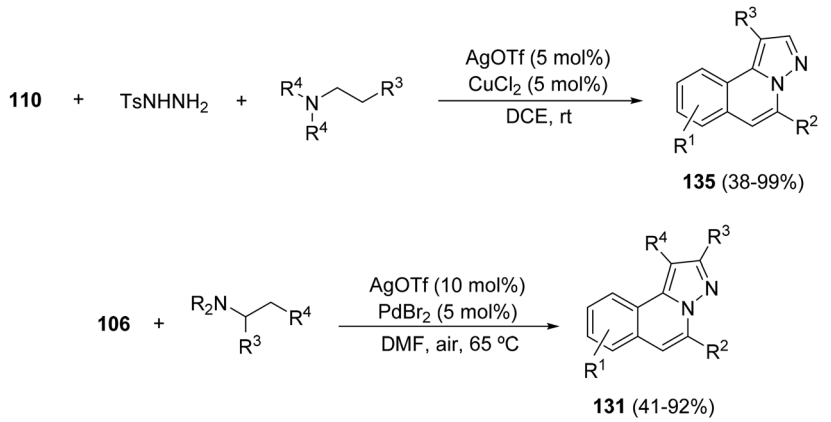
copper(II)-catalyzed oxidation of an aliphatic C–H bond of the tertiary amine in air (Scheme 53).[74] A related process using palladium dibromide as a cocatalyst gave isoquinolines **131**, which has been performed starting from the hydrazides **106** instead of aldehydes **110** (Scheme 53).[75a] The same transformation has been previously performed using $Fe_2(CO)_9$ as a cocatalyst (5 mol%) and *tert*-butyl hydroperoxide (3 equiv.) affording products **135** in 46–83% yields.[75b]

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).[76] In this case, the Wu *et al.*[56] 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**.

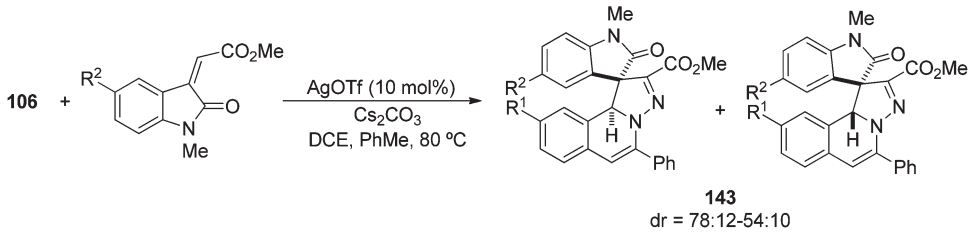
In general, these unsaturated isoquinolinium imides have been mainly used in [3 + 2] cycloaddition with acetylenic dipolarophiles. The only example of a [3 + 3] cycloaddition of azomethine imines **144** has been performed using cyclopropane diesters and a $Ni(ClO_4)_2$ complex with trisoxazoline derivatives **146** as a chiral ligand.[77] 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.*[78] with *N*-benzoyliminoisoquinolinium ylide and methyl 2-phenylcyclopropane-1,1-dicarboxylate catalyzed by $Ni(ClO_4)_2$ in a modest yield (21%).

3.3 Pyridinium and quinolinium imides

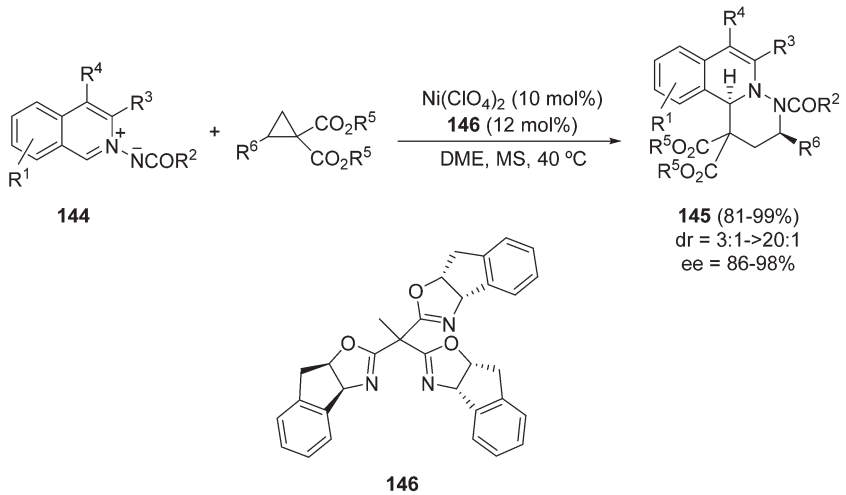
Pyridinium imides **147**, also called *N*-iminopyridinium ylides or pyridin-*N*-imines, are masked cyclic azomethine imines incorporating C–N into the ring, which react mainly with acetylenic dipolarophiles.[10] They are unstable and have to be generated *in situ* from *N*-aminopyridinium halides and since the



Scheme 53 Amines as reagents for the synthesis of compounds **131** and **135**.

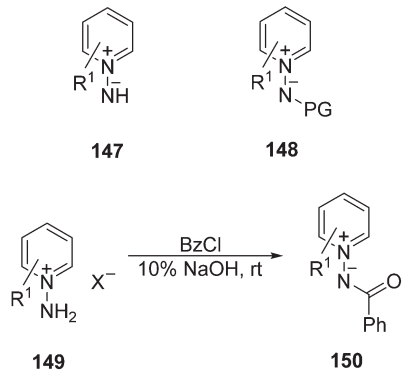


Scheme 54 Preparation of fused spirooxindoles **143**.

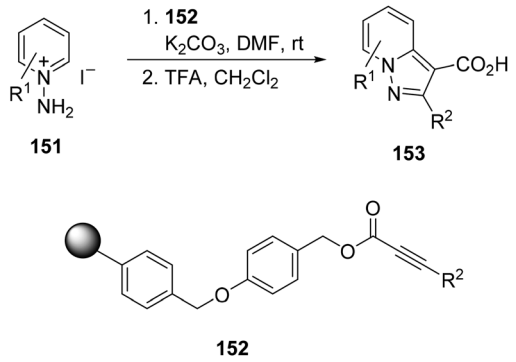


Scheme 55 Enantiocatalyzed [3 + 3] cycloaddition of azomethine imines **144** and cyclopropane diesters.

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 afford ylides **148**. *N*-Benzoyliminopyridinium ylides **150** have been the most used imines of this family. They can be prepared by benzoylation of the corresponding *N*-aminopyridinium salts **149** (Scheme 56) easily accessible by direct *N*-amination of pyridine using hydroxylamine-*O*-sulfonic acid.[79–81] Alternatively, *N*-aminopyridinium salts **147** can be prepared using different electrophilic amination reagents, especially efficient being *O*-(2,4-dinitrophenyl) hydroxylamine, which gave good yields with



Scheme 56 Synthesis of *N*-benzoyliminopyridinium ylides **150**.



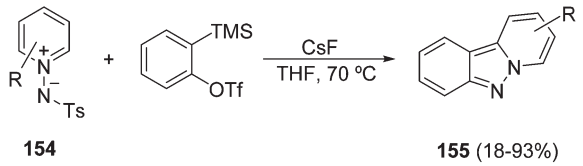
Scheme 57 Solid-phase synthesis of pyrazolopyridines **153** by a [3 + 2] cycloaddition of pyridinium imides with polymer-bound propiolates **152**.

several types of substituted pyridines, quinolines and isoquinolines.[82]

By using alkynes as dipolarophiles pyrazolopyridines can be prepared[83] 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 antiherpetic[87] and antiallergenic[88] 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 *in situ* generation of pyridinium imides **147** from *N*-aminopyridinium salts **151** followed by TFA cleavage (Scheme 57). Alternatively, by using NaOMe in THF/MeOH the corresponding methyl esters can be isolated.[89]

In the case when arynes are used as dipolarophiles and pyridinium imides **148** with different electron-withdrawing groups on the imide nitrogen, it was found that the pyrido[1,2-*b*]-indazoles **155** are obtained in high yields (Scheme 58) using the tosyl derivatives **154**, whereas the benzoyl, pivaloyl, benzyloxycarbonyl, and *tert*-butyloxycarbonyl ones gave lower results.[90] This methodology has been also used with *N*-tosylisoquinolinium imides to afford indazolo[3,2-*a*]isoquinolines.



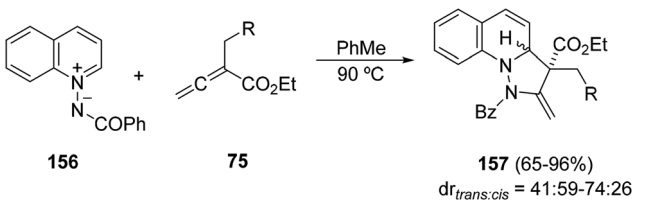
Scheme 58 Synthesis of pyrido[1,2-*b*]indazoles **155** by aryne [3 + 2] cycloaddition with *N*-tosyl pyridinium imides.

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.

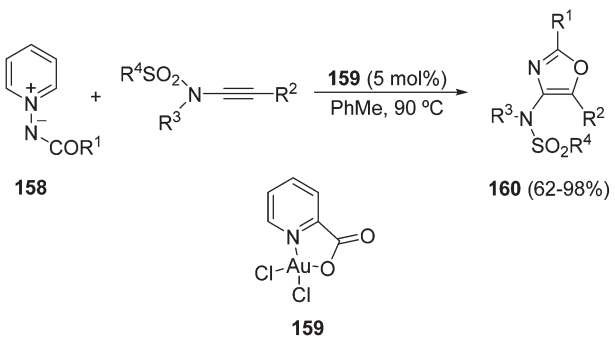
A formal [3 + 2] cycloaddition catalyzed by a gold complex **159** between *N*-benzoyliminopyridinium ylides **158** and *N*-alkynylsulfonamides gave 2,4,5-trisubstituted oxazoles **160** in high yields (Scheme 60).[92]

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] This cycloaddition has also been performed with the *N*-benzoylisoquinolinium ylide with a modest yield (21%).

