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Metal-catalyzed [3+2] cycloadditions of azomethine imines

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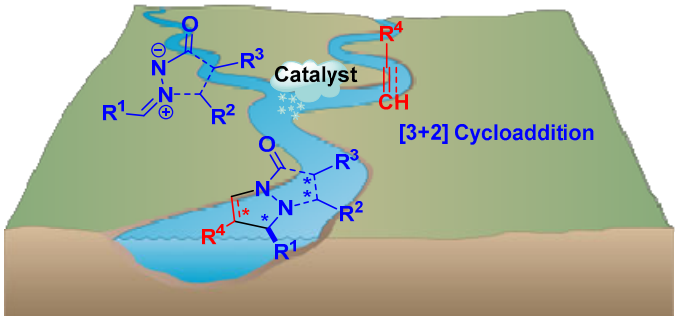


In the last decade, metal-catalyzed [3+2] cycloadditions of azomethine imines have emerged as a regioselective and stereoselective method for the synthesis of pyrazolidines and pyrazolines. A considerable number of asymmetric reactions proved the viability of metal-catalyzed [3+2] cycloadditions of azomethine imines for the synthesis of nonracemic cycloadducts. This review covers around 50 examples of title reactions that have been published since 2002.

Keywords: azomethine imines, pyrazolines, transition metals, catalysis, cyclization, [3+2] cycloadditions.

[3+2] Cycloadditions of various 1,3-dipoles to olefins, acetylenes, and other dipolarophiles are a powerful synthetic tool for the preparation of five-membered heterocycles.[1–4] Since these cycloadditions provide high regioselectivity and stereoselectivity toward (partially) saturated five-membered systems with multiple stereogenic centers they are generally considered as concerted processes.[5–9] In this context, the chemistry of azomethine ylides, nitrones, and nitrile oxides is well elaborated, whereas the chemistry of azomethine imines remains relatively less explored.[1–4,10–12]

Azomethine imines are 1,3-dipoles of azaallylic type, which can be represented by four mesomeric structures. One pair represents iminium ylide structures **I** and **II** and the other diazonium ylide structures **III** and **IV**. Most frequently, azomethine imines are represented as the iminium ylide structure **I** with the negative charge residing on the terminal nitrogen atom and the positive charge on the central nitrogen atom. This mesomeric structure is also in agreement with the charge distribution determined by quantum-chemical methods.[5–9] Structurally, azomethine imines are divided into four groups: acyclic imines **Ia**, C,N-cyclic imines **Ib**, N,N-cyclic imines **Ic**, and C,N,N-cyclic imines **Id** (Fig. 1).[10–12]

There are several methods for the generation of azomethine imines, which have already been reviewed by Grashey[10] and Schantl.[11] Nevertheless, a condensation of a disubstituted hydrazine derivative with an aldehyde or ketone remains the most widely used method, which also

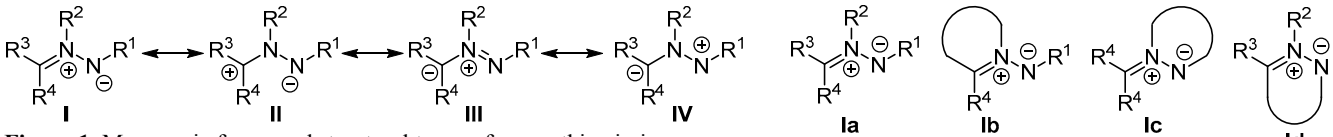


Figure 1. Mesomeric forms and structural types of azomethine imines.

* Здесь и далее в номере фамилия автора, с которым следует вести переписку, отмечена звездочкой.

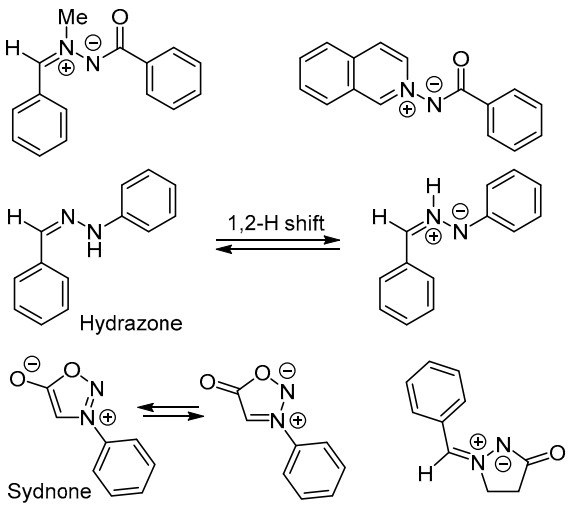


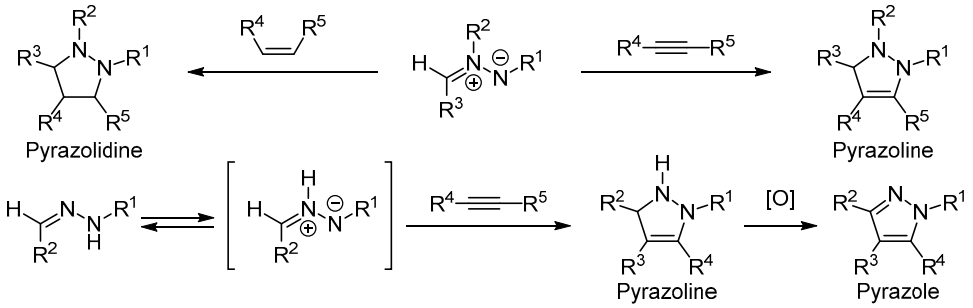
Figure 2. Typical structural types of azomethine imines.

enables *in situ* formation of azomethine imines. Although these 1,3-dipoles are generally considered to be unstable, there are many types of stable and isolable azomethine imines. For example, stable dipoles prepared by condensation of 3-pyrazolidinones with aldehydes and ketones are used as model dipoles for studying [3+2] cycloadditions of azomethine imines. Notably, hydrazones are also azomethine imine equivalents because they undergo acid-induced 1,2-prototropy to form the azomethine imine structure.[10–12] Similarly, sydnones are also regarded as azomethine imine equivalents.[10–13] Few typical azomethine imines are presented in Figure 2.

[3+2] Cycloadditions of azomethine imines to olefins and acetylenes offer a straightforward route to pyrazolines and pyrazolidines, respectively. Through their reactions with other dipolarophiles, such as nitriles, imines, and thiones, other five-membered N,N-based heterocycles are also accessible. Although diazoalkanes and nitrile imines are also useful 1,3-dipoles in the synthesis of pyrazole derivatives. The advantage of using azomethine imines lies in the possibility of obtaining either fully or partially saturated pyrazoles in a single synthetic step, due to the primarily formed pyrazoline which can be oxidized *in situ* into the corresponding pyrazole derivative (Scheme 1).[10–12]

Although pyrazoles are rarely found in natural products they are, as analogs of naturally abundant pyrroles and imidazoles, attractive scaffolds in the synthesis of synthetic bioactive compounds (pharmaceuticals, agrochemicals, etc.) and materials.[14–16] Two general methods of preparation are usually employed – cyclocondensation of a 1,3-dicarbonyl compound (or it's analog) with a hydrazine derivative and [3+2] cycloaddition of azomethine imine, diazoalkanes, or nitrile imine to an olefin or an acetylene. Although both methods are comparable in terms of simplicity and availability of starting materials, the cyclocondensation method is generally used for the preparation of fully unsaturated pyrazoles, whereas the cycloaddition route is more suitable for the synthesis of (partially) saturated pyrazole derivatives. Both methods may suffer from low regioselectivity when nonsymmetrical dicarbonyls or dipolarophiles are used. However, in this respect the cycloaddition route is advantageous, since regioselectivity can possibly be improved by metal catalysis. In contrast to the "traditional" cyclocondensation method, the cycloaddition method has had enormous progress in the last 15 years due to the introduction of metal-catalyzed variants, which are highly regio- and stereoselective. The first report dated back to 2002, when Kobayashi and coworkers reported asymmetric intramolecular acylhydrazone–olefin [3+2] cycloadditions catalyzed by $Zr(OPr)_4$/BINOL (1,1'-bi-2-naphthol). The corresponding cycloadducts were obtained in up to 96% *ee*.[17] Soon after, in 2003 Fu and Shintani published the first example of an asymmetric copper-catalyzed azomethine imine–alkyne cycloaddition (CuAIAC), which gave the corresponding 2,3-dihydropyrazolo[1,2-*a*]pyrazolones regioselectively in high yields and enantioselectivities.[18] By analogy with its famous "big sister", copper-catalyzed azide–alkyne cycloaddition (CuAAC), the CuAIAC reaction, too, is considered as a "click" reaction. Later on, Kobayashi and coworkers demonstrated that CuAIAC is also catalyzed by silver(I) with concomitant reversal of regioselectivity. Unlike cycloadditions to acetylenes, which are catalyzed only by group IB elements, examples of metal-catalyzed reactions with olefins include a wider array of metals, such as cobalt, copper, gold, lanthanides, magnesium, nickel, palladium, silver, silicon, titanium, zinc, and zirconium. Until now, around 50 metal-catalyzed [3+2] cycloadditions of azomethine imines have been reported. Unlike thermal noncatalyzed reactions, which are considered to be concerted, the metal-catalyzed reactions are usually better explained through a stepwise mechanism. Unfortunately, only a few mechanistic studies have been published with respective explanations serving mostly as a plausible mechanistic rationale.

Scheme 1. Synthesis of pyrazoles by [3+2] cycloadditions of azomethine imines



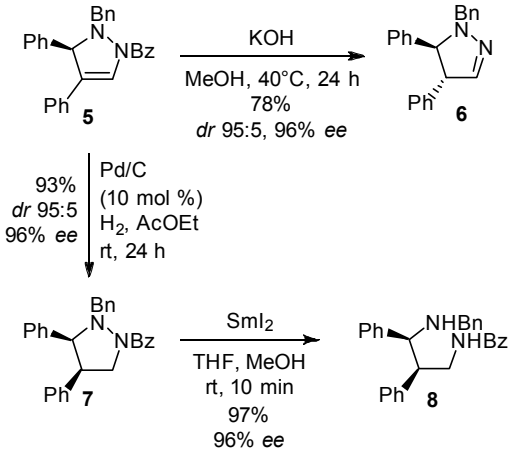
This review covers metal-catalyzed cycloadditions of azomethine imines published up to December 2017. The reactions include regioselective preparation of fully unsaturated pyrazoles, as well as regio- and stereoselective cycloadditions including the asymmetric reactions. As mentioned before, the purpose of this review is also to show the simplicity, efficacy, and viability of the [3+2] cycloaddition approach in the synthesis of pyrazole derivatives with a variable degree of saturation. Hopefully, the readers of this review will be appetized to consider [3+2] cycloadditions of azomethine imines as a suitable alternative in their endeavor respective fields, when pyrazole synthesis is required.

1. [3+2] CYCLOADDITIONS OF AZOMETHINE IMINES TO ACETYLENES

1.1. Reactions of acyclic dipoles

The first and the only example (up to date) of a 1,3-dipolar cycloaddition of *in situ* formed acyclic dipoles from aldehydes and hydrazides with alkynes was described by Maruoka et al.[19] The transformation was carried out enantioselectively using PyBox–Cu(I) complex as a catalyst and a chiral binaphthyl dicarboxylic acid as a cocatalyst. N^1-Benzylbenzoylhydrazide (**1**) was used for the formation of the corresponding acyclic azomethine imine intermediates, which reacted with terminal alkynes **3** providing pyrazolines **4** in a chemoselective manner (*dr* >95:5). However, only a small amount of acyclic condensation side product, arising from the nucleophilic addition of copper acetylide to azomethine imine intermediate, was noticed. Both, aromatic and aliphatic aldehydes **2** were applicable in the presence of MS 4 Å to eliminate the water formed during the reaction. Additionally, aromatic and aliphatic alkynes were successfully used affording the corresponding pyrazolines **4** in good to excellent yields (48–98%) and enantioselectivity (88–99% *ee*) (Scheme 2).

Scheme 3. Synthesis of enantioenriched 3,4-disubstituted pyrazolines

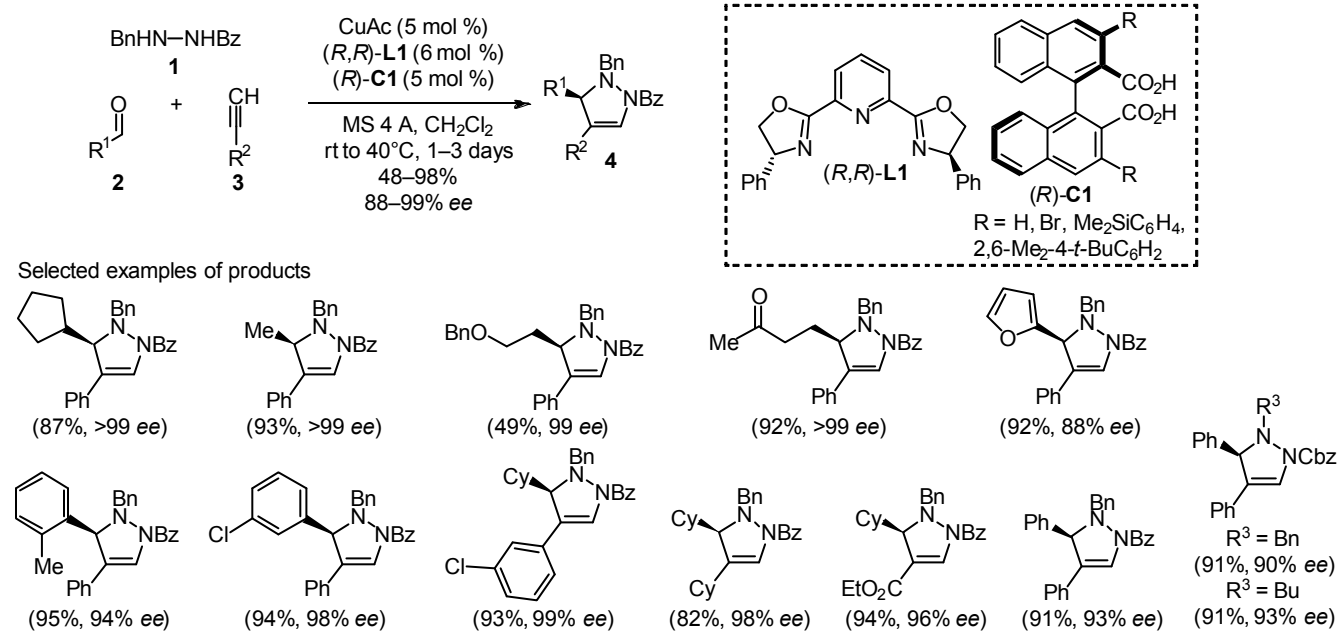


The enantioenriched 3,4-disubstituted pyrazolines were used to approach different chiral heterocyclic compounds, as well as chiral acyclic 1,3-diamine derivatives.[19] The *N*-benzoyl protecting group was easily removed under basic reaction conditions to yield pyrazoline **6** having two phenyl groups in the *trans* orientation (*dr* 95:5). In additional example, hydrogenation of (2-benzyl-3,4-diphenyl-2,3-dihydro-1*H*-pyrazol-1-yl)(phenyl)methanone (**5**) furnished pyrazolidine **7** with *cis*-oriented phenyl groups. Finally, acyclic 1,3-diamine **8** was obtained (97% yield, 96% *ee*) by SmI_2-mediated cleavage of pyrazolidine N–N bond (Scheme 3).

1.2. Reactions of C,N-cyclic dipoles

N-Iminoisoquinolin-2-ium ylides and their unsaturated analogs, isoquinolinium-2-yl imides, which are generally prepared *in situ* in a two- or three-component reaction, represent cyclic azomethine imines bearing a C–N bond in

Scheme 2. Py-Box–Cu(I)-catalyzed 1,3-dipolar cycloaddition of *in situ* formed acyclic dipoles

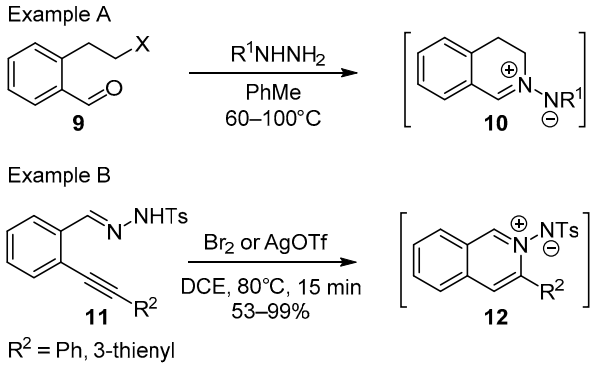


the ring.[11] A direct method to access *N*-iminoisoquinolin-2-ium ylide intermediates **10** is the cascade cyclization reaction of the corresponding aldehydes **9** with hydrazines (Scheme 4, example A). On the other hand, the saturated analogs, isoquinolinium-2-yl imides **12**, are in general prepared *in situ* by halogen- (Br_2 or I_2) or AgOTf-promoted 6-*endo* cyclization of *N*'-(2-alkenylbenzilidene)hydrazides **11** (Scheme 4, example B). Additionally to the former methods for the *in situ* generation of isoquinolinium-2-yl imides **12**, these azomethine imines have been also prepared and isolated in pure form by a one-pot synthetic procedure reacting 2-alkynylbenzaldehydes and hydrazides followed by silver(I) triflate-catalyzed cyclization.[20]

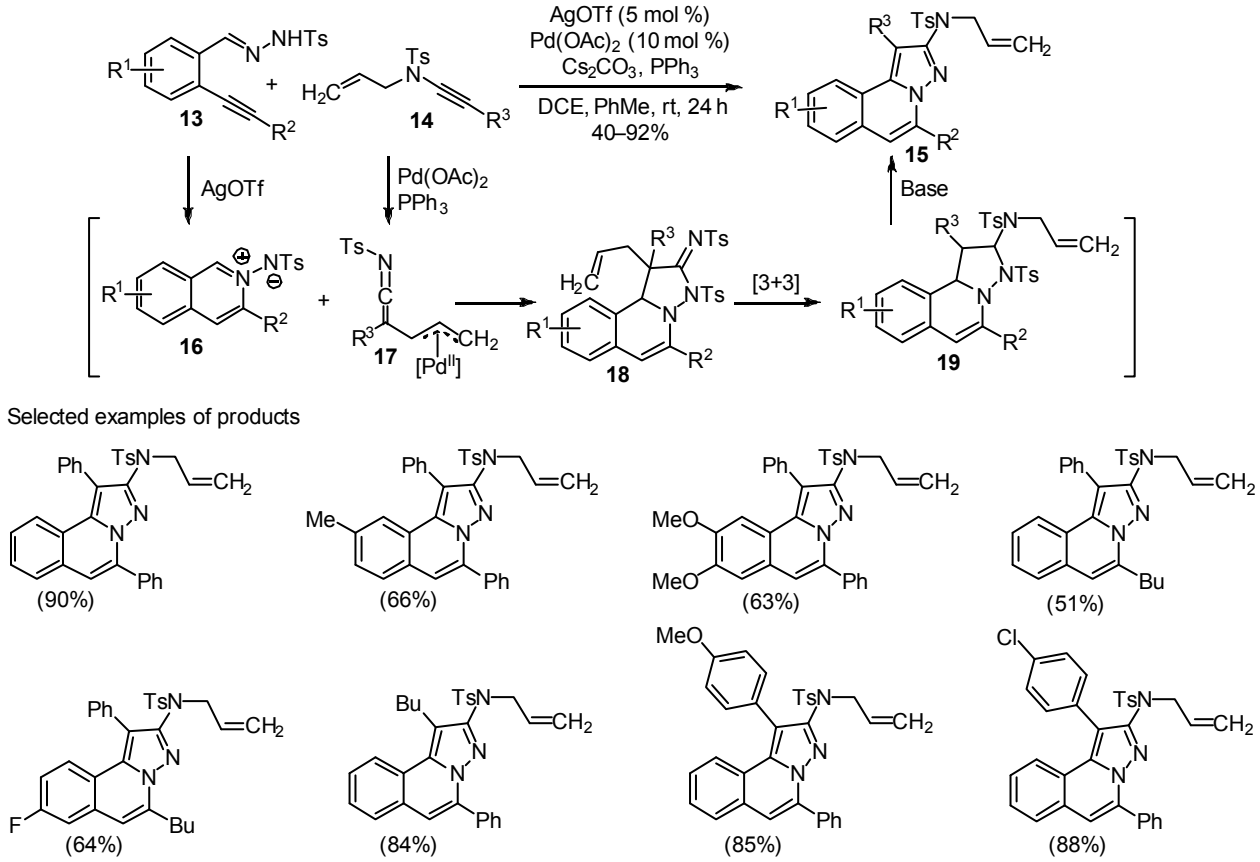
Peng et al. developed a silver triflate- and palladium acetate-cocatalyzed reaction of *N*'-(2-alkynylbenzylidene)-hydrazide with *N*-allyl ynamides.[21] The transformation enables the synthesis of differently substituted 2-amino-pyrazolo[5,1-*a*]isoquinolines **15** in good to excellent yields (40–92%, Scheme 5). It is worth mentioning that when *N*-(3'-methylallyl) ynamides were used instead of simple *N*-allyl ynamides, two isomeric products in ratio ranging from 5:3 to 3:1 were isolated. Mechanistic investigations provide some insight into the reaction pathway of the transformation. In the presence of the Pd(0) catalyst the reactive ketenimine **17** is derived from *N*-allyl-*N*-tosyl ynamide **14** *via* ynamido-Pd-π-allyl complex and subsequent allyl migration from the nitrogen to the carbon atom. Isoquinolinium-2-yl amide **16** is formed *via* Ag(I)-catalyzed 6-*endo* cyclization of *N*'-(2-alkynylbenzylidene)-hydrazide **13** (Scheme 5). The intermolecular [3+2] cyclization reaction generates the key intermediate **18**, followed by an intramolecular [3+3] sigmatropic rearrangement to yield intermediate **19** which undergoes base-promoted elimination of the tosyl group providing aromatized product **15** (Scheme 5).

