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Comprehensive Review on Huisgen's Cycloaddition Reactions

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Abstract: The 1,3-Dipolar cycloaddition reactions are the classic reaction in modern synthetic organic chemistry. The concept of these reactions was introduced by Huisgen and his co-workers in the early 1960's. 1,3-Dipolar cycloaddition reactions are simple but powerful tool for the construction of five membered heterocycles such as isoxazoles, isoxazolines, pyrazoles, pyrazolones, 1,2,4-oxadiazolines etc. This review comprises of illustrious history, mechanistic path, FMO approach, stereochemistry and synthetic applications of 1,3-dipolar cycloaddition reactions. Recent developments in asymmetric 1,3-dipolar cycloaddition reactions were also discussed.

Key Words: Dipolar, regioselectivity, thermal, photolytic, pericyclic, stereoselectivity.

Introduction:

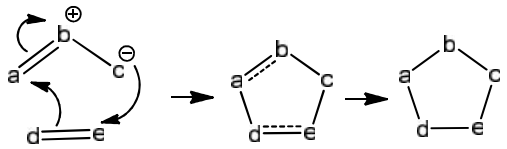
Most of the organic reactions occur in several steps, the reaction mechanism involve, either intermediates or polar transition states or free radicals. But there are some reactions that give no evidence of involving intermediates when they are subjected to usual probes for studying the mechanisms. The lack of evidence for the existence of intermediates leads to the conclusion that, the reactions follow concerted mechanisms. An important class of concerted reactions is pericyclic reactions; the present understanding of the mechanism of pericyclic reactions is mainly due to the ingenious work of Woodward and Hoffman. Accordingly, the pathways of such reactions were determined by the symmetry properties of the orbitals, that are directly involved and that the symmetry of the each participating orbital must be conserved during the concerted process.[1]

Cycloaddition reactions:

Cycloaddition reaction is a process in which two or more π systems combine to form a stable cyclic molecule, during which sigma bonds are formed between the termini of π systems without loss of any fragment, that follow a concerted mechanism. These reactions proved to be a powerful tool in the construction of cyclic systems. The most familiar of these cycloadditions are Diels-Alder reaction [4π + 2π]; extensively used in the stereospecific construction of 6-membered ring systems, and 1,3-dipolar cycloaddition [3 + 2]; used in the construction of 5-membered ring systems.

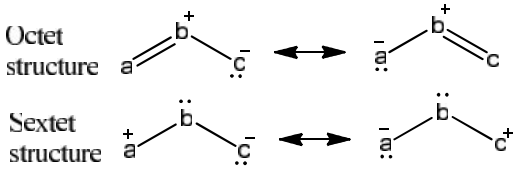
1,3-Dipolar cycloaddition reactions:

The concept of 1,3-Dipolar cycloaddition reactions now known as Huisgen cycloaddition reactions was the monumental work by Huisgen and his Co-workers.[2] Here, a five membered ring is formed by the cycloaddition of 1,3-dipole molecule (a three atom entity; *a-b-c*) and dipolarophile (a two atom entity; *d-e*) (Scheme-1).



Scheme-1

1,3-Dipolar molecule is a species represented by zwitter ionic octet and sextet structures as shown (Scheme-2). The three atoms can be a wide variety of combination of C, O and N.



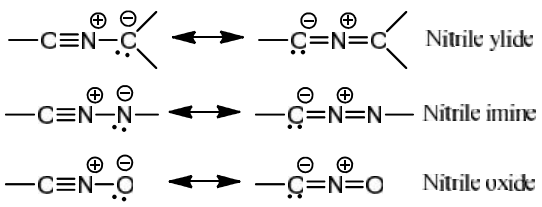
Scheme-2

In all 1,3-dipoles, there are four electrons in three parallel π-orbitals and are both nucleophilic and electrophilic in nature. This ambivalence of the 1,3-dipole is of key importance in understanding its reactivity. The nucleophilic character of the 1,3-dipole may be stronger than its electrophilic quality. Compounds such as nitrile ylides or diazomethane will cycloadd to electron deficient dipolarophiles much faster than with electron rich multiple bonds. The opposite is true for ozone, which combines preferably with electron rich dipolarophiles.

The 1,3-dipoles can be basically divided into two different types: the allyl anion type such as nitrones, azomethine ylides, nitro compounds, bearing a nitrogen atom in the middle of the dipole, carbonyl ylides, or carbonyl imines, bearing an oxygen atom in the middle of the dipole and the linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkanes, or azides. Some typical 1,3-dipolar species are shown in table-1,table-2 and table-3.

Table-1: Propargyl-allenyl type 1,3-dipoles

Nitrilium betaines



Diazonium betaines

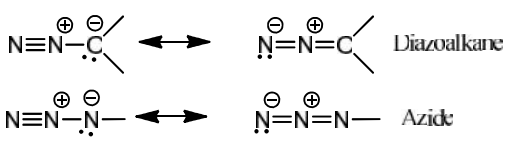


Table-2: Allyl type 1,3-dipoles

Nitrogen functions as middle ion

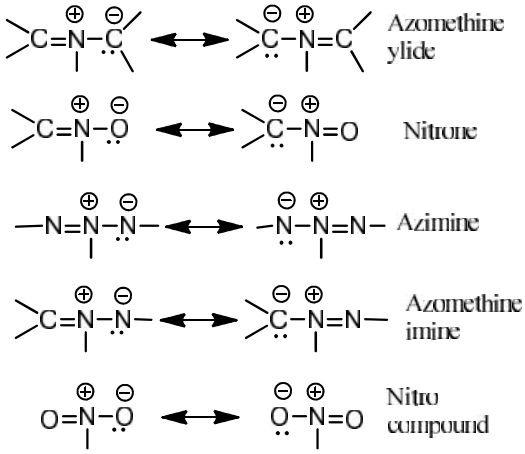
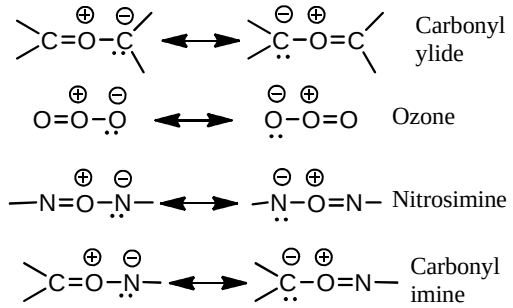


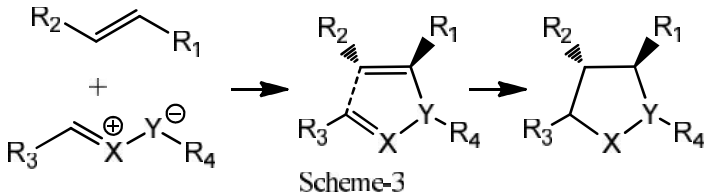
Table-3: 1,3-dipoles with oxygen as middle ion



The dipolarophile can be virtually any double or triple bonded species. The more common are alkenes, alkynes, carbonyls and nitriles. Other multiple bonded functional groups such as imines, azo and nitroso can also act as a dipolarophiles.

Mechanism of 1,3-dipolar cycloaddition reactions:

2 π-electrons of the dipolarophile and 4 electrons of the dipolar compound participate in a concerted, pericyclic shift. The addition is stereoconservative (suprafacial), and the reaction is therefore a $[2_s+4_s]$ cycloaddition (Scheme-3), and is similar to the Diels-Alder reation.