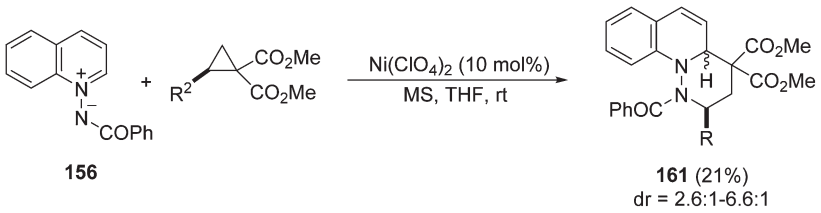
An enantioselective formal [3 + 3] cycloaddition has been performed also with *N*-benzoylpyridinium ylides **158** and sily-



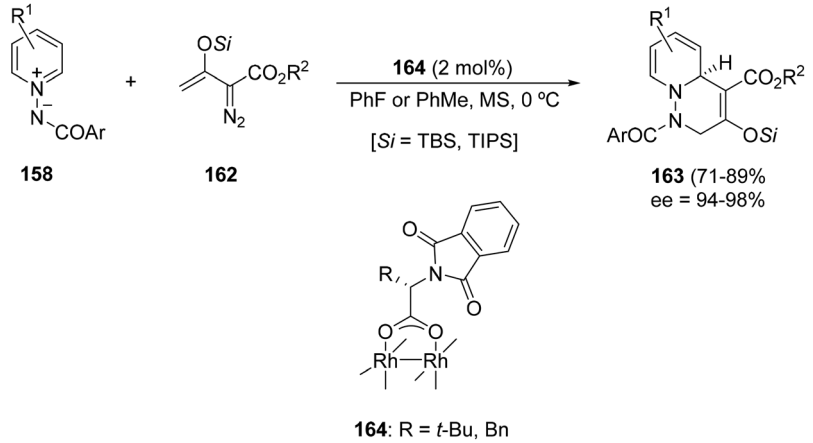
Scheme 59 Thermal [3 + 2] cycloaddition of *N*-benzoylquinolinium imide **156** with allenoates.



Scheme 60 Gold-catalyzed formal [3 + 2] cycloaddition of *N*-benzoyliminopyridinium ylides **158** with *N*-alkynyl sulfonamides.



Scheme 61 Ni-catalyzed formal [3 + 3] cycloaddition of quinolinium imides and 1,1-cyclopropane diesters.



Scheme 62 Rh-catalyzed formal [3 + 3] cycloaddition of *N*-acylpyridinium ylides **158** with silylated enol diazoacetates **162**.

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.

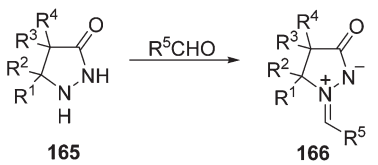
4 Cyclic azomethine imines incorporating a N–N bond in a ring

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 tetrahydropyrazolopyrazolones, -pyridazinones, -diazepinones, and -diazocinones, which are important products or intermediates for the preparation of useful chemicals and diverse bioactive molecules.

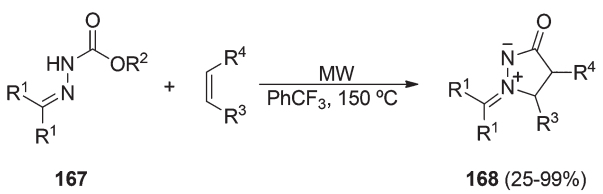
4.1 *N*-Alkylidene-3-oxopyrazolidin-1-ium-2-ides

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



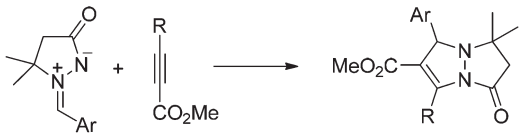
Scheme 63 Synthesis of azomethine imines **166** from pyrazolidin-3-ones **165**.



Scheme 64 Synthesis of azomethine imines **168** from hydrazones **167** and alkenes.

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-1*H*,5*H*-pyrazolo[1,2-*a*]-pyrazol-1-ones **170** (Scheme 65).[94]

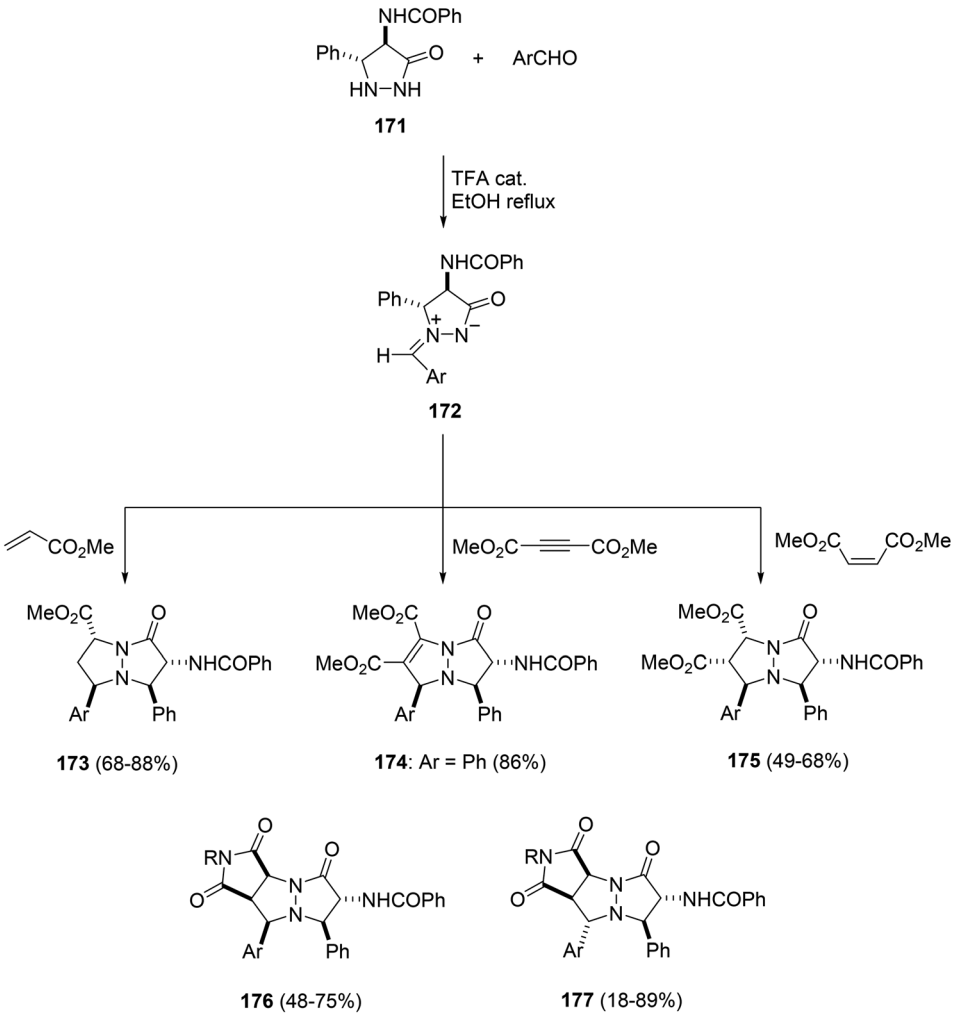


169 **170** (20-97%)

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]

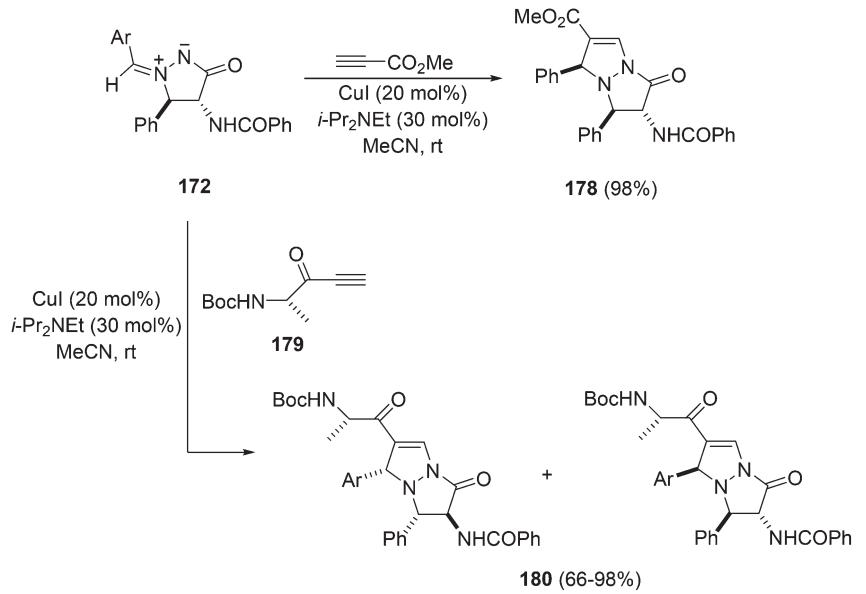
In the case of the Cu(I)-catalyzed [3 + 2] cycloaddition of azomethine imines **172** (Ar = Ph) it takes place at room temperature in acetonitrile using Hünig's base with methyl propio-



173 (68-88%) **174**: Ar = Ph (86%) **175** (49-68%)

176 (48-75%) **177** (18-89%)

Scheme 66 Diastereoselective [3 + 2] cycloaddition of azomethine imines **172** with dipolarophiles.