Subsequently, the same research group developed a AgOTf- and CuI-catalyzed direct alkynylation and cyclization reaction of *in situ* formed *N*-iminoisoquinolinium ylides with bromoalkynes leading to diverse pyrazolo-[5,1-*a*]isoquinolines (Scheme 6).[22] Optimization of the reaction conditions revealed that other Cu(I) and Cu(II) sources such as CuBr, CuCl, $Cu(OTf)_2$, or $Cu(OAc)_2$ were much less efficient, producing the final product in lower yields. Various substituted *N*'-(2-alkynylbenzylidene)-

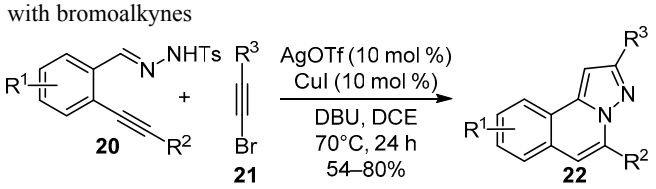
Scheme 4. Synthesis of C,N-cyclic dipoles



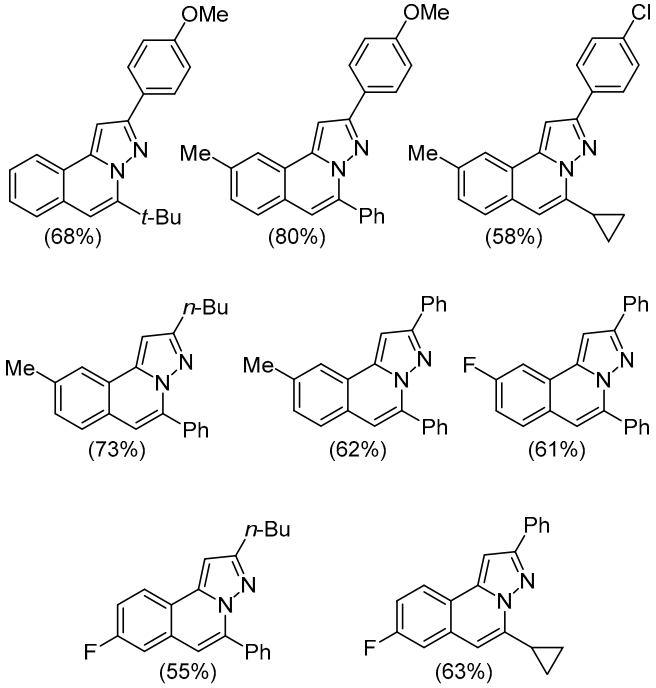
Scheme 5. A silver triflate- and palladium acetate-cocatalyzed reaction of *N*'-(2-alkynylbenzylidene)hydrazide with *N*-allyl ynamides



Scheme 6. Alkynylation followed by cyclization reaction of *in situ* formed *N*-iminoisoquinolinium ylides with bromoalkynes



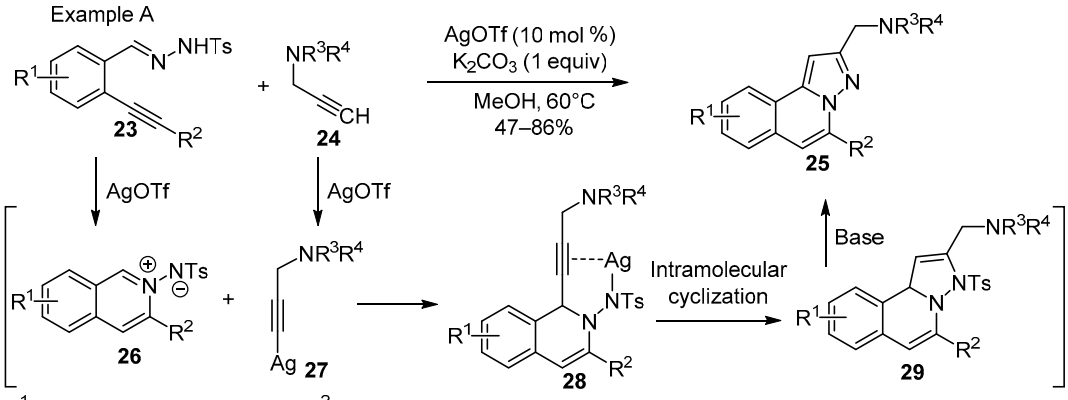
Selected examples of products



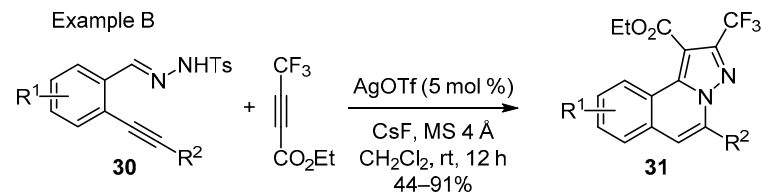
hydrazides **20** and not only 2-aryl-substituted bromoalkynes **21**, but also 2-alkyl-substituted analogs were shown to be applicable partners in the reaction providing pyrazolo[5,1-*a*]isoquinolines **22** in good yields (Scheme 6). Although the exact mechanism of the transformation has yet to be established, it has been suggested that the reactive intermediate, *N*-iminoisoquinolinium ylide, undergoes a C–H activation/alkynylation by preformed alkynyl cuprate (formed by oxidative addition of the copper(I) catalyst to haloalkynes[23]) followed by Ag(I)-catalyzed 5-*endo* cyclization to furnish the final products.

Not only ynamides, but also propargyl amides were investigated in a silver(I)-catalyzed tandem reaction of *N*'-(2-alkynylbenzylidene)hydrazides.[24] A variety of *N*'-(2-alkynylbenzylidene)hydrazides **23** was successfully reacted with propargyl amine derivatives **24** at a catalyst loading of 10 mol % yielding the desired pyrazolo[5,1-*a*]-isoquinolines **25**. The reaction proceeds through a tandem 6-*endo* cyclization, yielding intermediate **26**, followed by nucleophilic addition of compound **27**, then 5-*endo* cyclization of intermedaite **28** and aromatization of the resulting tricyclic compound **29**, leading to cycloadducts **25** in good to excellent yields and exclusive regioselectivity (Scheme 7, example A). Another example involving a silver(I) triflate-catalyzed tandem reaction protocol is the synthesis of trifluoromethyl-substituted pyrazolo[5,1-*a*]isoquinolines starting from *N*'-(2-alkynylbenzylidene)hydrazides **30** and ethyl 4,4,4-trifluorobut-2-ynoate.[25] The range of *N*'-(2-alkynylbenzylidene)hydrazides **30** were successfully applied to provide trifluoromethylated pyrazolo[5,1-*a*]isoquinoline derivatives **31** in a regioselective manner ranging from 44 up to 91% yield (Scheme 7, example B). However, no mechanistic evidence was provided by the authors that the catalyst is involved in a concerted [3+2] cycloaddition

Scheme 7. A silver(I)-catalyzed tandem reaction of *N*'-(2-alkynylbenzylidene)hydrazides with propargylamides



R^1 = H, 4-MeO, 5-Me, 5-F, 4-F; R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, *n*-Bu, *c*-Pr, *t*-Bu
R^3 = Ph, Bn, *n*-Bu; R^4 = Me, Ts, Boc

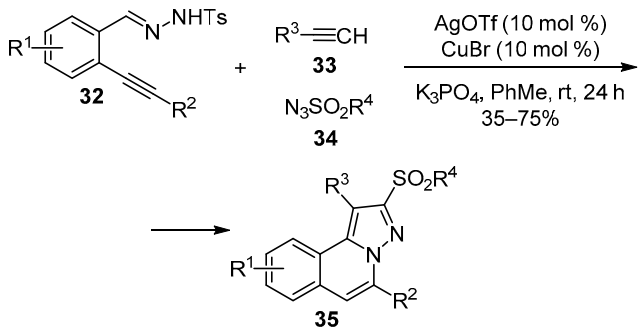


R^1 = H, 5-F; R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4; 4-FC_6H_4, 4-$O_2NC_6H_4$, 4-$MeCOC_6H_4$, *c*-Pr

synthetic step, nor that the transformation proceeds *via* stepwise or polar-synchronous reaction mechanism.

Wu et al. described a synthetic approach for the synthesis of 2-aminopyrazolo[5,1-*a*]isoquinolines *via* three-component reaction of *N*'-(2-alkynylbenzylidene)hydrazide **32**, alkyne **33**, and sulfonyl azide **34**.[26] The transformation tolerated a wide variety of substituted acetylenes and *N*'-(2-alkynylbenzylidene)hydrazides yielding cycloadducts **35** (Scheme 8) in moderate to good yields. Regarding sulfonyl azides **34**, only tolyl, phenyl, 4-bromophenyl, and 4-nitrophenylsulfonyl azides were explored. The key intermediates in the transformation are believed to be isoquinolinium-2-yl amide and ketenimine, formed by copper(I)-catalyzed azide–alkyne cycloaddition.

Scheme 8. Synthesis of 2-aminopyrazolo[5,1-*a*]isoquinolines *via* three-component reaction



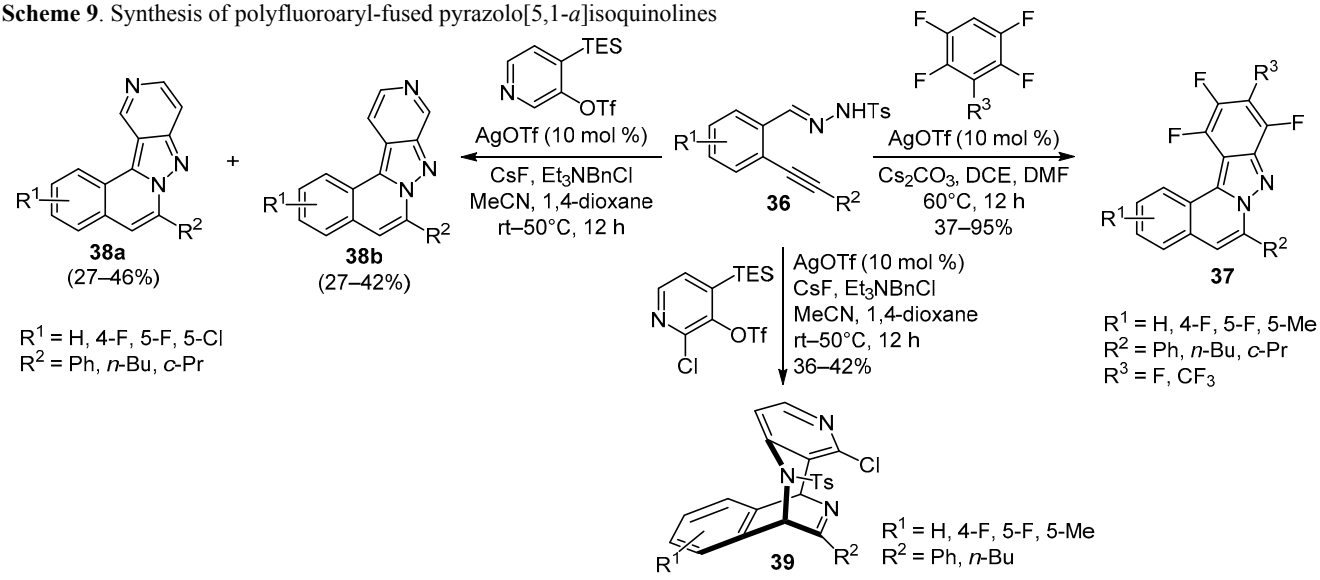
R^1 = H, 4-F, 4-MeO, 5-Me, 5-F, 5-NO_2;
R^2 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, *c*-Pr
R^3 = Ph, *c*-Pr; R^4 = Ph, 4-MeC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$

Polyfluoroarenes were found to react under the silver(I) triflate-catalyzed reaction conditions with *N*'-(2-alkynylbenzilidene)hydrazide leading to polyfluoroaryl-fused pyrazolo[5,1-*a*]isoquinolines in good yields.[27] The presence of a base was demonstrated to be essential for the transformation, while the best results were obtained with cesium carbonate. The reaction pathway was envisaged as follows – pentafluorobenzene first undergoes a base-promoted elimination to generate a polyfluorinated benzyne intermediate which subsequently undergoes [3+2] cycloaddition with isoquinolinium-2-yl amide, formed from *N*'-(2-alkynylbenzilidene)hydrazides **36** as a result of AgOTf-catalyzed 6-*endo* cyclization, to provide the intermediate which is spontaneously aromatized to furnish final pyrazolo[5,1-*a*]isoquinolines **37** in moderate to excellent yields (Scheme 9). The same research group also explored a silver(I) triflate-catalyzed tandem reaction of *N*'-(2-alkynylbenzilidene)hydrazides with pyridine derivatives.[28] The choice of the solvent was found to be crucial when 4-(triethylsilyl)pyridin-3-yl trifluoromethanesulfonate was reacted with *N*'-(2-alkynylbenzilidene)hydrazides, whereas a mixture of the solvents MeCN/1,4-dioxane enabled the highest yields of the transformation. In all cases a mixture of isomers **38a**,**b** was formed from which individual pure compounds were isolated by chromatography in yields up to 46% (Scheme 9). However, unexpected results were obtained when the chloropyridine analog was used and, as established by X-ray diffraction analysis, 6,11-dihydro-5*H*-11,6-(azenometheno)benzo[*e*]-pyrido[4,3-*b*]azepines **39** were isolated in moderate yields (Scheme 9). Again, different groups were compatible under the standard silver(I) triflate-catalyzed reaction conditions in the presence of CsF. As suggested by authors, the presence of a chloro substituent in the intermediate formed after the [3+2] cycloaddition step would promote the cleavage of the N–N bond to generate the corresponding radical, which undergoes an intramolecular addition to provide the final product.

1.3. Reactions of N,N-cyclic dipoles

The synthetic approach toward pyrazolidinone and pyrazolone heterocycles is of significant importance because they have been used as dyes, pharmaceuticals, and agrochemicals.[29] In particular, N,N-bicyclic pyrazolidinone derivatives show important biological activities and have

Scheme 9. Synthesis of polyfluoroaryl-fused pyrazolo[5,1-*a*]isoquinolines



R^1 = H, 4-F, 5-F, 5-Cl
R^2 = Ph, *n*-Bu, *c*-Pr

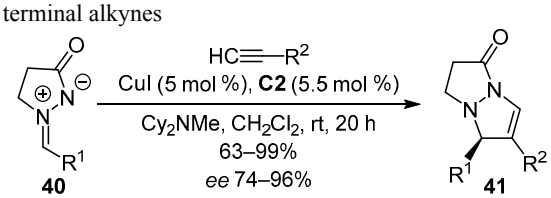
R^1 = H, 4-F, 5-F, 5-Me
R^2 = Ph, *n*-Bu, *c*-Pr
R^3 = F, CF_3

R^1 = H, 4-F, 5-F, 5-Me
R^2 = Ph, *n*-Bu

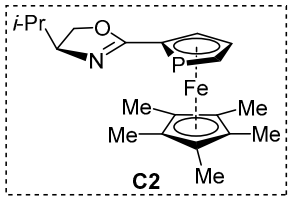
been investigated as pesticides, herbicides, and as analogs of β-lactam antibiotics, such as penicillin and cephalosporin.[30] The 1,3-dipolar cycloaddition of azomethine imines to alkynes, first reported by Dorn and Otto in 1968,[31] is one of the most attractive and useful methods for the synthesis of N,N-bicyclic pyrazolidinone derivatives due to the tolerance of a wide variety of functional groups and the usage of mild reaction conditions. However, this uncatalyzed cycloaddition yields, in majority of cases, a mixture of regioisomers in the case of unsymmetrically substituted alkynes.[32] Generally, it is widely accepted that the 1,3-dipolar cycloaddition of organic azides to terminal alkynes proceeds regioselectively in the presence of copper(I) catalysts and that *in situ* generated copper(I) acetylide is the catalytically active species.[33] In 2003, Fu and Shintani described the development of a new copper-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine imines **40** to terminal alkynes which proceeded regio- and enantioselectively in the presence of nitrogen-based chiral bidentate ligands such as phosphaferroceneoxazoline **C2**[18] (Scheme 10). With regard to the alkyne, the best results are obtained when this coupling partner is electron-deficient in its nature. Thus, if the alkyne bears a carbonyl and an electron-deficient (hetero)aromatic substituent, the *ee* of cycloaddition product **41** is high. Simple aryl- and alkyl-substituted alkynes are also suitable reacting partners, although they require a slightly higher reaction temperature and an erosion in the regioselectivity is observed (6:1, R^2 = Ph or *n*-pentyl, Scheme 10).

In 2005, the same group developed a kinetic resolution of azomethine imines **42** by CuI–phosphaferroceneoxazoline **C3**-catalyzed cycloaddition with propiolate derivatives (Scheme 11).[34] The process likely involves a reaction of dipole **42** with *in situ* generated copper acetylide giving bicyclic pyrazolidinone derivatives **44**. The

Scheme 10. Phosphaferroceneoxazoline–Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine imines to terminal alkynes

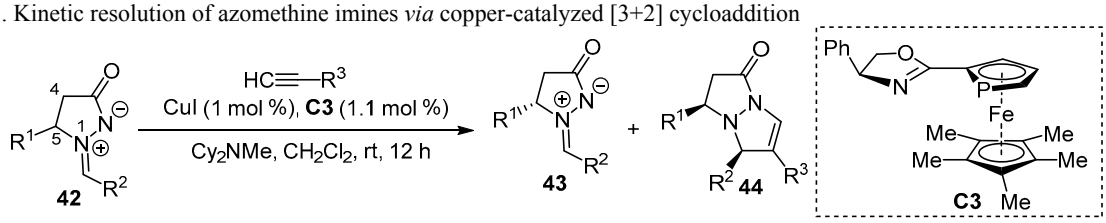


R^1 = Ph, 2-FC_6H_4, 3-BrC_6H_4, 4-$F_3CC_6H_4$, 1-cyclohexenyl, *n*-pentyl, cyclohexyl; R^2 = CO_2Et, COMe, CONMePh, 4-$F_3CC_6H_4$, 4-$EtO_2CC_6H_4$, 2-Py, Ph, *n*-pentyl

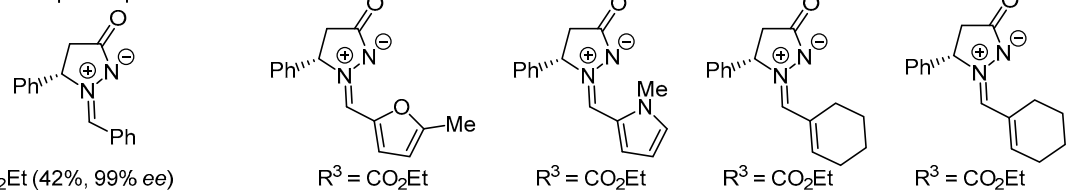


catalytic system CuI–**C3** furnishes a selectivity factor (*s* – rate of fast-reacting enantiomer/rate of slow-reacting enantiomer) in the range from 15 to 96. A variety of electron-poor alkynes enable useful selectivity, with ethyl propiolate and 4-(trifluoromethyl)phenylacetylene being the most efficient. Good selectivity is observed for azomethine imines that possess a variety of substituents on the N-1 atom. Therefore, highly enantioenriched (91–99% *ee*) dipoles **43** can be isolated in yields between 31 and 48%. The kinetic resolution of azomethine imines substituted on the C-4 and C-5 atoms was also investigated, however, C-4-substituted (e.g., cyclohexyl) analogs did not undergo kinetic resolution with reasonable selectivity ($s < 2$). On the other hand, C-5-substituted dipoles with (hetero)aryl or branched alkyl substituents can also be efficiently resolved (Scheme 11).