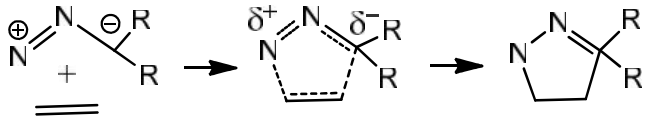
Scheme-3

A condition for such a reaction to take place is a certain similarity of the interacting HOMO and LUMO orbitals, depending on the relative orbital energies of both the dipolarophile and the dipole. Electron-withdrawing groups on the dipolarophile normally favor an interaction of the LUMO of the dipolarophile with the HOMO of the dipole that leads to the formation of the new bonds, whereas electron donating groups on the dipolarophile normally favour the inverse of this interaction.

Based on kinetic measurements, stereochemical results, solvent effects and substituent effects; the mechanism for the 1,3-dipolar cycloaddition (DC) was elegantly demonstrated by Huisgen *et al*. In most of 1,3-DC, the reaction rate is not markedly influenced by the dielectric constant of the solvent. The independence of the solvent polarity; the very negative entropy of activation; the stereospecificity and all regiospecificity point to a highly ordered transition state.[3] However, this mechanism was passionately disputed for years between

Huisgen and Firestone. Firestone favored the formation of a diradical intermediate in which the mechanism involves two stages.[4]

The experimental efforts of several groups involved in this dispute lent support to the concerted mechanism based on the stereospecificity of the reaction.[5] However, the general agreement that, the reaction is a [3+2] cycloaddition reaction and in terms of orbital symmetry classification, it is classified as a [$\pi^4_s + \pi^2_s$] cycloaddition reaction analogous to that of Diel's-Alder reaction (Scheme-4).



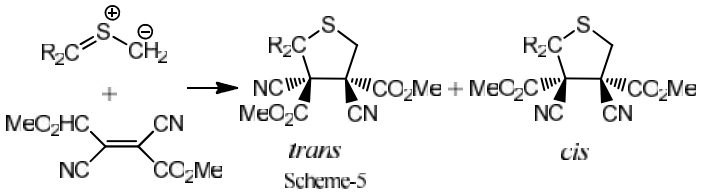
Scheme-4

Criteria for the mechanism of 1,3-DC are provided by the stereoselectivity observed with cis-trans isomeric dipolarophiles; by the effect of solvent and substituents on the rate constants, activation parameters, and orientation phenomena. A concerted addition, which can also be described in terms of molecular orbitals and in which the two new σ-bonds are formed simultaneously, although not necessarily at equal rates, offers the best explanation of the experimental facts.[6] An appreciation of the stereospecificity of these cycloadditions can be illustrated through the use of FMO theory as well as experimental outcomes.

The most of 1,3-DC would proceed through a concerted reaction mechanism. Similar to the Diels-Alder reaction, this results in a stereospecific *syn* addition of the 1,3-dipole to the dipolarophile. By making the dipole electron deficient and the dipolarophile electron rich (or vice versa) the bond formation in the concerted reaction will become asynchronous. When this is taken to the extreme, the bond formation becomes so asynchronous that a zwitterionic intermediate is formed and nonstereospecific 1,3-DC occur. Interestingly, similar treatment of Diels-Alder dienes and dienophiles has resulted in similar loss of stereospecificity, showing that these ideas can be applied to other cycloaddition reactions.[7]

Stereochemistry of Huisgen cycloaddition reactions:

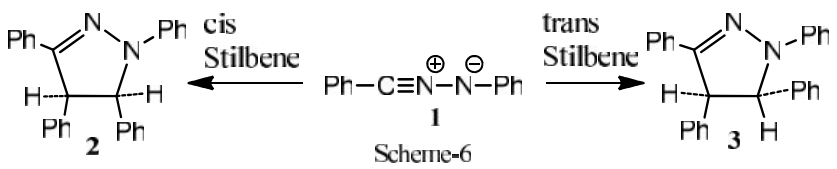
Huisgen reported the first non-stereospecific two-step 1,3-dipolar cycloadditions, along with mechanistic and FMO rationalization. He found that by creating a large difference in electron demand between an electron-rich thiocarbonyl ylide dipole and electron-poor dicyano-substituted dipolarophile. He created a reaction that scrambled stereochemistry in the products; the *E*-alkene dipolarophile gave rise to both *cis* and *trans* products (Scheme-5).[8]



trans *cis*

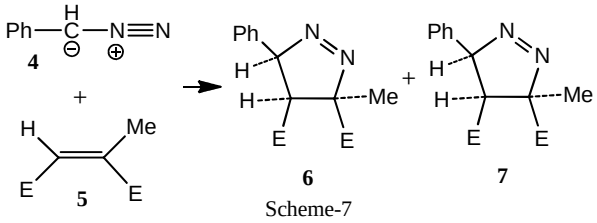
Scheme-5

The stereochemistry of 1,3-DC reaction is a stereospecific *syn* addition with respect to dienophile. For example, addition of *cis* and *trans* stilbenes to diphenyl nitrile imine (**1**) gives tetraphenyl pyrazines (**2**) and (**3**) respectively (Scheme-6).[9]



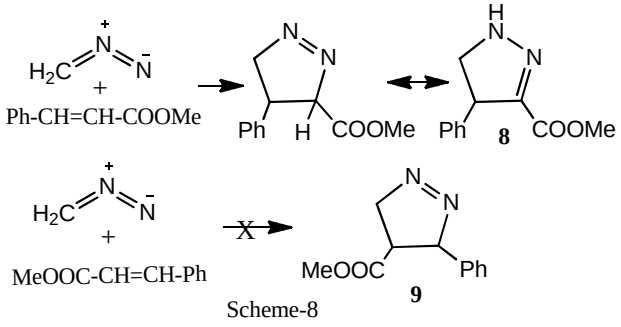
Scheme-6

With some dipoles, two possible diastereomers can be formed by *syn* addition. These result from two differing orientations of the reactant molecules. For example, phenyl diazomethane (**4**) gives diastereomers, (**6**) and (**7**) on addition with dienophile (**5**) (Scheme-7).[10]



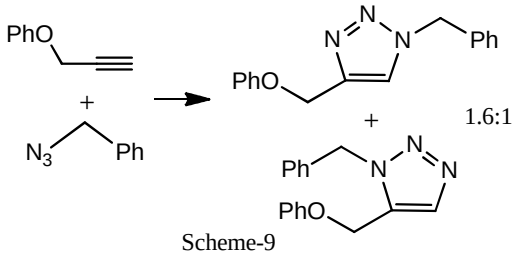
Scheme-7

The regioselectivity can be interpreted in terms of interaction between the FMO of 1,3-dipole and dienophile. Usually, for dipolarophiles with electron-attracting groups; the dipole-HOMO and dipolarophile-LUMO interaction is dominant. The reverse is true for dipolarophiles with electron-donating groups. However, there are HOMO-LUMO interactions of comparable magnitude. According to the principle of maximum overlap, the preferred isomers of each interaction can be predicted by union of two sites of the reactants having the largest coefficient value. For instance; due to the two different possible orientations of methyl cinnamate, the formation of two regioisomers namely pyrazoline-3-carboxylic ester (**8**) and pyrazoline-4-carboxylic ester (**9**) is possible, but not (**8**) (Scheme-8).[11]



Scheme-8

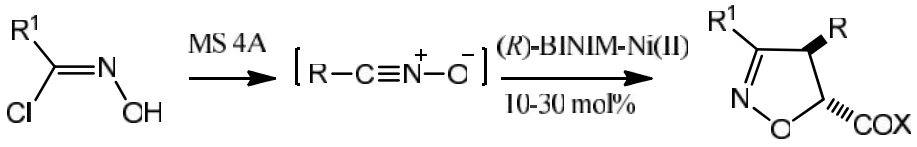
The regioselectivity of the reaction depends on electronic and steric effects. For instance, the addition of alkynes to azides, which is an interesting reaction for the generation of 1,2,3-triazole libraries by the simple reaction of two molecules leads to regioisomers (Scheme-9).[12]