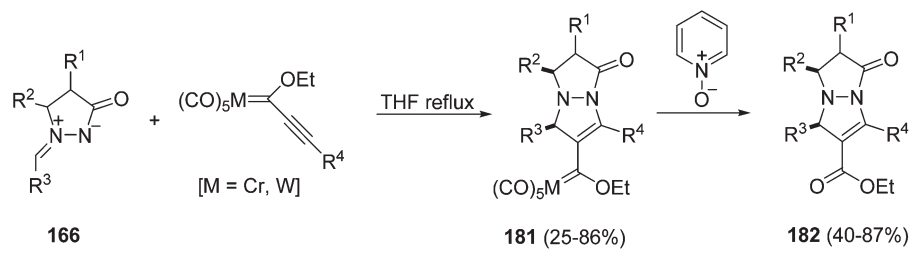


Scheme 67 Diastereoselective Cu(I)-catalyzed [3 + 2] cycloaddition of azomethine imine **172** with acetylenic dipolarophiles.

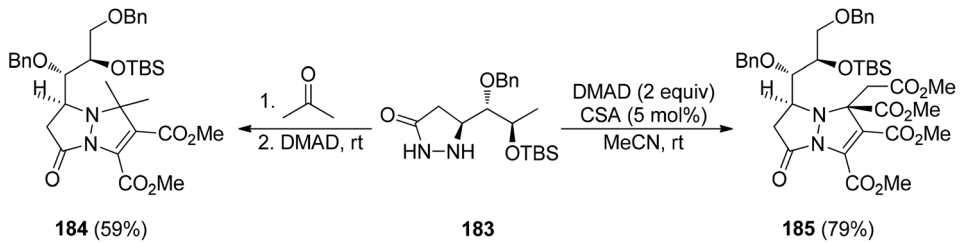
late giving the product **178** (Scheme 67).[101] When the chiral ynone **179** was allowed to react with **172** a mixture of diastereomeric cycloadducts **180** was obtained.

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.[102] 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).[103]

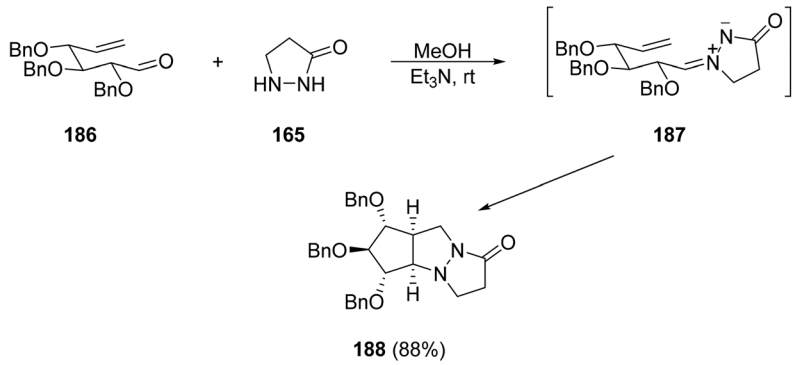
Several pyrazolidin-3-ones bearing a chiral chain have been applied as precursors of chiral azomethine imines in diastereoselective [3 + 3] cycloadditions. Thus, 5-substituted pyrazolidin-3-ones **183** derived from 2,3-unsaturated sugar 1,5-lactones react at room temperature with acetone and then with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



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



Scheme 69 Diastereoselective [3 + 2] cycloaddition of **183** with DMAD.



Scheme 70 Synthesis of polyoxygenated diazatriquinane **188** *via* intramolecular diastereoselective [3 + 2] cycloaddition.

cycloadduct **184** or two equivalents of DMAD, under camphorsulfonic 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.

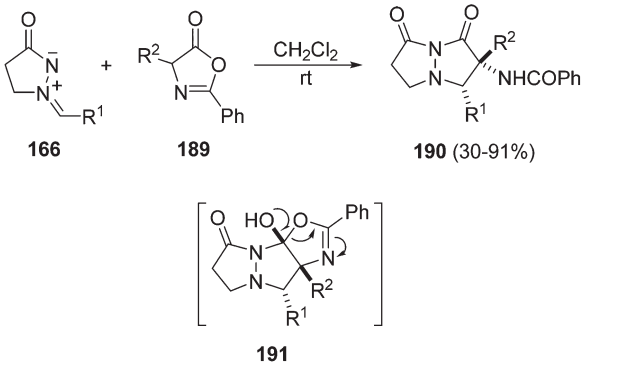
Different types of dipolarophiles have been investigated under thermal conditions with azomethine imines **166** derived from unsubstituted **165**, for example, acetylenic sulfones,[106] arynes,[107] β-nitrostyrenes,[108] cyclic vinyl sulfones,[109] and trifluoroethylidene malonates.[110] In the case 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 = Ph) with ethyl acrylate at room temperature in the presence of 0.5 equivalent of Cy_2NMe in dichloromethane, giving regioselectively the corresponding cycloadduct in 88% yield. After establishing these reaction conditions, different chiral ligands were assayed, the phosphaferrocene 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]

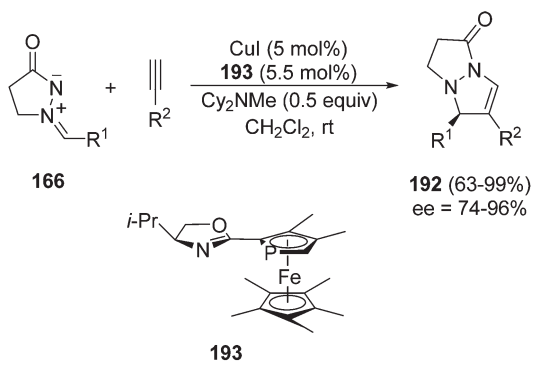
The [3 + 2] cycloaddition of azomethine imines **169** with the *N*-acryloylpyrazolidinone **194** catalyzed by the chiral complex Cu(OTf)$_2$·bisoxazoline **196** gave regio- and diastereoselectively *exo*-cycloadducts **195** in good yields (Scheme 74).[114] These processes have been performed only 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]

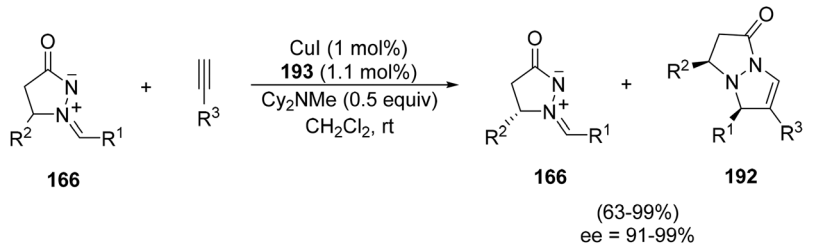
The same group developed a better ligand PyBodine (L-Ala) **199**, which is able to perform this cycloaddition with Cu(OAc)$_2$ as a metallic salt in better yields and enantioselectivities (Scheme 76).[116]



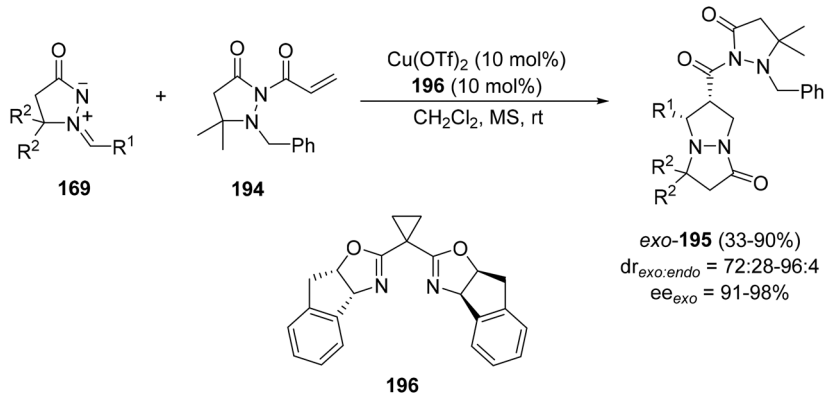
Scheme 71 [3 + 2] Cycloaddition of azomethine imines **166** with azlactones **189**.



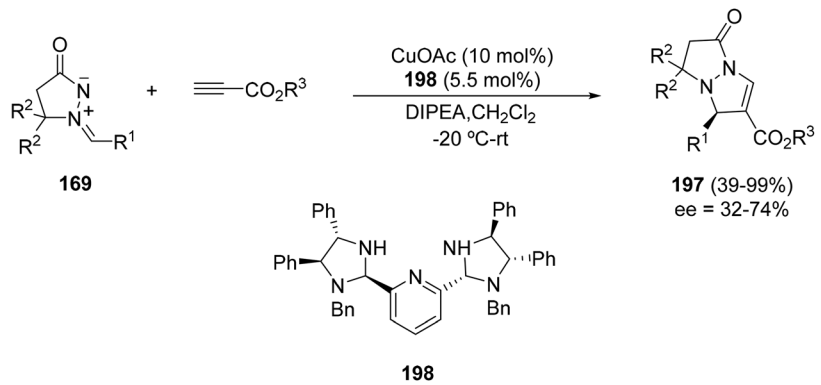
Scheme 72 Enantioselective copper-catalyzed [3 + 2] cycloaddition of azomethine imines ylides **166** with terminal alkynes.



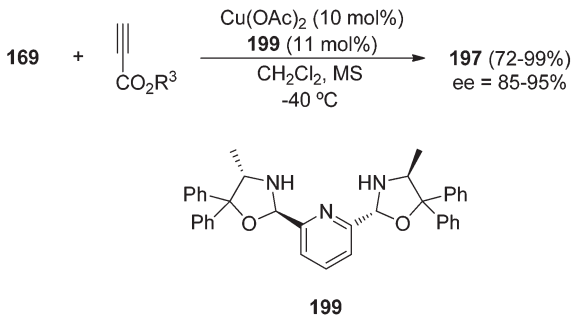
Scheme 73 Kinetic resolution of azomethine imines *via* a copper-catalyzed [3 + 2] cycloaddition.