Scheme 11. Kinetic resolution of azomethine imines *via* copper-catalyzed [3+2] cycloaddition



Selected examples of products



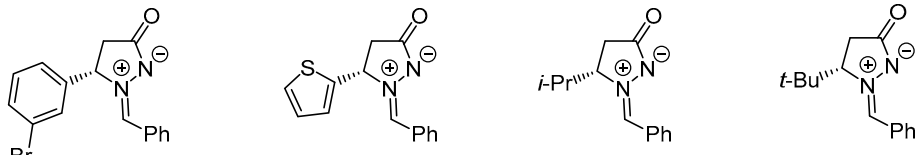
R^3 = CO_2Et (42%, 99% *ee*)
R^3 = CONMePh (42%, 91% *ee*)
R^3 = 4-$(CF_3)C_6H_4$ (39%, 99% *ee*)

R^3 = CO_2Et (48%, 95% *ee*)

R^3 = CO_2Et (31%, 99% *ee*)

R^3 = CO_2Et (36%, 95% *ee*)

R^3 = CO_2Et (36%, 91% *ee*)



R^3 = CONMePh (44%, 99% *ee*)

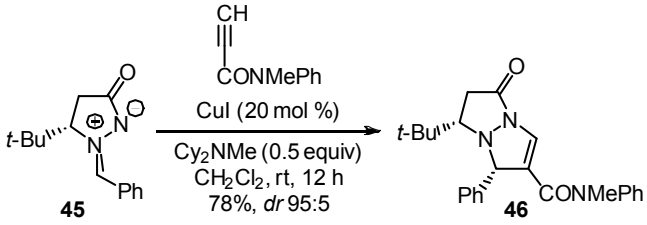
R^3 = CO_2Et (31%, 98% *ee*)

R^3 = CONMePh (40%, 97% *ee*)

R^3 = CONMePh (48%, 93% *ee*)

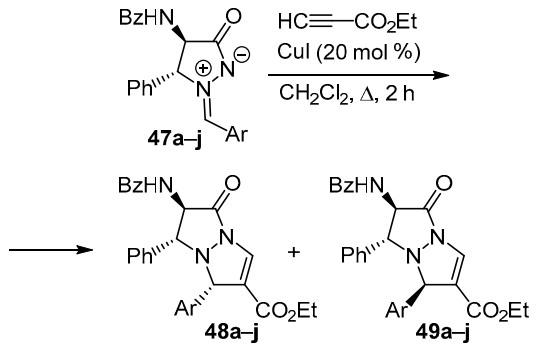
The highly enantioenriched dipoles **45** that are generated by the above described methodology undergo efficient Cu(I)-catalyzed diastereoselective [3+2] cycloaddition with amide-substituted alkynes to produce bicyclic pyrazolidinones **46** (Scheme 12).

Scheme 12. [3+2] Cycloaddition of enantiopure azomethine imine to *N*-methyl-*N*-phenylpropiolamide



In 2009, Svete et al. reported that, in contrast to non-catalyzed [3+2] cycloaddition, reactions of 4-amino-5-aryl-substituted azomethine imines with propiolates,[35] the corresponding CuI-catalyzed reaction proceeds with high regio- and stereoselectivity.[36] Starting azomethine imines were prepared by a parallel solution-phase synthesis from racemic pyrazolidinones and aromatic aldehydes.[37] In the [3+2] cycloaddition reactions, 4-benzoylamino-5-aryl-substituted azomethine imines **47a**–**j** were reacted with ethyl propiolate in the presence of 20 mol % of CuI in refluxing dichloromethane. Under these conditions, the corresponding cycloadducts, (1*R**,6*S**,7*S**)-1-aryl-6-benzamido-5-oxo-7-phenyl-1,5,6,7-tetrahydropyrazolo[1,2-*a*]pyrazole-2-carboxylates **48a**–**j** or their (1*R**,6*R**,7*R**)-epimers **49a**–**j** were obtained as the single, 2-CO_2Et regioisomers (Scheme 13). The exclusive formation of regioisomers **48a**–**j** and **49a**–**j** is in agreement with the regiochemistry of copper(I)-catalyzed cycloadditions of azomethine imines to terminal acetylenes. Reactions of dipoles **47a**–**h** with at least one *ortho* position free gave (1*R**,6*S**,7*S**)-isomers **48a**–**h**, whereas reactions of *ortho*-disubstituted dipoles **47i** and **47j** yielded the major (1*R**,6*S**,7*R**)-isomers **49i** and **49j**.

Scheme 13. Cu(I)-catalyzed cycloadditions of 4-benzoylamino-5-aryl-substituted azomethine imines with ethyl propiolate



Ar = Ph (51%, **48a**:**49a** = 1:0)
Ar = 2-furyl (35%, **48b**:**49b** = 1:0)
Ar = 2-MeOMeC$_6$H$_4$ (32%, **48c**:**49c** = 1:0)
Ar = 4-MeOC$_6$H$_4$ (60%, **48d**:**49d** = 1:0)
Ar = 4-MeC$_6$H$_4$ (43%, **48e**:**49e** = 1:0)
Ar = 3,4,5-(MeO)$_3$C$_6$H$_2$ (55%, **48f**:**49f** = 1:0)
Ar = 3-FC$_6$H$_4$ (65%, **48g**:**49g** = 1:0)
Ar = 3-Me-2-thienyl (11%, **48h**:**49h** = 1:0)
Ar = 2,6-(Cl)$_2$C$_6$H$_3$ (8%, **48i**:**49i** = 0:1)
Ar = 2,4,6-(MeO)$_3$C$_6$H$_2$ (50%, **48j**:**49j** = 1:5.7)

Recently, the same group reported a Cu(I)-catalyzed [3+2] cycloaddition of 4,5-substituted azomethine imines to (*S*)-*N*-Boc-alanine-derived ynone,[38] which afforded separable mixtures of diastereomeric cycloadducts (Scheme 14).[39] Azomethine imines **50a**–**l** with variable substituents at C-4 and C-5 atoms and bearing typically aryl residues at position C-1' were reacted with *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate in the presence of 20 mol % of CuI and 30 mol % of Hünig's base in MeCN as the optimal solvent at room temperature. The corresponding mixtures of diastereomers (+)-**51a**–**l** and (–)-**51a**–**l** were isolated in excellent yields (66–99%). The mixtures of diastereomers (+)-**51a**–**l** and (–)-**51a**–**l** were further separated, either by SiO_2 column chromatography (CC) or by medium-pressure liquid chromatography (MPLC) to furnish diastereomerically pure compounds (+)-**51a**–**l** and (–)-**51a**–**l** in 5–44% yield (Table 1).

Scheme 14. Cu(I)-catalyzed synthesis of nonracemic highly substituted 5-oxo-2,3-dihydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles

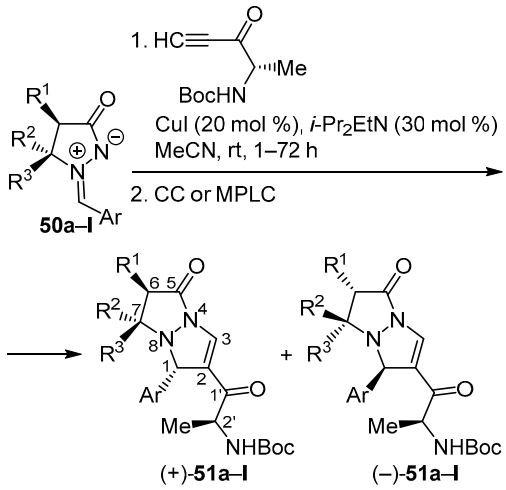


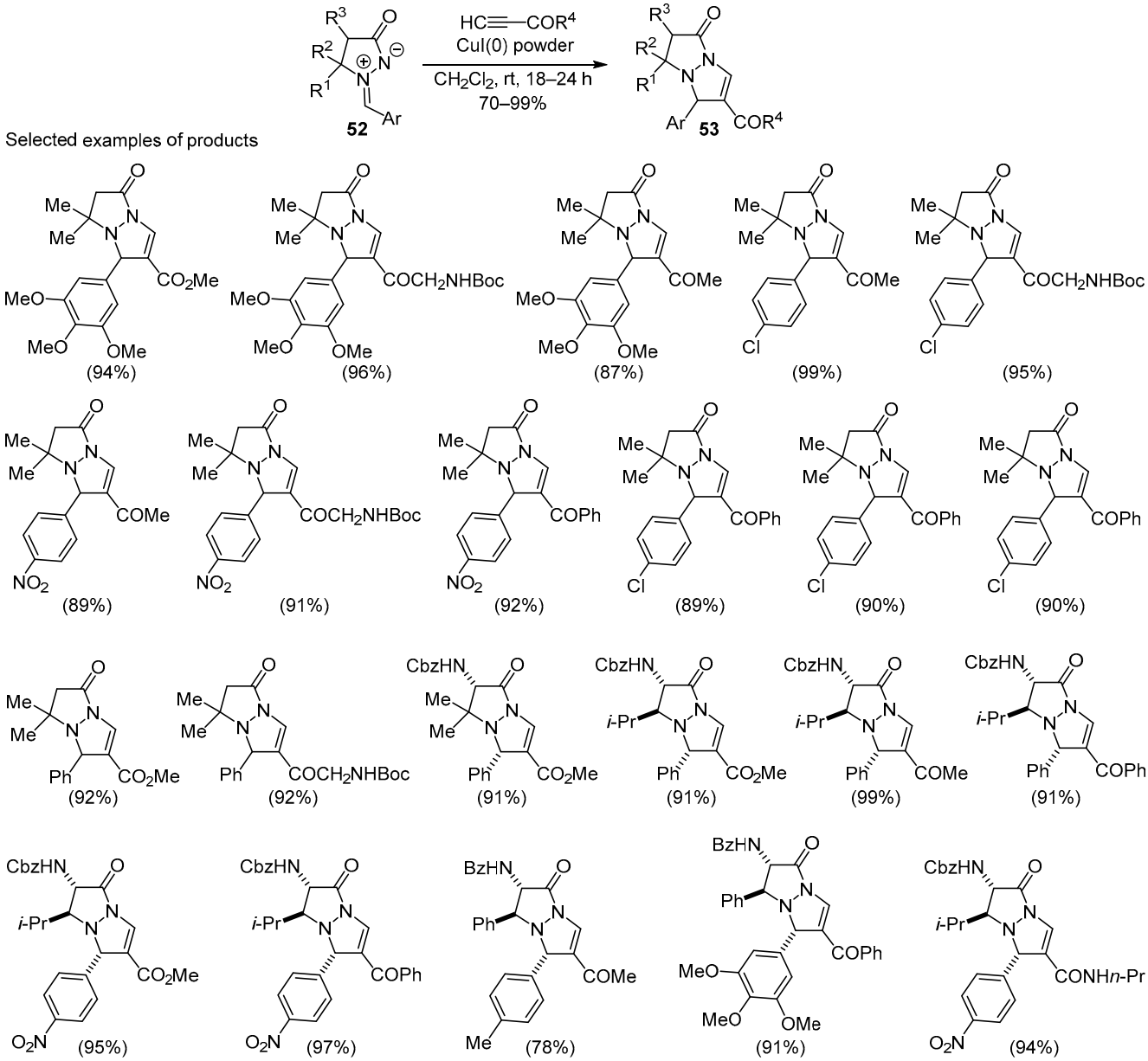
Table 1. Substituents and yields of compounds **51a**–**l**

Compound	R^1	R^2	R^3	Ar	Yield, %		
					(±)-**51**	(+)-**51**	(–)-**51**
51a	NHBz	Ph	H	Ph	91	44	5
51b	NHBz	Ph	H	4-O$_2$NC$_6$H$_4$	95	39	17
51c	NHBz	Ph	H	4-MeC$_6$H$_4$	98	25	14
51d	NHBz	Ph	H	3,4,5-(MeO)$_3$C$_6$H$_2$	66	30	14
51e	NHCbz	*i*-Pr	H	4-ClC$_6$H$_4$	99	44	30
51f	NHCbz	*i*-Pr	H	4-O$_2$NC$_6$H$_4$	99	42	32
51g	NHCbz	Ph	H	Ph	96	42	21
51h	H	Ph	H	4-O$_2$NC$_6$H$_4$	97	39	37
51i	NHBz	Me	Me	4-O$_2$NC$_6$H$_4$	95	35	30
51j	NHBz	Me	Me	2,4-(Cl)$_2$C$_6$H$_3$	79	27	23
51k	NHBz	Me	Me	3,4,5-(MeO)$_3$C$_6$H$_2$	89	29	31
51l	H	Me	Me	4-O$_2$NC$_6$H$_4$	93	36	28

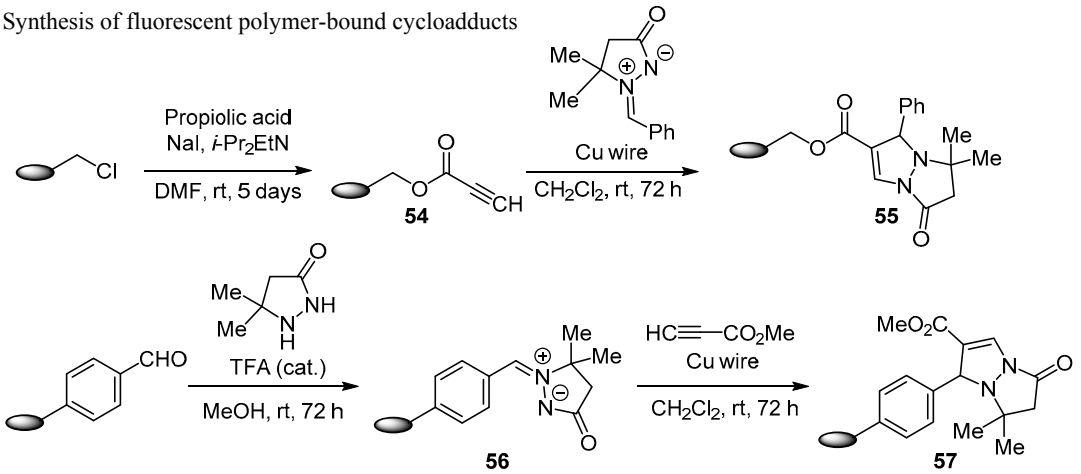
The relative configurations of diastereomeric cycloadducts (+)-**51** and (–)-**51** were initially determined by NOESY experiments and by inspection of vicinal coupling constants $^3J_{6\text{-CH}-7\text{-CH}}$.[38,40–42] In compound **51h**, a NOE between 1-CH and 7-CH atoms supported the *syn* orientation of the two hydrogens. In compound **51i**, the *anti* orientation of 1-CH and 6-CH atoms was established by NOE between 1-CH and 7-CH_{3A} atoms as well as between 7-CH_{3B} and 6-CH atoms. In compounds **51e**–**g**, the value of the vicinal coupling constant, $^3J_{H(6)-H(7)} \approx 12$ Hz is in line with the *trans* configuration around C-6–C-7 bond. The correlation also reveals a significant difference in chemical shifts, $\Delta\delta > 0.3$ ppm, for protons H-3 and 6-CH in diastereoisomeric pairs **51a**–**g** and **51i**–**k** with the present 6-acylamino moiety. The structure and absolute configurations of cycloadducts (+)/(–)-**51f** ((–)-**51f**, (2'*S*,1*R*,6*S*,7*S*)) and (+)/(–)-**51h** ((–)-**51h**, (2'*S*,1*R*,6*R*); (+)-**51h**; (2'*S*,1*S*,7*S*)) were unambiguously established by X-ray analysis by VCD and ECD spectroscopy. Correlation between the absolute configuration and specific rotation in compounds **51a**–**l** revealed substantially different contributions of each stereogenic center to the overall sign and the magnitude of specific rotation of isomers, thus, all 1-(*S*)-isomers are strongly dextrorotatory (+117 to +758°), whereas all 1-(*R*)-isomers are strongly levorotatory (–194 to –769°).

The first examples where copper metal was applied as a precatalyst in CuAIAC reaction and its applicability in "click" chemistry was recently reported.[43,44] A library of cycloadducts **53** (Scheme 15) was prepared by reacting the corresponding 4,5-disubstituted dipoles **52** with terminal alkynes bearing different acyl groups. The reaction was performed with a substoichiometric amount (40 mg Cu powder/1 mmol of dipole) of Cu(0) in dichloromethane as the optimal reaction solvent at room temperature.

Scheme 15. Cu(0)-catalyzed [3+2] cycloadditions of azomethine imines with substituted acetylenes



Scheme 16. Synthesis of fluorescent polymer-bound cycloadducts

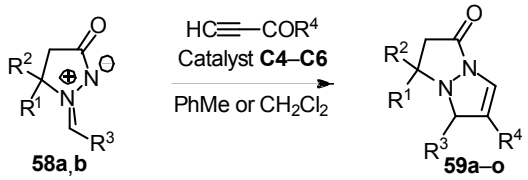


A simple workup comprised the removal of the catalyst by filtration, followed by evaporation yielding in majority of cases pure products as a single regioisomer. The scalability was tested on 20 times larger scale (20 mmol of dienophile) without any effect on the conversion or yield. The authors also tested other forms of heterogeneous copper metal catalysts such as 10% Cu–graphite (Cu/C) and copper-coated iron powder (Cu/Fe). Cycloaddition of azomethine imines to methyl propiolate catalyzed by Cu/C proceeded similarly as with Cu powder. Furthermore, the recovered catalyst could be reused three additional times without loss of its activity. The Cu/Fe catalyst which was easily prepared by stirring iron powder in an aqueous solution of $CuSO_4$ enabled quantitative formation of cycloadducts in 24 h at room temperature and could be reused several times after simple magnetic separation.

To test the applicability of CuAIAC reaction as a ligation tool the authors successfully functionalized polymeric material *via* attachment of the ynone component to Merrifield resin or *via* polymer-bound benzaldehyde modification (Scheme 16).[43] Treatment of chloromethylated polystyrene with propiolic acid in the presence of NaI and Hünig's base provided polymer-bound propiolate **54** which was then reacted with azomethine imine in dichloromethane in the presence of copper wire for 5 days to give the yellow fluorescent polymer-bonded cycloadduct **55**. The alternative approach consisted of polymer-bound dipole **56** which readily reacted with methyl propiolate in the presence of copper wire, affording the corresponding polymer-bound cycloadduct **57** (Scheme 16).