Scheme-9

The lack of stereospecificity in some cases leads to the consideration of a non-concerted mechanism. In order to decide if the reaction is really nonconcerted, other possible reasons for the apparent nonstereospecificity must first be ruled out. For instance, in the case of enamines, the reactions were carried out with the (*E*)-isomer and under reaction conditions; no (*Z*)-isomers were observed. Therefore, it is believed that the stereochemical integrity of the reactants was maintained under the reaction conditions. If cycloreversion was occurring then the more thermodynamically stable isomer would be allowed to form. Finally, a trapping experiment was performed using the highly reactive dipolarophile cyclooctyne, the results revealed that no cycloaddition products were found between the product and the newly introduced dipolarophile. These findings were consistent with the idea that no cycloreversion followed by recyclization was happening. Therefore it was concluded that stereochemical leakage was not occurring prior to or after the cyclization reaction.

Asymmetric cycloaddition reactions between nitrile oxides and 3-(2-alkenoyl)-2-oxazolidinones and 2-(2-alkenoyl)-3-pyrazolidonone derivatives carried out in the presence of binaphthylidiimine (BINIM)-Ni(II) complexes as catalysts. Using (*R*)-BINIM-4-(3,5-xylyl)-2QN-Ni(II) comple (30 mol%), good regioselectivity (4-Me/5-Me = 85:15) along with high enatioselectivity (96% ee) of the 4-Me adduct were obtained for the reaction between isolable 2,4,6-trimethylbenzonitrile oxide and 3-crotonoyl-5,5-dimethyl-2-oxazolidinone (Scheme-10).[13]



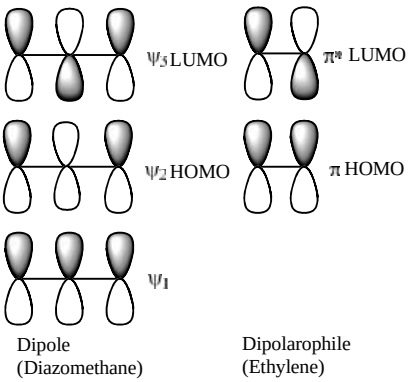
Scheme-10

rs: >99 : 1-85 : 15
96-42% ee

FMO symmetry analysis of 1,3-dipolar cycloaddition reaction:

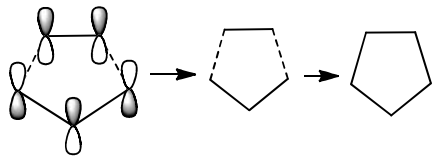
The synchronicity and regioselectivity of 1,3-dipolar cycloaddition reactions are rationalized through FMO theory. Generally, the orbital coefficients of HOMO-LUMO interaction will determine the regioselectivity. The atoms with the largest coefficients on the HOMO and on the LUMO will combine with each other preferentially and determine the regioselectivity.[14] The concerted reaction results from the overlap of orbitals of one molecule (dipolar) with the orbitals of the other (dipolarophile). Similar to electrocyclic reactions, here also each HOMO has to overlap with an empty orbital. Therefore, a HOMO picks up the most stable of the empty orbitals LUMO. In the transition state; stabilization chiefly comes from the overlap between the HOMO of one reactant (dipole or dipolarophile) with the LUMO of the other (dipolarophile or dipole) in bonding fashion. FMO orbitals diagram of dipole and dipolarophile is depicted in Figure-1.

Fig-1: FMO diagram of dipole and dipolarophile



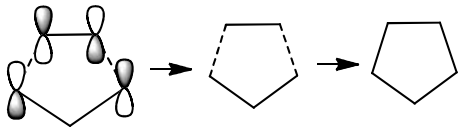
The LUMO of dipole's interation with HOMO of dipolarophile is depected in Figure-2.

Fig-2: The LUMO (dipole)-HOMO (dipolarophile) interaction



The HOMO of dipole's interation with LUMO of dipolarophile is depicted in Figure-3.

Fig-3: The HOMO (dipole)-LUMO (dipolarophile) interaction



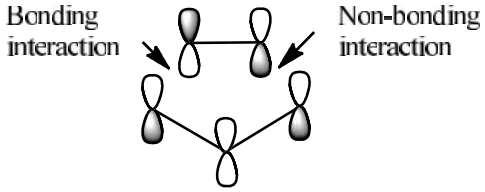
Thus, 1,3-dipolar cycloaddition is a thermally allowed reaction.

In the cases, where the FMO energies of the dipole and the dipolarophile are very similar, a combination of both modes of interactions can occur, and are referred to as either *exo* or *endo*, where the *endo* transition state is stabilised by small secondary π-orbital interactions or via an *exo*-transition state lacking such a stabilisation. However, steric effects can also be important factors for the *endo*/*exo* selectivity. Depending on the substitution pattern in the reacting partners, the process gives rise to either the *endo*- or *exo*-cycloadducts.

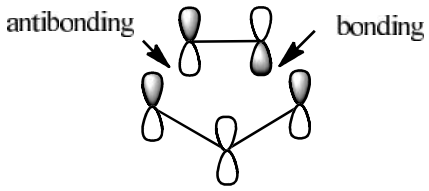
The presence of a metal, such as a Lewis acid; alter both the orbital coefficients of the reacting atoms and the energy of the frontier orbitals of both the 1,3-dipole or the dipolarophile, depending on the electronic properties of these reagents or the Lewis acid. The coordination of a Lewis acid to one of the two partners of the cycloaddition is of fundamental importance for asymmetric 1,3-DC. Furthermore, the Lewis acid also have influence on the selectivity of the cycloaddition reaction, since the regio-, diastereo- and enantioselectivity can all be controlled by the presence of a metal–ligand complex.

1,3-Dipolar cycloaddition reactions are photochemically forbidden. For photochemical process; HOMO in excited state of one reactant (dipole/dipolarophile) and LUMO in ground state of another (dipolarophile/dipole) has to be considered.

HOMO of excited state of 1,3-dipole is ψ_3 and LUMO of ground state of dipolarophile is π*.



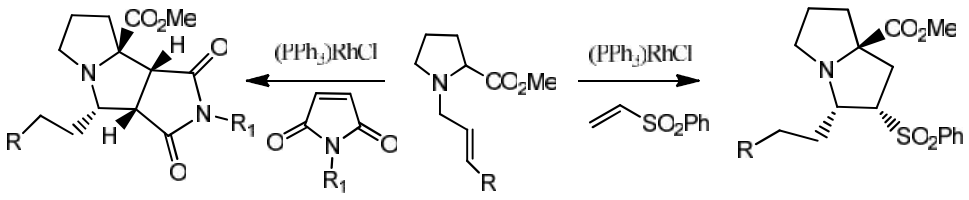
HOMO of excited dipolarophile is π* and LUMO of ground state of 1,3-dipole is ψ_3



Here, there is an antibonding situation on one side, hence no product is formed. Therefore, $[\pi^4_S + \pi^2_S]$ photochemical reaction is forbidden.

