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Progress in classical chemistry of metal-carbenoids from α-diazocarbonyls

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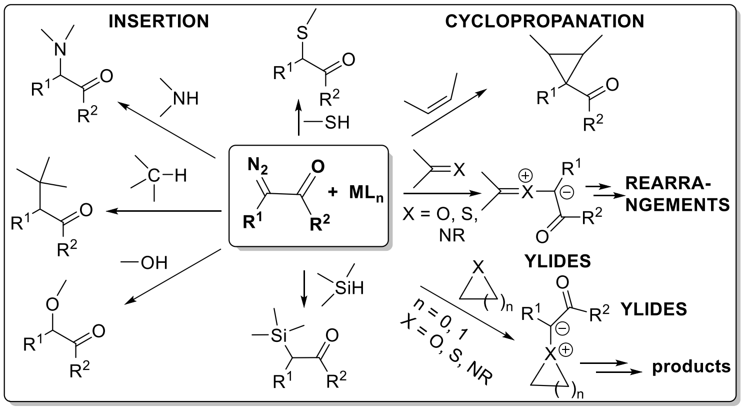
Abstract

α-Diazocarbonyls are well known precursors of reactive intermediate carbenes that coordinate with metal salts and complexes to react as metal-carbenoids. Insertion into carbon-hydrogen and heteroatom-hydrogen bonds, and addition across various multiple bonds are the classical reactions of metal-carbenoids. These reactions have been widely employed as a key reaction in the synthesis of diverse classes of biologically relevant natural and synthetic scaffolds. Recent years have seen design and development of novel α-diazocarbonyl molecules, metal complexes and cooperative catalysis concept to achieve construction of complex molecular structures from insertion, addition, and cascade reactions. The reactions of ylides, generated from the reaction of metal-carbenoids with carbon-heteroatom (C-N, C-O, C-S) have also led to the synthesis of several novel heterocyclic motifs. The present review article discusses the recent progress in study of such reactions of metal-carbenoids from α-diazocarbonyls.



Keywords: α-Diazocarbonyls, carbenoids, insertion, addition, cyclopropanation, ylides.

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1. Introduction

α-Diazocarbonyls are powerful synthons in the arsenal of synthetic organic chemists that is evident from plethora of literature on their synthesis and chemistry from the mid-1980s till date.[1-4] Many of them are commercially available while others are easily accessible in the laboratory by simple synthetic procedures. α-Diazocarbonyls undergo thermal, photochemical, and microwave-assisted decomposition generating α-carbonylcarbenes. In many cases, these carbenes undergo the Wolff-rearrangement to form ketenes, another important class of reactive intermediates.[5-7] However, several metal salts and complexes are known to coordinate with carbenes preventing the Wolff-rearrangement and generating metal-carbenoids with enhanced electrophilicity making it more reactive towards nucleophiles. Although copper and rhodium catalysts have been more popular traditionally, other metals such as cobalt, nickel, silver, gold, iron, and ruthenium, etc. have been employed in recent years. Also, several new and novel chiral metal complexes have been developed for stereoselective synthetic protocols employing diverse types of α-diazocarbonyl compounds (Figure 1).[8,9] Common synthetic methods involve benchmark reactions of metal-carbenoids such as insertion into C-H and X-H (X = O, N, S, and Si, etc.) bonds, cyclopropanation, and ylide generation followed by cyclization and cycloaddition reaction (Scheme 1).[10] These reactions have led to the synthesis of diverse classes of biologically relevant natural products (Figure 2) and synthetic molecules of complex architecture.[11]

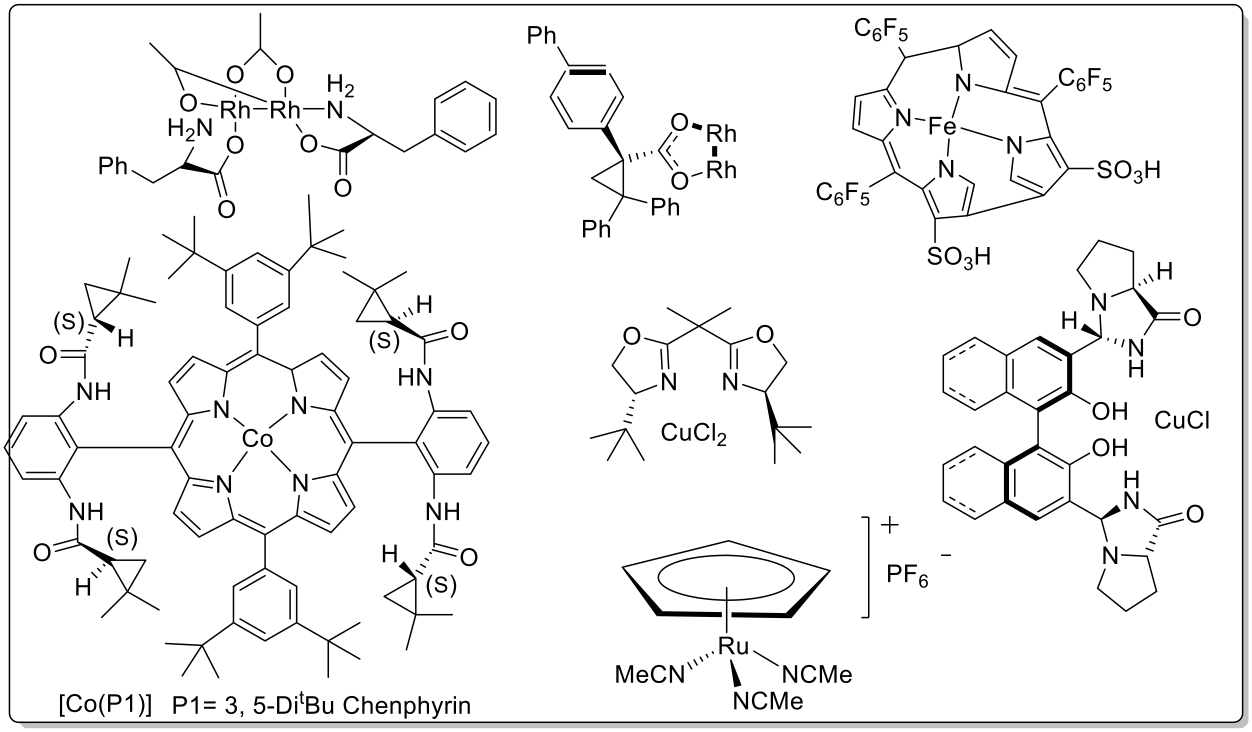
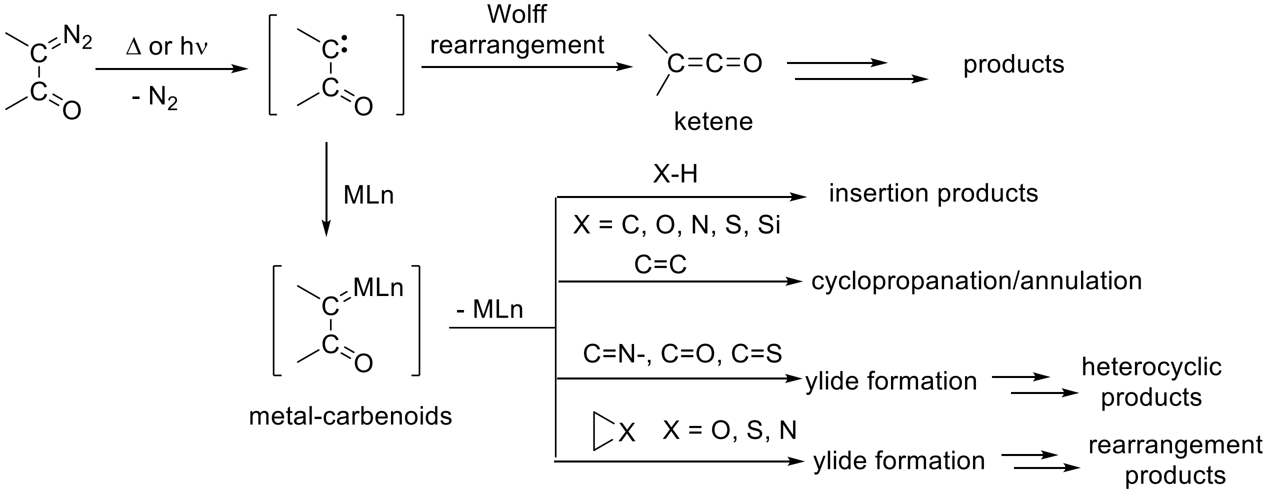


Figure 1. Some metal complexes and ligands used in carbene chemistry.



Scheme 1

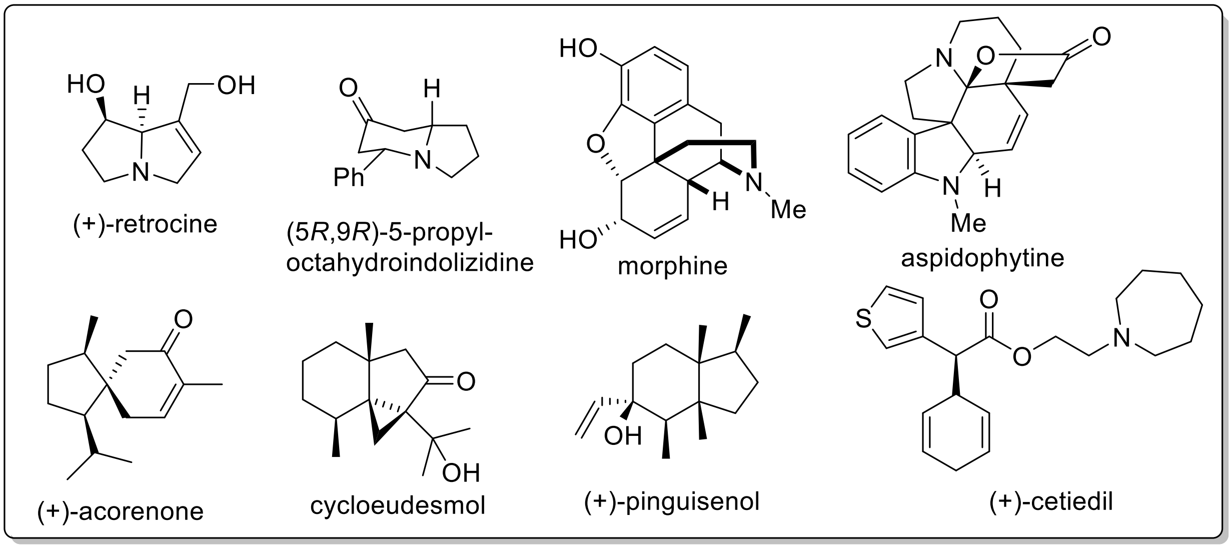


Figure 2. Some natural molecules synthesized using chemistry of metal-carbenoids.

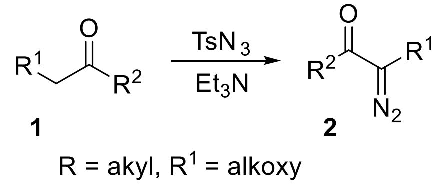
The chemistry of different types of diazo compounds focusing on different aspects have been reviewed from time to time. Gurmessa and Singh published a review on the insertion and cyclopropanation reactions employing α-diazocarbonyls in the presence of metal salts and complexes in 2017, covering literature till 2016.[8] The application of microwave irradiation in the reactions of α-diazocarbonyl compounds has also been reviewed by me recently.[12] Two brief accounts on different aspects of metal-carbenoids chemistry from diazo compounds have been published by Harada and coworkers.[13,14] The synthesis and chemistry of diazoketones was reviewed in 2019 by Arora *et.al*.[15] The chemistry of silver carbenoids from diazo compounds has been reviewed by Zhang and coworkers.[6] Recently, Soam and coworkers have published their review on Rh-catalyzed cascade reactions using diazo compounds as carbene precursor to construct diverse heterocycles.[16] Xiang and coworkers have reviewed the application of diazo compounds in synthesis of nitrogen heterocycles via transition metal-catalyzed cascade C–H activation/carbene insertion/annulation reactions.[17]

The bulk of literature appearing in this research area in recent years necessitates a more frequent review. The aim of the present article is to update the chemistry of metal-carbenoids generated from α-diazocarbonyl compounds and present an overview of the development since 2016 till date.

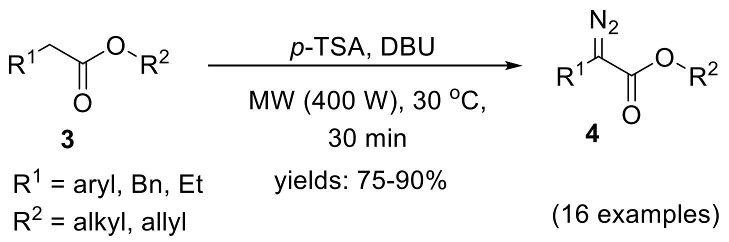
2. Synthesis of α-Diazocarbonyl Compounds

Although the objective of this article is not to review the synthetic methods for getting access to α-diazocarbonyl compounds it is pertinent to mention about some methods of preparation of these reagents whose reactivity is being discussed. Acylation of diazomethane with acyl chloride in the presence of bases (The Arndt-Eistert method) and the diazo-transfer reactions of carbonyl compounds **1** (Scheme 2) are the two long-known classical methods for the preparation of α-diazocarbonyls **2**.[18] A range of sulfonyl azides are commercially available as diazo-transfer reagents that transfer diazo group to methylene carbon α to carbonyl groups. Yi and coworkers have used microwave irradiation for the preparation of α-diazoesters **4** from the reaction of 2-phenyl acetates **3** by diazo-transfer reaction (Scheme 3).[19] Another common method that our group has been using is the metal-catalyzed dehydrogenation of α-carbonyl hydrazones.[20,21] More recently, Tanbouza and coworkers have developed a new bismuth(V) catalytic system for oxidation of hydrazones **5** to diazo compounds **6** including α-

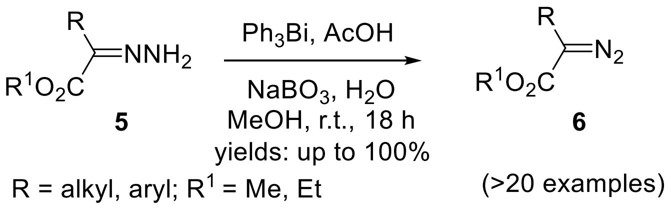
diazocarbonyls (Scheme 4).[22] Use of low catalytic amounts of triphenylbismuth and acetic acid with sodium borate hydrate as a terminal oxidant leads to *in situ* generation of $Ph_3Bi(OAc)_2$ that is capable to oxidize hydrazones in excellent yields. Sharma and coworkers have developed a metal-free method for a quick oxidation of alkynyl hydrazones **7** to alkynyl diazoesters **8** using phenyliodine(III) diacetate (PIDA) (Scheme 5).[23]