As successfully shown for the "click" Huisgen reaction, the zeolite framework was investigated as a ligand toward copper(I) for stabilization of this inherently labile Cu(I) species and thus avoiding the addition of stabilizing and activating ligands. Among the tested Cu(I)-modified zeolites (H-Y, H-MOR, H-ZSM5, and H-β), Cu(I)-USY zeolite (**C4**) was proven to be the most successful catalyst for the [3+2] cycloaddition of azomethine imines **58a**,**b** to electron-deficient acetylenes resulting in regioselective formation of the corresponding cycloadducts **59a**–**o** in good to high yields (30–95%, Table 2, catalyst **C4**).[45] Cage-type zeolites having larger pore size possess better catalytic activity than smaller channel zeolites. Size discrimination

Table 2. Substituents and yields of compounds **59a**–**o**



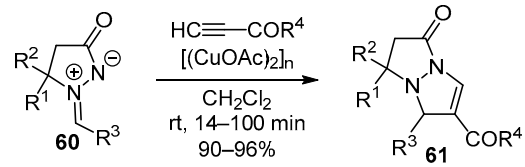
Compound	R^1	R^2	R^3	R^4	Catalyst*	Yield, %
59a	H	H	Ph	CO_2Et	**C4**	80
59a	H	H	Ph	CO_2Et	**C5**	98
59a	H	H	Ph	CO_2Et	**C6**	95
59b	Me	H	Ph	CO_2Et	**C4**	63
59b	Me	H	Ph	CO_2Et	**C5**	97
59b	Me	H	Ph	CO_2Et	**C6**	98
59c	Me	Me	Ph	CO_2Et	**C4**	90
59c	Me	Me	Ph	CO_2Et	**C5**	>99
59c	Me	Me	Ph	CO_2Et	**C6**	80
59d	Me	Me	4-$MeOC_6H_4$	CO_2Et	**C4**	67
59e	H	H	4-$MeOC_6H_4$	CO_2Et	**C5**	97
59e	H	H	4-$MeOC_6H_4$	CO_2Et	**C6**	93
59e	H	H	4-$Et_2NC_6H_4$	CO_2Et	**C4**	30
59f	Me	Me	4-ClC_6H_4	CO_2Et	**C4**	82
59g	H	H	4-ClC_6H_4	CO_2Et	**C5**	99
59g	H	H	4-ClC_6H_4	CO_2Et	**C6**	92
59h	Me	Me	*n*-C_5H_{11}	CO_2Et	**C4**	63
59i	H	H	*n*-C_5H_{11}	CO_2Et	**C5**	>99
59i	H	H	*n*-C_5H_{11}	CO_2Et	**C6**	85
59j	Me	Me	Cy	CO_2Et	**C4**	50
59k	H	H	Cy	CO_2Et	**C5**	89
59k	H	H	Cy	CO_2Et	**C6**	88
59l	H	H	Ph	Ac	**C4**	97
59l	H	H	Ph	Ac	**C5**	97
59m	H	H	Ph	Bn	**C4**	92
59m	H	H	Ph	Bn	**C6**	55
59n	H	H	Ph	Ts	**C5**	96
59n	H	H	Ph	Ts	**C6**	88
59o	Me	Me	Ph	CO*i*-Pr	**C4**	77

* **C4** = Cu(I)-USY heterogeneous zeolite catalyst, **C5** = $[[Cu(\mu\text{-}OH)(tmen)]_2Cl_2]$, **C6** = $Cu(OH)_x/Al_2O_3$ heterogeneous catalyst.

was not the sole factor influencing the activity. Catalyst efficiency of the Cu(I)-modified zeolites could be also correlated to the Si/Al ratio, whereas the lower the Si/Al ratio, the better the catalyst performance. The Si/Al ratio is linked to the number of acid sites, and thus to the number of copper ions present in the Cu(I)-modified zeolites. Additionally, dinuclear copper complex $[Cu[Cu(\mu\text{-}OH)(tmen)]_2Cl_2]$ was described by Mizuno et al.[46] as an efficient precatalyst for the 1,3-dipolar cycloaddition of pyrazolidinone-based dipoles to electron-deficient terminal alkynes (Table 2, catalyst **C5**). The catalyst activity was superior when compared to that of $TBA_4[\gamma\text{-}H_2\text{-}SiW_{10}O_{36}\{Cu_2(\mu\text{-}1,1\text{-}N_3)_2\}]$. The 1,3-dipolar cycloadditions efficiently proceeded typically applying 1 mol % Cu with respect to the dipole to give the corresponding bicyclic pyrazolidinone as a single regioisomer. The active Cu(I) species is initially formed by the alkyne homocoupling reaction *via* the Cu(II)–alkynyl intermediate $[Cu_2(\mu\text{-}C{\equiv}CR)_2]$, followed by the formation of the corresponding diyne and catalytically active Cu(I) species.[47] However, the catalyst amount could be reduced significantly in a scale up experiment using only 0.1 mol % of $[Cu[Cu(\mu\text{-}OH)(tmen)]_2Cl_2]$ where the TOF (based on initial rates) reached 305 h^{-1} and TON was 860. The same research group later on disclosed a heterogeneous $Cu(OH)_X/Al_2O_3$ catalyst[48] which was applied to the same set of substrates for comparative reasons. Also in this case, the cycloaddition reactions proceeded with various 4,5-substituted azomethine imines and electron-deficient alkynes with excellent conversions and TON up to 646 (Table 2, catalyst **C6**). It was clearly shown that also in this case the reduction of copper(II) into copper(I) species occurs producing the active species needed for the catalytic cycle to proceed. The generation of a highly dispersed copper hydroxide species on the surface of support (Al_2O_3) also plays an important role in achieving high catalyst performance. In all the above-described cases (Table 2) when 2-arylbenzylidene-3-methyl-substituted azomethine imines were used, a highly *anti*-diastereoselective addition occurred with the substituted acetylenes producing *syn* diastereomers as the major isomers.

A copper(I) acetate-catalyzed cycloaddition between simple azomethine imines and propiolates yielding the corresponding cycloadducts as a single regioisomer under mild reaction conditions was introduced by Wang and Hu et al.[49] The transformation proceeded smoothly in dichloromethane at room temperature in the presence of 0.02 equiv of $[(CuOAc)_2]_n$ with a variety of C1'-substituted (phenyl, pyridyl, and alkyl) azomethine imines **60** (Scheme 17). No significant effect on the yield of cycloadducts **61** was noticed when C-5 carbon in azomethine imine bears a single substituent (methyl or phenyl). However, the use of substrates with two substituents at the C-5 position required longer reaction times and provided products in lower yields. The mechanistic investigations suggest the presence of $(CuC{\equiv}CCOR^4)_2$ which upon the cyclization with azomethine imine **60** gives the corresponding 3-cuprous dihydropyrazolo[1,2-*a*]pyrazol-1-one which undergoes protonation yielding the final cycloadduct **61**. Copper(I) acetate is a conjugate base of acetic acid that is strong enough to form copper(I) acetylide. Additionally, the acetic acid formed during the transformation not only activates the polymer $[(CuC{\equiv}CCOR^4)_2]_n$, but also accelerates the protonation of the formed cyclic cuprous intermediate.

Scheme 17. A copper(I) acetate-catalyzed cycloaddition between simple azomethine imines and propiolates

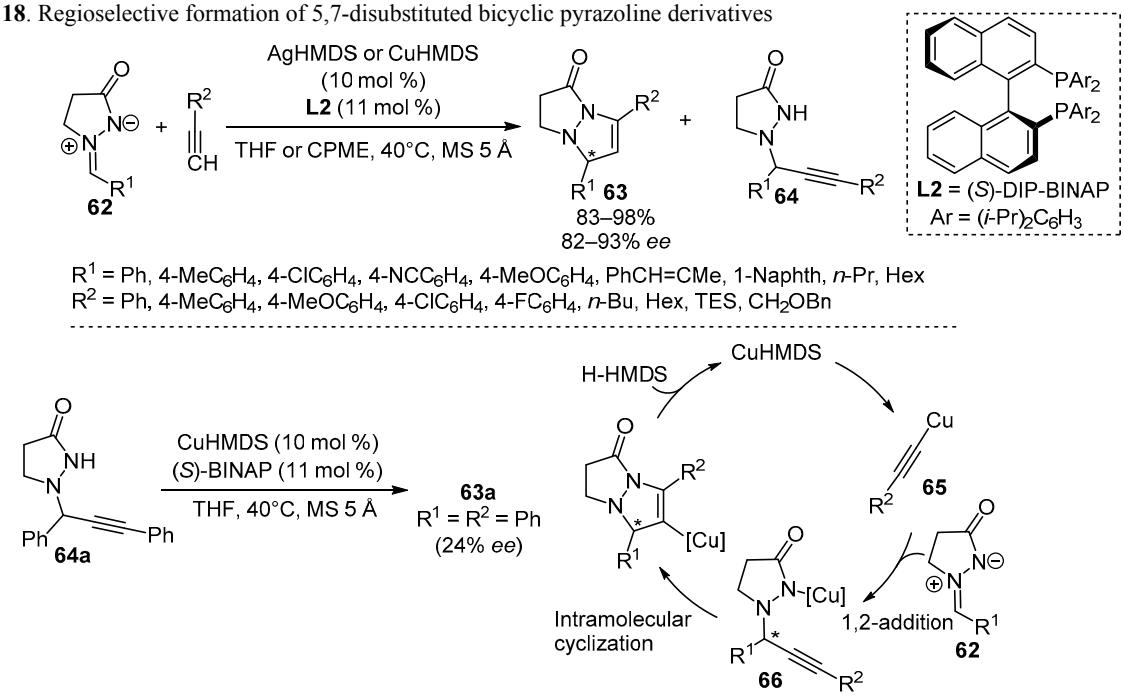


R^1, R^2 = H, Me, Ph; R^3 = Ph, 2-Py, Cy; R^4 = OEt, Me

Recently, solvent-free 1,3-dipolar cycloaddition of azomethine imines to terminal alkynes promoted by calcium fluoride was developed.[50] The reaction was catalyzed by cuprous salts in the presence of additives such as Et_3N, D-proline, TIBAF, CaF_2, KF, and $Ca(OAc)_2$ at room temperature under the ball-milling conditions. Typically, a mixture of azomethine imine, ethyl propiolate, Cu(I), SiO_2, and CaF_2 was milled vigorously at a rate of 20 Hz at room temperature for 60 min. The silica was used as a grinding aid and was not expected to participate in the reaction. Various copper catalysts were examined (CuI, CuBr, CuOAc, $Cu(OAc)_2$, $CuSO_4$, $Cu(NO_3)_2$, and $CuCl_2$) among which CuOAc provided the highest yields of the cycloadducts. The optimized reaction conditions were applied to a range of azomethine imines and terminal alkynes (methyl propiolate, ethyl propiolate, and butyn-2-one) resulting in the formation of cycloadducts as a single regioisomer in 56 up to 96% yield.

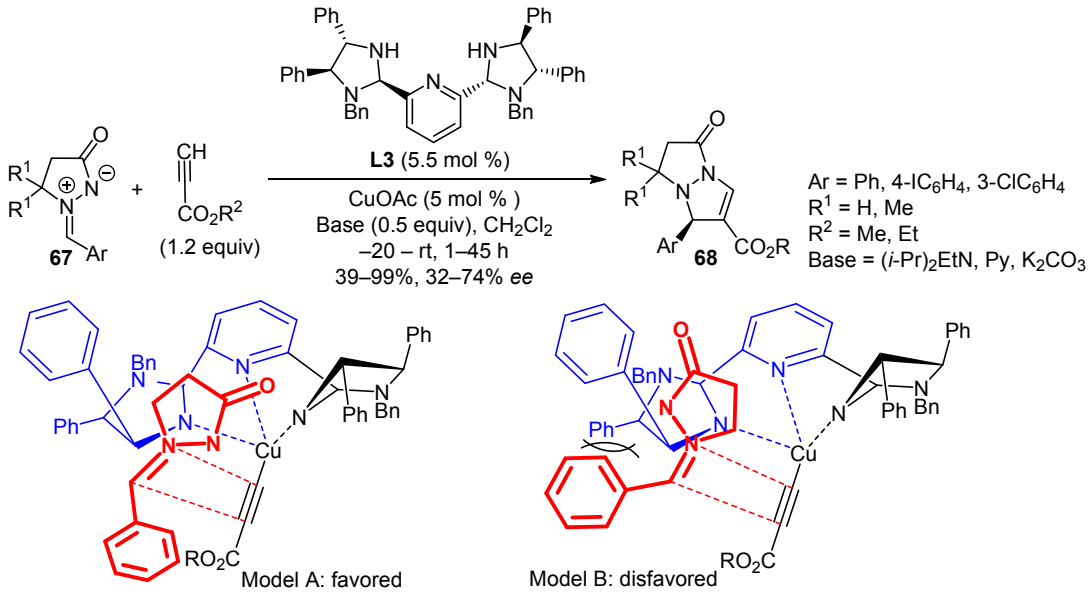
Copper(I)-catalyzed 1,3-dipolar cycloadditions of N,N-cyclic azomethine imines to terminal alkynes, which involves Cu(I)-acetylide intermediate, generally afford 5,6-disubstituted bicyclic products. However, Kobayashi et al. introduced silver(I) amide-catalyzed cycloaddition of cyclic azomethine imines **62** to the terminal alkynes in the presence of (*S*)-DIP-BINAP ligand to exclusively obtain isomeric 5,7-disubstituted bicyclic adducts **63** (Scheme 18).[51] Strong basicity of AgHMDS was found to be crucial for the cycloaddition to occur since no cycloadduct was formed when a less basic silver source (AgOAc) was used. Even the combination of AgOTf and an external source of base (DBU or KO*t*-Bu) showed lower reactivity and no cyclized product was obtained. In all cases, a small amount (less than 1%) of 1,2-adduct **64** was formed. To obtain a better understanding of the reaction mechanism, additional experiments were conducted. When 1,2-adduct **64a** was treated under the reaction conditions, cycloadduct **63a** was formed exclusively. Therefore, authors propose that the cyclized compounds are formed *via* a stepwise reaction mechanism involving 1,2-addition of metal acetylide **65** to azomethine imine **62**, followed by the intramolecular cyclization of intermediate **66**, that forms in a result of Lewis acid-activated alkyne addition.

Scheme 18. Regioselective formation of 5,7-disubstituted bicyclic pyrazoline derivatives

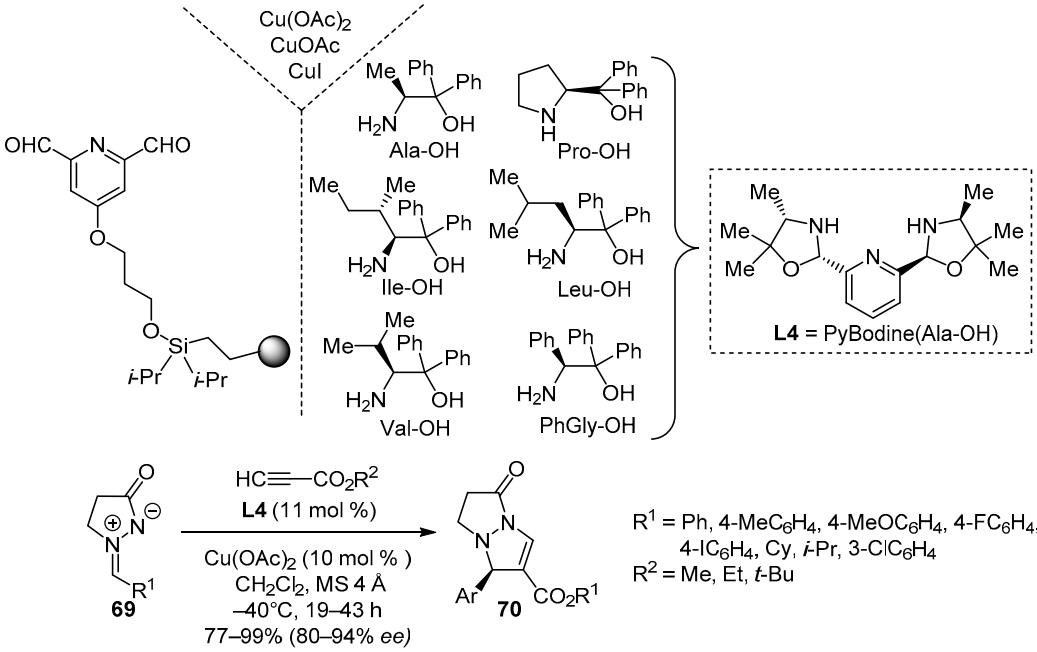


Asymmetric [3+2] cycloaddition of imino esters with nitroalkenes catalyzed by a bis(imidazolidine)pyridine–$Cu(OTf)_2$ complex was developed by Arai et al. in 2010.[52] The authors extended the catalytic system to the cycloaddition of N,N-cyclic azomethine imines to ethyl propiolate yielding enantioenriched pyrazolo[1,2-*a*]-pyrazolone derivatives.[53] Copper(I) salts showed good catalytic activity, and the PyBidine/CuI provided the corresponding product in a 99% yield and moderate enantioselectivity (44% *ee*). The PyBidine (**L3**) in the presence of CuOAc improved the catalyst performance to give the (*R*)-enriched product in high yield (99%) and with 60% *ee* (Scheme 19). Various solvents tested ($CHCl_3$, CH_2Cl_2, PhMe, THF, EtOH) were applicable to give the compounds in good chemical yield. However, the use of MeCN resulted in low yield of transformation. Among the tested solvents, the reaction in CH_2Cl_2 gave the product with the highest stereoselectivity. Moreover, a low reaction temperature (–20°C) was helpful for improving the enantiomeric excesses in particular cases, though the reaction time had to be prolonged to achieve reasonable yields. To accelerate the reaction at low temperature the presence of a base, such as Hünig's base, was beneficial also in terms of enantioselectivity reaching up to 74% *ee*. The authors also propose a model of action of the catalytic system based on the enantioselective outcome of the transformation. The

Scheme 19. Chiral PyBidine ligand in CuOAc-catalyzed cycloaddition of azomethine imines with alkyl propiolates



Scheme 20. Preparation of chiral polymer-supported PyBodine derivatives and participation of PyBodine(Ala-OH) (**L4**) in $Cu(OAc)_2$-catalyzed [3+2] cycloaddition reaction



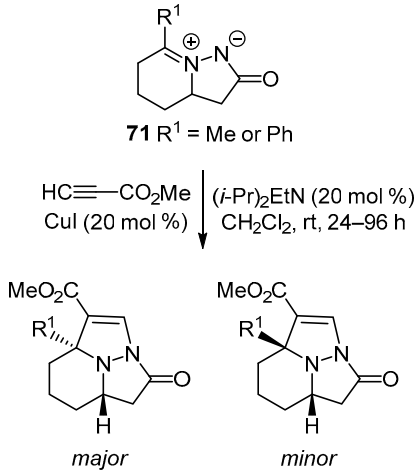
in situ generated copper acetylide coordinates to the PyBidine–Cu(I) complex, consequently azomethine imine **67** approaches in a way to minimize the steric repulsion between the phenyl ring of the PyBidine ligand and the aromatic ring of the azomethine imine (model A) resulting in bicyclic product **68** with *R* absolute configuration. On the other hand, as shown in model B, steric repulsion between phenyl groups is increased disfavoring the formation of the corresponding (*S*)-enantiomer (Scheme 19).

To further evaluate the versatility of tridentate chiral pyridine-derived ligands in asymmetric [3+2] cycloaddition of azomethine imines, the five-membered imidazolidine ring in ligand **L3** was replaced by differently substituted oxazolidine analogs.[54] The latter can be constructed in a straightforward manner and in high optical purity from the corresponding amino alcohols derived from L-amino acids and polymer-supported pyridine-2,6-dicarbaldehyde (Scheme 20). The combinatorial approach employing circular dichroism-high throughput screening was used to determine the most efficient catalyst prepared from the *in situ* generated chiral polymer-supported bis(oxazolidine)-pyridine ligands (PyBodine) and copper salts. The best performing bis(oxazolidine)pyridine ligand **L4** in the reaction of azomethine imine **69** (R^1 = Ph) with ethyl propiolate was PyBodine(Ala-OH) providing, in the presence of $Cu(OAc)_2$, (*R*)-cycloadduct **70** with high yield and excellent enantioenrichment (up to 94% *ee*). Surprisingly, the PyBodine tridentate chiral ligand made from proline-derived alcohol (Pro-OH) gave (*S*)-isomer of cycloadduct **70** as the major stereoisomer, although with significantly lower enantioselectivity (76% *ee*). The PyBodine(Ala-OH)–$Cu(OAc)_2$ catalytic system enabled, under the optimized reaction conditions, the reaction of a wide scope of azomethine imines **69** with different propiolates, providing various cycloadducts **70** in 77–99% yield and enantioselectivities up to 94% *ee* (Scheme 20).