Applications of Huisgen cycloaddition reactions:

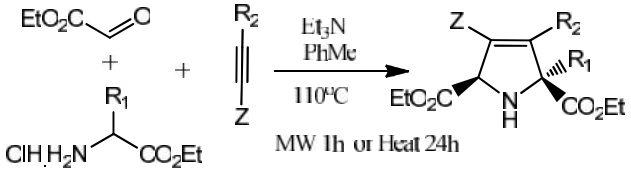
The simple, easy accessible and work up procedure involved in 1,3-dipolar cycloaddition reactions; makes it a useful tool for the synthesis of pharmacologically important five membered heterocycles, particularly with respect to the approach toward asymmetric syntheses is of major importance in both the pharmaceutical and agricultural industries. For instance; fused ring heterocycles were synthesised *via* the rhodium catalysed isomerisation/regio and stereoselective 1,3-DC cascades in good yields (Scheme-11).[15]



Scheme-11

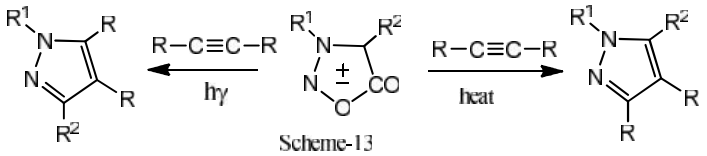
The thermal multicomponent 1,3-DC of diethyl aminomalonate or α-amino esters with ethyl glyoxylate and dipolarophile such as maleimides, methyl acrylate, methyl fumarate, (*E*)-1,2-bis(phenylsulfonyl)ethylene,

and electron deficient alkynes allows the diastereoselective synthesis of polysubstituted pyrrolidine derivatives. Microwave-assisted processes give better results affording *endo*-cycloadducts as major stereoisomers (Scheme-12). In general, 2,5-*cis*-cycloadducts are preferentially formed, but in the 1,3-DC of the disulfone with phenylglycine and ethyl glyoxylate the corresponding *exo-trans*-cycloadduct was isolated.[16]



Scheme-12

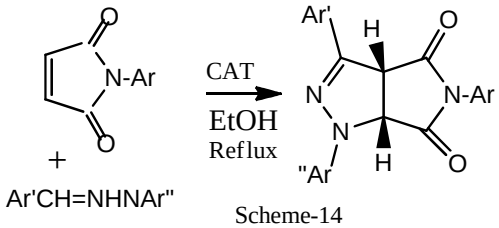
Sydnones are masked 1,3-dipoles that by photolysis give nitrile imine intermediates, or in thermal reactions react as cyclic azomethine imines. In the presence of acetylenic dipolarophiles, sydnones undergo 1,3-DC reactions, which can be induced thermally or photochemically, giving different pyrazole derivatives (Scheme-13).[17]



Scheme-13

Nitrile imines are a linear-type 1,3-dipoles and extensively used as versatile reactive intermediates in 1,3-DC reactions for constructing biologically potent five membered heterocycles such as pyrazolines and pyrazoles.[18] For example, Broggini *et al* reported an effective synthesis of enantiopure pyrazolo[1,5-*a*]-pyrrolo[2,1-*c*][1,4]benzodiazepines, by a diastereoselective intramolecular 1,3-DC of nitrilimines. The exclusive formation of the *trans* diastereoisomers was due to the bulky and rather rigid pyrrolidine moiety worked against the intramolecular approach of the dipole to the *re* face of the ethylenic bond.[19]

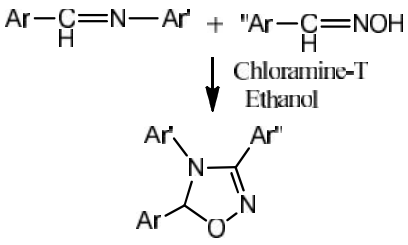
Rai and co-workers reported a new approach for the synthesis of pyrazoles via 1,3-DC of acetyl acetone and *in situ* generated nitrile imines. Their reaction afforded the regioselective cycloadducts in good yield.[20] Very recently Kumar *et al* reported the synthesis of 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-*d*]-7,8-dihydropyrazoles that showed promising antibacterial, antifungal and antioxidant activities by Huisgen cycloaddition of *in situ* generated nitrile imines and *N*-aryl maleimides (Scheme-14).[21-22]



Scheme-14

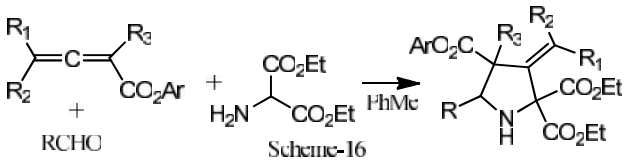
The one-step synthesis of bis[1,2,4-triazolo][4,3-*a*:3′,4′-*d*][1,5] benzodiazepines by way of completely regio- and diastereoselective 1,3-DC of nitrilimines to 2,4-dimethyl-3*H*-1,5-benzodiazepines is reported to be a tentative rationalization for the observed diastereoselectivity.[23] Aldehyde phenyl hydrazones undergo oxidative dehydrogenation with Chloramine-T to give nitrile imines, which are trapped *in situ* by ethyl oleate to afford 8-(5-Aryl-4-octyl-2-phenyl-3,4-dihydro-2H-pyrazol-3-yl)-octanoic acid ethyl esters in good yield and have showed moderate antimicrobial and antioxidant activities.[24-25]

Rai and co-workers reported the synthesis of series of trisubstituted 1,2,4-oxadiazoles via 1,3-DC reactions. They carried out a cycloaddition reaction of imines and nitrile oxides generated *in situ* by the catalytic dehydrogenation of aromatic aldoximes using chloramine-T reagent and obtained the cycloadducts in good yield. The cycloadducts have exhibited a promising antifungal and antibacterial activity (Scheme-15).[26]



Scheme-15

A bisphosphoric acid-catalysed 1,3-dipolar cycloaddition of buta-2,3-dienoates with azomethine ylides yields 3-methylenepyrrolidine derivatives with excellent enantioselectivity up to 97% ee (Scheme-16).[27]



Scheme-16

Solid-phase methods are of a great significance in organic synthesis. Recent developments of these methods are providing new ways to construct libraries of small organic molecules. Five-membered heterocyclic compounds are formed in the 1,3-DC reaction between dipolarophiles and dipoles on solid polymer support.[28]

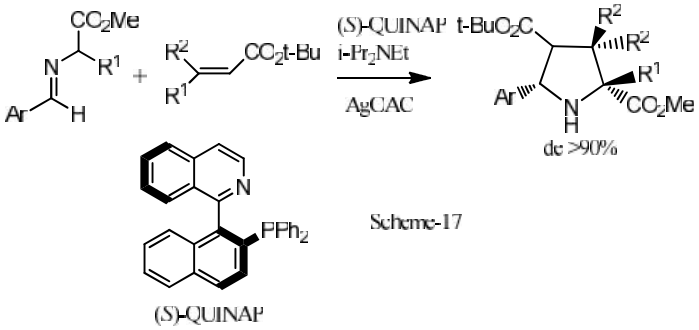
N-Alkylation of optically active 1-benzyl-4-phenyl-4,5-dihydroimidazole with active alkyl halides and then treatment with DBU in the presence of a range of alkene dipolarophiles, constitutes a one-pot cascade terminating in a 1,3-DC reaction that affords optically active pyrrolo[1,2-*a*]imidazoles. The cycloaddition follows an *endo* approach of dipole and dipolarophile with *anti* geometry of the dipole.[29] The 1,3-DC reaction of nitrones with dipolarophiles has received considerable attention in asymmetric. Regio- and stereoselective nitrone cycloaddition followed by reduction of the N-O bond to produce both an amino and a hydroxyl function. One of the reasons for the success of the synthetic applications of nitrones is that, most nitrones are stable compounds that do not require an in situ formation.[30]

Metal-catalysed asymmetric 1,3-DC have become an important research field in recent times.[31] The efficiency of chiral catalysts relies not only on the capability of the enantiopure catalyst to help discriminate between the two π-faces of the dipolarophile, but also on its ability to control both the *exo*/*endo* selectivity and the regiochemistry as well as the yield. Effective catalysis by the use of a wide variety of chiral Lewis-acid catalysts has been reported for the nitrone cycloaddition reactions using both electron-deficient and rich alkene dipolarophiles.