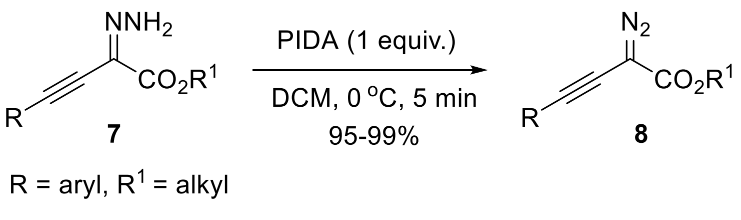
Scheme 2



Scheme 3



Scheme 4



Scheme 5

3. Insertion Reactions

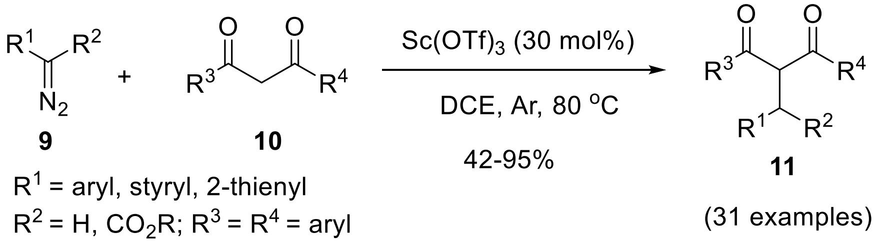
Insertion reactions are powerful tools for construction of C-C and C-heteroatom (N, O, S, and Si) bonds. The reactions of metal-carbenoids, generated *in situ* from the decomposition of α-diazocarbonyls at C-H, N-H, O-H, S-H, and Si-H bonds alkylating them are very common and well-established synthetic protocols. However, insertion is not limited only to these listed bonds. Metal-catalyzed carbene insertions are also reported in P-H, B-H, C-C, Sn-H, Ge-H, F-H and metal-metal bonds, but they are yet referred as "uncommon".[24,25] The electronic demand of the substituent attached to the carbene carbon atom affects the selectivity of insertion reactions. Highly electrophilic carbenoid intermediates display little regioselectivity and stereoselectivity, favoring the occurrence of side reactions. A less electrophilic carbenoid intermediate, on the other hand, has a lower reactivity, but its regioselectivity and stereoselectivity are better.[26]

Despite the importance of electronic factors to the reactivity and selectivity of carbenoid intermediates, steric and conformational effects are also determining factors in carbenoid chemistry. Steric as well as electronic factors and the chemical properties of the ligands around the metal center also significantly determine the type of insertion by the carbenoid intermediate. The complexes used for the formation of carbenoids in enantioselective insertion reactions must present a balance between steric and electronic factors, to promote the formation of a specific enantiomer.[27] The succeeding paragraphs discuss selected examples of common insertion reactions useful to organic chemists.

3.1 C-H bond insertion reactions

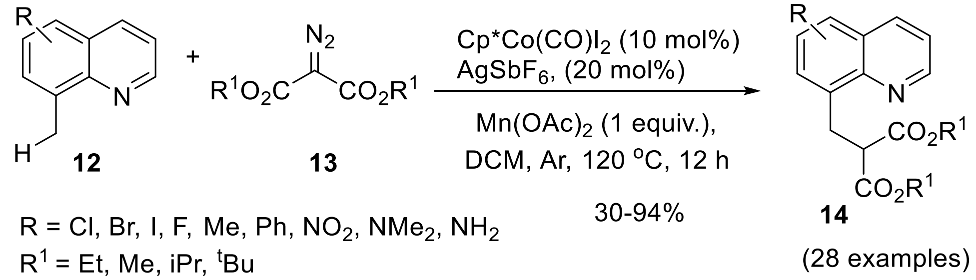
For decades, the stereoselective carbon–carbon bond formation by activation of a C-H bond in the synthesis of pharmaceuticals, natural products, and other industrially relevant target molecules has been a challenging aspect in organic chemistry. A powerful approach to achieve such useful C-H functionalization is via C-H insertion of metal carbenoids.[28] The activation of the C-H bond needs an appropriate interaction between the carbenoid intermediate and the carbon atom of the C-H bond. The mechanistic details of this reaction have been discussed previously.[8] Recent literature shows some excellent reports on the application of C(sp3)-H and C(sp2)-H insertion/activation/annulation reactions in synthesis of complex molecules that are discussed below. The literature is arranged mostly according to the metal catalyst used beginning with less common metal catalysts for the reactions of α-diazocarbonyls.

Liu and coworkers have investigated the reactions of α-diazocarbonyl compounds **9** with 1,3-dicarbonyl compounds **10** in the presence of silver and scandium catalysts.[29] The formal C-H insertion led to the formation of 2-alkylated 1,3-dicarbonyl compounds **11** in the presence of Sc(III) triflate (Scheme 6). In the presence of silver(I) triflate, however, the reaction switched to insertion into the C(=O)-C bond of the 1,3-dicarbonyl substrate forming a 1,4-dicarbonyl product (in up to 96% yield). This was the first example of a C-C bond insertion of metal-carbenoid from diazo compound in acyclic C-C bonds.



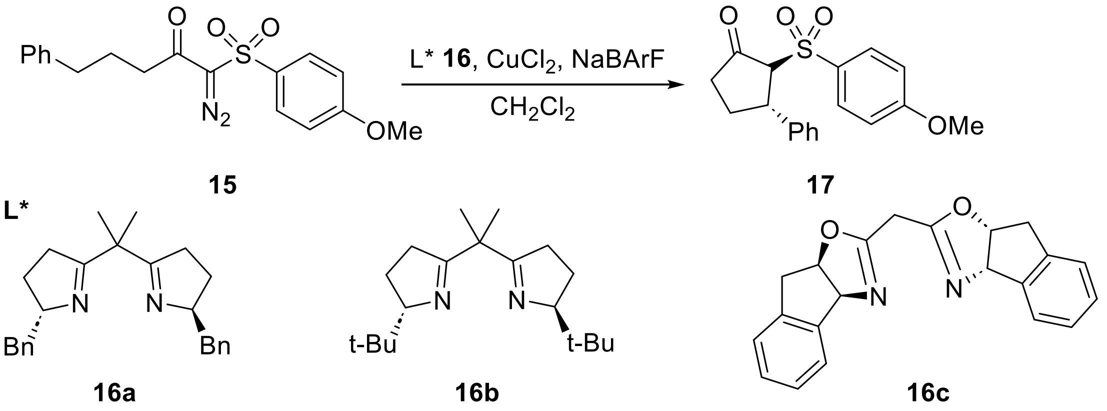
Scheme 6

Yan and coworkers have reported an efficient Cp*Co(III)-catalyzed reaction of α-diazocarbonyls **13** with 8-methylquinoline **12** resulting into insertion at the methyl group forming quinoline derivatives **14**.[30] The protocol tolerates a variety of functional groups (Scheme 7) and can be scaled up easily. The alkylated products can be used to synthesize important intermediates of azatricyclic antibiotic compounds. According to the proposed mechanism, the reaction proceeds through a quinolyl-directed C(sp3)–H activation by cobalt, cobalt-carbenoid formation, migratory insertion, and subsequent protonation. The active catalyst [Cp*Co(III)OAc$^+$] was generated by the ligand abstraction with $AgSbF_6/Mn(OAc)_2$.



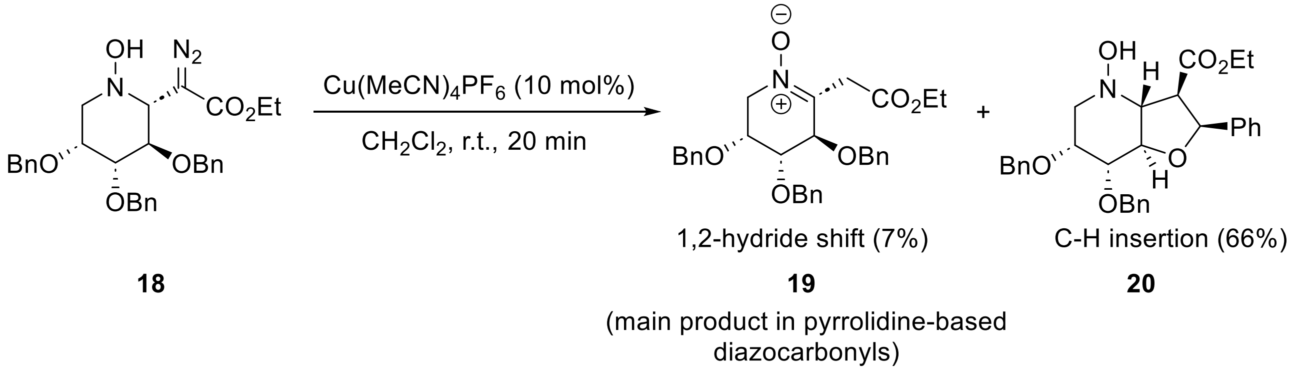
Scheme 7

A ligand-dependent enantioselectivity has been demonstrated in copper-bisoxazoline systems in studies reported by the Ford group.[31] The α-diazo-α-sulfonyl ketone substrate **15** is just one example in a recent report on copper-catalyzed 1,5-C–H insertion product **17** formation that was investigated with three different commercially available bisoxazoline ligands **16**. A wide variation in enantioselectivity was observed with the different ligands employed; the highest asymmetric induction (87%) was achieved with the indane-derived bisoxazoline ligand **16c** (Scheme 8).



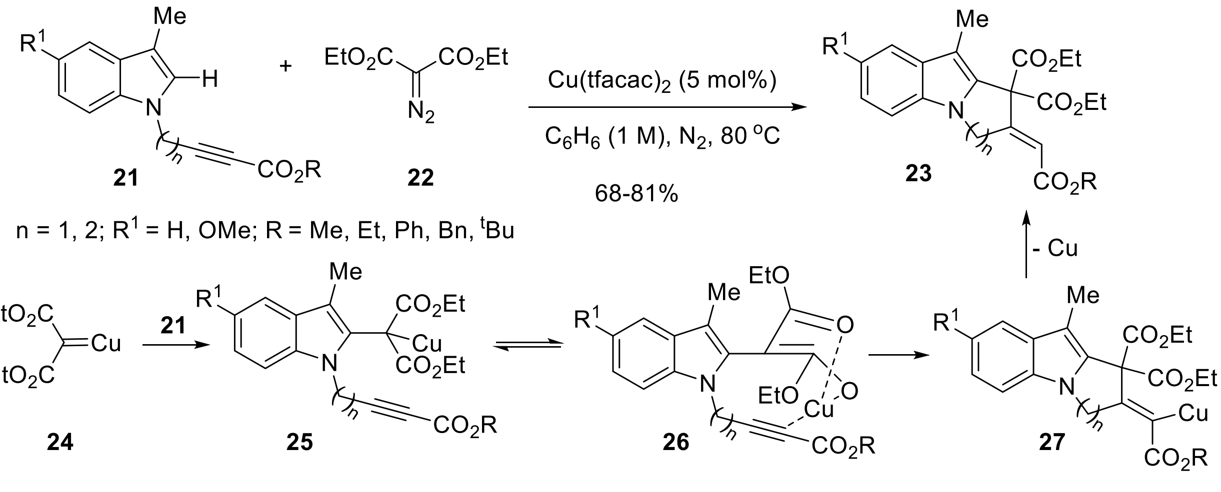
Scheme 8

Kui and coworkers have studied the metal-catalyzed reactions of α-diazo-β-hydroxyamino esters **18**. An intramolecular 1,5-C-H insertion forming fused cyclic product **20** was the principal reaction in copper-catalyzed reaction of piperidine-based substrate (Scheme 9) while a selective 1,2-hydride shift forming ketonitrones **19** was observed in pyrrolidine-based substrates.[32]



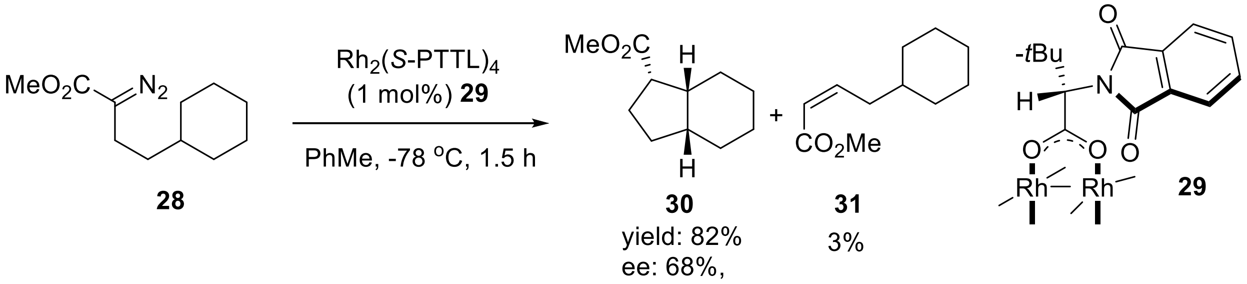
Scheme 9

Bhat and coworkers have developed a copper-catalyzed arene C(sp2)–H insertion/Michael-type annulation reaction involving α-diazocarbonyl compounds.[33] The reactions of α-diazocarbonyl compounds **22** with suitably substituted indoles **21** containing alkynyl ester electrophiles yield a variety of fused indole **23** scaffolds in a stereoselective manner by varying the location of the electrophile on the indole derivatives (Scheme 10). The method features low catalyst loadings, reasonable yields, and excellent regio- and stereoselectivity. Further, a one-pot copper carbene coupling/base promoted annulation sequence, which extended the electrophile scope past alkynyl-ester, was developed to synthesize a series of interesting, cyclized products. The electron-deficient internal alkynes appeared central to the success of the copper cascade conditions. Switching the ester group at the terminal end of the alkyne acceptor for an alkyl group resulted in formation of C-H insertion product only. The copper catalyst has been proposed to play dual role in the mechanistic pathway. First, it activated the diazocarbonyl to generate the copper-carbenoid **24** for C-H functionalization **25** and then double activated the enolate and alkyne electrophile in **26** invoking 5-exo-dig *syn* addition furnishing cyclized intermediate **27** which underwent protodemetalation to give cyclized *Z*-alkene isomer and regenerate the catalyst.