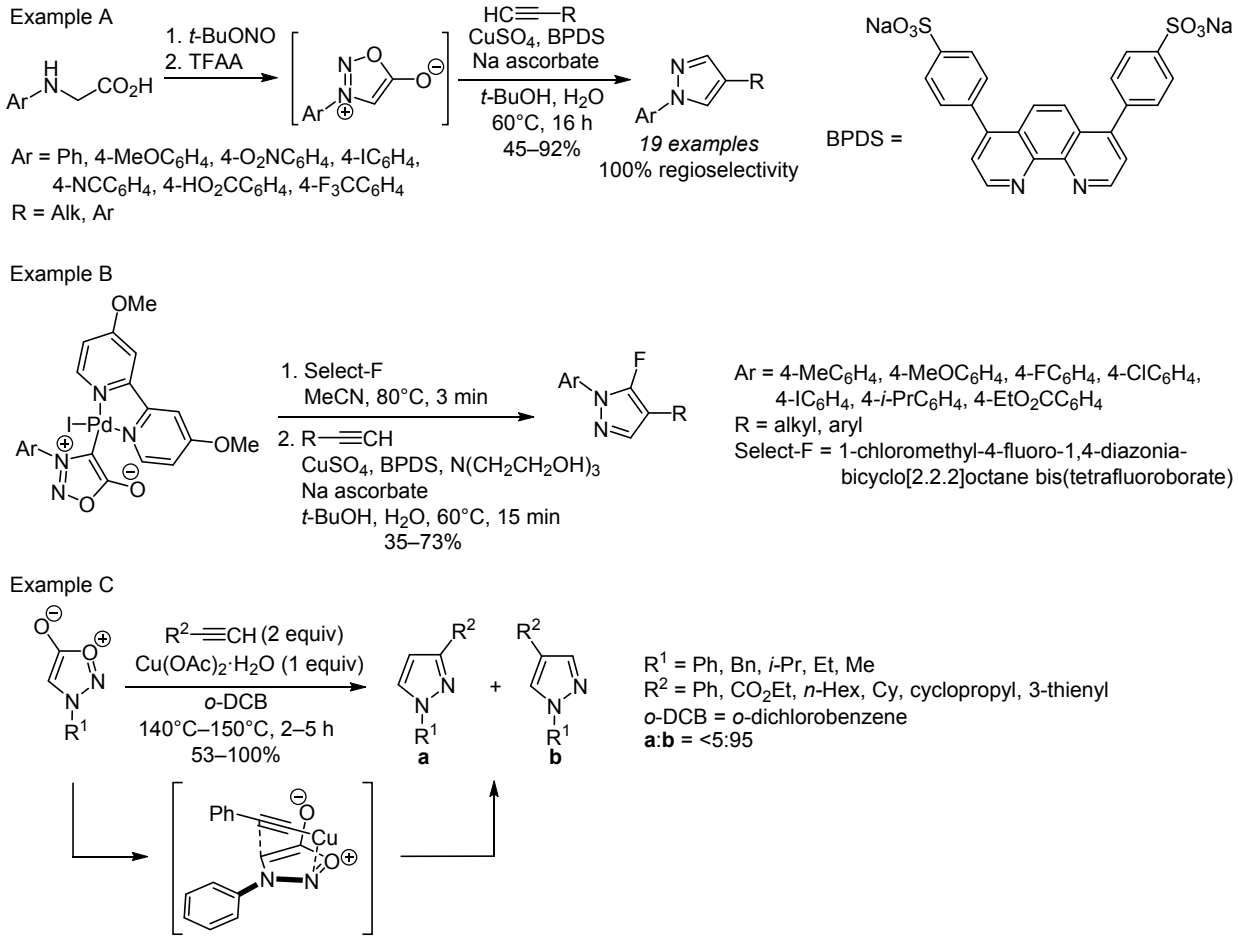
1.4. Reactions of C,N,N-cyclic dipoles

Recently, examples of [3+2] cycloaddition of C,N,N-cyclic azomethine imines **71** to methyl propiolate catalyzed by CuI were described.[55] The transformation occurred at room temperature to yield a mixture of diastereomers **72** (*dr* 93:7) and **73** (*dr* 85:15) in moderate yields. The methodology enables the synthesis of diazacyclopenta[*cd*]indene-3-carboxylates, which are unexplored saturated heterocycles, able to serve as a starting point in the search of novel lead compounds in medicinal chemistry, chemical biology, or materials science (Scheme 21).

Scheme 21. [3+2] Cycloaddition of C,N,N-cyclic azomethine imines with acetylenes catalyzed by CuI



Scheme 22. Examples of copper-catalyzed [3+2] cycloaddition of sydnones with acetylenes



The 1,3-dipolar cycloaddition reaction of sydnones with alkynes appeared as an attractive alternative to construct pyrazoles. However, these uncatalyzed reactions are limited to electron-deficient alkynes, suffer from lack of regioselectivity, and usually require harsh reaction conditions. Recently Taran et al. described a one-pot synthesis of 1,4-disubstituted pyrazoles from arylglycines *via* copper-catalyzed sydnone–alkyne cycloaddition (CuSAC). Various electron-rich and electron-poor *N*-arylsydnones were successfully reacted with a variation of the acetylene component yielding 1,4-pyrazoles as the sole product (Scheme 22, example A).[56] The methodology was successfully applied in a bioconjugation protocol. Bovine serum albumin (BSA) and sydnone conjugate was obtained through standard peptide coupling using an excess of 4-carboxyphenylsydnone. Under CuSAC conditions the sydnone moiety on BSA was then transformed into pyrazole yielding the densylated protein.[57]

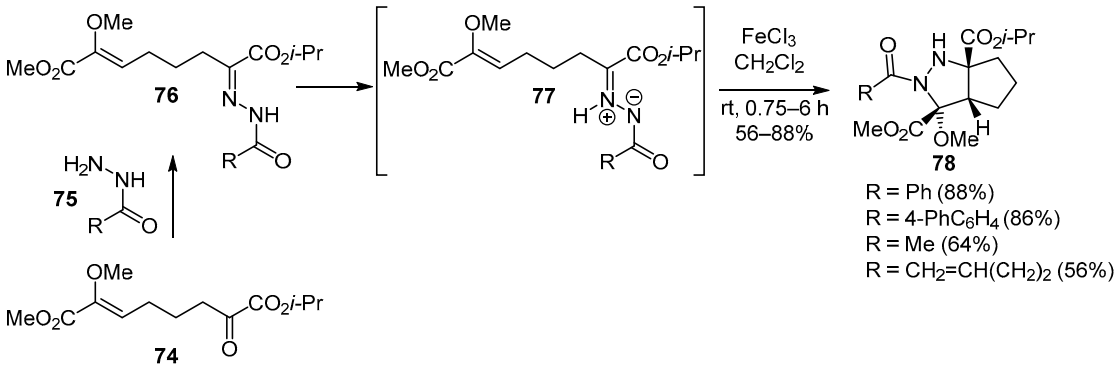
The same research group later on described a surprisingly fast, regioselective, copper-catalyzed cycloaddition of 4-fluorosydnones, which were successfully generated from the corresponding 4-bromo- or 4-iodosydnones *via* Pd complexes, with a variety of acetylenes (Scheme 22, example B).[58] Aminopyrazoles were also very recently prepared from readily accessible sydnones and sulfonyl ynamides using either a copper-mediated sydnone–alkyne cycloaddition or *in situ* generated strained cyclic ynamides.[59] However, copper salts have been found to promote the cycloaddition reaction of sydnones and terminal alkynes, resulting in significant reduction in reaction time. The use of $Cu(OTf)_2$ facilitates the formation of 1,3-disubstituted pyrazoles, whereas the $Cu(OAc)_2$ promoter system allows the corresponding 1,4-isomer to be formed (Scheme 22, example C). The mechanistic experimental and theoretical studies revealed that $Cu(OTf)_2$ functions as a Lewis acid activator of the sydnone, whereas $Cu(OAc)_2$ enables the formation of reactive Cu(I) acetylides.[60]

2. [3+2] CYCLOADDITIONS OF AZOMETHINE IMINES TO OLEFINS

2.1. Reactions of acyclic dipoles

Overman et al. studied intramolecular cycloadditions of acyclic azomethine imines **77**, generated *in situ* from hydrazones **76** *via* thermal or acid-induced 1,2-prototropy, to form *cis*-cyclopentapyrazolidines **78**. Hydrazones **76**, in turn, were prepared from alkene-tethered α-ketocarboxylic acid derivative **74** and monosubstituted hydrazines **75**. Under optimized reaction conditions, cycloadditions of hydrazones **76** proceeded smoothly under prolonged heating (100–115°C, 18–60 h). On the other hand, $FeCl_3$-promoted cycloadditions of hydrazones **76** furnished

Scheme 23. $FeCl_3$-promoted intramolecular cycloadditions of acyclic azomethine imines

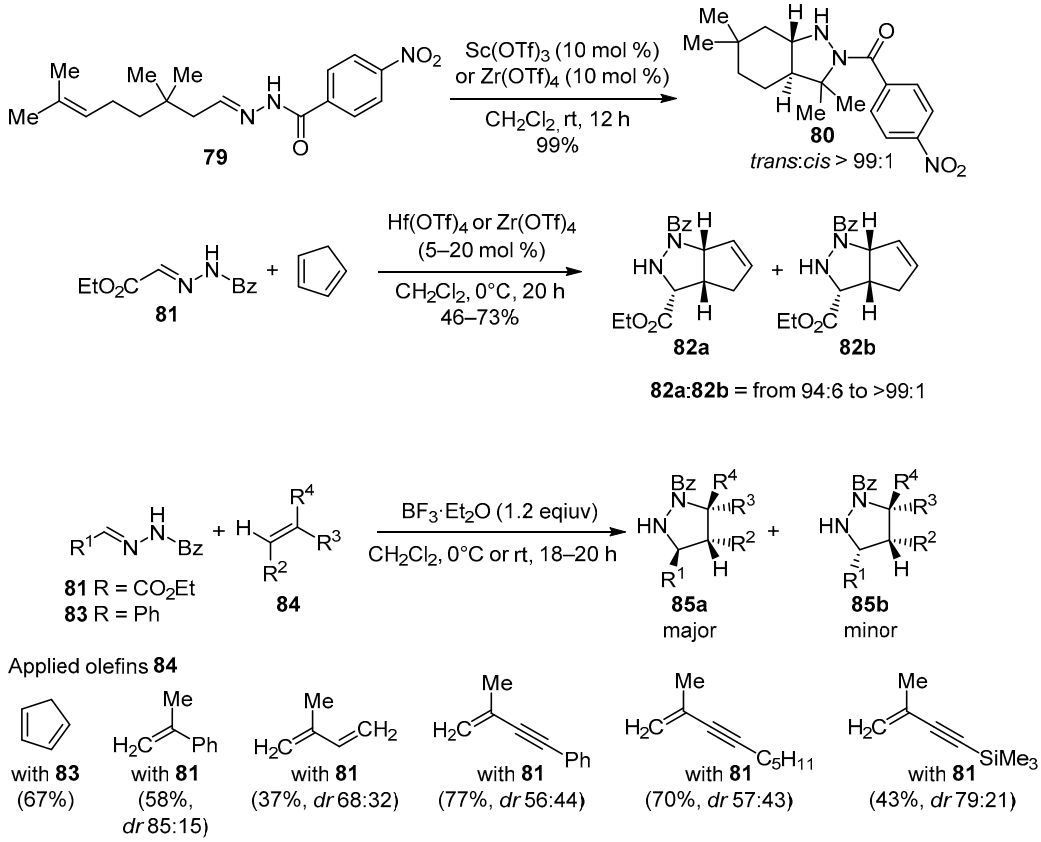


cis-cyclopentapyrazolidines **78** (56–88% yield) in 0.75–6 h at room temperature in CH_2Cl_2. The authors reported only four $FeCl_3$-promoted cycloadditions (Scheme 23), while other hydrazones (trifluoroacetyl, Cbz, 3-pyridylcarbonyl, and formyl) were either unreactive or unstable under these reaction conditions.[61]

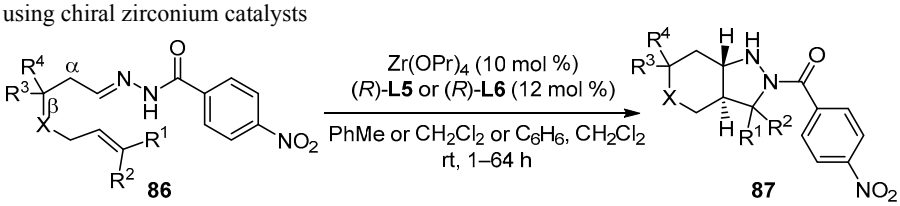
Kobayashi and coworkers demonstrated the utility of Lewis acids in [3+2] cycloadditions of hydrazine-derived acyclic azomethine imines under mild reaction conditions. Thus, intramolecular cycloaddition of hydrazone **79** using catalytic amounts of either $Sc(OTf)_3$ or $Zr(OTf)_4$ at room temperature proceeded quantitatively to give pyrazolidine **80** with excellent diastereoselectivity (*trans*:*cis* = >99:1). On the other hand, cycloaddition of hydrazone derived from ethyl glyoxylate **81** to cyclopentadiene yielded the desired bicyclic product **82** with high diastereoselectivity (**82a**:**82b** = from 94:6 to >99:1) in 46–73% yields applying various catalytic amounts of either $Zr(OTf)_4$ or $Hf(OTf)_4$ in CH_2Cl_2 at 0°C. When cycloadditions of ethyl glyoxylate-derived hydrazone **81** or benzaldehyde-derived hydrazone **83** were performed with cyclopentadiene or acyclic olefins **84**, a stoichiometric amount of $BF_3{\cdot}Et_2O$ was needed to achieve satisfactory reactivity. Cycloadducts **85** were formed in 37–77% yields with low to moderate diastereoselectivity (*dr* from 56:44 to 85:15) (Scheme 24).[62]

In 2002, Kobayashi et al. described asymmetric intramolecular [3+2] cycloaddition reactions of 4-nitrobenzoyl hydrazone-tethered olefins **86** using chiral zirconium catalysts obtained from $Zr(OPr)_4$ and BINOL-derived ligands (*R*)-**L5** or (*R*)-**L6**. The scope of their investigation

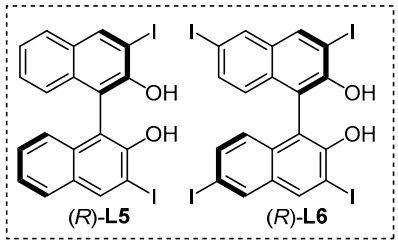
Scheme 24. Lewis acid-mediated cycloadditions between hydrazones and olefins



Scheme 25. Asymmetric intramolecular [3+2] cycloaddition reactions of 4-nitrobenzoyl hydrazone-tethered olefins using chiral zirconium catalysts



	Yield, %	*cis*:*trans*	*ee*, % *trans*
$R^1 = R^2 = R^3 = R^4 = Me$, X = CH_2	99	1:99	96
$R^1 = R^2 = Me$, $R^3 = R^4 = H$, X = CH_2	62	29:71	92
$R^1 = R^2 = Me$, $R^3 + R^4 = SCH_2CH_2S$, X = CH_2	91	1:99	97
$R^1 + R^2 = SCH_2CH_2S$, $R^3 = R^4 = H$, X = CH_2	57	1:99	72
$R^1 = R^2 = R^3 = R^4 = Me$, X = O	38	1:99	81

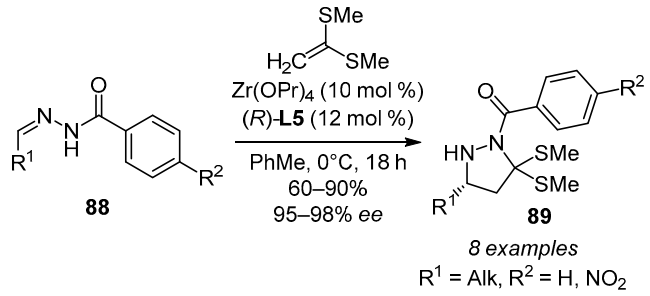


is presented in Scheme 25. The corresponding bicyclic pyrazolidine products **87** were formed in 38–99% yields, good to excellent enantioselectivities (72–97% *ee*), and *cis*:*trans* diastereoselectivities ranging from 29:71 to 1:99 (Scheme 25). The lack of substituents in the β-position or terminal olefin positions had a significant effect on both the reactivity and diastereoselectivity of the respective intramolecular cycloadditions.[17]

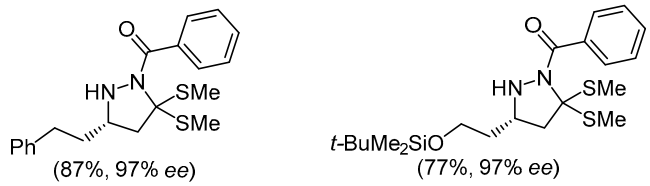
Later in 2004, Kobayashi et al. developed a zirconium-catalyzed enantioselective intermolecular [3+2] cycloaddition of hydrazones to olefins. Thus, benzoyl and 4-nitrobenzoyl hydrazones **88**, derived from various aliphatic aldehydes (α- and β-branched, sterically hindered, enolizable, and functionalized aldehydes), reacted smoothly with 1,1-bis(methylsulfanyl)ethane in the presence of catalytic amounts of chiral zirconium catalyst prepared from $Zr(OPr)_4$ and BINOL-derived ligand (*R*)-**L5**. The corresponding pyrazolidine derivatives **89** were formed in high yields (60–90%) and excellent enantioselectivities (95–98% *ee*) (Scheme 26).[63]

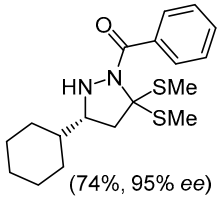
On the other hand, cycloadditions of vinyl ethers **91** (and ethyl vinyl sulfide) proceeded only with more reactive 4-nitrobenzoyl hydrazones **90** in the presence of chiral zirconium catalyst prepared from $Zr(OPr)_4$ and ligand (*R*)-**L6**. The respective pyrazolidine products **92** containing *N*,*O*-acetal structural motif were formed in low to moderate diastereoselectivities (*dr* from 50:50 to 81:19), high yields (65–95%), and excellent enantioselectivities for both diastereomers (84–99% *ee*) (Scheme 27). Reaction of propyl vinyl ether with aromatic hydrazone (derived from benzaldehyde and 4-nitrophenylhydrazine) gave the corresponding cycloadduct in 70% yield, *dr* 1:1, and decreased

Scheme 26. Zirconium-catalyzed enantioselective [3+2] cycloaddition of hydrazones to ketene dimethyl dithioacetal

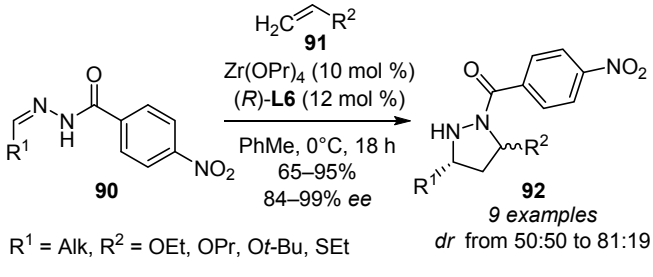


Selected examples of products

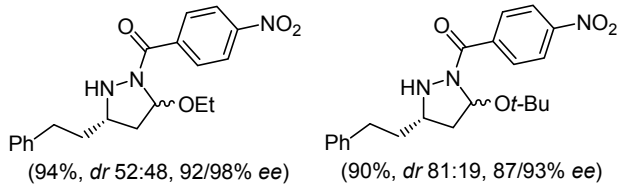


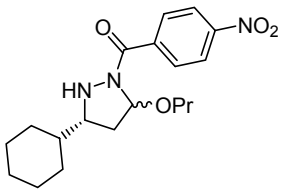


Scheme 27. Zirconium-catalyzed enantioselective [3+2] cycloaddition of hydrazones to vinyl ethers and ethyl vinyl sulfide