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



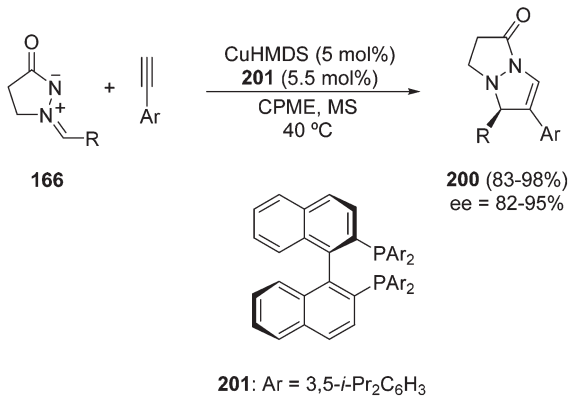
Scheme 75 Enantioselective copper-catalyzed [3 + 2] cycloaddition of azomethine imines **169** with propiolates using ligand **198**.



Scheme 76 Enantioselective copper-catalyzed [3 + 2] cycloaddition of **169** with propiolates using ligand **199**.

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.

By using propiolylpyrazoles **202** as acetylenic dipolarophiles, terminal and internal alkynes gave very good enantio-



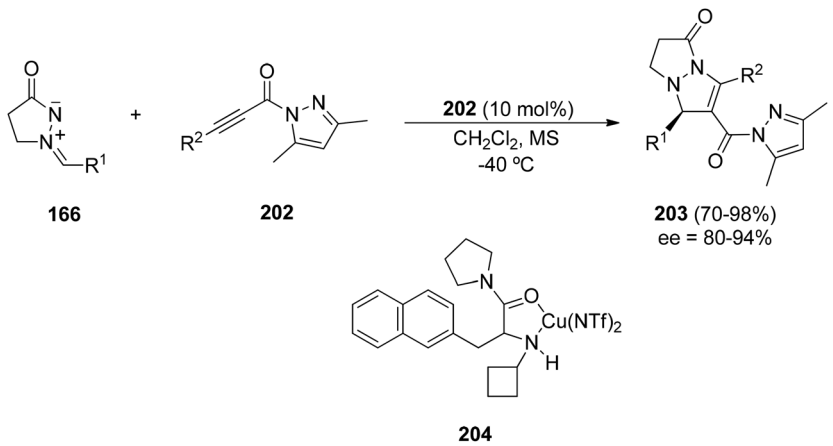
Scheme 77 Enantioselective copper-catalyzed [3 + 2] cycloaddition of azomethine imines **166** with terminal alkynes.

selection in the [3 + 2] cycloaddition of azomethine imines **166** catalyzed by a chiral π-cation catalyst **204** (Scheme 78).[119] 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).

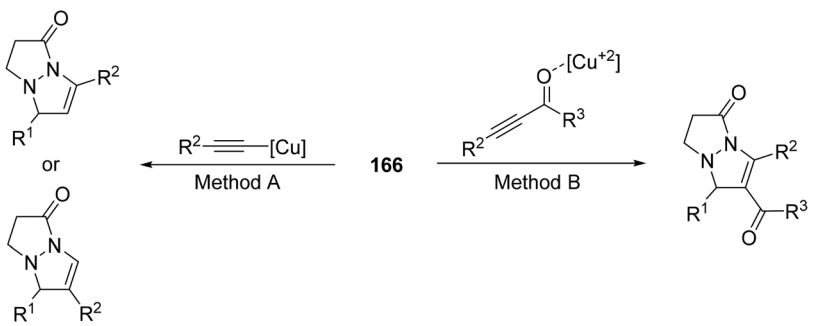
The racemic copper-catalyzed [3 + 2] cycloaddition has been performed not only with CuI but also with Cu(I) zeolites as the heterogeneous ligand-free catalysts.[120,121] They are easy to be removed by simple filtration and can be recycled up to six times without decreasing the efficiency. Heterogeneous supported copper hydroxide $Cu(OH)_x/Al_2O_3$ has also been used as an efficient reusable catalyst.[122]

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_P)-*t*-Bu-Phosferrox **207** as a ligand and AgOAc or $Cu(MeCN)BF_4$ 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).[123]

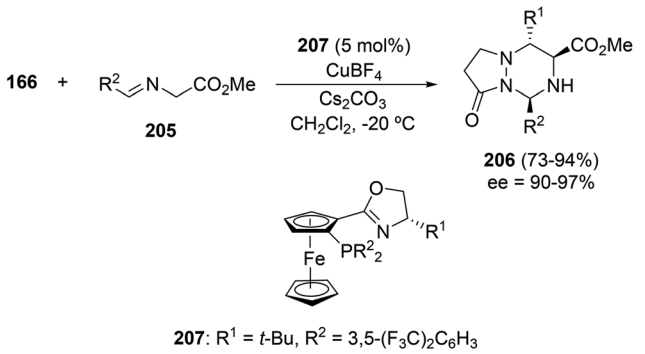
Independently, a similar [3 + 3] cycloaddition has been performed using the ferrocenyl P,N-chiral ligand **208** and the $Cu(MeCN)_4ClO_4$ salt as a catalyst. This process takes place giving products **206** with good yields (71–89%), diastereo- (>20 : 1) and enantioselectivities (50–96%).[124]



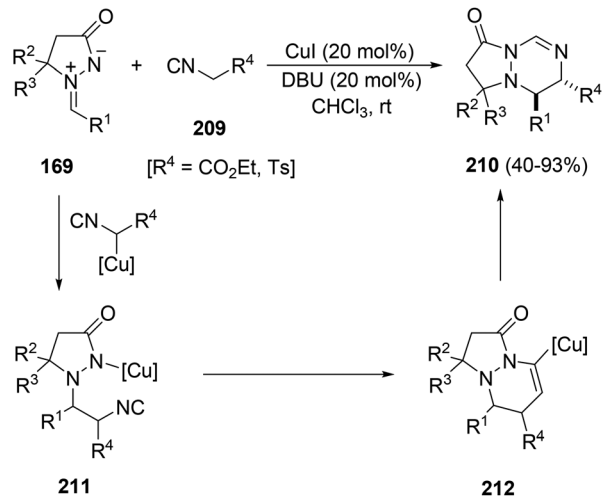
Scheme 78 Enantioselective copper-catalyzed [3 + 2] cycloaddition of **166** with propiolylpyrazoles catalyzed by the chiral complex **202**.



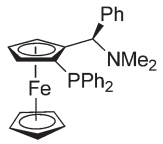
Scheme 79 Strategies for the copper-catalyzed [3 + 2] cycloaddition of azomethine imines **166** with alkynes.



Scheme 80 Enantioselective copper-catalyzed [3 + 3] cycloaddition of azomethine ylides and azomethine imines.



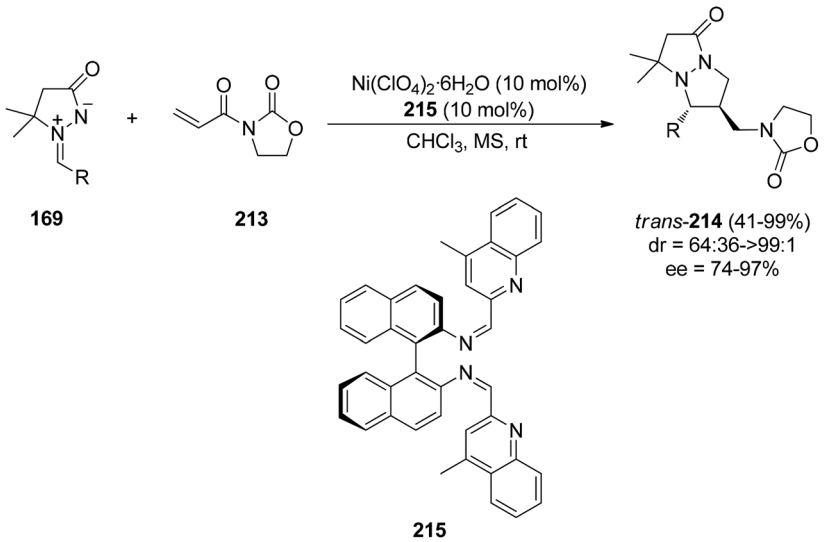
Scheme 81 [3 + 3] Cycloaddition of azomethine imines **169** and isocyanides **209** catalyzed by CuI.



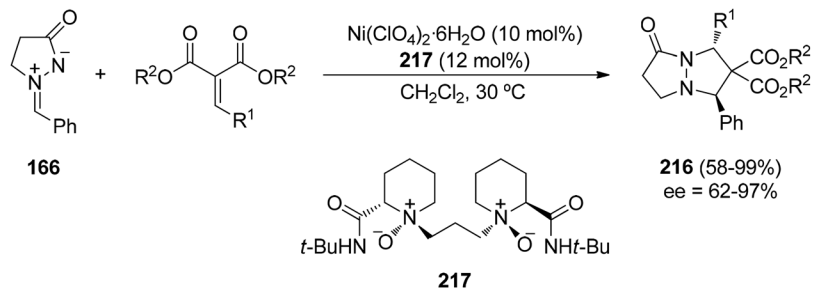
Isocyanides **209** and azomethine imines **169** gave a [3 + 3] cycloaddition to give pyrazole[1,2-*a*]triazin-8(4*H*)-ones **210** (Scheme 81).[125] The process takes place with high stereocontrol using CuI as a catalyst and DBU as a base at room temperature. Silver salts and other copper salts provided lower yield than CuI. The proposed mechanism involves the formation of the α-cuprioisocyanide followed by nucleophilic addition to the imine and final insertion of the isonitrile **211** into the N–Cu bond to give the imidoyl-copper intermediate **212** 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 cycloadducts *trans*- and *cis*-**214** (Scheme 82).[126] 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(II) atom of the acryloyloxazolidinone. A dipole–HOMO/dipolarophile–LUMO controlled asymmetric 1,3-DC is proposed.

Recently, a Ni(II)-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).[127] The reaction also proceeds by a dipole–HOMO/dipolarophiles–LUMO inter-



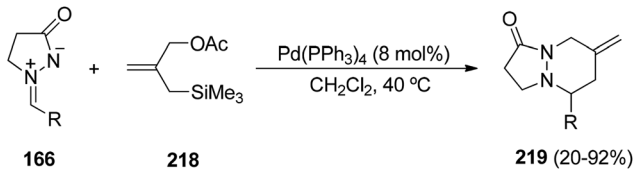
Scheme 82 Enantioselective Ni(II)-catalyzed [3 + 2] cycloaddition of azomethine imines **169** and 3-acryloyl-2-oxazolidinone **213**.