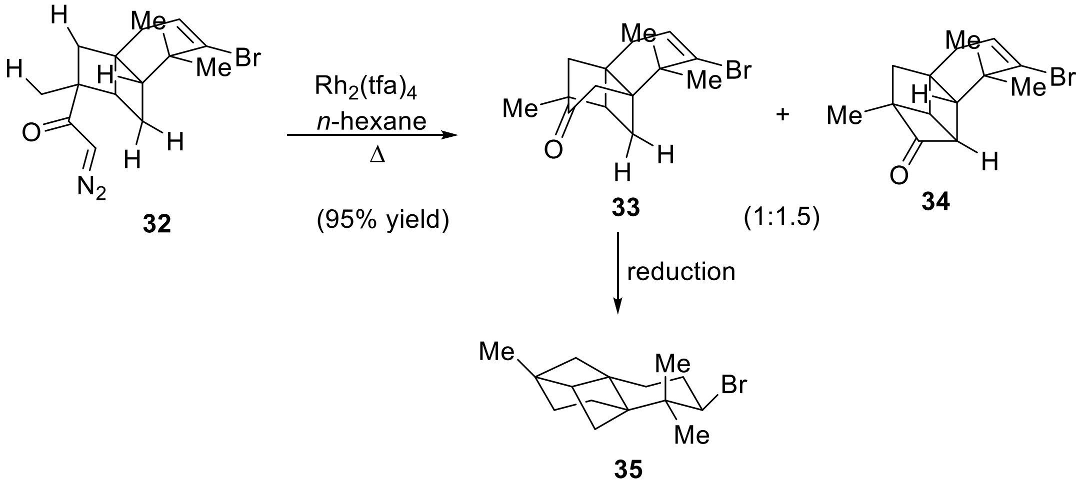
Scheme 10

Several studies have shown application of different rhodium catalysts for intramolecular C(sp3)-H and intermolecular C(sp2)-H insertion reactions of α-diazocarbonyl compounds. Miyazawa and coworkers have reported application of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate, Rh$_2$(S-PTTL)$_4$ **29** as a catalyst in enantio- and diastereoselective construction of fused bicyclic ring systems with three contiguous stereocenters via intramolecular C-H insertion of σ–symmetric α-alkyl α-diazoesters.[34] The C-H insertion proceeded in a chemoselective manner to furnish methyl bicyclo[3,3,0]oct-7-ene-2-carboxylate and bicyclo[4,3,0]nonane-7-carboxylate derivatives with *cis*-selectivity in up to 99% ee. A representative example of intramolecular C-H insertion in 2-diazo-4-cyclohexylbutanoate **28** catalyzed by Rh_2(S-PTTL)$_4$ **29** affording bicyclic ester **30** as a single diastereomer in 82% yield and 68% ee along with 3% of (*Z*)-alkene **31** is shown in scheme 11.



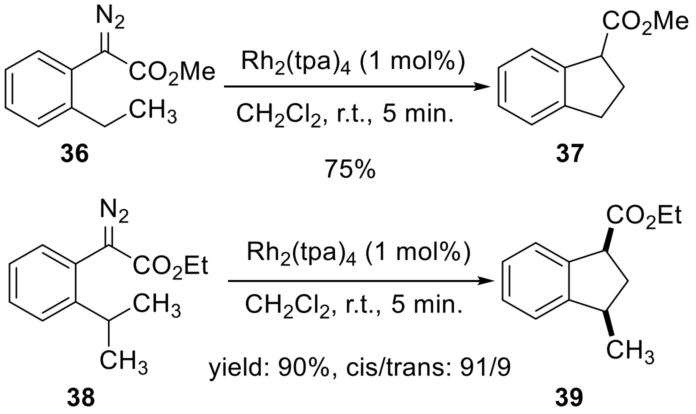
Scheme 11

In 2017, Zhang and coworkers reported the total synthesis of aplydactone, which involved an unusual intramolecular Rh-catalyzed C-H insertion reaction to construct the highly strained tetracyclic core.[35] The reaction of 2-diazoketone **32**, containing a [2]-ladderane skeleton, in the presence of $Rh_2(tfa)_4$ in hexane under reflux afforded the desired six-membered isomer **33** (95%, **33:34** = 1:1.5, Scheme 12). The reduction of the carbon skeleton of **33** furnished aplydactone **35**.



Scheme 12

Dirhodium(II) tetrakis(triphenylacetate), $Rh_2(tpa)_4$-catalyzed site-selective intramolecular insertion of aryl diazoacetates into a nonactivated primary C−H bond has been reported recently.[36] The insertion reaction of rhodium-carbenoids from aryldiazoacetates **36** and **38** into the C-H bonds of 2-ethyl or 2-isopropyl groups present on the phenyl ring of the substrates proceeded at room temperature to furnish indane-1-carboxylates **37** and **39**, respectively, in very good yields (Schemes 13). The *cis*-isomer **39** was the major product in the reaction of ethyl 2-diazo-2-(2-isopropylphenyl)acetate **38**.

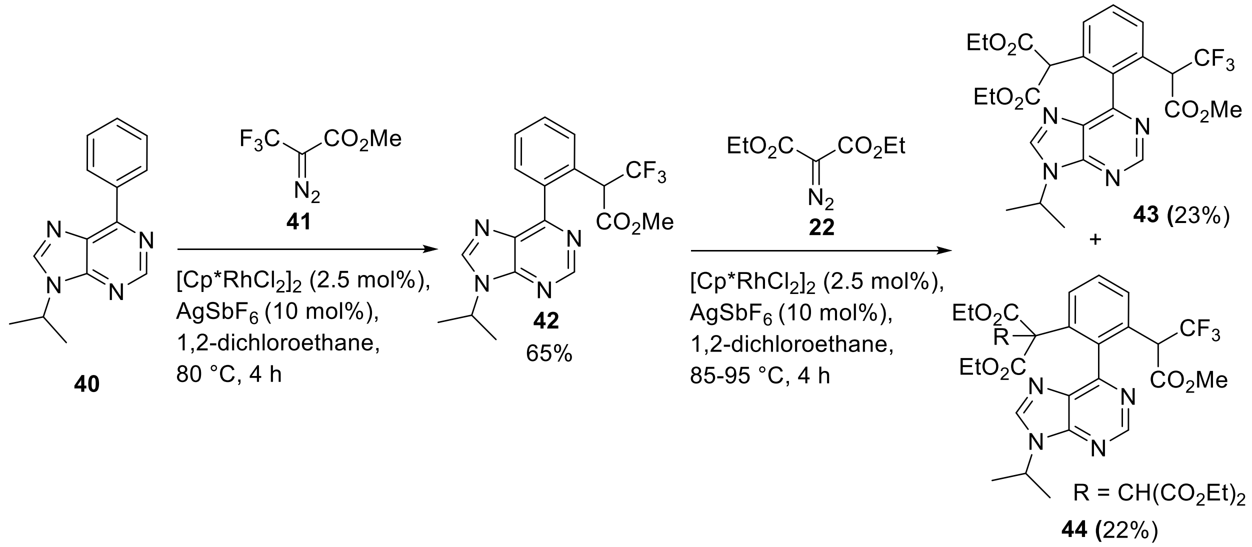


Scheme 13

Merey and coworkers have studied the rhodium and copper-catalyzed reactions of α-diazoesters bearing a tertiary amide group in which the nitrogen atom was substituted with an alkoxy group having a carbon-carbon double bond together with another group.[37] In the presence of $Rh_2(OAc)_4$, intramolecular 1,5-C-H insertion product isooxazolidinone was obtained predominantly while cyclopropanation was the main course of reaction in the presence of CuCl/$AgSbF_6$. A $Rh_2(OAc)_4$-catalyzed intermolecular cyclization of pyrazol-5-amine and cyclic 2-diazo-1,3-diketones in *N,N*-dimethylformamide (DMF) has been developed.[38] Various pyrazolo[3,4-*b*]pyridine derivatives were obtained in this reaction under mild conditions. Interestingly, the metal-carbenoid underwent C-H insertion with methyl group of DMF. Thus, DMF provided a carbon atom in the construction of pyridine ring.

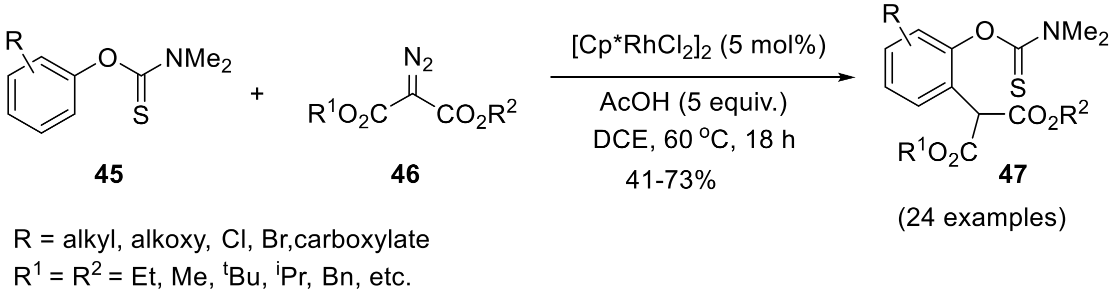
In a recent communication, Sihag and coworkers have reported insertion of rhodium-carbenoids from α-diazocarbonyls into an allylic C-H bond of unactivated alkenes.[39] In this protocol acceptor-acceptor diazo compounds bypassed cyclopropanation. Further, the method was compatible with diverse unactivated alkenes functionalized with different sensitive functional groups. A rhodacycle π-allyl intermediate has been proved to be an active intermediate in the mechanistic pathway.

A copper-catalyzed C(sp2)-H insertion has been described previously.[32] Several other reports have appeared on Csp^2-H insertion reactions of α-diazocarbonyl compounds using rhodium, gold, iron, and iridium catalysts. Vinogradov and coworkers have reported consecutive alkylation of 9-isopropyl-6-phenyl-9*H*-purine **40** on treatment with diethyl diazomalonate **22** and then with methyl 2-diazo-3,3,3-trifluoropropionate **41** at the *ortho*-positions of the phenyl substituent furnishing product **43** via the first insertion product **42**.[40] This reaction proceeded under chelation assistance of the purine core that led to high regioselectivity at the *ortho*-position of phenyl substituent. The dimeric rhodium(III) complex $[Cp^*RhCl_2]_2$ was discovered as the most efficient catalyst. However, when the sequence of diazocarbonyls was reversed then an unusual triple alkylation product **44** was obtained because of the third alkylation due to simple electrophilic metal carbenoid insertion to the C−H bond of the malonate moiety (Scheme 14).[41]

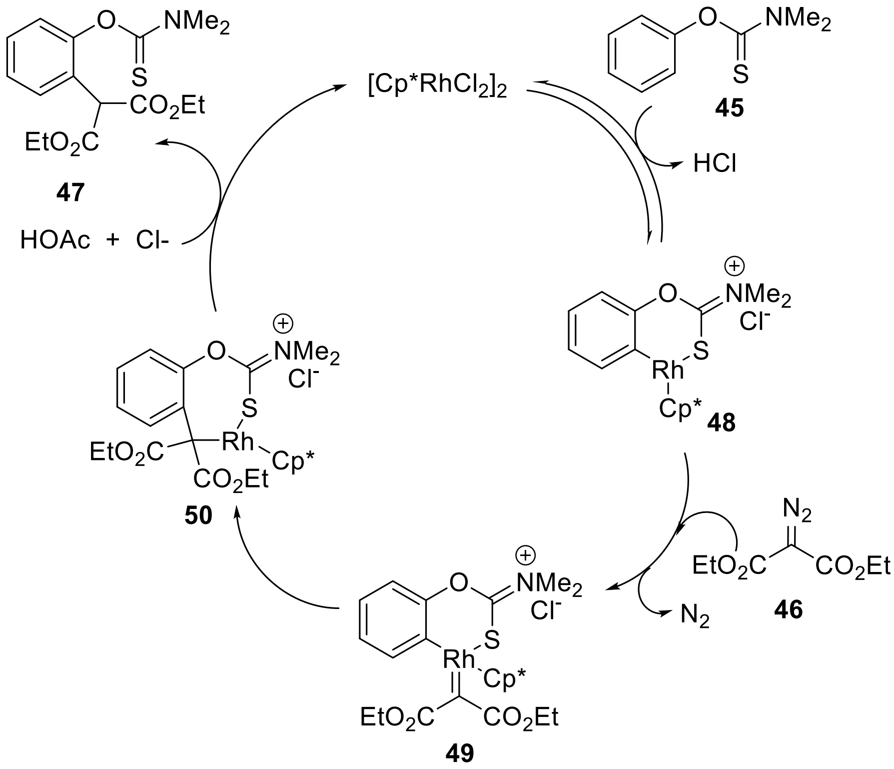


Scheme 14

The reactions of dialkyl diazomalonates (dimethyl diazomalonate **46**) with *O*-aryl *N,N*-dimethylthiocarbamates **45** using $[Cp^*RhCl_2]_2$ in acetic acid as a catalytic system is reported.[42] The reaction was directed by thiocarbamate group leading to alkylation of aromatic C-H *ortho* to thiocarbamate group in moderate to good amounts (Scheme 15). The plausible mechanism involved the ligand exchange of enolate form of thiocarbamate group with $[Cp^*RhCl_2]$2 inducing a reversible *ortho* C−H activation via electrophilic metalation to form a six-membered cyclorhodium species **48**. This species reacted with diazomalonate to afford the key Rh-carbenoid intermediate **49** accompanied with the nitrogen release. Next migratory insertion and protonation by acetic acid furnished the alkylation product **47** and the catalyst is generated by attack of chloride ion on the rhodium center in the complex **50** (Scheme 16).

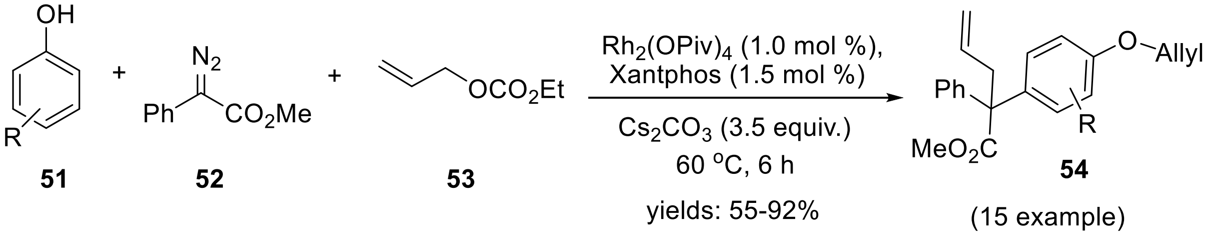


Scheme 15



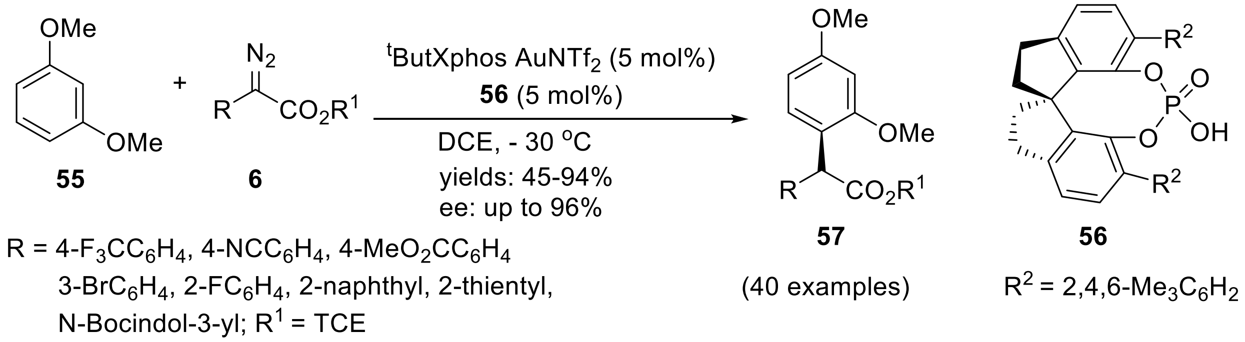
Scheme 16

Phenols are important motifs in natural products and pharmaceutical products. The C-H functionalization of phenols employing metal-carbenoids is a challenging endeavor due to competing insertion into the O-H bond. Toward this end, Yang and coworkers have developed a novel multicomponent reaction of free phenols **51**, methyl 2-diazo-2-phenylacetate **52**, and allylic carbonate **53** in the presence of Rh(II) and a Xantphos ligand as the catalyst, furnishing a wide range of phenol derivatives **54**, bearing an all-carbon quaternary center and a synthetically useful allylic unit (Scheme 17).[43] Probably, the reaction proceeds via a tandem process of carbene-induced *para*-selective C−H functionalization, followed by Rh(II)/Xantphos-catalyzed allylation.