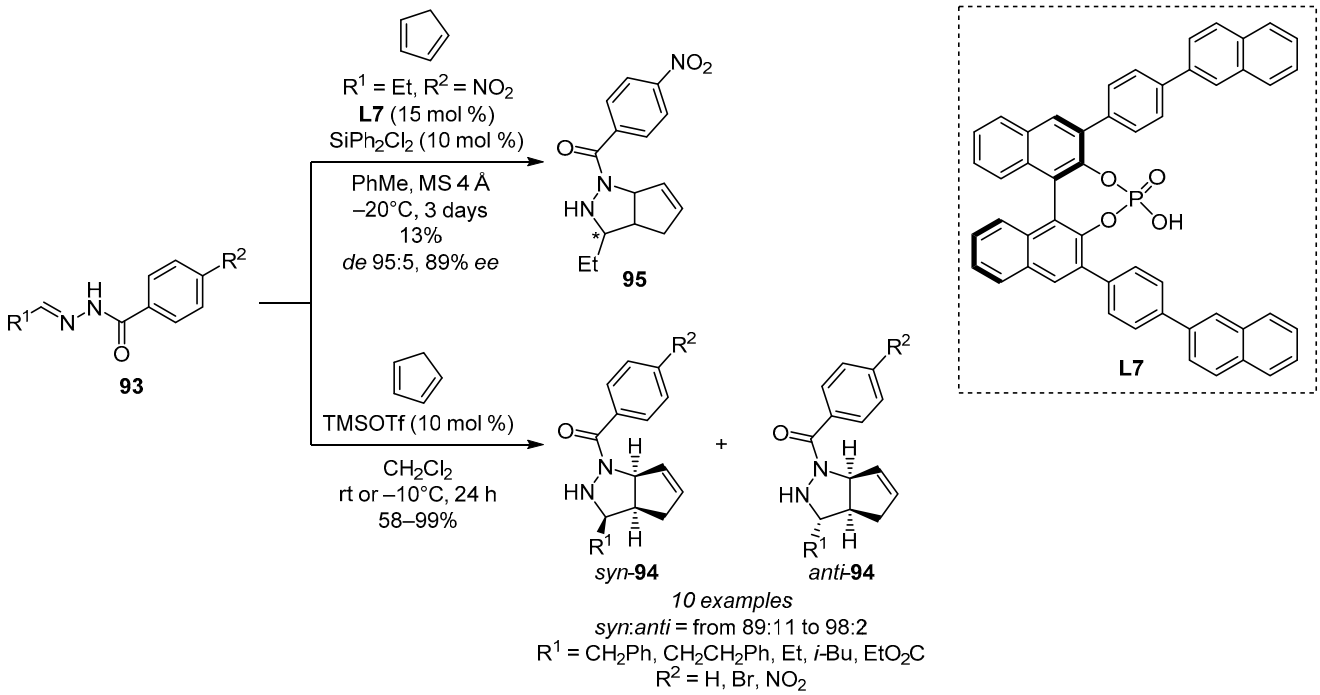


Selected examples of products





Scheme 28. Cycloaddition reaction between aliphatic aldehyde-derived *N*-acyl hydrazones and cyclopentadiene catalyzed by silicon-based Lewis acids



enantioselectivities (42 and 81% *ee*). Based on several experiments, a concerted [3+2] reaction mechanism has been proposed.[63]

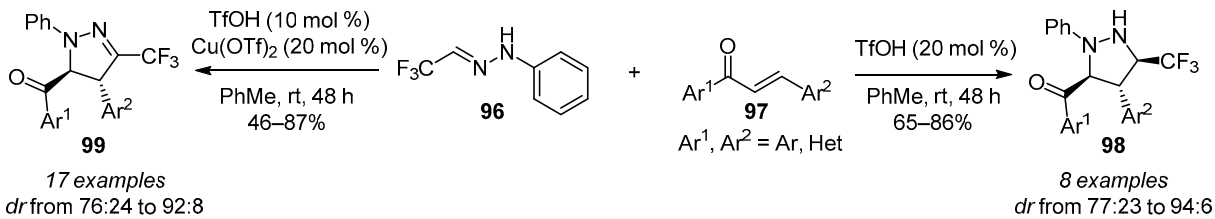
Tsogoeva and Zamfir developed a cycloaddition reaction between aliphatic aldehyde-derived *N*-acyl hydrazones **93** and cyclopentadiene applying catalytic amounts of trimethylsilyl triflate (TMSOTf) as Lewis acid. The corresponding cycloadducts **94** were formed in good to excellent yields (58–99%) and diastereoselectivities (*dr* from 89:11 to 98:2) (Scheme 28). Next, a chiral silicon-based Lewis acid, prepared *in situ* from BINOL-phosphate ligand **L7** and $SiPh_2Cl_2$, was applied in enantioselective cycloaddition between 4-nitrobenzoyl hydrazone **93** (prepared from propionaldehyde) and cyclopentadiene in the presence of MS 4 Å. Cycloadduct **95** was formed in a very low yield (13%), though very promising stereoselectivity (*dr* 95:5 (*syn*), 89% *ee*) (Scheme 28).[64]

Wu et al. studied cycloaddition reactions of trifluoroacetaldehyde-derived phenyl hydrazone **96** with α,β-ethenyl ketones **97**. Under optimized reaction conditions, triflic acid-catalyzed reactions led to the expected pyrazolidines **98** in 65–86% yields with good diastereoselectivity (*dr* from 77:23 to 94:6). If the same reactions were conducted in the presence of catalytic amount of copper(II) triflate, pyrazoline derivatives **99** were obtained in 46–87% yields and *dr* from 76:24 to 92:8. Both, electron-withdrawing and -donating substituents on the benzene ring as well as heterocyclic substituents of dipolarophiles **97** were compatible with the optimized reaction conditions. The formation of pyrazolines **99** was reasoned to be the consequence of a copper(II) triflate-promoted oxidation of the corresponding pyrazolidines **98** (Scheme 29).[65]

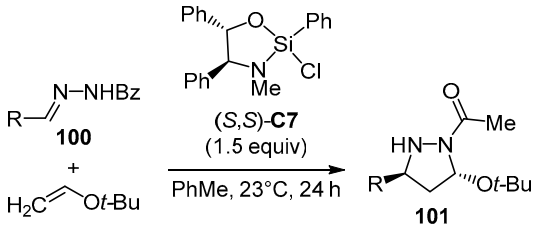
Leighton and coworkers developed an enantioselective [3+2] acyl hydrazine–enol ether cycloaddition, where chiral phenyl silane (*S*,*S*)-**C7** was found to efficiently mediate the reaction and to induce the enantioselection (Scheme 30).[66] A variety of aliphatic, aromatic, and heteroaromatic aldehyde-derived benzoyl hydrazones **100** reacted well with *tert*-butyl vinyl ether to give the corresponding *N*-acetyl-pyrazolidines **101** with high *dr* and *ee* values. Despite the requirement for a full equivalent of the silane (*S*,*S*)-**C7**, the chiral pseudoephedrine backbone can be easily recovered, thus rendering this methodology highly practical. This method was also applicable to β-substituted enol ether **102** which gave, after cycloaddition to hydrazone **100a**, pyrazolidine **103** bearing three stereocenters.

Later on, the same authors applied the developed chiral silane-promoted enol ether–acyl hydrazone [3+2] cyclo-

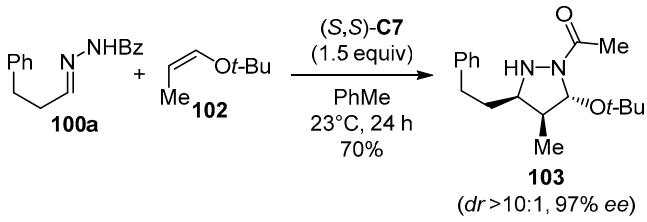
Scheme 29. Cycloaddition reactions of trifluoroacetaldehyde-derived phenyl hydrazone with α,β-ethenyl ketones



Scheme 30. Chiral silane-mediated 1,3-dipolar cycloaddition of acyl hydrazones to enol ethers



R	Yield, %	*dr*	*ee*, %
$PhCH_2CH_2$	84	96:4	90
$BnOCH_2$	85	>97:3	90
i-Pr	76	96:4	94
Cy	79	>97:3	95
t-Bu	76	>97:3	98
Ph	80	>97:3	94
p-FC_6H_4	66	>97:3	93
2-Fur	81	95:5	95

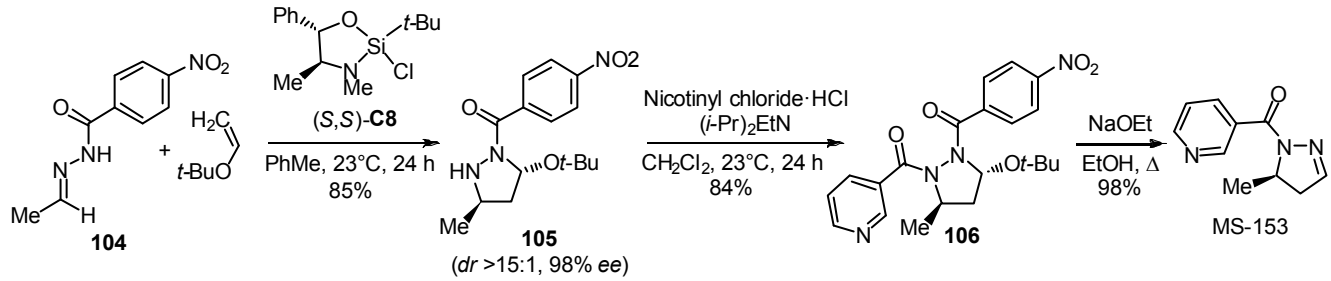


addition reaction to a brief synthesis of the neuroprotective agent MS-153 (Scheme 31).[67] *N*-Acyl hydrazone **104** was first reacted with *tert*-butyl vinyl ether in the presence of silane **C8** to give pyrazolidine **105**, which was transformed into *N*,*N*′-diacylated pyrazolidine **106**. Finally, removal of *p*-nitrobenzoyl group with concomitant elimination of *tert*-butoxy group gave the target compound MS-153. The use of *p*-nitrobenzoyl group in hydrazone **104** was necessary to enhance its reactivity in the reaction with enol ether.

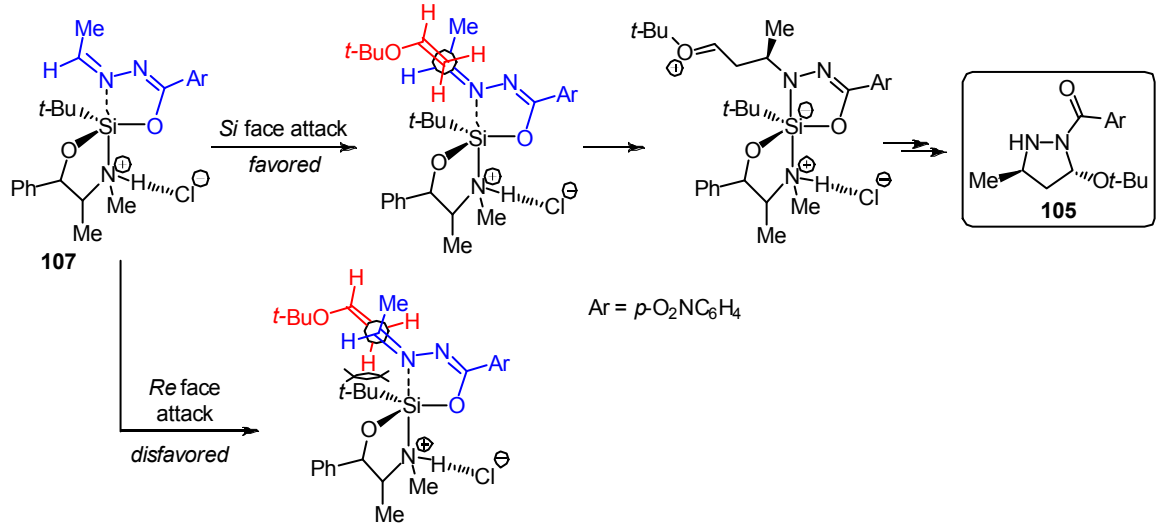
They also proposed a mechanism, where the reaction proceeds in a stepwise fashion, which assures the observed stereochemical outcome (Scheme 32). First, a trigonal bipyramidal complex **107** of acyl hydrazone **104** and silane (*S*,*S*)-**C8** is formed. Then *tert*-butyl vinyl ether attacks the C=N bond of acyl hydrazone **104** from less crowded *Si* face and the ring closure gives pyrazolidine product **105** as a key intermediate in the synthesis of MS-153.

Asymmetric cycloaddition reaction of *N*-acyl hydrazone **108** with silyl ether **109** was used as a crucial transformation in a six-step synthesis of manzacidin C,[68] a representative of tetrahydropyrimidine alkaloids displaying various biological activities (Scheme 33).[69] The chiral silane (*S*,*S*)-**C9** itself was found to promote the cycloaddition, furnishing satisfactory enantioselectivity in the model reaction. To increase the activity of silane, catalyst (*S*,*S*)-**C9** was preactivated with AgOTf, and the resulting chiral Lewis acid successfully promoted the reaction of thienyl hydrazone **108** with alkene **109**. The advantage of

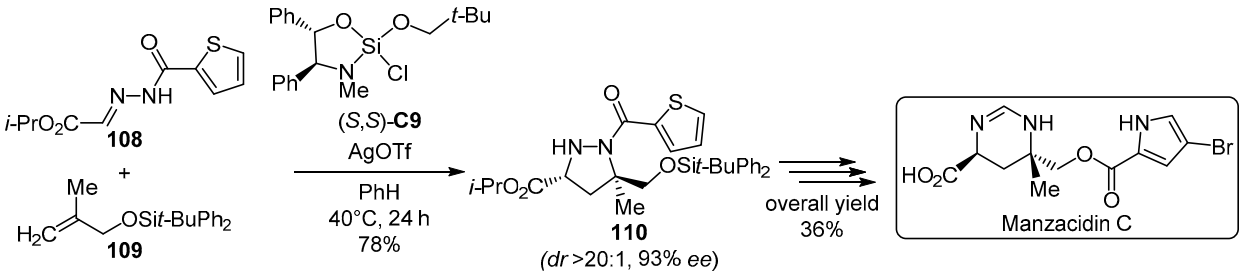
Scheme 31. Silane-promoted asymmetric [3+2] cycloaddition as a crucial step in neuroprotective agent MS-153 synthesis



Scheme 32. Mechanism of chiral silane-mediated [3+2] cycloaddition of acyl hydrazone with enol ether



Scheme 33. Synthesis of manzacidin C *via* Ag–silane-catalyzed asymmetric 1,3-dipolar cycloaddition



this cycloaddition is the formation of two stereocenters in a single highly diastereo- and enantioselective step to give pyrazolidine product **110** with excellent *dr* and *ee* values, which was used as the key intermediate in the synthesis of manzacidin C.

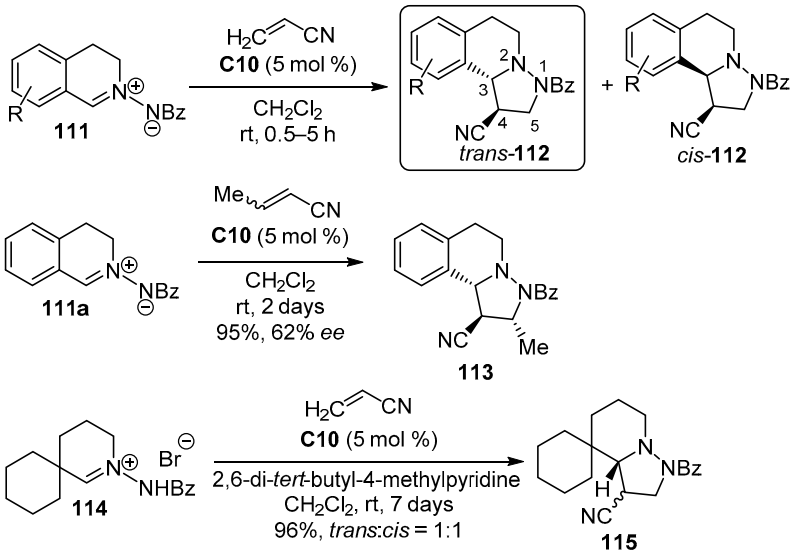
2.2. Reactions of C,N-cyclic dipoles

Togni and coworkers reported an enantioselective [3+2] cycloaddition of C,N-cyclic azomethine imines **111** to α,β-unsaturated nitriles catalyzed by a dicationic Ni(II) complex **C10** containing a chiral phosphine ligand.[70] The addition of azomethine imines **111** bearing different electron-donating or electron-withdrawing groups to acrylonitrile occurred readily (0.5–5 h) at room temperature in a regio- and diastereoselective manner. Although the steric effect of a small activated cyanoolefin is low, the corresponding *trans*-3,4-cycloadducts **112** were obtained in high yields and satisfactory enantiomeric excesses, ranging from 66 up to 88% *ee* (Scheme 34). The addition of unsubstituted azomethine imine **111a** to acrylonitrile resulted in cyanopyrazolidine **112a** (R = H) with excellent *ee* (96%) and *dr* values (*trans*/*cis* 92:8). High efficiency of the catalyst **C10** was demonstrated in decreasing the catalyst loading from 5 to 1 mol % without a significant loss of yield, diastereoselectivity, or enantioselectivity. When crotononitrile (*trans*/*cis* mixture) was used in cycloaddition to azomethine imine **111a**, much lower enantioselectivity was observed (62% *ee* for compound **113**), indicating that the steric size of the dipolarophile is a crucial factor in these 1,3-dipolar cycloadditions. The azomethine imine substrate without the fused aromatic ring, prepared *in situ* from the parent salt **114**, reacted with acrylonitrile at room temperature very slowly to give full conversion only after 7 days. The *trans*- and *cis*-3,4-cycloadducts **115** were obtained in equal amounts as racemic mixtures (Scheme 34).

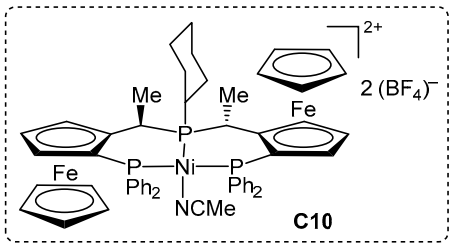
Similarly, C,N-cyclic azomethine imines **111** were employed in 1,3-dipolar cycloadditions to α,β-unsaturated aldehydes **116** as dipolarophiles to obtain optically active tetrahydroisoquinoline derivatives **117** (Scheme 35).[71] Reactions proceeded smoothly in the presence of the 1:2 complex of Ti(O*i*-Pr)$_4$ and (*S*)-BINOL and gave the corresponding cycloadducts in high enantioselectivities and diastereoselectivities in most cases. The generality of this asymmetric cycloaddition was demonstrated in reactions of azomethine imines **111** containing substituents in positions 6, 7, and 8 and using aldehydes containing a β-alkyl or β-aryl group. α,β-Disubstituted aldehydes also gave cycloadducts with high *ee* and *exo*/*endo* values, while α,β-unsaturated aldehydes lacking a β-substituent, furnished almost equal amounts of two diastereomers. This suggests the importance of the steric factor for the *exo* selectivity (Scheme 35).