Metal-free and metal-mediated routes for 1,3-DC of nitrone-type dipoles to substrates bearing the C≡N triple bond are studied extensively. In 1,3-DC of nitrones to RCN species, the outcome of the reaction is determined by a degree of activation of the dipolarophile, the activation was greatly enhanced either by introduction of electron-withdrawing substituents into a nitrile molecule or coordination of RCN to a metal center, or by both methods. The ligation makes favorable the 1,3-DC of nitrones to a wide range of RCN substrates; which forms the basis for the synthesis of 2,3-dihydro-1,2,4-oxadiazoles, 2,3-dihydro-1,2,4-oxadiazole-based heterocycles, and 2,3-dihydro-1,2,4-oxadiazole ligand systems.[32]

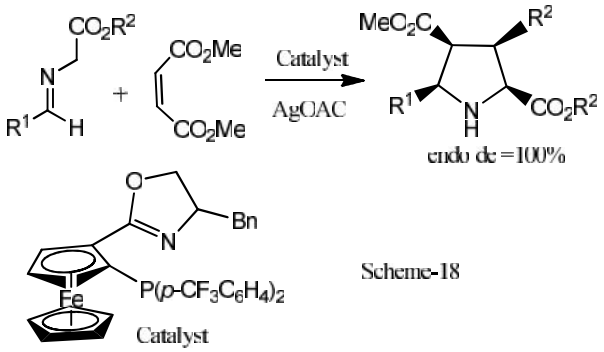
Varieties of Lewis acids have provided excellent results in the stereoselective metal-catalysed 1,3-DC of azomethine ylides. However, among them, the Ag(I)-based processes stand out as the most used. For example, the 1,3-DC of 4-oxoazetidine-2-carbaldehyde-derived azomethine ylides with a variety of dipolarophiles in the presence of $AgOAc/Et_3N$, affording the corresponding chiral pyrrolidinyl-β-lactams with reasonable diastereoselectivities and moderate to good yields.[33] The AgOAc-catalysed 1,3-DC of azomethine ylides to vinyl sulfoxides evolved with complete regio- and *endo*-selectivities. The stereoselectivity could, however, be controlled by using THF or MeCN as solvents. This methodology applied in the synthesis of highly substituted pyrrolidines.[34]

(*S*)-QUINAP was successfully used as effective catalyst in the 1,3-DC of azomethine ylides derived from α-iminoesters with various α,β-unsaturated esters, giving excellent levels of diastereoselectivity (>90% de) and enantioselectivity (96% ee) (Scheme-17).[35]



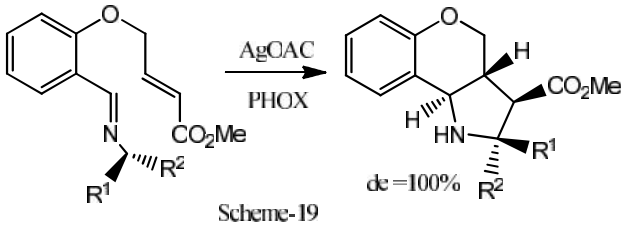
Scheme-17

A chiral ferrocenyloxazoline-derived N,P-ligand was found to be an efficient chiral catalyst in the presence of AgOAc to perform 1,3-DC reactions. The reactive metal-bound azomethine ylide dipole was formed by deprotonation with acetate that played the role of base. Indeed, the AgOAc, bearing a weakly basic charged acetate ligand, facilitated the deprotonation of iminoesters to generate the azomethine ylides. This method provided a total *endo* diastereoselectivity in all cases, furnishing enantiopure highly substituted pyrrolidine derivatives (Scheme-18).[36]



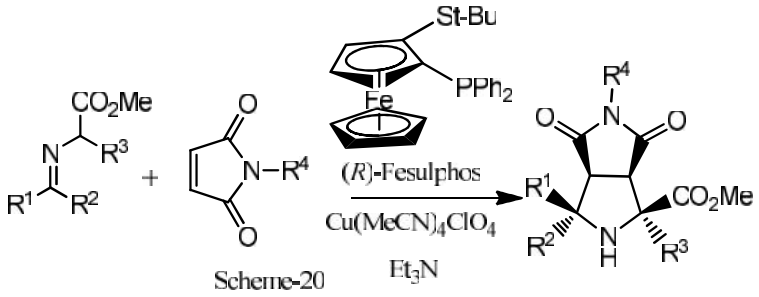
Scheme-18

The intramolecular version of the enantioselective silver-catalysed 1,3-dipolar cycloaddition performed in the presence of a chiral ligand phosphino-oxazoline (PHOX), giving access to chiral tricyclic compounds with perfect diastereoselectivity and high levels of enantiocontrol (Scheme-19).[37]



Scheme-19

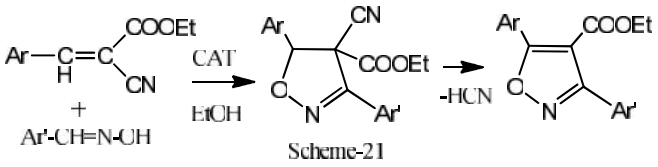
Cu–Lewis acids in combination with a variety of chiral ligands have been studied in the enantioselective cycloadditions of azomethine ylides. For instance, 1,3-DC of azomethine ylides and maleimide dipolarophiles in the presence of copper(I) salts and a Fesulphos ligand displaying exceptional enantioselectivities with assymmeric inductions. (Scheme-20).[38]



Scheme-20

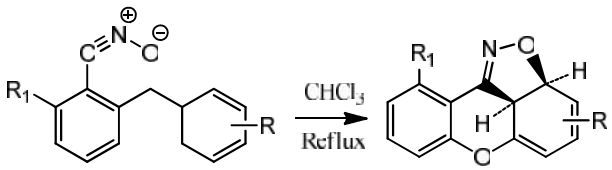
Nitrile oxides are reactive, relatively unstable, linear molecules, which may be generated from nitro compounds, hydroxymoyl halides, and aldoximes by treatment with various reagents. It is important to note that nitrile oxides are prone to dimerisation or polymerisation, especially upon heating and hence are usually generated *in situ*. Nitrile oxides were considered as useful intermediates in 1,3-dipolar cycloaddition reactions leading to the formation of five membered heterocycles such as isoxazole and oxadiazole derivatives.[39-42]

Nitrile oxides generated *in situ* by the oxidative dehydrogenation of aldoximes with chloramine-T reacted with α,β-unsaturated compounds to afford ethyl 3,5-diarylisoxazole-4-carboxylates, which exhibited remarkable antimicrobial activity (Scheme-21).[43]



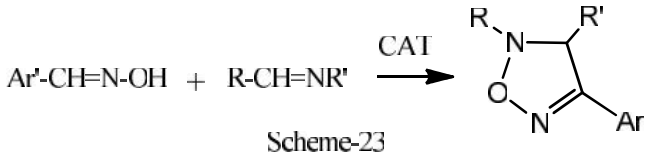
Scheme-21

Intramolecular 1,3-DC of 2-phenoxy benzonitrile *N*-oxides to benzene rings, accompanied by dearomatisation, formed the corresponding isoxazolines in high yields (Scheme-22). The substituents on the benzene ring markedly affected the reaction rate, yield and structure of the final product.[44]