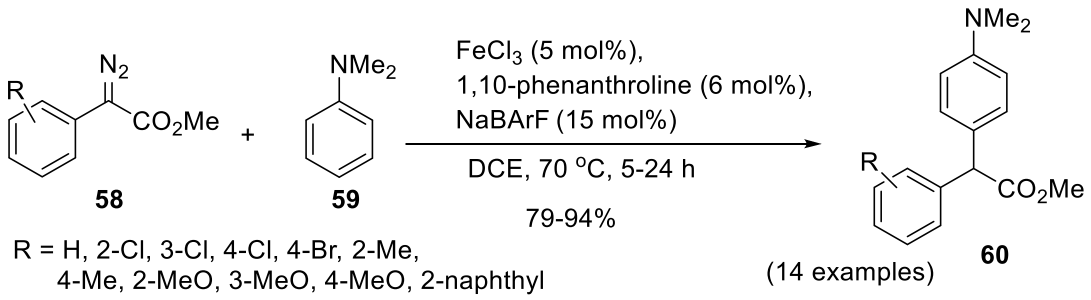
Scheme 17

An example of Csp^2-H bond insertion of metal-carbenoids involves the reaction of aryl diazoacetates **6** with anisole **55** in the presence of an achiral gold complex and chiral phosphoric acid **56** as a cooperative catalytic system (Scheme 18).[44] This reaction offers a protocol for an enantioselective synthesis of α,α-diary acetates **57**. The reactivity and enantioselectivity of this reaction have been explained by DFT calculations. More recently, a Csp^2–H activation on 2-aryl group of 2-arylbenzimidazoles with α-trifluoromethyl-α-diazoketones followed by defluorinative annulation is reported.[45] The reaction sequence leads to easy access to 6-fluorobenzimidazo[2,1-*a*]isoquinolines in high yields and excellent functional group compatibility.



Scheme 18

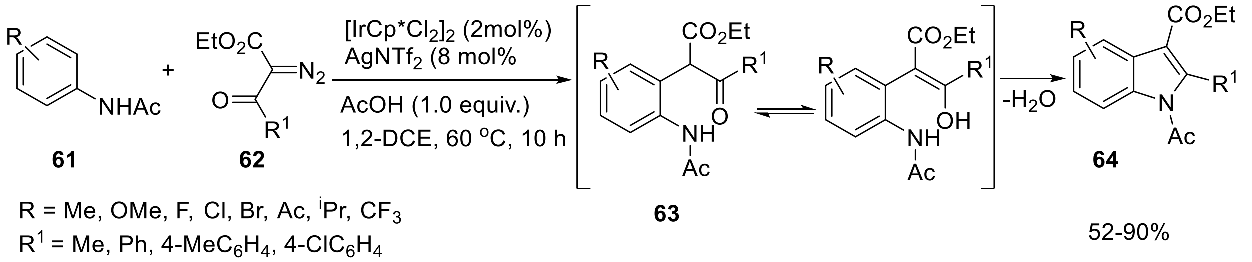
Yang and coworkers reported the application of $FeCl_3$ for a chemo- and regioselective arylation of α-aryl diazoacetates **58** using *N,N*,dimethylaniline **59**.[46] The group has used iron(III) chloride in combination with 1,10-phenanthrolene and NaBArF as the catalytic system. The reaction led to exclusive formation of 4-substituted *N,N*,dimethylanilines **60** in very good yields (Scheme 19). No 2-substitution or insertion into C-H bond of methyl group was observed. The diazo compounds with fused ring or heteroaromatic ring also worked efficiently.



Scheme 19

Balhara and Jindal published their density functional theory (DFT) study of indole alkylation with diazoacetates catalyzed by $Fe(ClO_4)$TMEDA/spirobisoxazoline and myoglobin catalytic system. This study was conducted to get a clue of low stereoselectivity in C-H functionalization of indoles with Fe-carbenoids. Three mechanistic pathways: nucleophilic, radical, and oxocarbenium routes were explored. The nucleophilic pathway is the most feasible involving an enol species that furnishes the alkylated indole on tautomerization. The present study showed that the conventionally proposed enol pathway was not responsible for the low enantiomeric excess. The enol intermediate can stay coordinated to the catalyst via different binding sites placing the enol in proximity to the chiral environment and affecting the stereoselective proton transfer. Both the binding strength and the chiral environment were crucial for obtaining high selectivity. This study might be helpful in finding an efficient catalytic system for efficient enantioselective C-H insertion.[47]

Patel and Borah have reported Ir(III)-catalyzed reactions of α-diazocarbonyl compounds **62** with readily available acetanilides **61**.[48] The reaction resulted into C-H insertion at ortho to anilide group forming **63** and annulation under mild conditions allowing direct access to indoles **64** (Scheme 20). Diverse types of *N*-substituted indoles, including *N*-acetyl, *N*-pivolyl, and *N*-benzoyl indoles, were obtained in good yields.

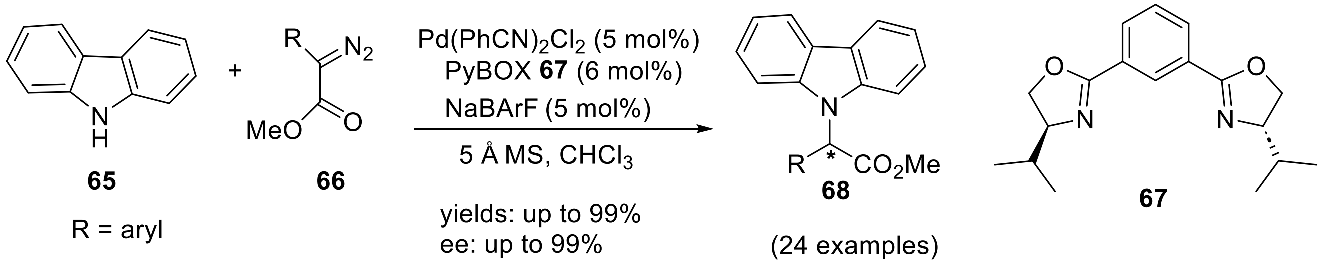


Scheme 20

3.2 N-H bond insertion reactions

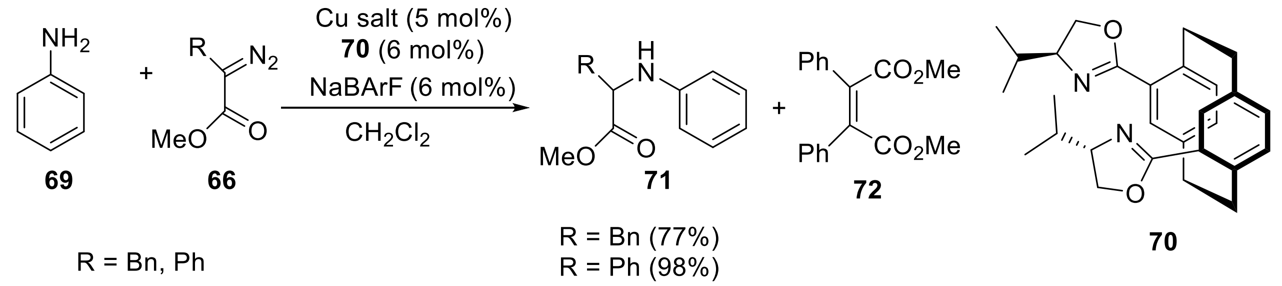
One of the most efficient methods for the construction of the carbon–nitrogen bond is through N–H bond insertion reactions of metal-carbenoids, generated from metal-catalyzed reactions of diazo compounds.[8] Recent literature shows notable development in this area of research. Chemoselective and in some cases enantioselective N-H bond insertion reactions have been reported with primary and secondary amines, heterocyclic amines, imines, and ammonia as well. Copper, rhodium, iron, and silver catalysts have been employed to achieve the reaction. The N-H bond insertion of the metal-carbene from diazocarbonyls has been reviewed by Jiajun *et al*. in Chinese language.[49] The products obtained from the N–H insertion reaction are useful building blocks in organic synthesis. The N-H insertion reaction provides an attractive access for the synthesis of α-amino esters, dipeptides, nitrogen-containing heterocycles, and other amino acid derivatives.

Arredondo and coworkers reported that Pd(II)-chiral biosoxazoline **67** catalyzed highly enatioselective N-H bond insertion of the metal-carbenoids from α-diazoesters **66** into N-H bonds of aromatic heterocycles such as C-3 substituted indoles and carbazoles **65** (Scheme 21).[50] The products **68** were obtained in good yields and ee up to 99%. The method was applied to the synthesis of the core of a bioactive carbazole derivative.



Scheme 21

Knoll and coworkers in 2019 reported a new class of planar chiral [2.2]paracyclophane-based bisoxazoline (BOX) ligand **70** for the $Cu(MeCN)_4PF_6$ complex showing good selectivity in N-H insertion reactions of methyl 2-diazo-2-benzyl/phenyl esters **66** into the N-H bond of aniline **69**.[51] Lowering the temperature to room temperature increased the selectivity to an excellent ratio of 93:5 with $Cu(MeCN)_4PF_6$. When β-hydrogen lacking **66** (R = Ph) was used, product **72** was detected from the dimerization of the α-diazocarbonyl compound. Dropwise addition of **66** (R = Ph) to the reaction mixture alleviated this issue for the most part. With these optimized reaction conditions, the same copper catalyst $Cu(MeCN)_4PF_6$ led to excellent yields of 98% for the desired insertion products (Scheme 22). Notably, in both cases the product was formed even in the absence of the ligand in 13% and 40% yields, respectively.



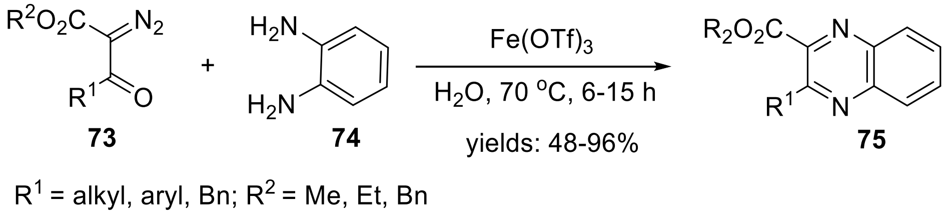
Scheme 22

Earlier in 2017, Ramakrishna and Sivasankar had reported an efficient green method for acceptor/acceptor type carbene insertion into the N–H bonds of various anilines in water. The study revealed that the $[(COD)IrCl]_2$ catalyzed the N-H insertion furnishing product in up to 98% yields.[52]

Aliphatic amines strongly coordinate, and therefore easily inhibit the activity of transition-metal catalysts, posing a marked challenge to N–H insertion reactions. Toward this challenge Li et al. used two catalysts in tandem: an achiral copper complex and a chiral amino-thiourea and developed highly enantioselective carbene insertion into N–H bonds of aliphatic amines.[53] Coordination by a homoscorpionate ligand protects the copper center that activates the carbene precursor. The chiral amino-thiourea catalyst then promotes enantioselective proton transfer to generate the stereocenter of the insertion product. This reaction couples a wide variety of diazo esters and amines to produce chiral α-alkyl α–amino acid derivatives.

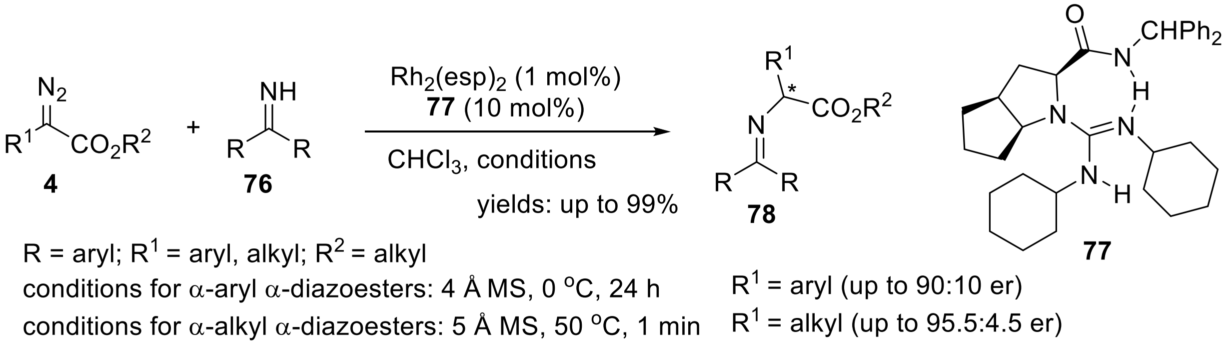
Tanbouza *et al.* in their study on N-H bond insertion of Fe-carbenoids, generated from the $Fe(OTf)_2$-catalyzed decomposition of methyl 2-diazo-2-phenyl acetate, observed that the reactions were strongly dependent on the type of amine used. Secondary amines afforded moderate yields of (57-68%) of *tert*-amine, with prolonged reaction time (72 h) and increased temperatures (80 °C) to reach completion. Primary aromatic amines offered improved yields of the insertion products, *sec*-amines (74-84%). It is noteworthy that in case of primary amines, the reaction was selective toward a single-insertion with no sign of a double insertion product.[54]

Pandit and coworkers have used iron(III) catalyst, $Fe(OTf)_3$ in the reaction of α-diazocarbonyls **73** and *o*-phenylenediamines **74** in water.[55] The reaction proceeds by a domino N−H insertion, cyclization, and oxidation reactions resulting in construction of polyfunctionalized quinoxalines **75** in high yields (Scheme 23). A total of 41 compounds were synthesized using monocyclic and bicyclic diamines. This methodology also allows the synthesis of biologically relevant pyrazines and benzoquinoxalines.



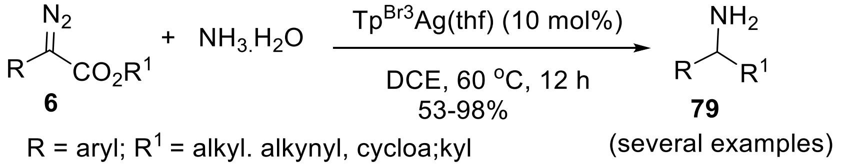
Scheme 23

The reaction of α-diazoesters **4** with benzophenone imines **76** using $Rh_2(esp)_2$ and chiral guanidine **77** cooperative catalysis results into an efficient enantioselective N–H bond insertion.[56] Both aliphatic and aromatic substituted α-amino esters **78** were obtained in high yields (up to 99%) and good enantioselectivities (up to 95.5: 4.5 er) under mild reaction conditions (Scheme 24).



Scheme 24

Insertion of metal-carbenoids into the N−H bond of ammonia persists as a longstanding challenge in carbene chemistry because of the tendency of Lewis basic ammonia (NH_3) to bind with metal and inhibit metal catalysis. To address this challenge, Liu and coworkers investigated the reactions of diverse diazo compounds **6** with ammonia using a Tp^{Br3}Ag-catalyzed two-phase system (Scheme 25).[57] These reactions resulted in a chemoselective carbene N−H bond insertion of $NH_3{\cdot}H_2O$. Coordination of silver to a homoscorpionate Tp^{Br3} ligand renders silver compatible with NH_3 and H_2O and enables the generation of electrophilic silver-carbenoid. Water promotes subsequent [1,2]-proton shift to generate N−H insertion products **79** with high chemoselectivity.