Scheme 83 Enantioselective Ni(II)-catalyzed [3 + 2] cycloaddition of the azomethine imine **166** and alkylidene malonates.

action, the Ni-complex acting as a chiral Lewis acid coordinating the two carbonyl groups of the alkylidene malonate.

The palladium-catalyzed [3 + 3] cycloaddition of trimethylenemethane (TMM) with azomethine imines **166** led to the formation 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 hexahydropyridazines in high diastereoselectivity. However, using substituted TMM different products are formed.



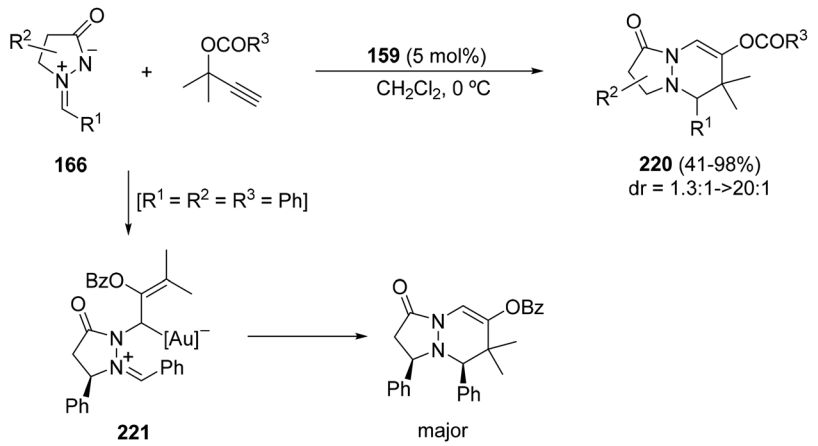
Scheme 84 Palladium-catalyzed [3 + 3] cycloaddition of trimethylenemethane with the azomethine imines **166**.

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 intermediate. 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]

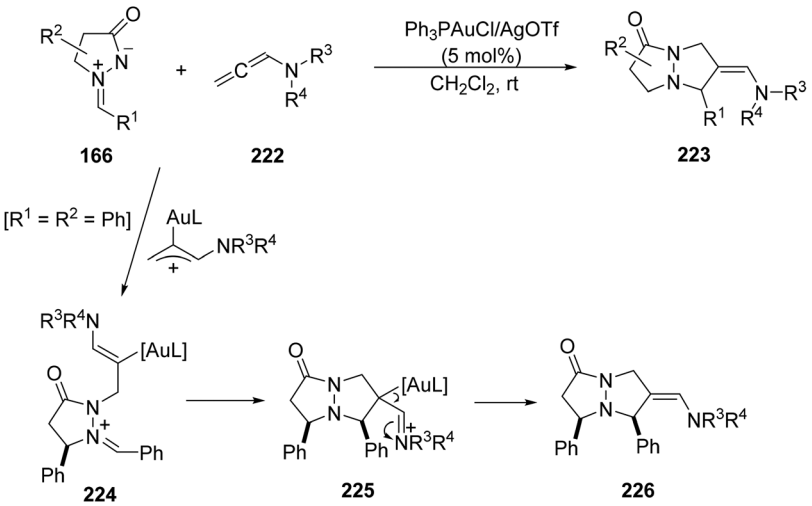
N-Allenyl amides **222** underwent 1,3-DC of azomethine imines **166** under gold(I) catalysis to provide [3 + 2] cycloadducts **223** (Scheme 86).[131] This process can occur through a gold allene intermediate, which can give another intermediate **224** by an outer-sphere nucleophilic addition. Subsequent intramolecular cycloaddition of **224** yielded the iminium intermediate **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]

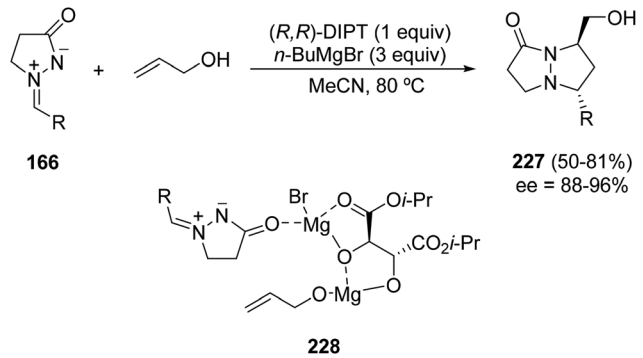
Under similar reaction conditions homoallylic alcohols have been used for this type of [3 + 2] cycloaddition. In this



Scheme 85 Gold(III)-catalyzed [3 + 3] cycloaddition of azomethine imines **166** with propargyl esters.

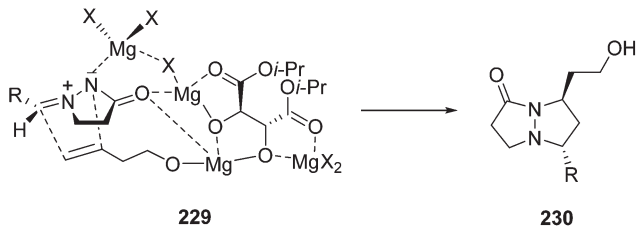


Scheme 86 Gold(I)-catalyzed [3 + 2] cycloaddition of **166** with *N*-allenyl amides **222**.



Scheme 87 Enantioselective [3 + 2] cycloaddition of azomethine imines **166** with allyl alcohol catalyzed by magnesium diisopropyl (*R*,*R*)-tartrate.

case only 20 mol% of DIPT, one equivalent of $MgBr_2$ 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 coordinated 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]



Scheme 88 Enantioselective [3 + 2] cycloaddition of azomethine imines **166** and homoallyl alcohol catalyzed by magnesium diisopropyl tartrate.

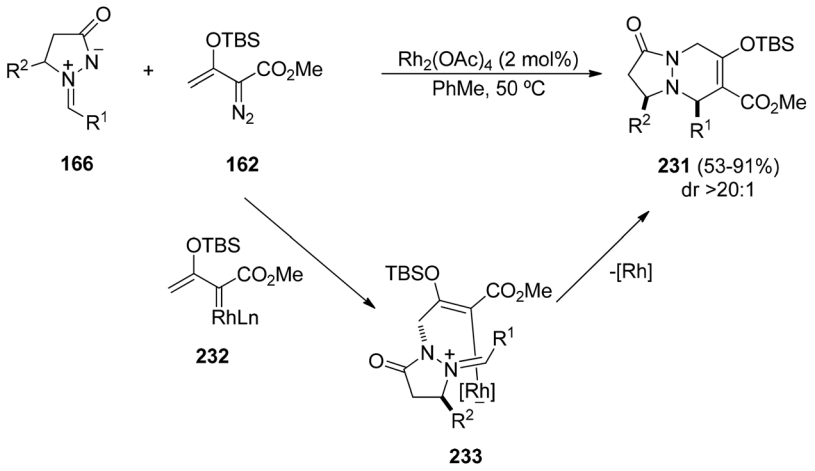
Doyle *et al.* have studied enol diazoacetate **162** as a dipolarophile for the [3 + 2] cycloaddition with azomethine imines **166** catalyzed by $Sc(OTf)_3$ or $In(OTf)_3$ as Lewis acids.[136] The corresponding cycloadducts **232** are obtained diastereoselectively in good yields. Selective 1,2-C→C and N→C migrations catalyzed by rhodium(II) salts or $CuPF_6$ 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 azomethine imine attacks the vinylogous position of the Rh(II)-vinyl carbine **232** to give the intermediate **233**, which after subsequent 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.**

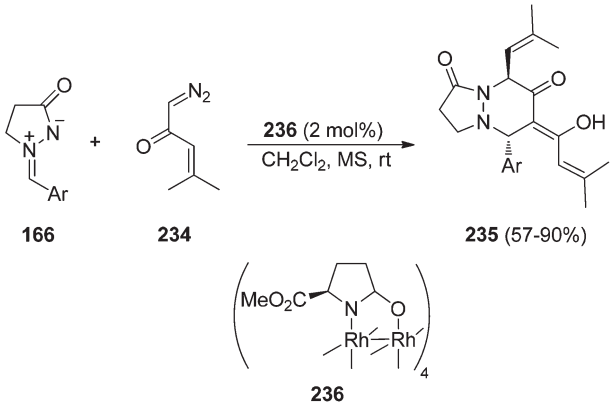
4.1.4 Metal-free-catalyzed cycloadditions. Different types of Lewis bases such as amines, phosphines and Lewis and Brønsted acids have been used for the racemic and enantioselective 1,3-DC of azomethine imines with dipolarophiles.

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 activation takes place by iminium formation giving the corres-

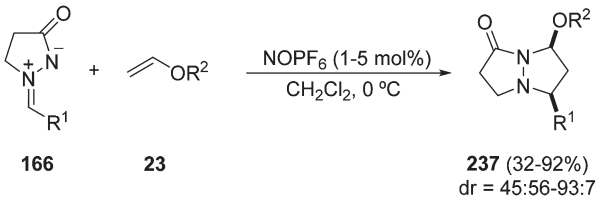


Scheme 89 Rh-catalyzed [3 + 3] cyclization of enol diazoacetate **162** with azomethine imines **166**.