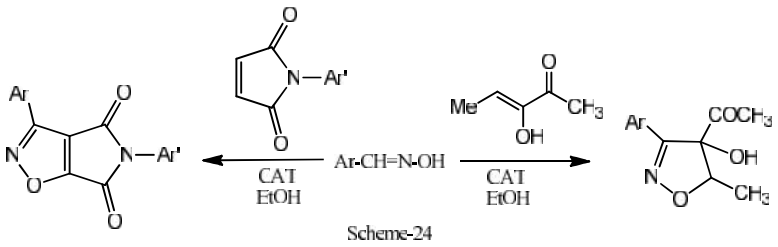
Scheme-22

A series of 3-aryl-5-(4-methoxyphenyl)-isoxazole-4-carbonitriles have been synthesized by the *in situ* generated nitrile oxides and 3-(4-methoxyphenyl)propiolonitrile in moderate yield. The products screened for their antibacterial and antifunal activity against different organism.[45] A series of 1,2,4-oxadiazolines have been synthesized by the intermolecular 1,3-DC of *in situ* generated nitrile oxides with imines in moderate yield (Scheme-23). The products have been evaluated for their antimicrobial activity against different bacteria and fungi species.[46]



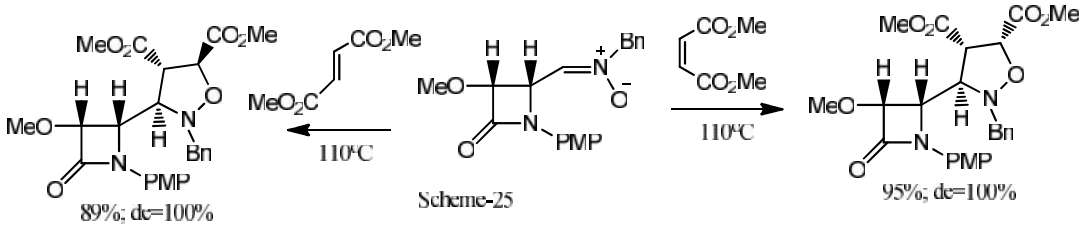
Scheme-23

Ajay kumar et al reported the synthesis of a series of thirteen cycloadducts 3-Aryl-5*N*-aryl-4,6-dioxo-pyrrolo*[*3,4-*d*]-7,8-dihydroisooxazolines by the reaction of *in situ* generated nitrile oxides and *N*-aryl maleimides (Scheme-24).[47] Later they demonstrated that the nitrile oxide gets added to enolic double bond of acetyl acetone in 1,3-dipolar cycloaddition and obtained the substituted isoxazolines in good yield (Scheme-24).[48]



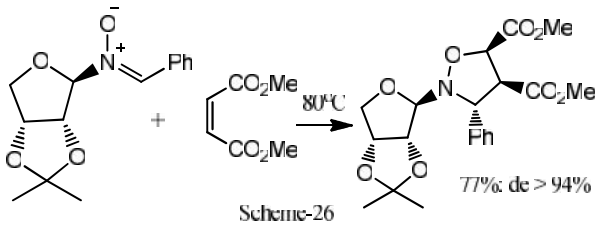
Scheme-24

In contrast to the cyclic dipoles, acyclic dipoles can undergo *Z*/*E* isomerisation around a double bond, this makes it difficult to realise a direct correlation between the product distribution and the *E*/*Z* isomer equilibrium distribution of the starting dipole, since one of the *Z*/*E* isomers can react faster under kinetic control. Various acyclic chiral nitrones have recently been involved in 1,3-DC reactions. For example, highly functionalised chiral β-lactams are obtained by regio- and stereoselective 1,3-DC reactions of optically active 2-azetidinone-tethered nitrones with electron-deficient alkenes such as dimethyl fumarate, dimethyl maleate (Scheme-25).[49]



Scheme-25

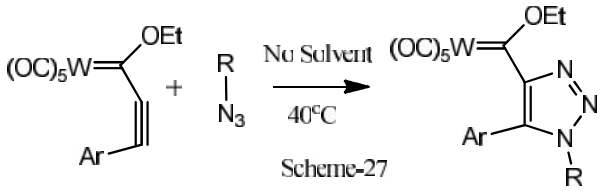
Nagasawa *et al* reported the synthesis of novel vitamin D_3 analogues by an asymmetric 1,3-dipolar cycloaddition reaction of a chiral nitrone derived from vitamin D_2 with methyl methacrylate, providing the corresponding isoxazolidine as a mixture of four diastereomers. The subsequent reduction of these compounds gave the corresponding lactams, which led to the formation of a novel series of 1α,25-dihydroxyvitamin D_3 antagonists.[50] Goti et al demonstrated the great potential of cycloaddition reactions applied to *C*-phenyl-*N*-glycosylnitrones. Indeed, *N*-glycosylnitrones underwent highly stereoselective 1,3-DC with dimethyl maleate, providing the corresponding 3,4,5-trisubstituted isoxazolidines (Scheme-26).[51]



Scheme-26

Stereocontrolled 1,3-DC reaction of a silyl ketene acetal to a D-glucose-derived nitrone, leading to a diastereomeric mixture of the corresponding *O*-silyloxy-β-amino esters with excellent yield and good diastereoselectivity in favour of the L-*ido* isomer (D-*gluco*/L-*ido*=23:77). These latter compounds were successfully used in the synthesis of the glycosidase inhibitors, D-*gluco*-homo-1-deoxynojirimycin and L-*ido*-homo-1-deoxynojirimycin.[52]

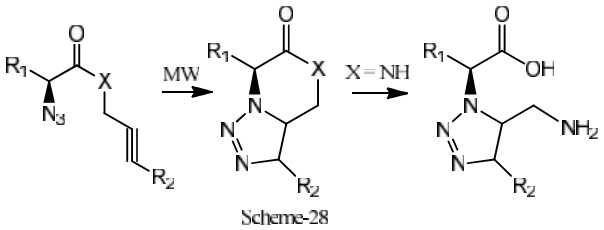
Baldwin and Long reported the cycloaddition reactions of a new chiral imidazolone-derived nitrone with a variety of alkenes, affording the corresponding chiral isoxazolidine cycloadducts in high yields and with high *exo* stereoselectivities. These latter products were readily transformed into the corresponding α-amino-γ-lactones, which were then easily converted into the corresponding γ-hydroxy-α-amino acids.[53] Regioselective 1,3-DC reactions between alkoxy alkynyl Fisher carbine complexes with a wide range of organic azides under solvent free conditions at moderate temperature (Scheme-27).[54]



Scheme-27

Asymmetric intramolecular 1,3-dipolar cycloadditions constitute an effective approach for the synthesis of enantiopure polycyclic compounds in a single step. In most cases, the reactions are known to proceed with higher diastereoselectivities than those of the intermolecular variant, because the flexibility of the reactant is much more restricted. Moreover, due to entropy factors, the activation barrier for the reaction is lower, allowing lower reaction temperatures and the use of dipoles and dipolarophiles of lower reactivity. Bhattacharya et al have demonstrated that highly stereoselective syntheses of chiral oxepanes and pyrans were possible through intramolecular nitrone cycloadditions performed in organised aqueous media.[55]