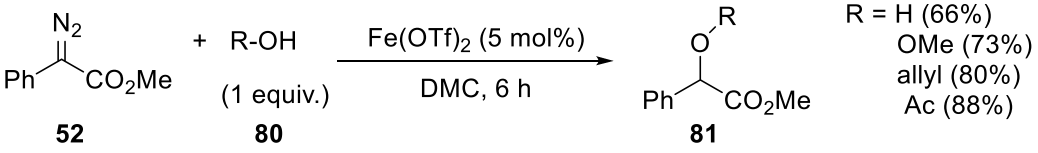
Scheme 25

Li and coworkers have reported an enantioselective N-H bond insertion to construct C-N bond by reaction of a wide variety of diazoesters with ammonia under the cooperative action of copper complexes and chiral hydrogen-bond donors.[58] The reaction resulted into formation of natural and nonnatural chiral α-amino acids in excellent yields and enantioselectivity.

3.3. O-H bond insertion reactions

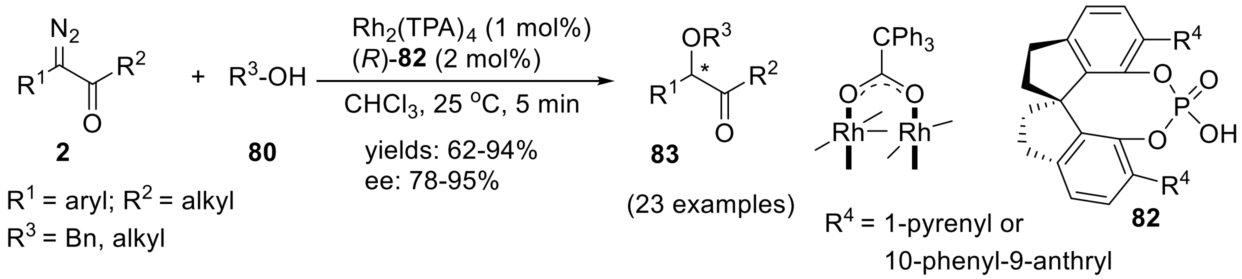
Carbenes can insert into O-H bond forming ethers. The mechanism involves usual addition of the oxygen lone pair into an empty *p*-orbital on the carbene, followed by proton transfer to generate a neutral molecule from the first formed ylide.

Tanbouza and coworkers have reported O-H bond insertion of iron-carbenoids, generated *in situ* from $Fe(OTf)_2$-catalyzed decomposition of methyl 2-diazo-2-phenyl acetate **52**, into the O-H bonds of water, alcohols and acetic acid **80**.[54] The products **81** were obtained in good yields in an emerging green solvent dimethyl carbonate (DMC) (Scheme 26). The catalyst and solvent were also good for N-H, Si-H, and S-H insertion reactions.



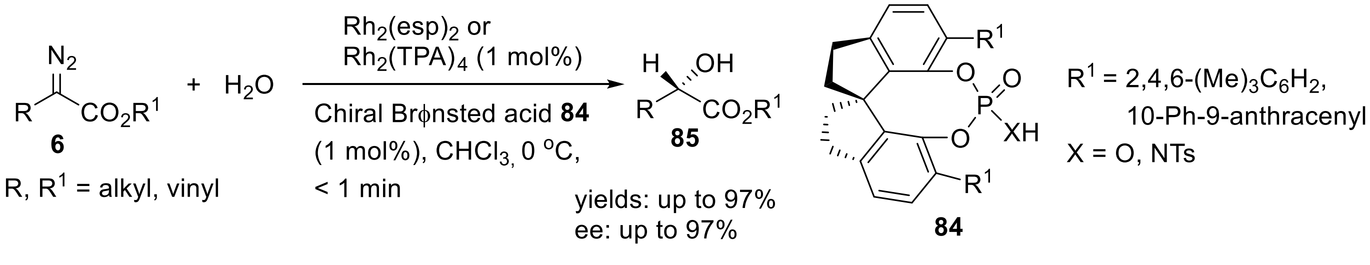
Scheme 26

In recent years cooperative catalysis by Rh(II)- chiral phosphoric acids has been employed in some enantioselective O-H insertion reactions. Li and coworkers reported the first asymmetric O—H insertion of metal-carbenes from α-diazoketones with alcohols co-catalyzed by achiral dirhodium complexes and chiral spiro phosphoric acids.[59] The products were obtained in high yields and high enantioselectivity (up to 95% ee) (Scheme 27). This reaction offers an efficient approach to the synthesis of very useful chiral α-alkoxy ketones, which are easily transformed to corresponding 1,2-diol derivatives with excellent diastereoselectivity. The DFT calculation revealed that the chiral spiro phosphoric acid can promote the proton transfer process of enol intermediates generated from rhodium carbene and alcohol like chiral proton-transfer shuttle and realize enantioselectivity control accordingly. Water is likely to participate in this proton transfer step and has a remarkable effect on the enantiocontrol of the reaction.



Scheme 27

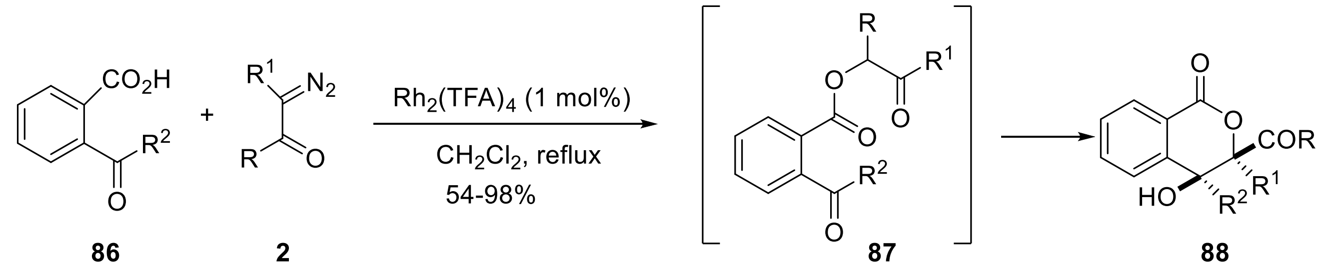
Recently, Li and coworkers have reported the first highly enantioselective O-H bond insertion reaction of metal-carbenoids from α-alkyl- and α-alkenyl-α-diazoesters **6** into the O-H bond of water using a combination of achiral dirhodium complexes and chiral phosphoric acids or chiral phosphoramides **84** as a catalytic system (Scheme 28).[60] The use of phosphoric acid or phosphoramide in the reaction was observed to suppress the side reactions such as carbene dimerization, olefin isomerization, and β-hydrogen shift. The products chiral α-alkyl- and α-alkenyl hydroxyl esters **85**, obtained in excellent yields readily undergo various transformations to give biologically relevant molecules.



Scheme 28

In a recent communication, Zheng and coworkers have reported Rh(II)-chiral phosphoric acid co-catalyzed three-component reaction of vinyl diazoacetates, alcohols and imines.[61] In situ generated vinyl rhodium-carbenoid formed oxonium ylides with alcohols that are intercepted by imines via a site-selective Mannich type reaction resulting into 1,3-difunctionalization of the vinyl carbene with excellent regio-, diastereo- and enantioselectivities (yields: 78-99%, rr: >95:5, dr: >20:1, ee up to 99%) for the first time. The protocol demonstrated a broad scope as diverse functional groups were tolerated (40 examples).

Massaro and coworkers have reported a convergent cascade approach for the stereoselective synthesis of diverse lactones.[62] The $Rh_2(TFA)_4$-catalyzed cascade reaction proceeds via a carboxylic acid O–H insertion furnishing **87** and aldol cyclization of insertion products **87** with high chemo-, regio-, and diastereoselectivity leading to a quick entry into highly functionalized γ-butyro- and δ-valerolactones **88** from readily accessible ketoacid **86** and diazo synthons **2** (Scheme 29). The reaction has wide scope as a range of ketoacids with electron-donating and electron-withdrawing groups, and diazocarbonyls react to provide functionalized lactones of varying ring sizes.

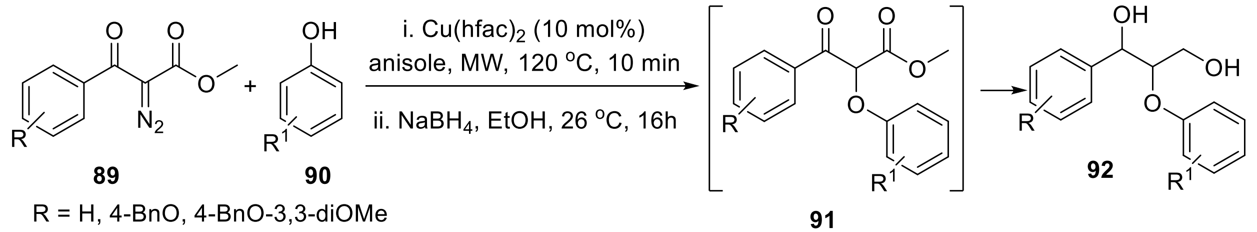


R = alkyl, alkoxy; R^1 = ; alkyl, aryl; R^2 = Me, cinnamyl

O-H insertion products

Scheme 29

Dias and coworkers have investigated the reaction of stable 2-diazo-1,3-diketones **89** with phenols **90**.[63] The optimization studies with different rhodium and copper catalysts established $Cu(hfac)_2$ as the most efficient catalyst. Anisole at 120 °C using microwave irradiation was discovered as the most efficient solvent. The copper-catalyzed insertion products **91** were obtained with substrates bearing diverse groups on the phenyl ring of phenol. The insertion products were reduced to obtain β-O-4-lignin models **92**, a sustainable source of aromatic compounds (Scheme 30).



R = H, 4-BnO, 4-BnO-3,3-diOMe

R^1 = H, 4-MeO, 4-^{n}Pr, 2-MeO, 3-MeO, 2,6-diMeO,

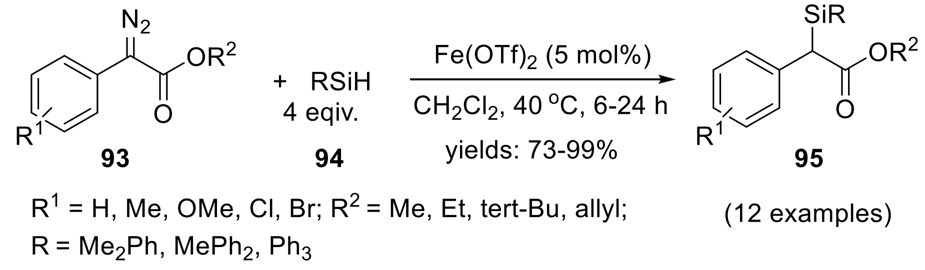
40-67%

Scheme 30

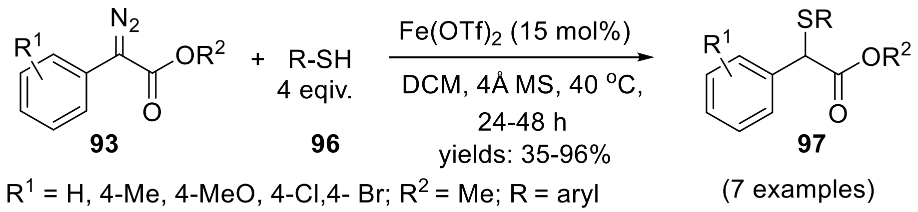
3.4 S-H and Si-H bonds insertion reactions

Insertion reactions of metal-carbenoids into the Si–H bond are known since 1988. However, they did not receive much attention compared to their N–H and O–H bonds counterparts. Recently, there have been a few notable developments, particularly in the field of asymmetric reactions of diazo compounds with substrates containing Si–H bond. Chiral copper, rhodium, iridium, ruthenium, and iron catalysts have shown to be very promising for the purpose.[19] Keipour and Ollivier reviewed the insertion reactions of metal-carbenoid from diazo compounds into the Si-H bond in 2017.[64]

Keipour and coworkers have reported iron- and copper-catalyzed carbenoid insertion reaction of α-diazo carbonyl compounds **93** into Si-H and S-H bonds of silanes **94** and thiols **96**, respectively.[65-67] Several α-silyllesters **95** (Scheme 31) and α-thioesters **97** (Scheme 32) were obtained in high yields from α-diazoesters **93** using a simple iron(II) salt as a catalyst. Substrates with electron-donating and electron-withdrawing groups were used in these studies. A 4-chloro group on the diazoester gave low yield of the corresponding α-thiolester in reaction with thiophenol (35%). A wide range of α-silylesters and α-thioesters was also obtained in high yields (up to 98%) from α-diazoesters using 5 mol% of a simple copper(I) salt as catalyst. Using 0.05 mol% of the same catalyst, α-diazoketones led to the formation of α-silylketones in low to good yields (up to 70%).



Scheme 31

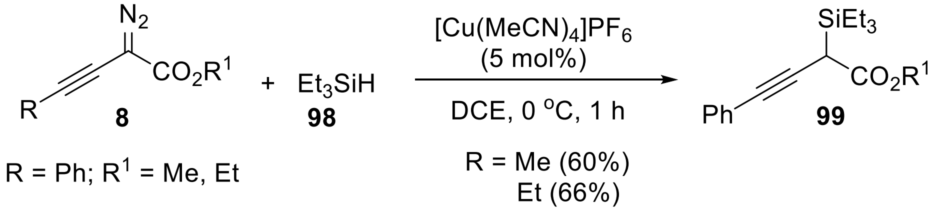


Scheme 32

Tanbouza and coworkers observed that the $Fe(OTf)_2$-catalyzed insertion using a wide range of diazo compounds into Si-H bond of silanes occurred in an emerging green solvent, dimethyl carbonate $(MeO)_2C{=}O$.[54] The α-silylated products were obtained in good to excellent yields. Kinetic studies of the reaction revealed that the extrusion of N_2 leading to the generation of iron-carbenoid was rate-limiting step.

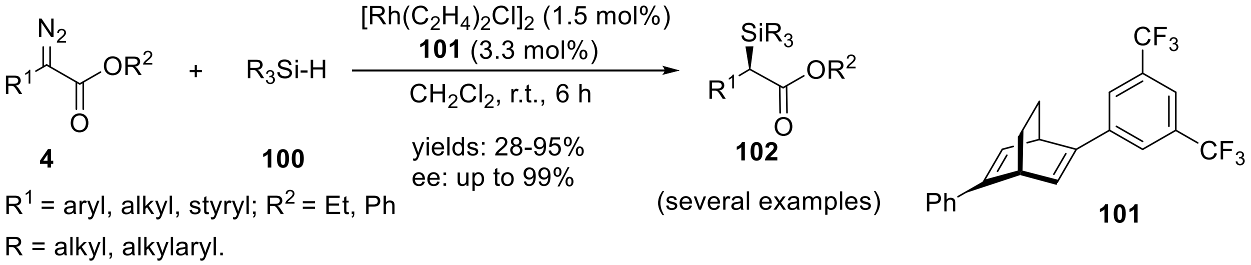
Komarova and coworkers have reported the cyclopentadienyl rhodium(III) complexes $[CpRhI_2]_2$ (Cp = cyclopentadienyl ring bearing five methyl groups) as catalysts for the insertion of rhodium carbenoids from phenyl diazoacetate into Si-H and N-H bonds.[68] Iodide complex was observed more efficient than common chloride complex. However, the C-H bond insertion with substrates 1,4-cyclohexadiene and with cycloheptatriene was not possible even on employing the most efficient catalyst of the series. Also, the catalysts of this class were less effective than Rh(II) carboxylates despite the higher oxidation state of the metal. The authors attributed the low electrophilicity of such carbenoids to electron donation from the anionic cyclopentadienyl and iodide ligands.