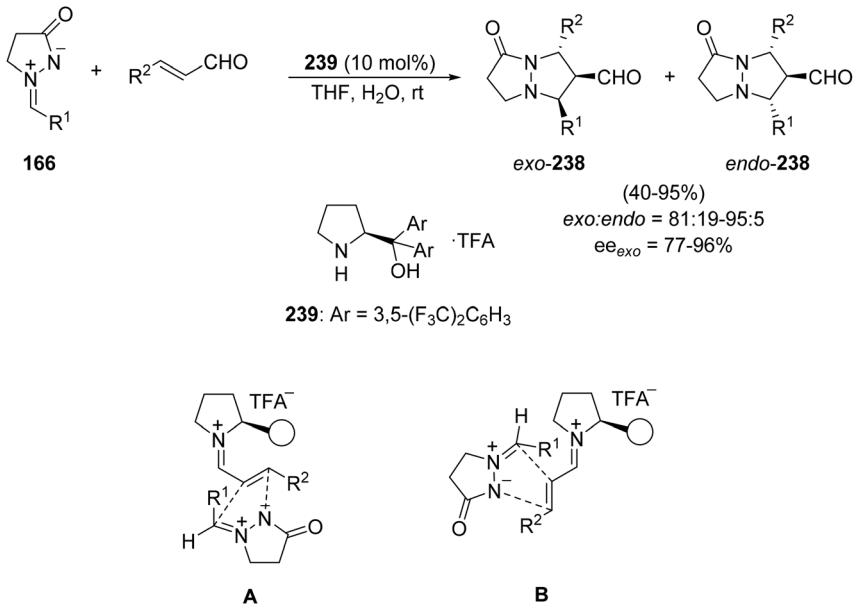


Scheme 90 Rh(II)-catalyzed formal [3 + 2 + 1] annulations of azomethine imines **166** and diazoketone **234**.

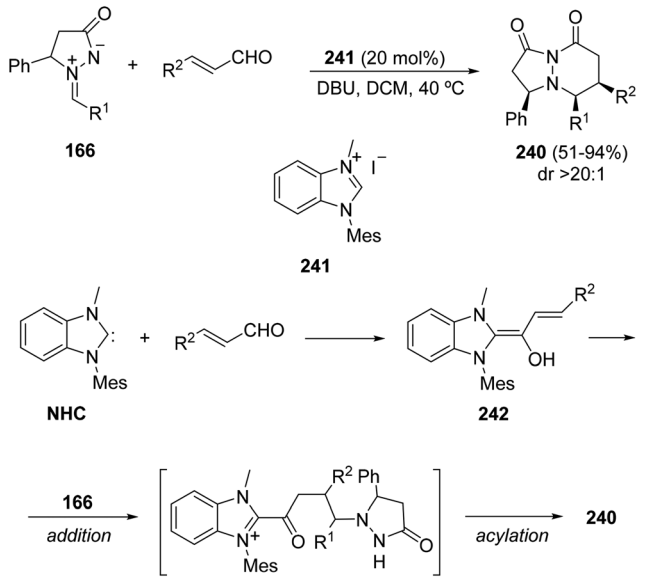
ponding fused pyrazolidinones **238** mainly with *exo*-selectivity and high enantioselectivities (Scheme 92).[140] The possible reaction models for this 1,3-DC are illustrated in Scheme 92:



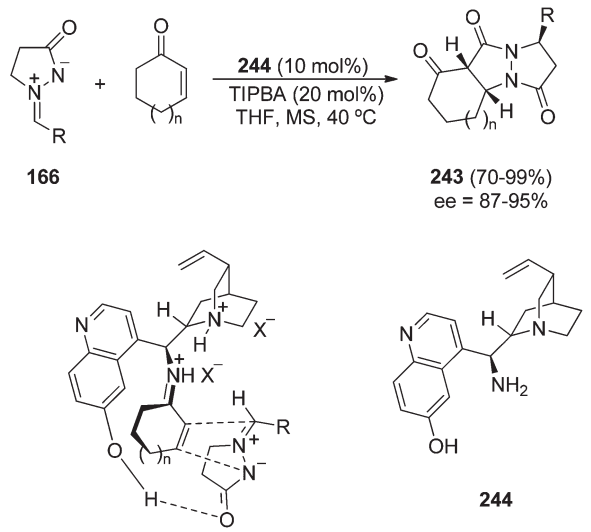
Scheme 91 NO cation-catalyzed [3 + 2] cycloaddition of azomethine imines **166** with vinyl ethers.



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



Scheme 93 NHC-catalyzed [3 + 2] cycloaddition of azomethine imines **166** with enals.



Scheme 94 Enantioselective organocatalyzed [3 + 2] cycloaddition of cyclic enones to **166**.

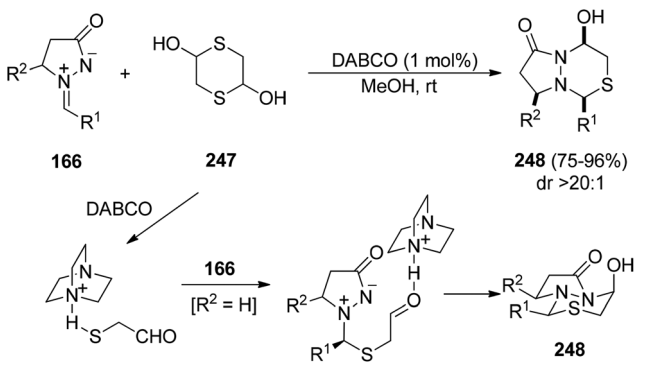
both transition states **A** and **B** with s-*cis* and s-*trans* conformations, respectively, would afford the *exo*-cycloadducts.

When this reaction is catalyzed by N-heterocyclic carbenes, a highly stereoselective formal [3 + 3] cycloaddition takes place to provide pyridazinones **240** (Scheme 93).[141] 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**.

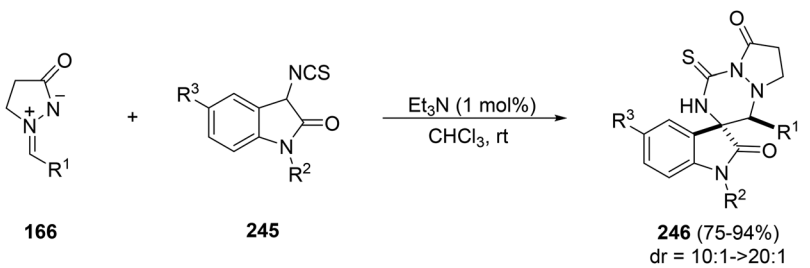
The enantioselective [3 + 2] cycloaddition of cyclic enones and azomethine imines **166** has been performed in the presence of the chiral primary amine 9-amino-9-deoxyepiquinine **244** and 2,4,6-triisopropylbenzenesulfonic acid (TIPBA) as a catalyst (Scheme 94).[142] The corresponding tricyclic pyrazolidinones **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-isothiocyanatooxindoles **245** to azomethine imines **166** gave 3,3′-triazinyl spirooxindoles **246** (Scheme 95).[143] 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



Scheme 96 DABCO-catalyzed [3 + 3] cycloaddition of mercaptoacetaldehyde to **166**.



Scheme 95 Base-catalyzed [3 + 3] cycloaddition of isothiocyanatooxindoles **245** with **166**.

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.[144] 5-Methyl and 5-phenyl substituted azomethines **166** gave the all *cis*-cycloadducts **248**.

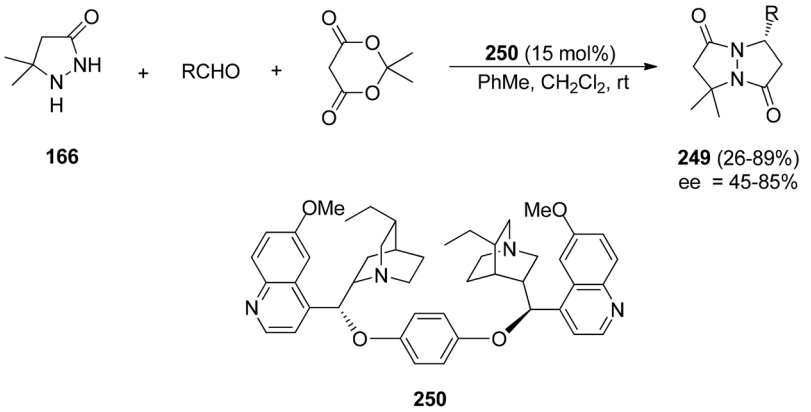
The multicomponent synthesis of pyrazolidinones **249** has been performed starting from **165**, the aldehyde and Meldrum's acid. This process was organocatalyzed by $(DHQ)_2PHAL$ **250** acting as a chiral base. A domino Knoevenagel-aza-Michael-cyclocondensation reaction gave the resulting cycloadducts **249** in good yields and enantioselectivities (Scheme 97).[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 β-carbon of the α-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).[42]

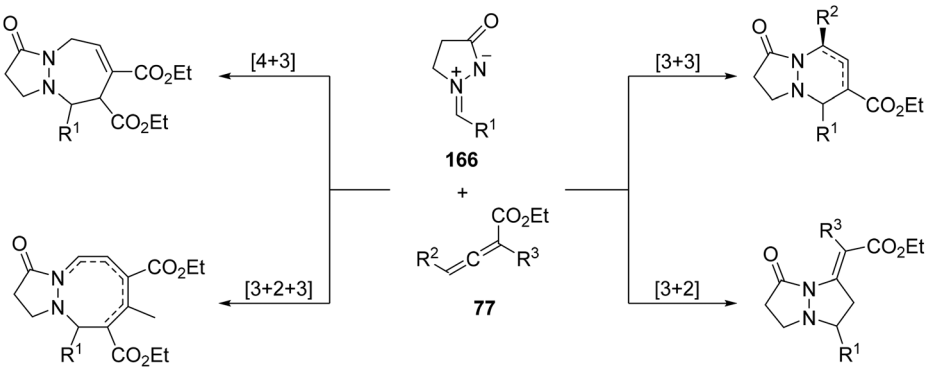
Ethyl 2-methylbuta-2,3-dienoate **75** reacted with azomethine imines **166** under tri-*n*-butylphosphine-catalyzed [3 + 2] cycloaddition to afford the exocyclic alkylidene adducts **251** as single isomers (Scheme 99).[146] By using a chiral phosphine **253**, the product **251** (with R^1 = Ph) was obtained in 56% yield and 89% ee. When azomethine imine **166** [with R = 4-$(O_2N)C_6H_4$] was allowed to react with other α-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).[146] It has been proposed that zwitterionic intermediates **A** and **B** gave the five- and the six- or seven-membered ring, respectively.