When alpha-azido propargyl esters were subjected to [3+2] cycloaddition in MeCN/H_2O under microwave dielectric heating, the expected 4*H*-[1,2,3]triazolo[5,1-c][1,4]oxazin-6-ones are not formed; rather, an oligomeric cyclic polyester is obtained via a prevailing intermolecular cycloaddition. The reaction provides access to new condensed triazoles that can be considered as conformationally constrained peptidomimetics. Moreover, the following microwave-assisted lactam ring opening provides 1,4-disubstituted and 1,4,5-trisubstituted triazole amino acids (Scheme-28).[56]

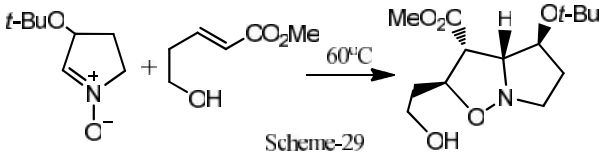


Scheme-28

An enamine-catalyzed strategy has been utilized to fully promote the Huisgen [3+2] cycloaddition with a broad spectrum of carbonyl compounds and azides, thereby permitting the efficient assembly of a vast pool of highly substituted 1,2,3-triazoles. In particular, the employment of commonly used carbonyl compounds has resulted in the introduction of a diverse set of functional groups, such as alkyl, aryl, nitrile, ester, and ketone groups, at the 1-, 4-, or 5-positions of the 1,2,3-triazole scaffold. Most significantly, the reaction process exhibits complete regioselectivity, with the formation of only one regioisomer.[57]

In recent times, azomethine ylides have become one of the most investigated classes of 1,3-dipoles. Their cycloadditions to olefinic dipolarophiles provide a direct and general method for the synthesis of pyrrolidine derivatives. Advances in this area have made cycloaddition reactions of azomethine ylides a powerful synthetic tool, extensively used in the synthesis of natural products and biologically active compounds.[58] The thermally induced 1,3-DC reaction of azomethine ylides and electron-deficient olefins and acetylenes gives the corresponding cycloadducts with *endo* selectivity. The diastereoselectivity of the reaction proved to be high, and a superior reactivity towards acetylenic compounds. The highly stereoselective reaction of *in situ* generated azomethine ylides was induced by microwave irradiation on the surface of silica gel, leading, in a short time, to the corresponding cycloadducts in good yields.

The *exo*-selective asymmetric 1,3-DC of alkylidene malonates with azomethine ylides catalyzed by AgOAc/TF-BiphamPhos has been reported in good yields and good to excellent enantio-/diastereoselectivities.[59] 1,3-DC reactions of chiral cyclic nitrones give generally a higher stereoselectivity than their acyclic counterparts, due to a more rigid skeleton, where one face of the molecule is often effectively shielded from attack by the chiral substituent. Chiral cyclic pyrroline *N*-oxides are the most-used chiral cyclic nitrones in 1,3-DC reactions. For instance, the 1,3-DC of (3*S*)-3-*tert*-butoxypyrroline *N*-oxide, obtained from L-malic acid, with 5-hydroxypentenoate was performed by Cordero *et al*. with complete regio-and stereoselectivity. (Scheme-29).[60]

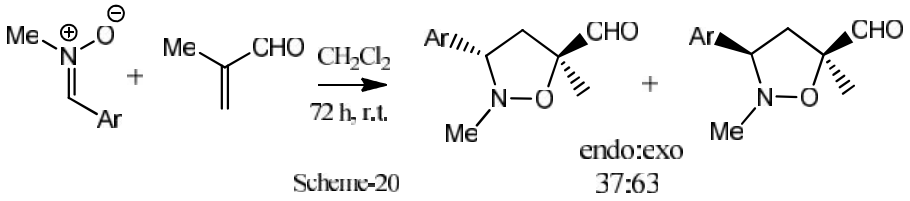


Scheme-29

A nonstabilized azomethine ylide reacts with a wide range of substituted isatoic anhydrides to afford novel 1,3-benzodiazepin-5-one derivatives, which are generally isolated in high yield. The transformations involve 1,3-DC reactions of the ylide with the anhydrides to give transient, and in a representative case spectroscopically observable, oxazolidine intermediates that undergo ring-opening-decarboxylation-ring-closing reaction cascades to yield the 1,3-benzodiazepin-5-one products.[61]

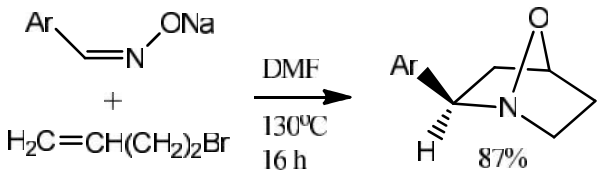
The rapid developments in the field of catalytic enantioselective 1,3-DC reactions of nitrones are reported. A series of catalysts has been applied for both the normal electron-demand and inverse electron-demand 1,3-DC reaction of nitrones with electron-deficient and electron-rich alkenes respectively. In several cases a high degree of control of both the diastereo- and enantioselectivity has been achieved. 1,3-DC of different hydrophobic nitrones with acrylates in both homogenous organic solutions and aqueous suspensions. Reactions in water suspensions showed great rate accelerations over homogenous solutions.[62]

Diazo compounds are shown to be extremely versatile dipoles in 1,3-DC reactions, their reactivity can be much greater or much less than its azide analog, and is enhanced markedly in polar-protic solvents. The most reactive diazo compound exhibited the highest known second-order rate constant to date for a dipolar cycloaddition with a cycloalkyne.[63] 1,3-DC afforded fast access to isoxazolidines bearing *N*-alkyl or *N*-benzyl substituents. The electronic effects of the substituents in the nitrones define the activity of the dipoles and modulate diastereoselectivity in the non-catalyzed reactions. Using a chiral one-point binding ruthenium Lewis acid catalyst, products were obtained in good yields and with excellent regio-, diastereo-, and enantioselectivity (Scheme-30).[64]



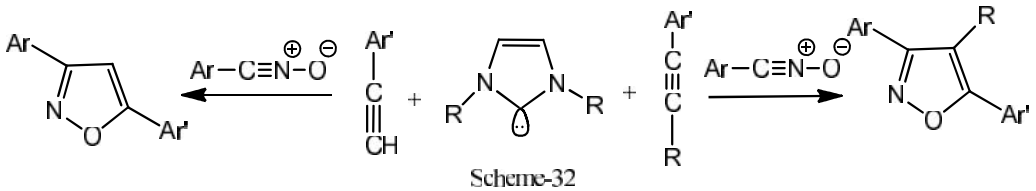
Scheme-20

Inter-or intra-molecular *N*-alkylation of oximes or their alkali metal salts furnishes nitrones; which can be trapped by activated and non-activated dipolarophiles in inter- and intra-molecular cycloaddition reactions in good yield (Scheme-31).[65]



Scheme-31

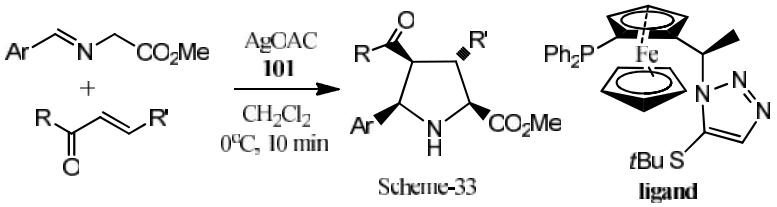
A first example of organo-*N*-heterocyclic carbene (NHC) catalyzed click-type fast 1,3-dipolar cycloaddition of nitrile oxides with alkynes was developed for the regioselective synthesis of 3,5-di- and 3,4,5-trisubstituted isoxazoles. Triethylamine (Et_3N) was employed as an effective base to generate both nitrile oxide and the organo-NHC catalyst *in situ*. This catalytic approach was used to attach a variety of substituents onto the isoxazole ring to selectively design multinucleus structures. A catalytic cycle is proposed and the remarkable regiocontrol in the formation of isoxazoles was ascribed to a beneficial zwitter ion intermediate developed by the interaction of the strongly nucleophilic organo-NHC catalyst withalkyne followed by nitrile oxide (Scheme-32).[66]