Sharma and coworkers have reported their preliminary study on oxidation of alkynyl hydrazones to alkynyl diazoesters and the application of the later compounds in synthesis. Copper-carbenoids, obtained from the $[Cu(MeCN)_4]PF_6$-catalyzed decomposition of alkynyl diazoesters **8**, reacted with triethylsilane **98** furnishing propargyl silanes **99** in 60-66% yields (Scheme 33).[23]



Scheme 33

Chen and coworkers reported the first rhodium(I)-catalyzed enantioselective insertion of carbenoids from α-diazoesters into Si-H bond.[69] This group used a C_1-symmetric chiral bicyclo[2.2.2]octadiene ligand **101** that enabled the reaction to proceed under extremely mild conditions to furnish diverse α-silyl esters **102** with excellent enantioselectivities. A wide range of substrates including both aryl- and alkyldiazoacetates **4** reacted with several trialkyl- and dialkylaryl silanes **100** to afford products **102** in moderate to good yields (Scheme 34).



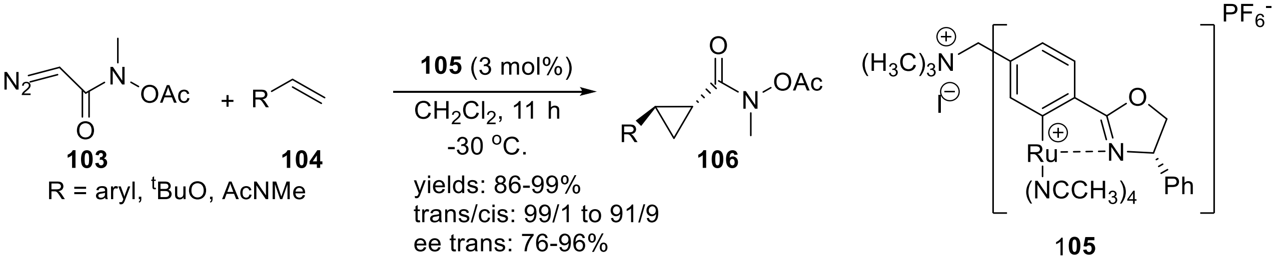
Scheme 34

4. Addition and Cascade Reactions

4.1 Cyclopropanation and other reactions across carbon-carbon multiple bonds

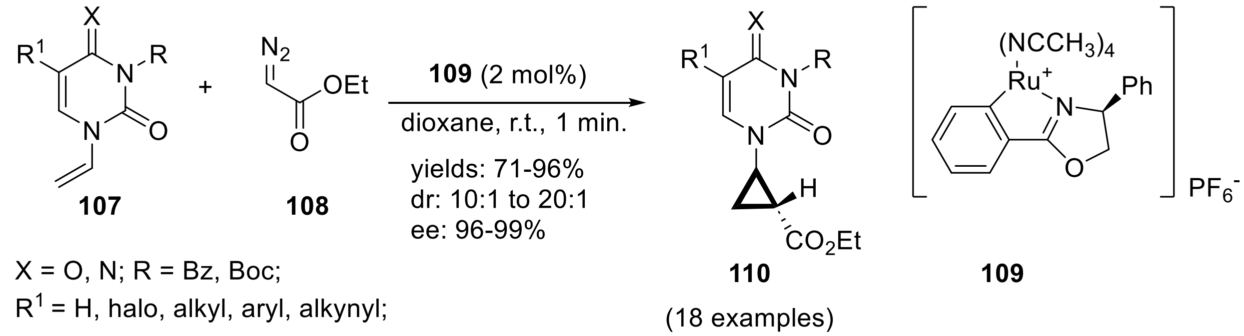
Along with insertion reactions, cycloprppanation is the oldest known classical reaction of carbenes. The cyclopropanation reactions of metal-carbenoids and its mechanistic aspects were discussed in detail in a review article by Gurmessa and Singh.[8] Several transition-metal-catalyzed asymmetric cyclopropanation of olefins with diazocarbonyls furnishing optically active cyclopropane derivatives were described. It is noteworthy that cyclopropane rings are highly strained and easily cleaved and hence serve as key building blocks.[70-72] Even though unstable and highly reactive, cyclopropane rings are prevalent structural unit in natural products and bioactive compounds.[73] Enantioselective cyclopropanation of a wide variety of olefins catalyzed by Ru(II)–Pheox complexes was accounted by Chanthamath and Iwasa in 2016.[74] Roy and coworkers have discussed the role of ligand types used in catalytic metal complexes in selectivity in asymmetric cyclopropanation reactions using diazo compounds.[75] A short review on cyclopropanation of semi-stabilized and non-stabilized diazo compounds was published by Allouche et al.[76]

Chanthamath group reported the first highly stereoselective cyclopropanation of diazo Weinreb amides **103** with olefins **104** using chiral Ru(II)–Amm–Pheox complex **105** to give the corresponding chiral cyclopropyl Weinreb amides **106** in high yields (up to 99%) with excellent diastereoselectivities (up to 99: 1 dr) and enantioselectivities (up to 96% ee) (Scheme 35).[77] The use of acetoxy-functionalized diazoacetamide as a carbene precursor was observed to be crucial for the high *trans*-selectivity of the cyclopropanation reaction. In another paper, this group has reported intramolecular cyclopropanation in *trans*-allylic diazo Weinreb amides using chiral ruthenium(II)-*Amm*-Pheox catalyst to give the corresponding chiral cyclopropyl Weinreb amides in excellent yield (up to 99%) with excellent enantioselectivity (up to 99% ee).[78] Using a catalyst (*p*-nitro-Ru(II)-diphenyl-Pheox) of same class, intermolecular cyclopropanations of diazo acetoxy acetone with various olefins were accomplished.[79] Optically active cyclopropane derivatives were obtained in good yields (up to 95%) with excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 98% ee).



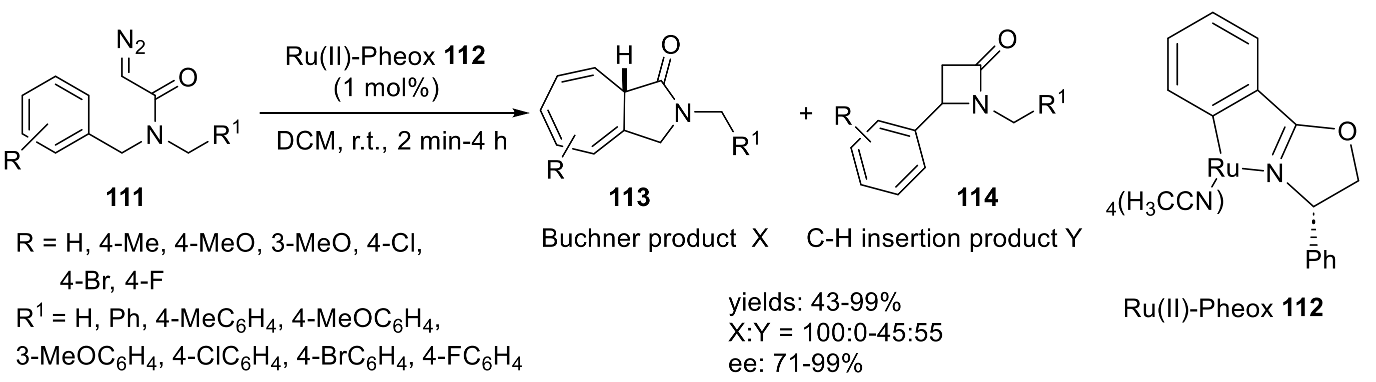
Scheme 35

Xie and coworkers have reported a highly enantioselective intermolecular cyclopropanation reactions of N1-vinylpyrimidines **107** with α-diazoesters (ethyl diazoacetate **108**) in the presence of chiral ruthenium(II)–phenyloxazoline complex **109** as the catalyst.[80] This reaction offered a direct route to nucleoside analogues **110** that were obtained in good yields (71–96% yields) with high levels of diastereo- and enantioselectivities (10:1 to >20:1 dr and 96–99% ee) in just one minute time (Scheme 36). In a most recent development, Davies group synthesized chiral bowl-shaped diruthenium catalyst and explored their utility for enantioselective cyclopropanation reactions with donor/acceptor carbenes generated from aryl diazoacetates.[81] Ru_2(*S*-TPPTTL)$_4$·BAr^F [*S*-TPPTTL = (*S*)-2-(1,3-dioxo-4,5,6,7-tetraphenylisoindolin-2-yl)-3,3-dimethylbutanoate,BAr^F = tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate] was observed as the most efficient catalyst that led to cyclopropanation of a range of substrates in up to 94% ee.



Scheme 36

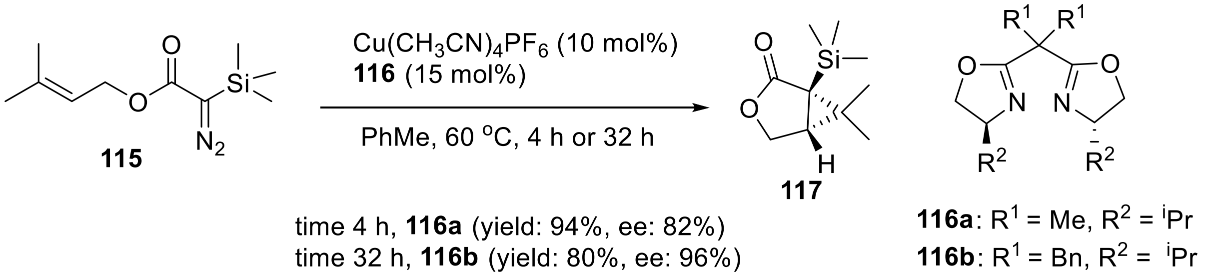
Thanh and coworkers have reported the development of an intramolecular cyclopropanation followed by ring-expansion (Buchner reaction) of a variety of *N*-benzyl diazoamide derivatives **111** in the presence of a chiral Ru(II)–Pheox catalyst **112**.[82] The aromatic rings are transformed into the corresponding γ-lactam-fused cycloheptatriene ring system **113** with high regio- and stereoselectivity (Scheme 37). The C-H insertion products, 2-azetidinones **114** were obtained as side-products in most cases. A substrate bearing a methyl group and a benzyl group on the amide nitrogen yielded insertion product and Buchner product in 55:45 ratio. The corresponding Buchner reaction products were obtained in excellent yields (up to 99%) and enantioselectivity (up to 99% ee) in case of substrates with electron-donating groups. In the case of substrates bearing an electron-withdrawing group, the rate of the Buchner reaction slightly decreased and formation of the C–H insertion product 2-azetidinones was observed. An asymmetric intramolecular Buchner ring expansion of α-alky-α-diazoesters has also been developed using rhodium(II) catalysts.[83]



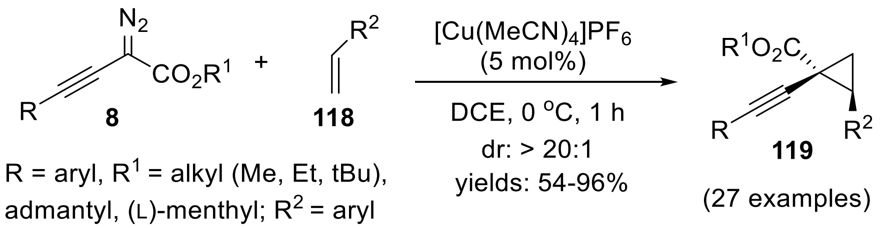
Scheme 37

Besides ruthenium, complexes of iron and copper with spirobisoxazolines have also shown good enantioselectivity in cyclopropanation reactions. Xu and coworkers reported the first intramolecular enantioselective cyclopropanation at C2-C3 double bond of indoles, which was achieved in good to high yields (up to 94%) with excellent enantioselectivity (ee: up to >99.9%) by using copper or iron complexes of chiral spiro bisoxazolines as catalysts.[84] This reaction offered a straightforward, efficient method for constructing polycyclic compounds with an all-carbon quaternary stereogenic center at the 3-position of the indole skeleton. Inoue and coworkers reported the copper(I)-catalyzed asymmetric intramolecular cyclopropanation using bis-oxazoline ligands.[85] The products 3-oxabicyclo[3.1.0]hexan-2-ones were obtained in 48-83% yields and up to 91% ee. In another communication, this group has reported intramolecular cyclopropanation of α-diazo-α-silyl acetate **115** using the same catalytic system **116** yielding cyclopropane-fused γ-lactone **117** (Scheme 38).[86] Cu(I) catalyst was found to play a crucial role in determining the yields and enantioselectivities. Anionic counteranions improved both yields and enantioselectivities.

The latest example of cyclopropanation reported involved the reaction of copper-carbenoid, obtained from the [Cu(MeCN)$_4$]PF$_6$-catalyzed decomposition of alkynyl diazoacetates **8**, with alkenes **118** furnishing alkynyl cyclopropane carboxylic esters **119** in good to excellent yields and with excellent diastereoselectivity (Scheme 39).[23] The steric effect on ester alkyl group led to reduced yield but the diastereselectivity was unaffected. The substrates alkenes and styrenes with wide variety of substituents reacted excellently. The authors attributed the observed high diastereoselectivity to the presence of the ester acceptor and alkynyl donor. The donor group could stabilize the electrophilic copper-carbenoid that attenuated the reactivity and enhanced the diastereoselectivity.