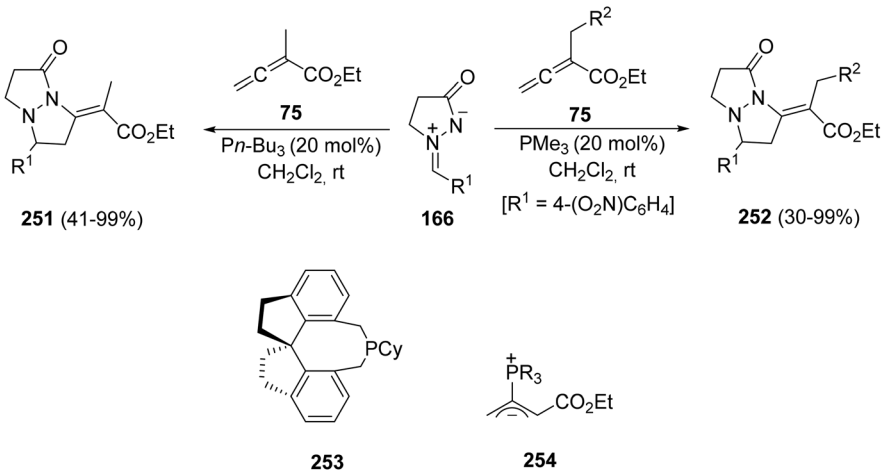
For unsubstituted ethyl 2,3-butadienoate **260**, a mixture of [3 + 2] and [3 + 3] cycloadditions **261** and **262** is formed in different proportions depending on the phosphine used as a catalyst. Trimethylphosphine favors the formation of the tetrahydropyrazolopyrazolone **261** and tri-*n*-butylphosphine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



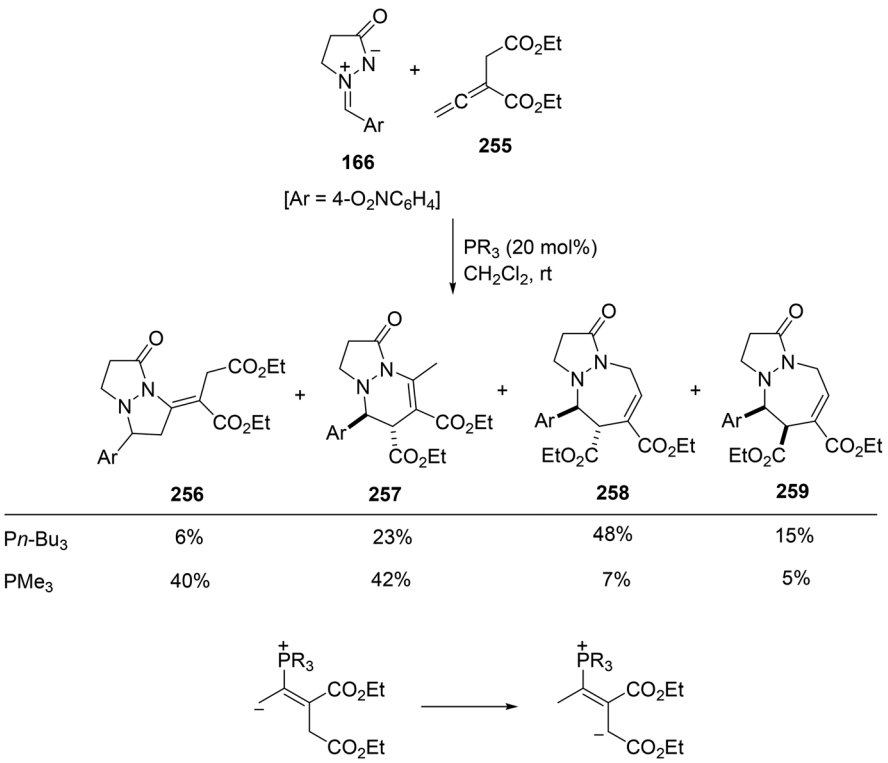
Scheme 97 Multicomponent enantioselective [3 + 2] cycloaddition of pyrazolidinones **165** with aldehydes and Meldrum's acid.



Scheme 98 Phosphine-catalyzed [3 + *n*] cyclization of azomethine imines **166** with allenoates.



Scheme 99 Phosphine-catalyzed [3 + 2] cycloadditions of allenoates **75** with azomethine imines **166**.

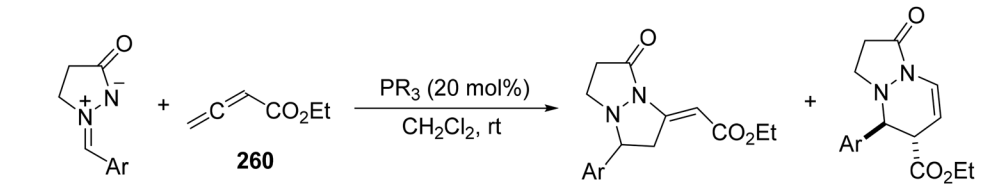


Scheme 100 Phosphine-catalyzed [3 + 2], [3 + 3] and [4 + 3] cycloadditions of azomethine imine **166** and diethyl 2-vinylidene succinate **255**.

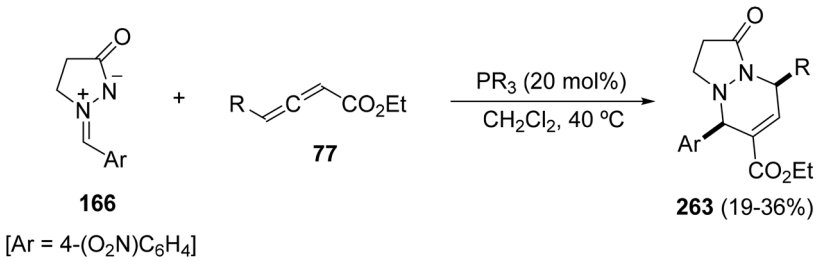
γ-carbon of the allenoate and the α-carbon, respectively (Scheme 101).[146]

When γ-substituted allenoates **77** are allowed to react with azomethine imine **166** [Ar = 4-$(O_2N)C_6H_4$], only the tetrahydropyrazolopyridazinones **263** were obtained in modest yields and with total diastereoselectivity, among other non-isolated products (Scheme 102).[146]

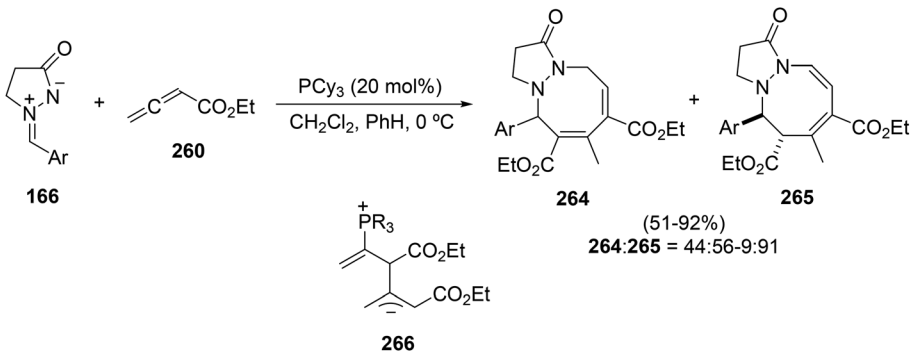
The reaction of ethyl 2,3-butadienoate **260** with different azomethine imines **166** was studied in more detail in order to determine the structure of secondary products. It was found that the formation of [3 + 2 + 3] products, such as 1-oxo-2,3,5,6-tetrahydro-1*H*-pyrazolo[1,2-*a*][1,2]diazines **264** 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]



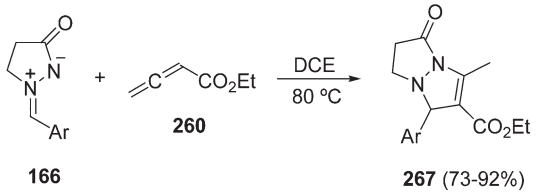
Scheme 101 Phosphine-catalyzed [3 + 2] and [3 + 3] cycloaddition of azomethine imine **166** and ethyl 2,3-butadienoate **260**.



Scheme 102 Phosphine-catalyzed [3 + 3] cycloaddition of **166** with γ-substituted allenoates **77**.



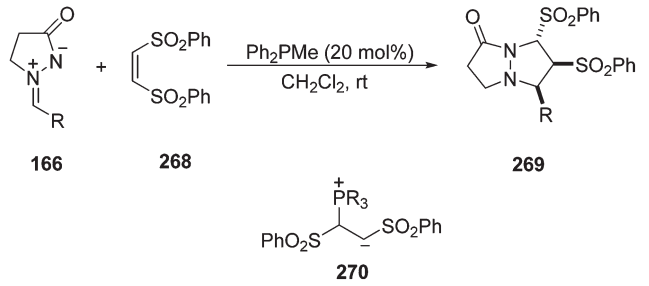
Scheme 103 Phosphine-catalyzed [5 + 3] cycloaddition of **166** with ethyl 2,3-butadienoate.



Scheme 104 Thermal [3 + 2] cycloaddition of **166** with ethyl 2,3-butadienoate **260**.