Scheme-32

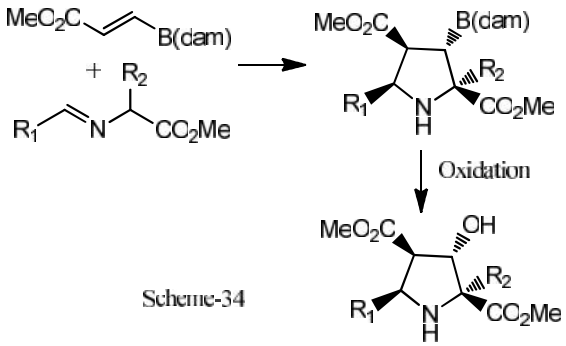
1,3-Dipolar cycloaddition of nitrile imines with 3-alkenyl-oxindoles was catalysed by chiral $Mg(ClO_4)_2$ complex of N,N'-dioxide ligand. The reaction is so far the sole catalytic synthesis of spiro-pyrazoline-oxindole the products obtained inexcellent enantioselectivities.[67] Lewis base catalysed 1,3-DC between α,β-unsaturated acyl fluorides and *N*-[(trimethylsilyl)methyl]amino ethers has been achieved using 1 mol% DMAP. The cycloaddition occurs preferentially between the α,β-unsaturated acyl fluoride and the unstabilised azomethine ylide.[68]

Sharpless and co-workers introduced a new approach in organic synthesis click chemistry that involves a handful of almost perfect chemical reactions. Huisgen 1,3-dipolar cycloadditions were shown to be the most effective and versatile and thus became the prime example of click chemistry. Hence, these long-neglected reactions were suddenly re-established in organic synthesis.[69] For instance, A highly *endo*-selective asymmetric 1,3-DC reaction of methyl *N*-benzylideneglycinate as source of azomethine ylides with (*E*)-acyclic α-enones is catalyzed by a silver(I)/ThioClickFerrophos complex to give highly functionalized *endo*-4-acyl pyrrolidines in good yields with high enantioselectivities (Scheme-33).[70]



Scheme-33

The Ag-catalysed 1,3-dipolar cycloaddition of (E)-β-boroacrylates with azomethine ylides results in 3-boropyrrolidine derivatives in high yields and complete endo selectivities using AgOAc/dppe as catalyst system and B(dam) as boryl group. Transformation of the B(dam) group into pinacol borane and oxidation afforded hydroxyproline derivatives (Scheme-34).[71]



Scheme-34

Intramolecular 1,3-DC proceed under microwave-assisted solvent-free conditions within 15-40 min in produce hexahydrochromeno[4,3-*b*]pyrroles.[72] A scope and limitations of these reactions including an influence of the dipolarophile geometry upon the cycloaddition selectivity and steric demands of the dipole upon its reactivity was reported. The rate enhancements caused by gradually increasing the mole fraction of water in the solvent for the cycloaddition reactions of pyridazinium-dicyanomethanide with ethyl vinyl ketone and methyl acrylate in the organic solvents such as acetonitrile, acetone, methanol at 37ºC are explored. The results showed that a dominant hydrogen-bonding effect operates in water-induced rate enhancements of 1,3-DC reactions with water-super dipolarophiles as well as the hydrophobic effect.[73]

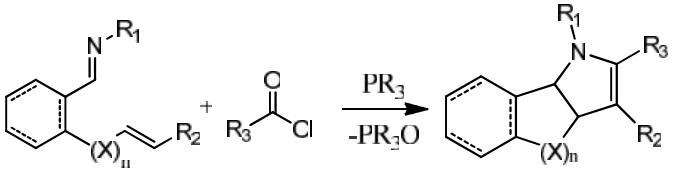
Synthesis of *sym*-1,4-diphenyl-1,4-dihydro-1,2,4,5-polytetrazine through 1,3-DC polymerization reactions. The tetrazine based polymers display high complexation potential with cobalt chloride demonstrating metal complexation capability.[74] A polymer supported catalyst for Huisgen's [3+2] cycloaddition reaction between azides and alkynes was prepared from copper(I) iodide and Amberlyst A-21. This catalyst was used in an automated synthesis of 1,4-disubstituted 1,2,3-triazoles giving access to these products in good yields.[75]

Tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol forms a stable complex with CuCl, which catalyzes the 1,3-DC of alkynes with azides on water or under neat conditions. Low catalyst loadings, short reaction times at room temperature, and compatibility with free amino groups make this complex an outstanding catalyst for CuAAC.[76] CuAAC catalysed cycloaddition reaction of azides and terminal alkynes in water in the presence of catalytic amount of β-cyclodextrin as a phase transfer catalyst produced 1,4-disubstituted-1,2,3-triazoles in high yields.[77] Cu(I)-catalyzed Huisgen cycloaddition reactions play a significant role as an emerging route for functionalization of carbon nanotubes for achieving their mechanical, electrical, and biological functions and enhancing their dispersion in a polymer matrix.[78]

The intramolecular alkyne-azide Huisgen [3+2] cycloaddition reaction as a click-reaction without a metal catalyst has been studied under aerobic conditions. The synthesis of various pyrrolidine–triazole hybrid compounds has also been achieved in water with complete 1,5-regioselectivity.[79] A copper(I)/ClickFerrophos complex catalyzed the asymmetric 1,3-DC of methyl *N*-benzylideneglycinates with electron deficient alkenes to give exo-2,4,5-trisubstituted and 2,3,4,5-substituted pyrrolidines with high diastereo- and enantioselectivities.[80]

Asymmetric 1,3-dipolar cycloaddition of *N*-unprotected 2-oxoindolin-3-ylidene with azomethine ylides for the construction of spirooxindole-pyrrolidines bearing four contiguous stereogenic centers has been achieved with AgOAc/TF-BiphamPhos complexes with excellent diastereoselectivities and moderate enantioselectivities.[81] Arynes formed through fluoride-promoted *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates undergo [3+2] cycloaddition with various azides to form substituted benzotriazoles. The rapid reaction times and mild conditions make this an attractive variation of the classical 'click' reaction of azides and alkynes.[82]

2-Pyrrolines can be generated by the PhP(2-catechyl) mediated coupling of alkene-tethered imines and acid chlorides. The reaction proceeds *via* phosphorus-containing 1,3-dipoles, which undergo cycloaddition with alkenes with high stereo- and regioselectivity. The modularity of this reaction is used to assemble a range of polysubstituted pyrrolines in one pot transformations (Scheme-35).[83]



Scheme-35

Summary:

Indeed, it is well known in recent years that; among the various methodologies are known in synthetic organic chemistry; 1,3-dipolar cycloaddition reactions occupies the top slot for the synthesis of five membered heterocycles and their analogs. The development in this research area, understading of stereochemical mechanistic path provided the chemists a platform for devise and synthesise a desired molecule of pharmacological interest. As this review discusses the background, advancements in methodology, clear mechanistic path, stereochemistry involved, and synthetic applications of 1,3-dipolar cycloaddition reactions in depth; this article might be very useful the researchers, academicians and students to understand 1,3-dipolar cycloaddition reactions.

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