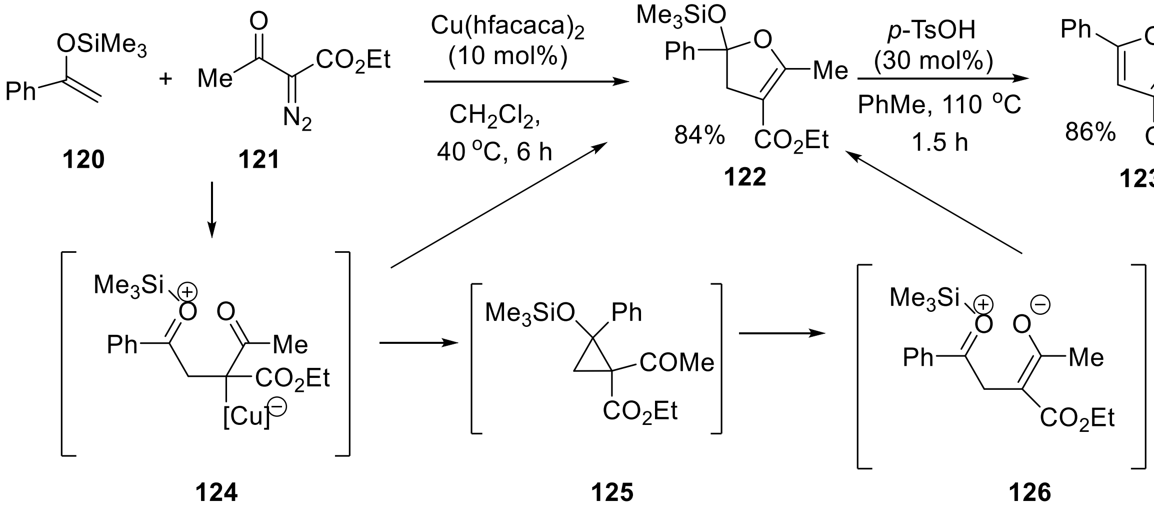


Scheme 38



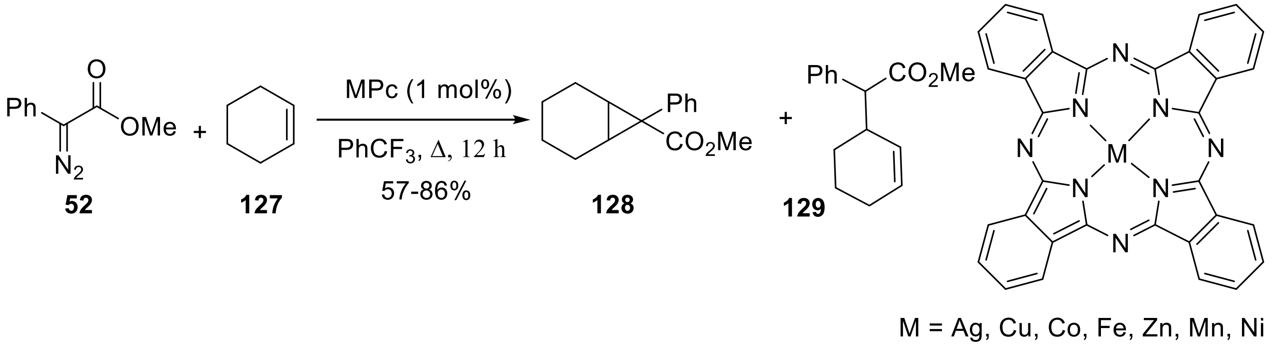
Scheme 39

Tan and Yoshikai employed Cu(hfacac)$_2$ over 4Å molecular sieves in dichloromethane at 40 °C for the coupling of 2-silyloxyalkenes **120** and α-diazo-β-ketoesters **121** or α-diazoketones to afford 2-siloxy-2,3-dihydrofuran derivatives **122** or 2,3,5-trisubstituted furans, respectively.[87] The former cyclization products serve as versatile 1,4-diketone surrogates, allowing facile preparation of 2,3,5-trisubstituted furans **123**, pyrroles, and thiophenes. A representative example of furan synthesis is shown here (Scheme 40). The reaction is proposed to occur via intermediate **124**, formed from nucleophilic attack of silyl enol ether on electrophilic copper-carbenoid. This intermediate may lead to the final product either directly or via cyclopropane **125** and intermediate **126**.



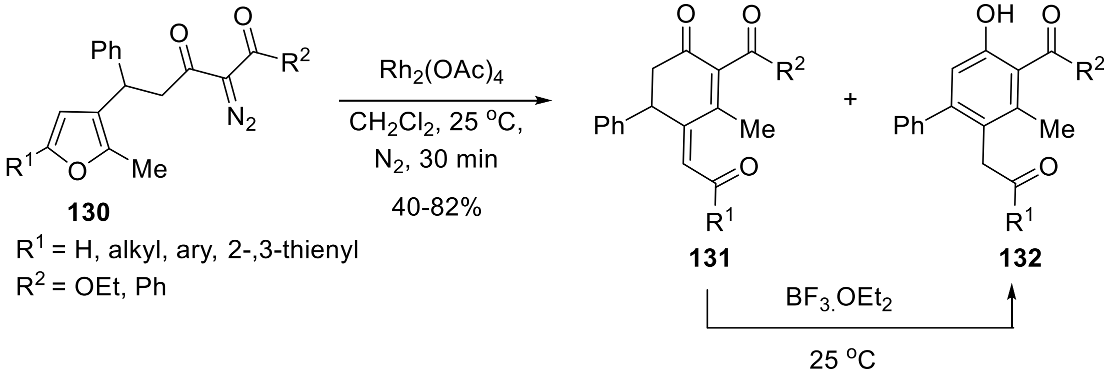
Scheme 40

Ventura and Lincourt reported on the use of metallophthalocyanines (MPc's) with different transition metal cores to investigate the ratio of intermolecular cyclopropanation and C-H insertion products upon reaction of cyclohexene **127** and the donor-acceptor methyl 2-diazo-2-phenyl acetate, **52** (Scheme 41).[88] The reactions displayed similar chemoselectivity furnishing cyclopropanation and allylic C-H insertion products **128**, and **129**, respectively, at a nearly 1:1 ratio except in case of CuPc where cyclopropanation was favored (6.4:1).



Scheme 41

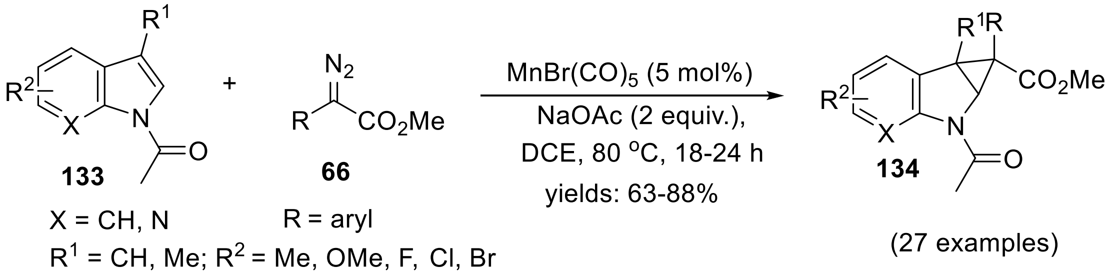
Rhodium carboxylates and complexes are among the oldest known catalysts for cyclopropanation of metal-carbenoids. Davies group developed a tandem reaction for the preparation of donor/acceptor-substituted α-diazocarbonyls in continuous flow coupled with dirhodium-catalyzed cyclopropanation of styrenes.[89] Hydrazones were oxidized in flow by solid-supported *N*-iodo-*p*-toluenesulfonamide potassium salt (PS-SO_2NIK) to furnish the α-diazocarbonyls, which were then purified by passing through a column of molecular sieves/sodium thiosulfate. A rhodium(II)-mediated cascade cyclopropanation/ rearrangement/isomerization of diazo 2,3,5-trisubstituted furans **130** yielding penta-substituted aromatic compounds is reported.[90] The reactions occurring under mild conditions show excellent chemoselectivity. No C(sp^2)-H insertion products were detected. In most cases, the reaction yielded either nonisomerization products **131** or pentasubstituted aromatic compounds **132** (Scheme 42). The former products could be isomerized using Lewis acid. The cyclopropanation of furan C=C bond by Rh-carbenoid followed by rearrangement and isomerization led to the formation of final product.



Scheme 42

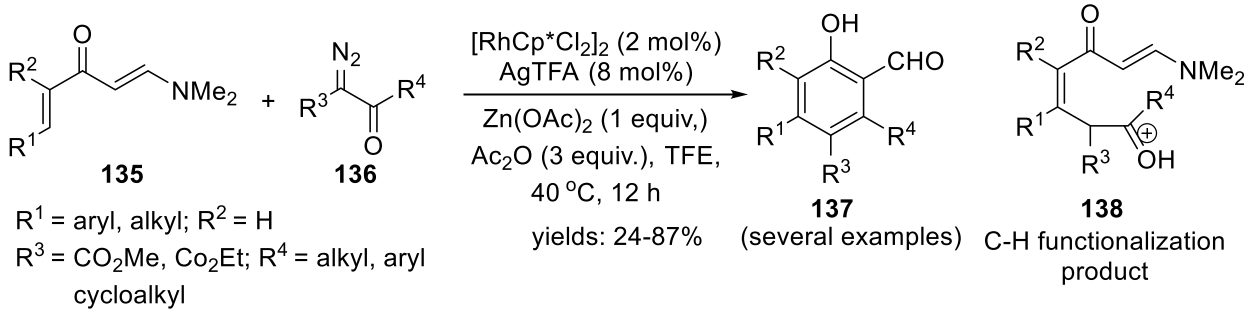
Dutta and coworkers have reported the first manganese catalyzed cyclopropanation of *N*-acylindoles **133** with several methyl 2-diazo-2-arylaceates **66** (Scheme 43).[91] Acetyl group has directing influence in this strategy.

In the absence of stereodirecting group the desired products **134** were obtained as a mixture of diastereomers (7:3 to 8:2). The reaction of unprotected indole yielded the desired product in trace amount. Also, N-benzoyl- and N-^{t}Boc-protected indoles were not found appropriate in this strategy.



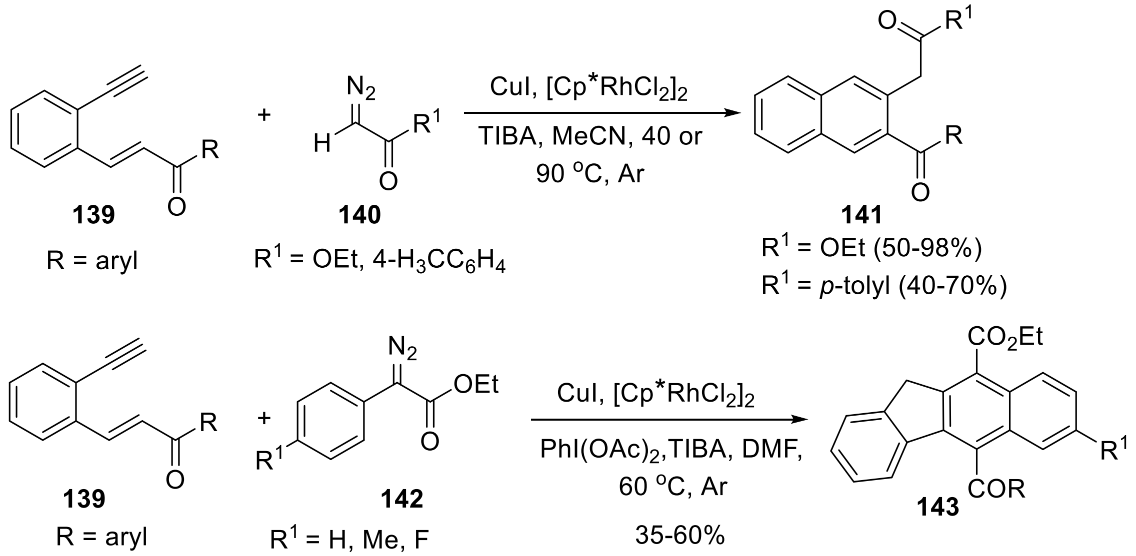
Scheme 43

Zhou and coworkers considered the development of the novel and practical [4 + 2] annulation via selective C−H bond functionalization of alkene as the key step for a possible strategy for the regiospecific synthesis of polyfunctionalized benzene rings in a one-step manner.[92] To explore this strategy, this group investigated the possibility of site-selective carbon insertion into the β-C-H bond of dialkenyl ketones with diazo compounds assisted by weak coordination of ketone to control the substitution patterns though it was challenging due to the different Csp2−H bonds and possible competition with the cyclopropanation of alkenes. The study resulted into development of a novel method for direct access to highly functionalized benzene rings **137** by regioselective formal [4 + 2] cycloaddition of enaminones **135** with diazocarbonyls **136** via C-H functionalization product **138** in the presence of a Rh(III) catalyst (Scheme 44). Deuterium labeling experiments supported the involvement of weakly directed site-selective alkenyl C−H bond functionalization as the key step. A broad range of substrates were tolerated under mild conditions, affording the desired products in good to excellent yields.

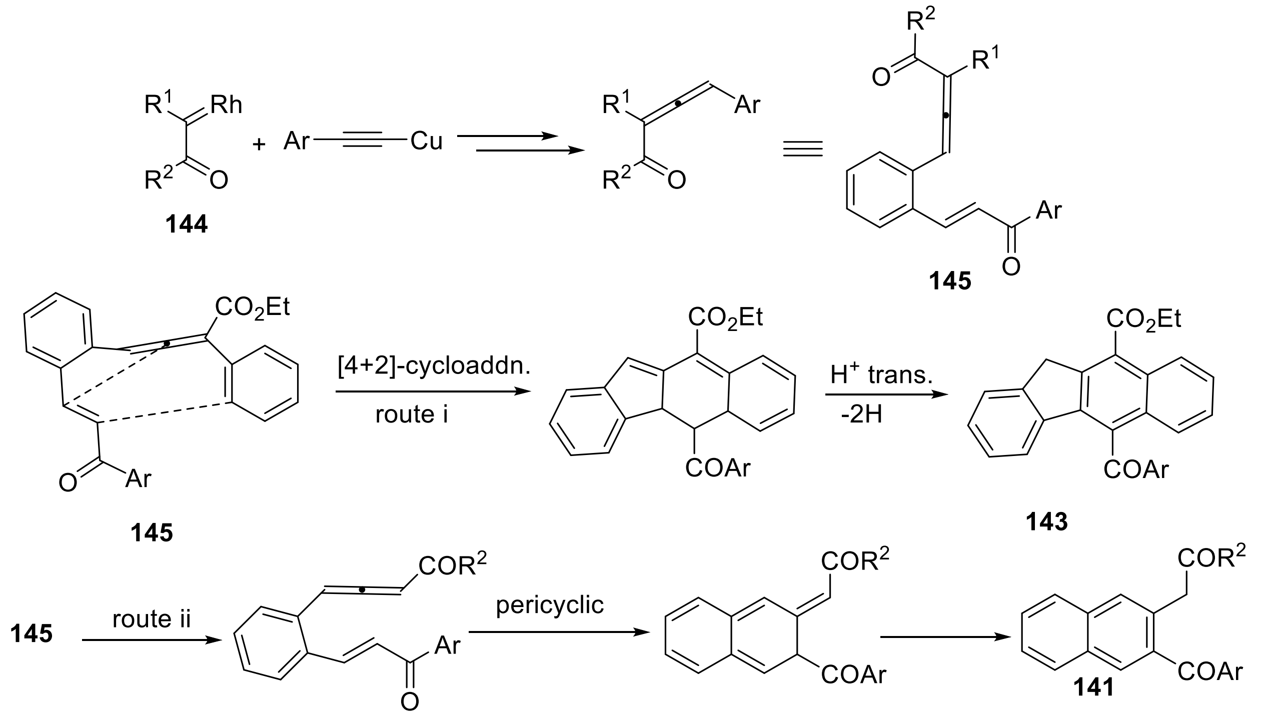


Scheme 44

Wu and coworkers have reported the cycloaddition reactions of α-daizocarbonyls with 1,5-enynes **139** in the presence of dual metal catalysts, rhodium, and copper.[93] The reaction was guided by the substituents on the α-diazocarbonyls. Ethyl diazoacetate and 2-diazo-1-(*p*-tolyl)ethan-1-one **140** yielded 2-naphthalenylmethanones **141** while ethyl diazoacetates **142**, bearing aryl groups on C-2, afforded a series of substituted benzo[*b*]fluorenes **143** (Scheme 45). Furthermore, the ethyl diazoacetate offered very good to excellent yields. The formation of products has been explained via an allene intermediate **145**, obtained from the reaction of rhodium-carbenoids **144** with enynes involving – ligand-exchange of Rh-carbenoids, migration insertion, enolization and H-abstraction. An intramolecular [4+2]-cycloaddition (route A) in allene followed by dehydrogenation affords the benzo[*b*]fluorenes **143** while a pericyclic reaction of allene furnishes naphthalene derivatives **141** (Scheme 46).