The methodology was extended to C,N-cyclic azomethine imines, which were not fused to the aromatic ring. Due to

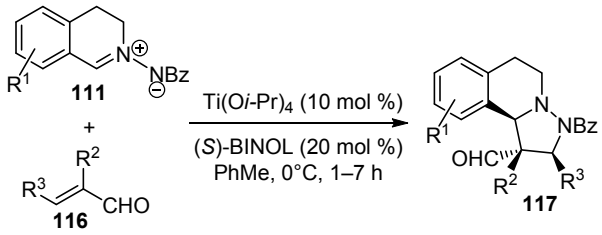
Scheme 34. Ni(II)–phosphine catalyst in enantioselective 1,3-dipolar cycloaddition of C,N-cyclic azomethine imines to unsaturated nitriles



R	Yield, %	*dr* (*trans*:*cis*)	*ee*, %
H	86	92:8	96
6-Me	95	93:7	72
7-Me	95	88:12	72
8-Me	90	87:13	88
6-Br	85	91:9	66
6-F	94	85:15	74



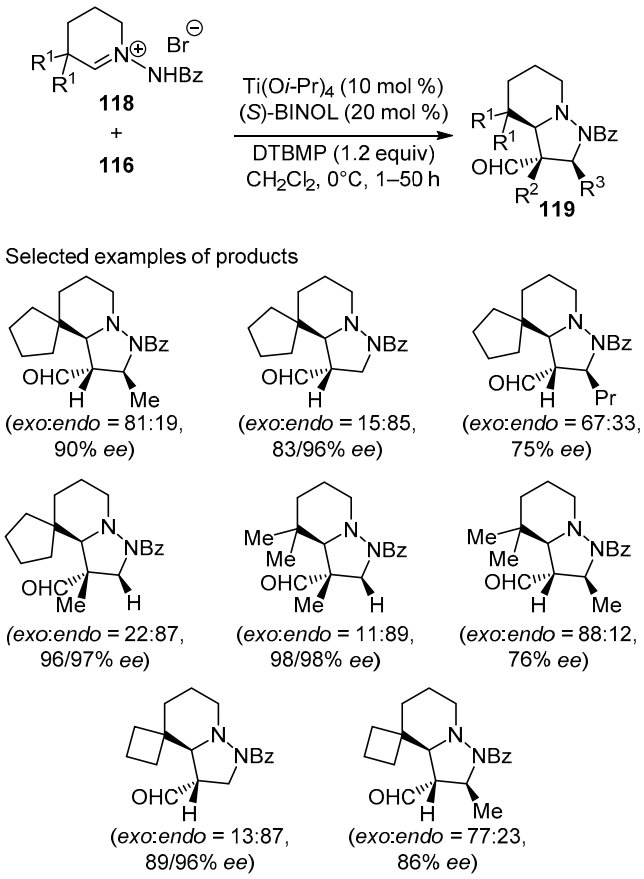
Scheme 35. Ti(IV)-catalyzed enantioselective cycloaddition of fused C,N-cyclic azomethine imines to α,β-unsaturated aldehydes



R^1	R^2	R^3	Yield, %	*exo*:*endo*	*ee*, %
5-Me	H	Me	85	>95:5	89
6-Me	H	Me	99	>95:5	92
7-Me	H	Me	93	>95:5	92
8-Me	H	Me	94	84:16	62/22
6-MeO	H	Me	96	>95:5	82
6-Br	H	Me	93	>95:5	95
7-Br	H	Me	92	>95:5	93
H	H	Pr	86	>95:5	85
H	H	Ph	94	>95:5	99
H	Me	Me	85	95:5	88
H	$(CH_2)_3$		93	92:8	89/86
H	Me	H	98	50:50	96/98
H	H	H	97	61:39	62/74

their low stability, they were prepared *in situ* from salts **118** in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base compatible with a Lewis acid catalyst. After reaction with α,β-unsaturated aldehydes **116**, cycloadducts **119** were obtained with satisfactory *dr* and *ee* values (Scheme 36).[71]

Scheme 36. Ti(IV)-catalyzed enantioselective cycloaddition of the *in situ* generated C,N-cyclic azomethine imines to α,β-unsaturated aldehydes

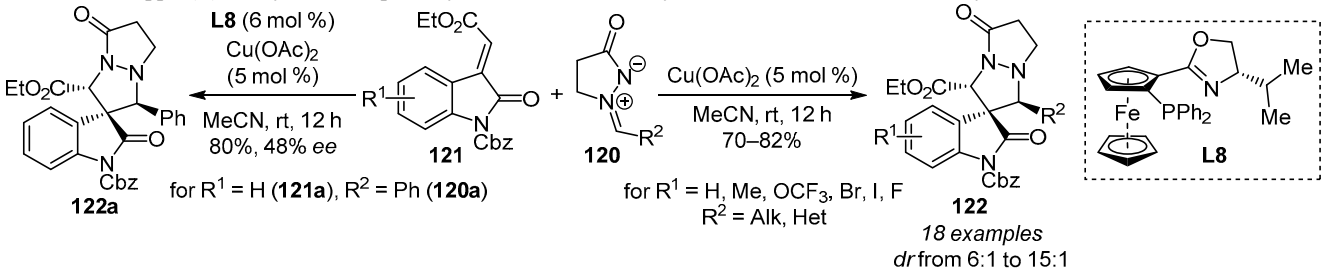


2.3. Reactions of N,N-cyclic dipoles

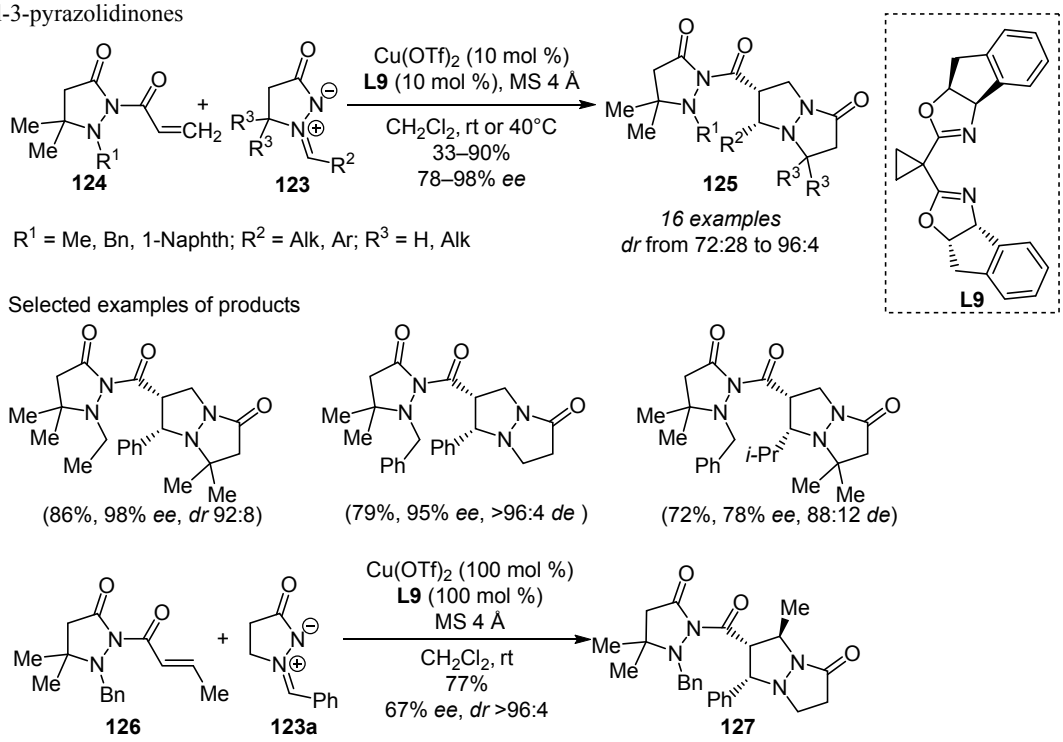
Sun and coworkers successfully utilized copper(II)-catalyzed 1,3-dipolar cycloaddition of N,N-cyclic azomethine imines **120** to methylidenindolinones **121** for the construction of spirocyclic oxindoles **122**. Products **122** were formed in good 70–82% yields and diastereoselectivities ranging from 6:1 to 15:1. The developed protocol tolerated both electron-donating and electron-withdrawing substituents on the aromatic ring of indolinone dipolarophiles **121**, as well as azomethine imines **120** bearing alkyl and differently substituted (hetero)aryl substituents. An enantioselective version of the above reaction between compounds **120a** (R^2 = Ph) and **121a** (R^1 = H), using *i*-Pr-Phosferrox ligand **L8**, gave spirocycloadduct **122a** in 80% yield and 48% *ee* (Scheme 37).[72]

Sibi and coworkers developed Cu(II)-catalyzed *exo*-diastereoselective and enantioselective cycloaddition of N,N-cyclic azomethine imines **123** to 2-acryloyl-3-pyrazolidinones **124**. The corresponding cycloadducts **125** were formed in 33–90% yields, in good to excellent enantioselectivities (78–98% *ee*), and diastereoselectivities ranging from 72:28 to 96:4. Interestingly, the authors observed occasional increase of enantioselectivity with the increased temperature (room temperature *vs.* 40°C) and the change of *exo* diastereoselectivity in the presence of MS 4 Å. Differently N^1-substituted dipolarophiles **124** were in line with the optimized reaction conditions, though N^1-Bn group showed the highest reactivity. Azomethine imines **123** bearing both electron-withdrawing and electron-donating substituents on the phenyl group as well as butyraldehyde-derived azomethine imine were compatible with the optimized reaction conditions. Expanding the

Scheme 37. Copper(II)-catalyzed 1,3-dipolar cycloaddition of N,N'-cyclic azomethine imines to methylidenindolinones



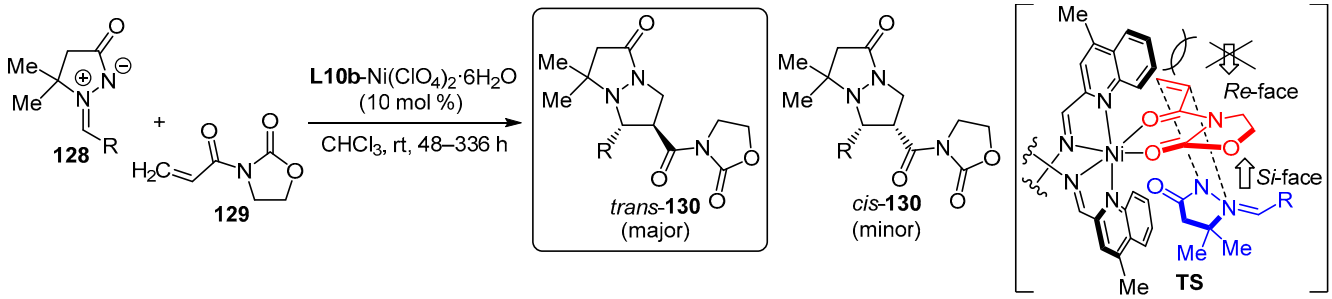
Scheme 38. Cu(II)-catalyzed *exo*-diastereoselective and enantioselective cycloaddition of N,N-cyclic azomethine imines to 2-acryloyl-3-pyrazolidinones



scope of reaction to β-substituted α,β-unsaturated pyrazolidinone imides, i.e., reaction of pyrazolidinone crotonate **126** with azomethine imine **123a**, met with decreased reactivity (100 mol % catalyst needed) to give the expected product **127** as a single *exo*-isomer in 77% yield, moderate 67% *ee*, and high *dr* >96:4 (Scheme 38).[73]

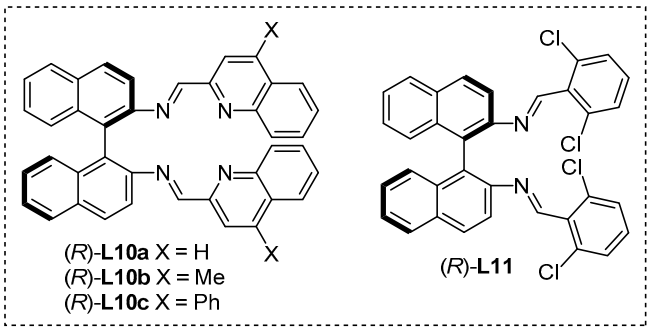
Chiral binaphthyldiimine–Ni(II) complex was applied as Lewis acid catalyst in a highly enantioselective and diastereoselective cycloaddition reaction between azomethine imines **128** and 3-acryloyl-2-oxazolidinone **129** (Scheme 39).[74] This represents yet another example of Ni(II)-catalyzed asymmetric 1,3-dipolar cycloaddition reaction of azomethine imines with electron-deficient dipolarophiles controlled by dipole-HOMO/dipolarophile-LUMO interactions. Asymmetric induction was achieved by the use of chiral bisimines **L10a–c** or **L11**, of which the quinoline-based ligand (*R*)-**L10b** exhibited the highest enantioselectivity and diastereoselectivity; the corresponding products **130** were obtained in *ee* values 75–97%, and *trans*/*cis* ratios from >99:1 to 64:36. For comparison, ligand (*R*)-**L11** gave 23% *ee* of the

Scheme 39. Chiral bisimines as ligands in Ni-catalyzed asymmetric [3+2] cycloadditions

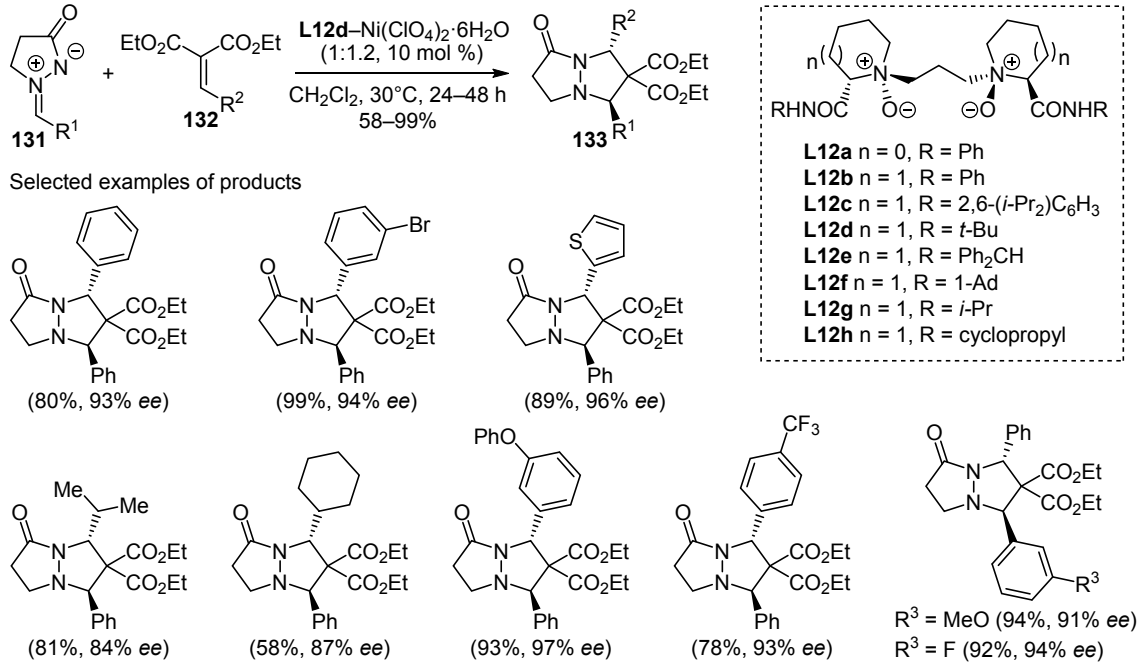


R	Yield, %	*dr*	*ee*, %
Ph	93	89:11	97
4-MeC_6H_4	99	91:9	93
4-NCC_6H_4	96	97:3	92
4-$MeOC_6H_4$	47	70:30	75
2-ClC_6H_4	63	>99:1	93
2-Naphth	quant.	93:7	96
2-Fur*	83	64:36	95

* Reaction run at 40°C, $Ni(BF_4)_2·6H_2O$ used.



Scheme 40. Ni(II)–*N*,*N*-dioxide-catalyzed asymmetric cycloaddition of alkylidene malonates with azomethine imines



product *trans*-**130** (R = Ph) in Ni(II)-catalyzed reaction of compound **128** (R = Ph) with compound **129**, whereas (*R*)-**L10b** furnished the same product in 97% *ee*. The only drawback of these reactions are relatively long reaction times (up to 336 h) at room temparature, but they can be shortened without a significant loss of enantioselectivity by running the reaction at 40 or 50°C in some cases.

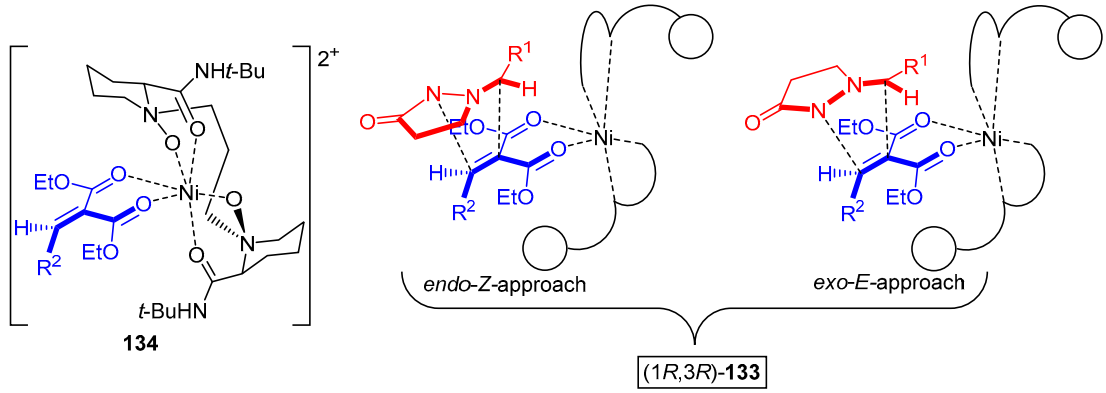
The high enantioselectivity of these cycloadditions might originate from transition state (**TS**) where quinoline moiety of **L10b**–Ni(II) complex efficiently shields the *Re* face of oxazolidinone **129**, and consequently the azomethine imine **128** adds to it from the *Si* face (Scheme 39).

Feng and coworkers utilized a chiral *N*,*N*-dioxide–Ni(II) complex in an asymmetric cycloaddition of azomethine imines **131** with alkylidene malonates **132** as typical electron-deficient olefins (Scheme 40).[75] Amongst *N*,*N*-dioxides **L12a–h** tested, ligand **L12d** gave the best performance in combination with $Ni(ClO_4)_2·6H_2O$, leading to high yields and *ee* values (84–97% *ee*) of bicyclic adducts **133**. The developed methodology was applicable to a wide range of alkylidene malonates **132** and azomethine imines **131** and furnished the corresponding fused pyrazolidine products **133** with extremely high diastereoselectivity (*dr* >99:1).

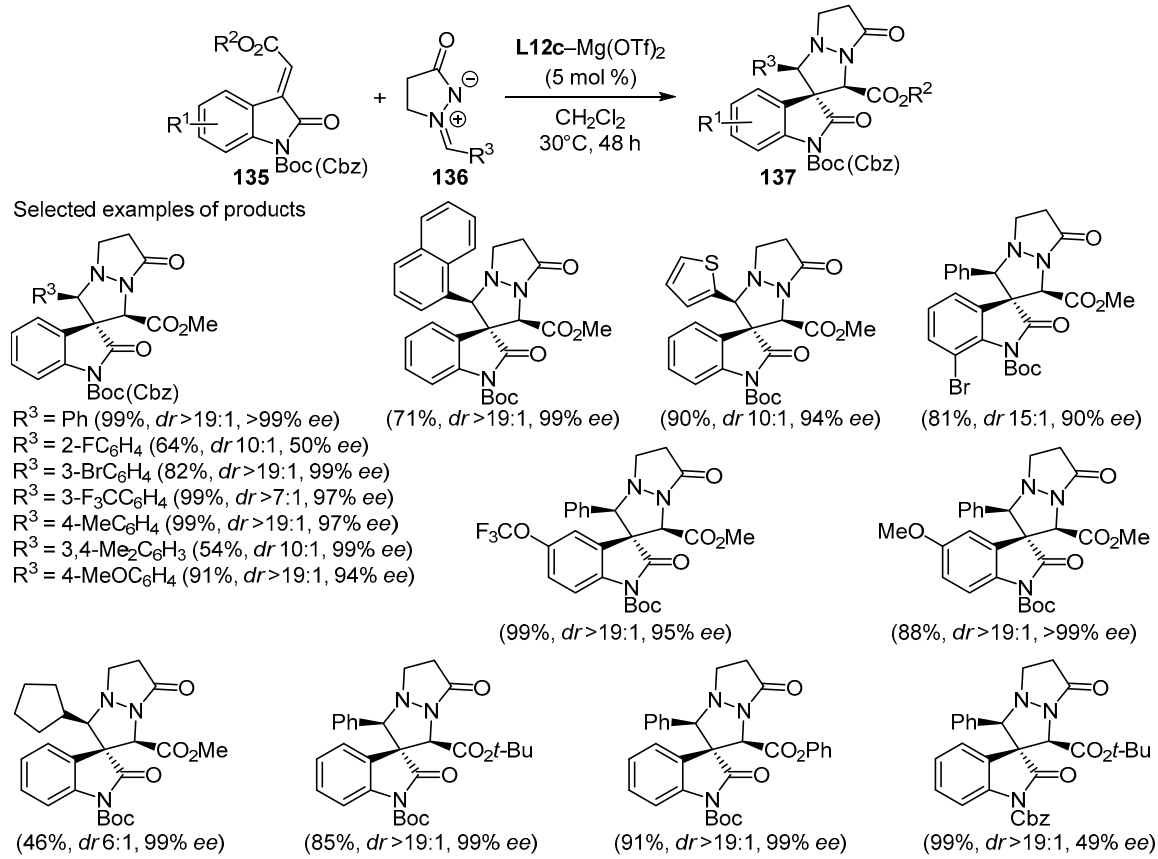
The authors also proposed a possible catalytic model, where a monomeric complex Ni(II)–**L12** would function as the most effective catalytic species in a concerted 1,3-cycloaddition mechanism as presented in Scheme 41. Malonate **132** first coordinates to Ni(II)–**L12d** complex in a bidentate manner, and the so formed complex **134** is attacked by azomethine imine **131** from the *Re* face. Taking into account also a possible isomerization of azomethine imine **131**, its *Z*-isomer could adopt the *endo* approach of malonate from the *Re* face, while *E*-isomer **131** could adopt the *exo* approach from the same side and, consequently, (1*R*,3*R*)-**133** product would be generated as the major diastereomer.