However, under thermal conditions, only the [3 + 2] cycloaddition products **267** were formed in high yields (Scheme 104),[41] whereas with α-, and γ-substituted allenoates 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**.[148]

Electron-deficient alkenes such as the (*Z*)-1,2-bis(phenylsulfonyl)ethylene **268** gave, under Ph_2PMe-catalysis at room

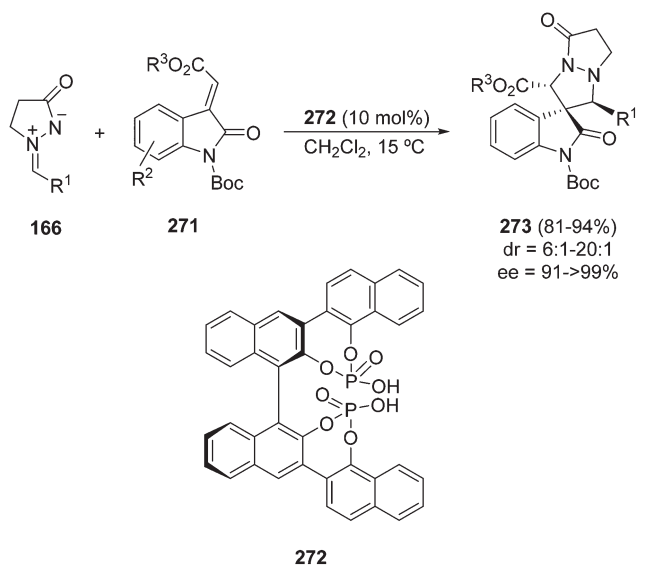


Scheme 105 Phosphine-catalyzed [3 + 2] cycloaddition of **166** with (*Z*)-bis-1,2-bis(phenylsulfonyl)ethylene **268**.

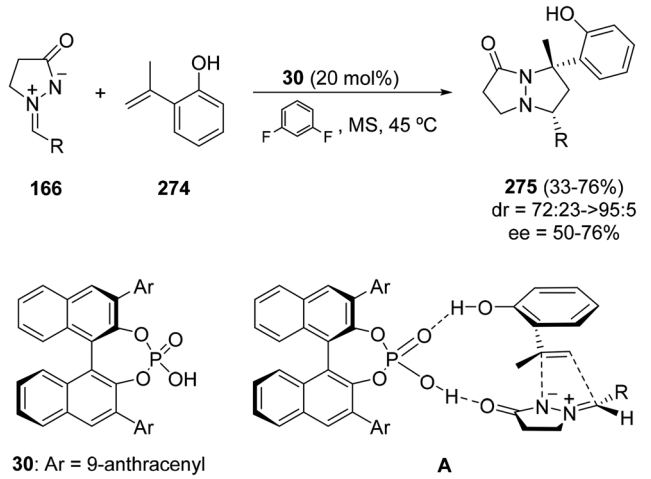
temperature, the corresponding [3 + 2] cycloaddition products **269** in the reaction with azomethine imines **166** (Scheme 105).[149] Products **269** were obtained with high diastereoselectivity and the relative configuration was the same when using (*E*)-**268**. In this case, the participation of 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 Brønsted acid catalyst for the 1,3-DC of alkylideindolinones **271** with azomethine imines **166** to afford 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



Scheme 106 Phosphoric acid-catalyzed enantioselective [3 + 2] cycloaddition of **166** with alkylideneindolinones.



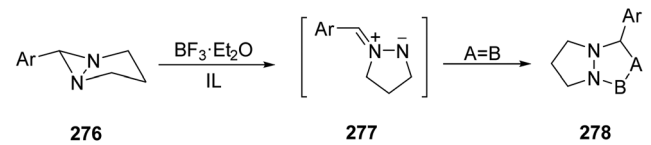
Scheme 107 Phosphoric acid-catalyzed enantioselective [3 + 2] cycloaddition of **166** with *o*-hydroxy-α-methylstyrene **274**.

organocatalyzed enantioselective inverse-electron-demanding 1,3-DC of azomethine imines **166** with *o*-hydroxy-α-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 *o*-hydroxy group played an essential role in the proposed transition state **A** (Scheme 107).[151]

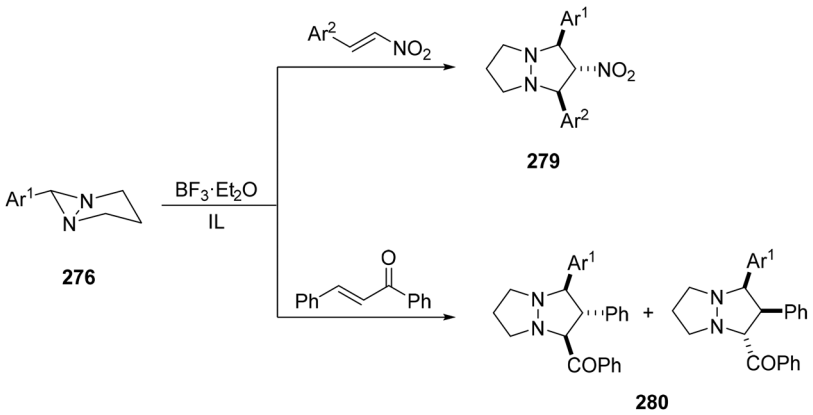
4.2 *N*-Alkylidenepyrazolidin-1-ium-2-ides

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 $BF_3{\cdot}Et_2O$ 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]

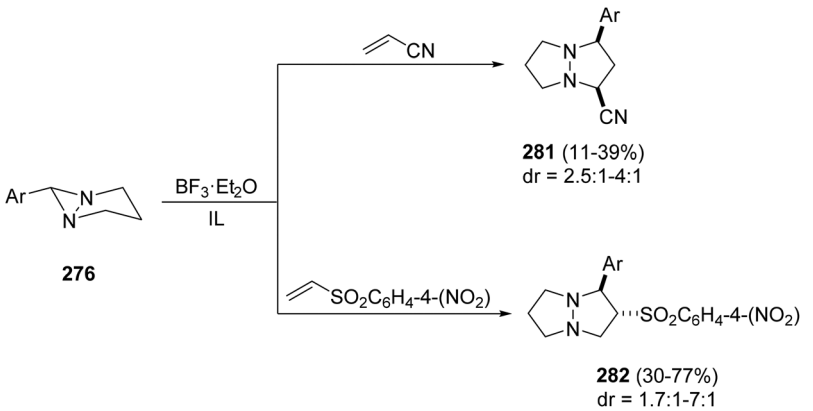
When acrylonitrile or 4-nitrophenyl vinyl sulfone was used as dipolarophiles the corresponding cycloadducts **281** or **282** were obtained with modest diastereoselectivity and with opposite regioselectivity in the first case (Scheme 110).[158,159]



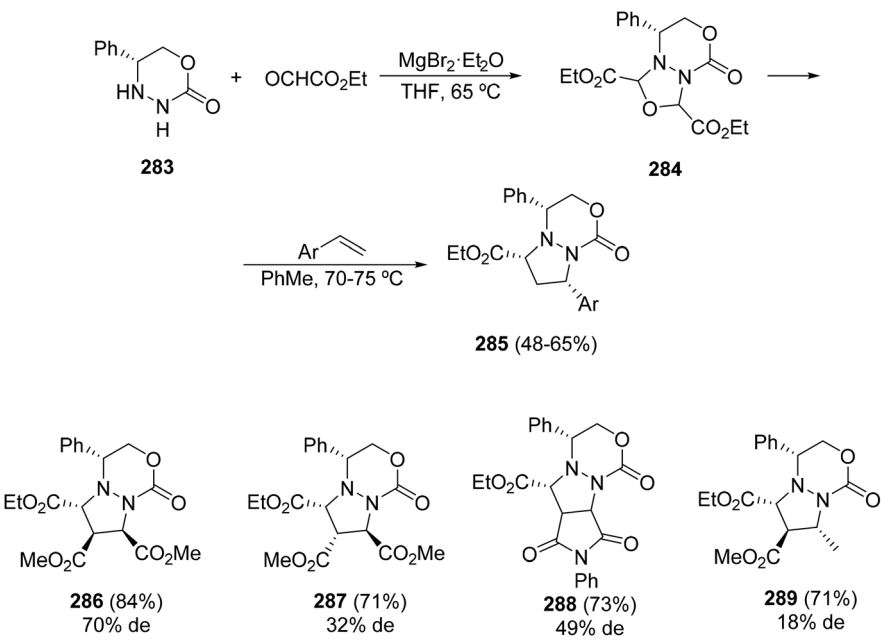
Scheme 108 [3 + 2] Cycloadditions of azomethine imines **277** generated from 1,5-diazabicyclo[3.1.0]hexanes **276**.



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-oxodiazolidin-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(6*H*)-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 Brønsted 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
Bn	Benzyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
CSA	Camphorsulfonic acid
DABCO	Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
1,3-DC	1,3-Dipolar cycloaddition
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	1,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DFT	Density functional theory
DIPEA	Diisopropyl ethyl amine
DIPT	Diisopropyl tartrate
DMAc	*N*,*N*-Dimethylacetamide
DMAD	Dimethyl acetylenedicarboxylate
DMF	*N*,*N*-Dimethylformamide
DMP	Dess–Martin reagent
2,4-DNBA	2,6-Dinitrobenzoic acid
DTBMP	2,6-Di-*tert*-butyl-4-methylpyridine
HDMS	Hexamethyldisilazane
ILs	Ionic liquids
MS	Mass spectrometry
NMP	*N*-Methylpyrrolidone
NPM	*N*-Phenylmaleimide
Py	Pyridine
rt	Room temperature
SEM	Scanning electron microscopy
TBS	*tert*-Butyldimethylsilyl
TIPBA	2,4,6-Triisopropylbenzenesulfonic acid
TIPS	Triisopropylsilyl
TMM	Trimethylenemethane
TMSOTf	Trimethylsilyl triflate
Troc	2,2,2-Trichloroethoxycarbonyl
Ts	*p*-Toluenesulfonyl

Acknowledgements

We acknowledge continued financial support from the Ministerio de Ciencia e Innovación (MICINN) (projects CTQ2007-62771/BQU, CTQ2010-20387, CONSOLIDER INGENIO 2010-CDS2007-00006, CTQ2011-24151, and CTQ2011-24165), the Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P, CTQ2014-51912-REDC, and CTQ2014-53695-P), FEDER, the Generalitat Valenciana (PROMETEO 2009/039 and PROMETEOII/2014/017), and the University of Alicante.

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