A chiral *N*,*N*-dioxide **L12c** proved to be a ligand of choice (Scheme 42) in $Mg(OTf)_2$-catalyzed asymmetric [3+2] cycloaddition of methylidenindolinones **135** to N,N-cyclic azomethine imines **136** (Scheme 42).[76] The corresponding

Scheme 41. Catalytic model for a highly diastereoselective 1,3-dipolar cycloaddition catalyzed by Ni(II)–*N*,*N*'-dioxide complex



Scheme 42. Mg-catalyzed cycloaddition of methylidenindolinones with N,N-cyclic azomethine imines

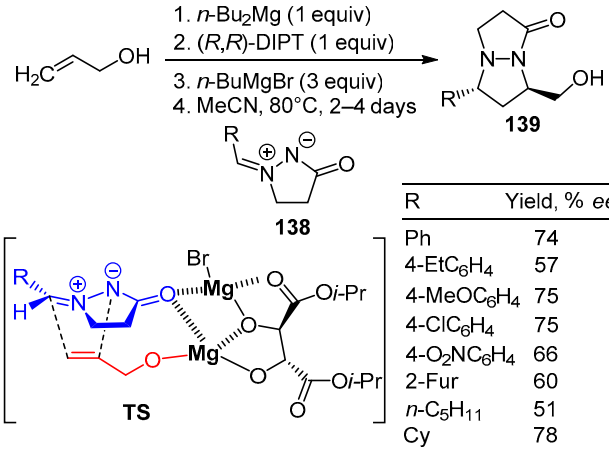


spiro products **137** were obtained with high *dr* and excellent *ee* values in most cases. The reaction is feasible with azomethine imines **136** bearing different alkyl, aryl, and heteroaryl R^3 groups, as well as with methylidenindolinones **135** having electron-donating or electron-withdrawing R^1 groups. Differently *meta*- and *para*-substituted phenyl moieties in substrate **136** did not affect the stereoselectivity, while *ortho* substitution caused a decrease in enantioselectivity (R^3 = 2-FC_6H_4, 50% *ee*). Moreover, R^2 of the ester group had no influence on the stereoselectivity, while changing the protecting group on the nitrogen of compound **135** from Boc to Cbz significantly affected the *ee* value of pyrazolidine derivatives **137** (99→49%).

Inomata and coworkers reported an asymmetric 1,3-dipolar cycloaddition of N,N-cyclic azomethine imines **138** to allyl alcohols where tartaric acid diisopropyl ester ((*R*,*R*)-DIPT) was utilized as the chiral auxiliary to afford the corresponding optically active *trans*-pyrazolidines **139** (Scheme 43).[77] It was found that magnesium-mediated system was effective in promoting the cycloaddition in a highly regio-, dia-, and enantioselective manner. Reactions were carried out in the presence of Grignard reagent as a magnesium source, and despite running them at elevated temperatures, relatively long reaction times (2–4 days) were required to achieve satisfactory yields of the isolated products **139**. Azomethine imines **138** bearing various R groups at the imine moiety were transformed with allyl alcohol into pyrazolidines **139** with *ee* values in the range of 88–96%. The authors speculated, that the 1,3-dipolar cycloaddition of compound **138** to allyl alcohol might proceed through transition state (**TS**), where the azomethine imine moiety is located further away from DIPT, thus ensuring high enantioselectivity of the reaction.

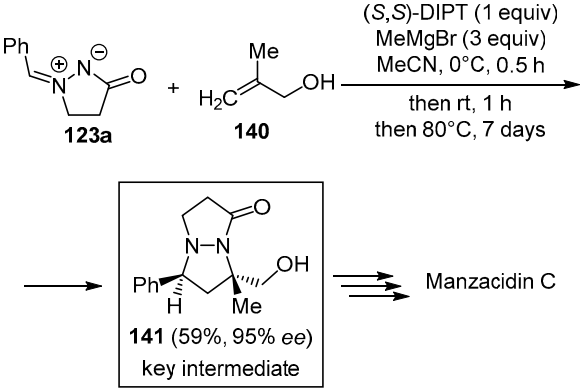
Thi Tong et al. utilized the previously developed Mg-mediated cycloaddition to build both stereocenters in a single step in another formal total synthesis of manzacidin C (Scheme 44).[78] To obtain the desired stereochemistry at the chiral carbon centers, (*S*,*S*)-DIPT was used as a chiral auxiliary in an asymmetric reaction between methallyl alcohol (**140**)

Scheme 43. Mg-mediated cycloaddition of allyl alcohol to N,N-cyclic azomethine imines



R	Yield, %	*ee*, %
Ph	74	95
4-EtC_6H_4	57	96
4-$MeOC_6H_4$	75	94
4-ClC_6H_4	75	94
4-$O_2NC_6H_4$	66	94
2-Fur	60	88
n-C_5H_{11}	51	96
Cy	78	94
t-Bu	50	96

Scheme 44. Manzacidin C synthesis *via* Mg-mediated asymmetric 1,3-dipolar cycloaddition of N,N-cyclic azomethine imines with methallyl alcohol

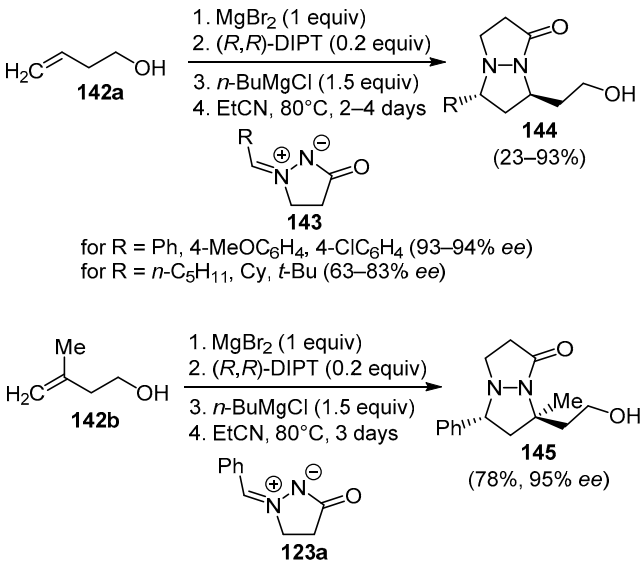


and 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide (**123a**). The synthesized intermediate **141** was further transformed *via* several synthetic steps into the target compound.

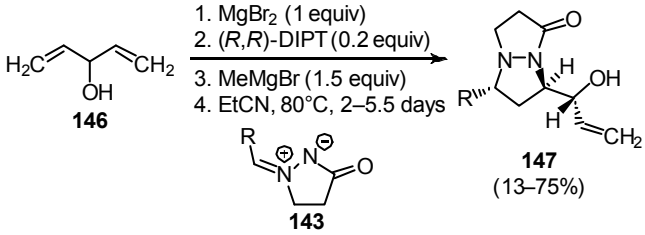
Tanaka research group extended the above-mentioned Mg-mediated cycloaddition to homoallylic alcohols **142a**,**b** (Scheme 45).[79] They improved the previously reported methodology by utilizing catalytic amount of (*R*,*R*)-DIPT and partially replacing Grignard reagent with $MgBr_2$. Although reactions of alcohol **142a** took place well with differently substituted azomethine imines **143**, considerably higher enantioselectivity was observed with azomethine imines bearing an aryl group. The corresponding pyrazolidine products **144** were obtained in 65–94% *ee*. Sterically more congested homoallyic alcohol **142b** also participated in the cycloaddition to 1-benzylidene-3-oxopyrazolidin-1-ium-2-ide (**123a**) to give product **145** with excellent 95% *ee* and complete regio- and diastereoselectivity.

The methodology described above allowed for the desymmetrization of 1,4-pentadien-3-ol (**146**) by the asymmetric 1,3-dipolar cycloaddition of azomethine imines **143**

Scheme 45. Mg-mediated cycloaddition of *N,N'*-cyclic azomethine imines with homoallylic alcohols



Scheme 46. Enantioselective desymmetrization of divinylmethanol *via* Mg–DIPT-promoted cycloaddition with N,N-cyclic azomethine imines



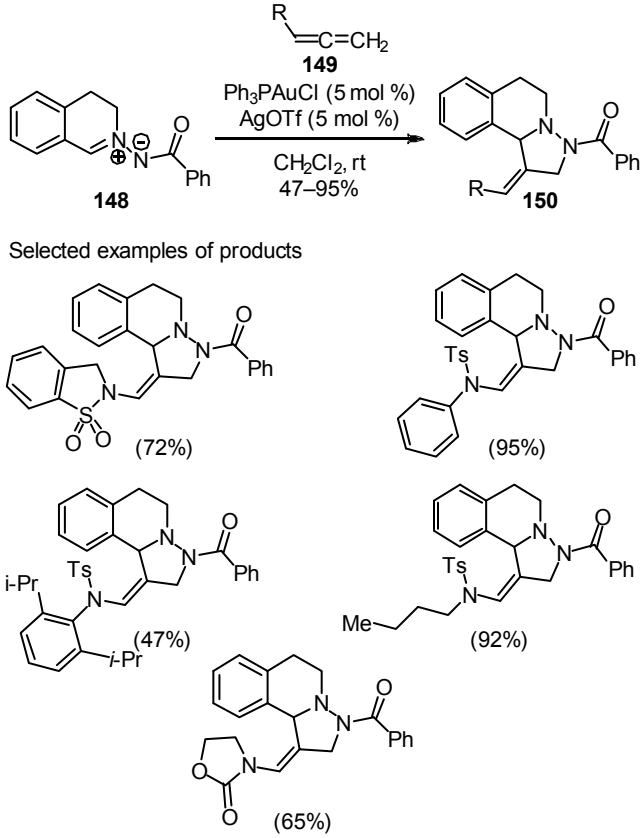
(Scheme 46).[80] Pyrazolidine products **147** containing three contiguous stereogenic centers were obtained as single diastereomers in high optical purity (79–98% *ee*).

3. [3+2] CYCLOADDITIONS OF AZOMETHINE IMINES TO OTHER DIPOLAROPHILES

3.1. Reactions of C,N-cyclic dipoles

Chen and coworkers reported gold-catalyzed [3+2] cycloadditions of C,N-cyclic azomethine imines to selected *N*-allenyl amides **149**. Under the optimized reaction conditions using Ph_3PAuCl/AgOTf in dichloromethane at room temperature, cycloadditions of 3,4-dihydroisoquinoline-derived azomethine imine **148** furnished (*Z*)-configured cycloadducts **150** in 47–95% yields (Scheme 47).[81]

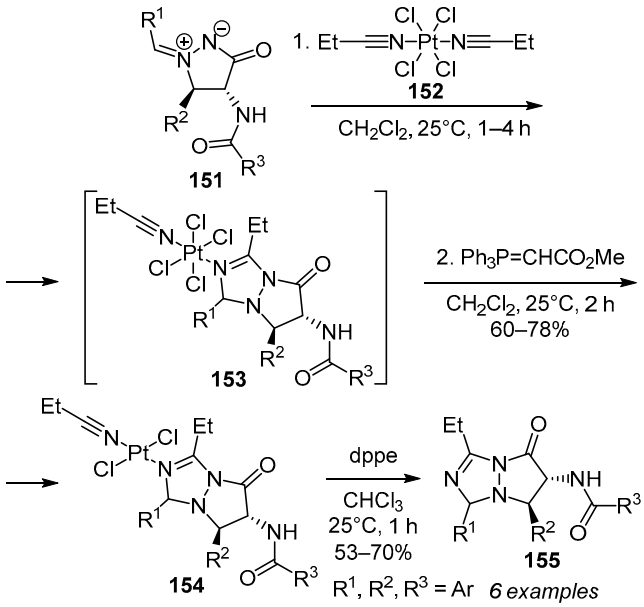
Scheme 47. Reactions of C,N-cyclic azomethine imines with selected *N*-allenyl (sulfon)amides



3.2. Reactions of N,N-cyclic dipoles

Kukushkin and coworkers applied platinum(IV)-bound nitrile, $[PtCl_4(EtCN)_2]$ (**152**), as a dipolarophile in 1,3-dipolar cycloaddition reactions to N,N-cyclic azomethine imines **151**. CN group coordinated to platinum(IV) center is activated enough to participate in 1,3-dipolar cycloadditions under mild reaction conditions. Thus, reactions between complex **152** and N,N-cyclic azomethine imines **151** proceeded rapidly at room temperature in a regio- and stereoselective fashion *via* unstable platinum(IV) species **153**, which were transformed in a one-pot two-step procedure into a stable and isolable platinum(II) species **154** in 60–78% yields. The final 6,7-dihydropyrazolo[1,2-*a*][1,2,4]-triazoles **155** were released after the treatment of Pt-complex **154** with 1,2-bis(diphenylphosphino)ethane (dppe) in 53–70% yields (Scheme 48).[82]

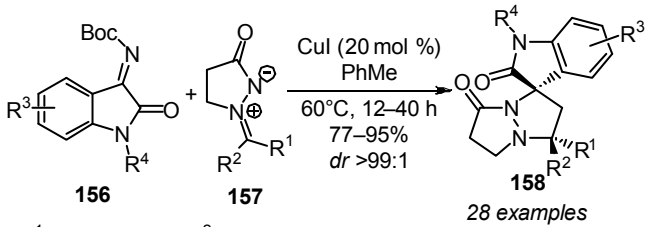
Scheme 48. Regio- and stereoselective 1,3-dipolar cycloadditions of N,N-cyclic azomethine imines to platinum(IV)-bound nitrile



Zhao and coworkers developed CuI-catalyzed diastereoselective 1,3-dipolar cycloaddition reaction between N,N-cyclic azomethine imines **157** and iminooxindoles **156**. Under optimized reaction conditions, the corresponding oxindole spiro-N,N-bicyclic heterocycles **158** were formed in good to excellent yields (77–95%) and excellent diastereoselectivities (*dr* >99:1). Thienyl- and alkyl-substituted azomethine imines **156** (R^1 = 2-thienyl, Me; R^2 = H, Me) failed to give the corresponding cycloadducts **158**. Otherwise, both electron-donating as well as electron-withdrawing substituents on the aromatic core of both reacting partners were well tolerated (Scheme 49). DFT calculation disclosed that the formation of products **158** is both, kinetically and thermodynamically favored.[83]

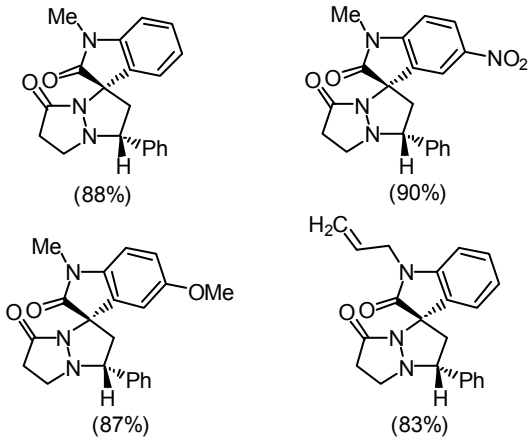
Chen et al. reported gold-catalyzed [3+2] cycloadditions of *N*-allenyl amides **160** to N,N-cyclic azomethine imines **159** (Scheme 50).[81] Under the optimized reaction conditions (Ph_3PAuCl/AgOTf, CH_2Cl_2, room temperature), *N*-allenyl sulfonamides **160** containing *N*-alkyl, substituted *N*-benzyl,

Scheme 49. CuI-catalyzed diastereoselective 1,3-dipolar cycloaddition reaction between N,N-cyclic azomethine imines and iminooxindoles

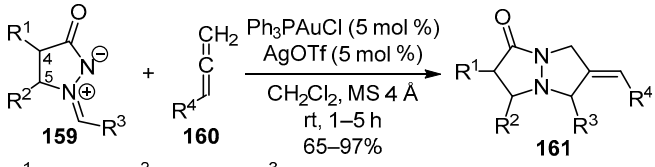


R^1 = Alk, Ar, Het; R^2 = H, Alk
R^3 = H, Me, F, Cl, Br, NO_2, OMe; R^4 = Me, MOM, Bn, allyl

Selected examples of products

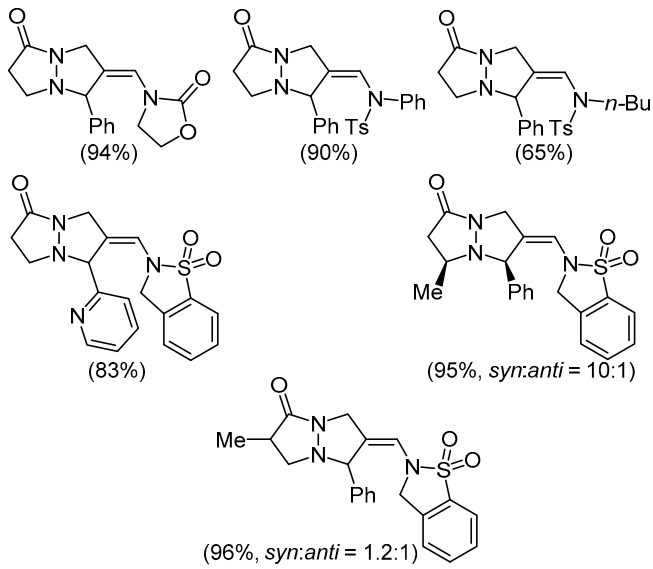


Scheme 50. [3+2] Cycloadditions of *N*-allenyl amides with N,N-cyclic azomethine imines



R^1 = H, Me; R^2 = Alk, Ph; R^3 = Ar, Het
R^4 = NTsAlk, NTsAr, etc.

Selected examples of products



and substituted *N*-phenyl groups, as well as 2-oxazolidinone-derived *N*-allenyl amide **160** reacted with azomethine imines **159** (containing both, electron-donating and -withdrawing phenyl substituents including pyridine functionality) furnishing the expected cycloadducts **161** in good to excellent yields (65–97%). These products feature exclusive (*Z*)-configuration around the exocyclic C=C bond. Reactions with C-5-substituted azomethine imines **159** (R^1 = alkyl, Ph) proceeded with diastereoselectivities ranging from 10:1 to >20:1, while reaction with C-4-substituted azomethine imine **159** (R^1 = Me) gave the corresponding product **161** in low *dr* (*syn*:*anti* = 1.2:1).

Since the seminal paper by Fu and Shintani in 2003, many examples of metal-catalyzed cycloadditions of azomethine imines to acetylenes and olefins have been reported. Much of the initial focus has been placed on copper-catalyzed azomethine imine–alkyne cycloaddition, which has now matured and become a viable alternative to azide–alkyne cycloadditions in "click" chemistry. As azomethine imines are neither explosive nor toxic, CuAIAC also allows large scale transformations, which are not safe with azides (CuAAC). However, regio- and stereoselective azomethine imine–alkyne cycloadditions to the nonterminal acetylenes remain challenging although recent examples may have showed the right path.

Beside reactions to acetylenes, many interesting examples of highly selective cycloadditions to olefins and other dipolarophiles have been reported. The catalysts employed were based on various transition and main group metals, that is advantageous in terms of catalyst diversity. On the other hand, higher diversity of catalysts and dipolarophiles within the same number of publications also means, that these cycloadditions are less systematically elaborated. Consequently, a lot of systematic work on cycloadditions of azomethine imines to olefins awaits to be done in order to obtain a general sight on reactivity and selectivity of these cycloadditions.

On the other hand, metal-catalyzed cycloadditions of all types of azomethine imines to other dipolarophiles containing C=X and C≡X multiple bonds including cumulenes and heterocumulenes are very scarce and need to be extensively elaborated both in terms of reactivity and selectivity.

The mechanism of metal-catalyzed [3+2] cycloadditions of azomethine imines is usually better explained by a stepwise than by a concerted mechanism. As already mentioned, mechanistic studies on this topic are scarce, while mechanistic explanations in the reported papers are in most cases used as a plausible rationale for the observed regioselectivity and stereoselectivity. The mechanism of metal-catalyzed [3+2] cycloadditions of azomethine imines is to be elucidated to obtain a basic figure on structure–reactivity–selectivity relationship. This improved understanding of the reaction mechanism will allow for a better catalyst and reaction design for practical applications.

Finally, the authors hope that this review will provide knowledge on recent progress in the field of [3+2] cycloadditions of azomethine imines that have emerged as useful methodologies for the construction of the pyrazole ring with all degrees of saturation including viable asymmetric versions. As azomethine imines are easily available from hydrazines and aldehydes/ketones, while numerous acetylenes and olefins are commercial, this approach toward pyrazole derivatives is unjustifiably neglected by the synthetic community in favor to the cyclocondensation method. However, the authors believe that the regioselectivity and the stereoselectivity of metal-catalyzed [3+2] cycloadditions of azomethine imines are the key advantages that will help this reaction to prevail in a long term.

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