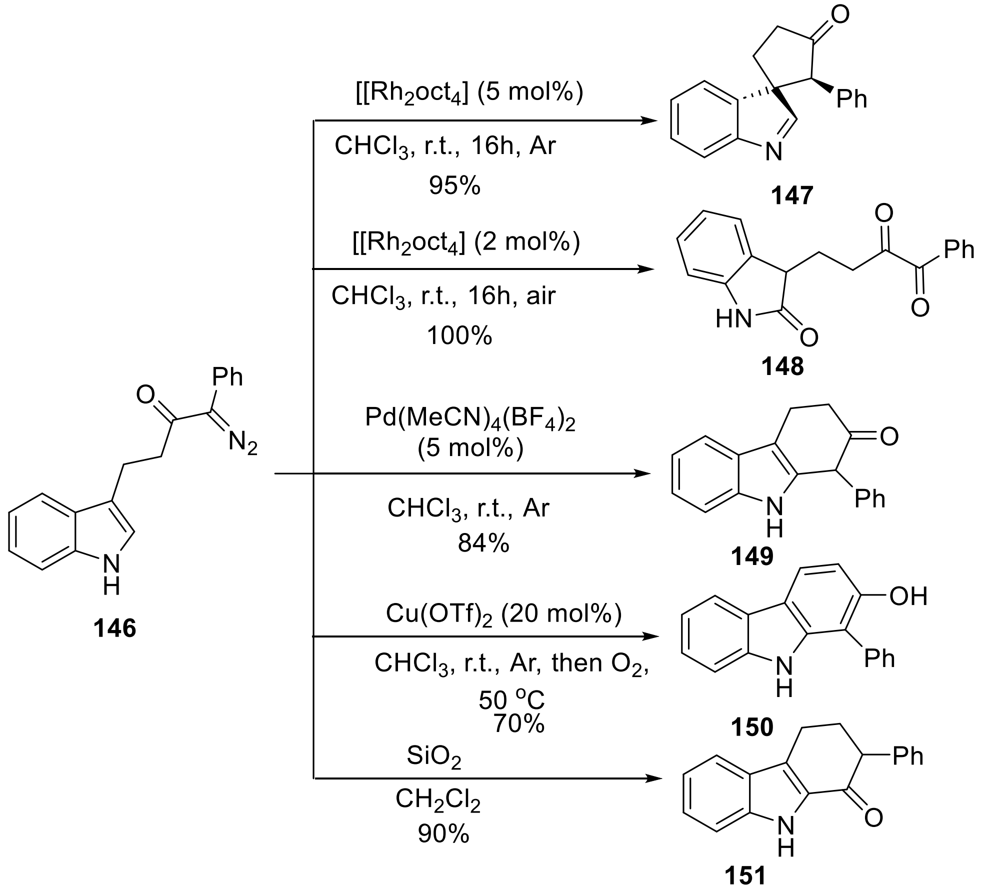
Scheme 45



Scheme 46

It is well known that the reactions of carbenoids depend on electronic factors as seen in the preceding example. However, they are also very sensitive to catalysts and reaction conditions. James and coworkers have reported synthesis of five different scaffolds **147**-**151** from a single indolyl α-diazocarbonyl precursor **146** using different catalysts and reaction conditions (Scheme 47).[94]_A range of catalysts including complexes of Rh(II), Pd(II), and Cu(II), as well as SiO_2, were used under argon or air to promote diazo decomposition and subsequent cyclization/ rearrangement of the diazocarbonyl precursor through different mechanistic pathways resulting into C-3 functionalization and C-2 annulation of indole ring. The product **148** could be further transformed to isomeric spirooxindoles by simple acidic and basic treatment.

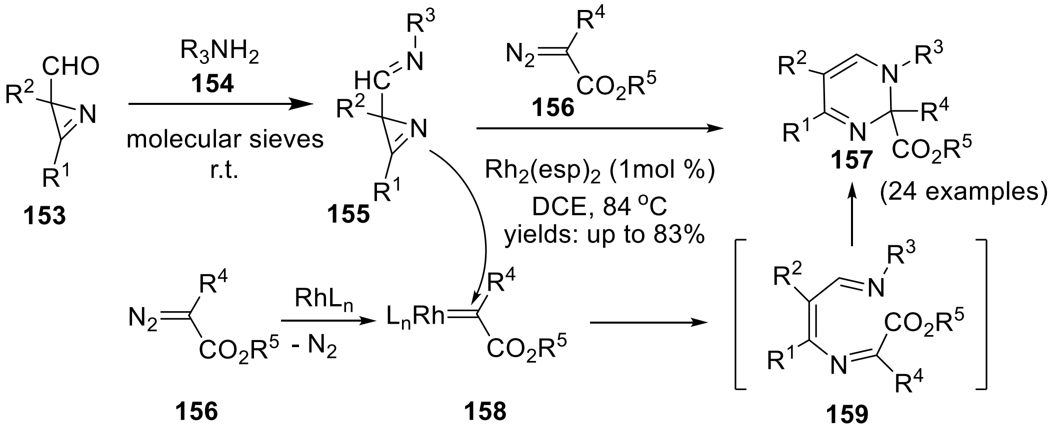
More recently, a catalyst dependent visible light-induced reaction of α-diazocarbonyls with different types of alkenes is reported.[95] The reaction in the presence of an Ir(III) catalyst yielded cyclopropanation products (up to 99% yield). A simple addition of $Rh_2(OAc)_4$ co-catalyst in the Ir(III)-catalyzed process yielded cyclobutanes by [2+2]-cycloaddition. However, both these processes have been explained through energy transfer in the presence of metal catalysts and not via metal-carbenoids.



Scheme 47

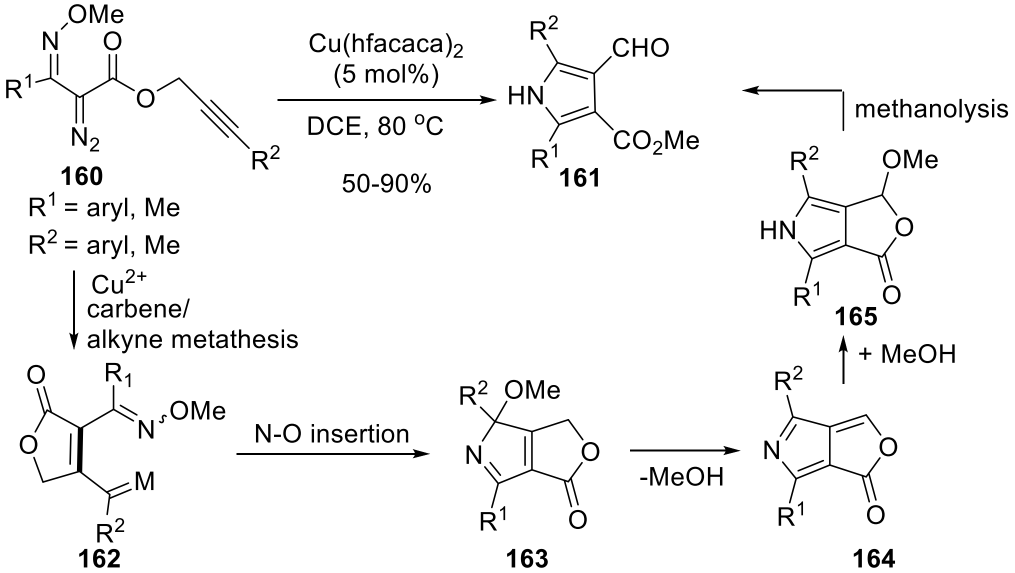
4.2 Addition reactions across carbon – heteroatom double bonds

Addition reactions of metal-carbenoids across carbon-heteroatom bonds occur via ylides. A regioselective addition of rhodium(II)-carbenoids **158** to 2*H*-azirine-2-carbaldimines **155** is reported leading to the synthesis of 1,2-dihydropyrimidine-2-carboxylates **157** (Scheme 48).[96] Azirine-2-carbaldimines **155**, formed in the first step from the condensation of azirine-2-carbaldehyde **153** with primary amines **154**, react with rhodium carbenoids **158**, generated from the diazocarbonyls **156** under $Rh_2(esp)_2$ catalysis. The reaction proceeds via 100% regioselective addition of the rhodium carbenoid to endocyclic nitrogen atom of the 2*H*-azirine-2-carbaldimine **155**. According to the DFT calculations the reaction proceeds via dissociation of the metal-bound complex of the azirinium ylide to metal-free azirinium ylide, ring-opening of the latter to give a 1,5-diazahexa-1,3,5-triene **159**, followed by 1,6-cyclization.



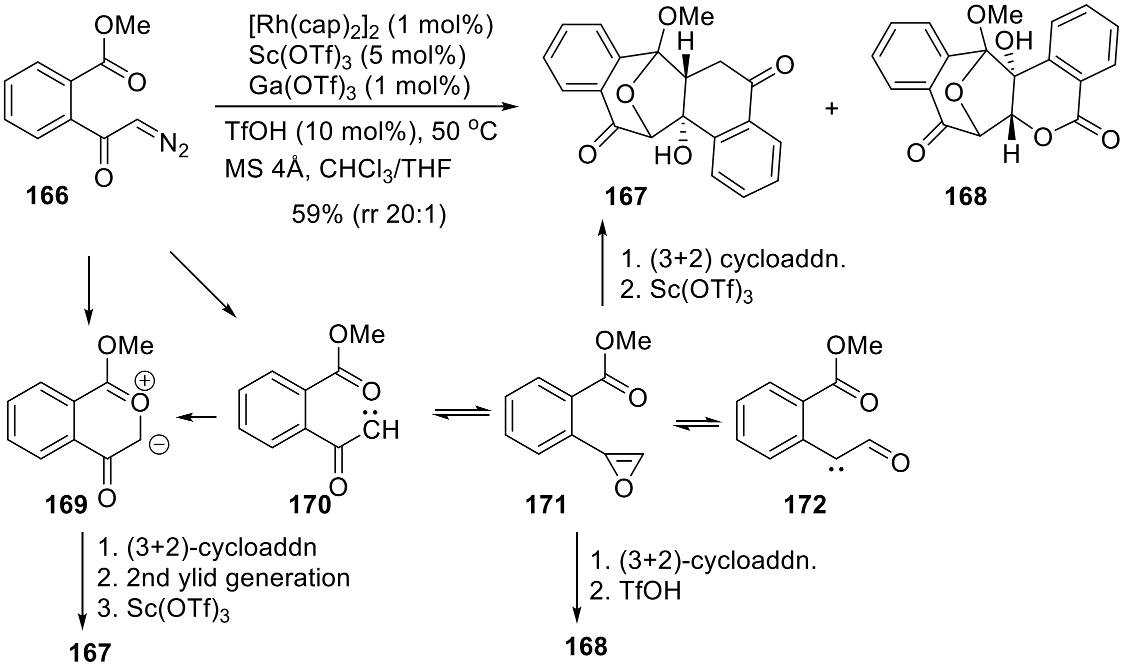
Scheme 48

Zhang and coworkers reported the synthesis of multi-substituted/fused pyrroles via copper-catalyzed carbene cascade reaction of propargyl α-iminodiazoacetates **160**.[97] The products **161** were obtained in high yields with broad substrate scope. Among the products were tetrasubstituted N–H 3-formylpyrroles (Scheme 49) as well, known to be synthesized with difficulty by alternate approaches. Mechanistic studies indicated that these transformations were initiated by a Cu-catalyzed carbene/alkyne metathesis furnishing **162** and followed by two disparate cascade transformations via products **163**-**165**.



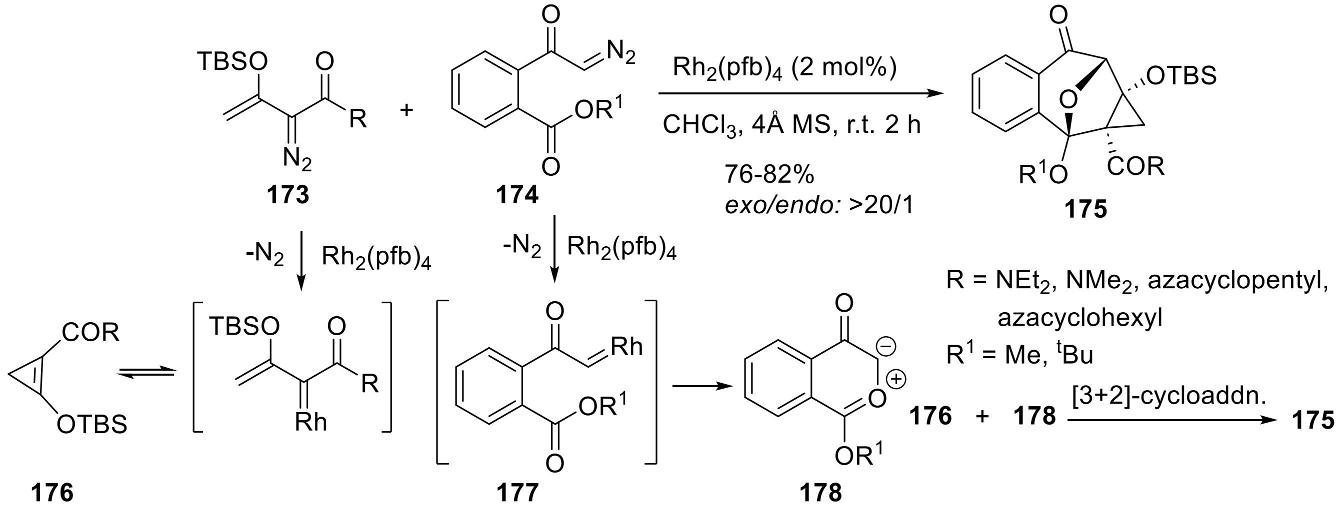
Scheme 49

Petzold and coworkers have employed cooperative Rh(II), Lewis and Brønsted acid catalysis in the decomposition of readily available *O*-diazoacyl-substituted arene carboxylate **166** to obtain scaffolds **167** and **168** with the 5,9-epoxycyclohepta[b]pyran-2(3*H*)-one core (Scheme 50).[10] This regio- and diastereoselective protocol led to the formation of four new bonds, three functional groups (lactone, ketal, and alcohol) and four contiguous stereocenters in a single synthetic step. The reaction is proposed to proceed via carbonyl ylide **169** and transient species **171**-**172** of the ketocarbene **170** equilibrium that undergo a cascade of cycloaddition and skeletal rearrangements giving the desired products.



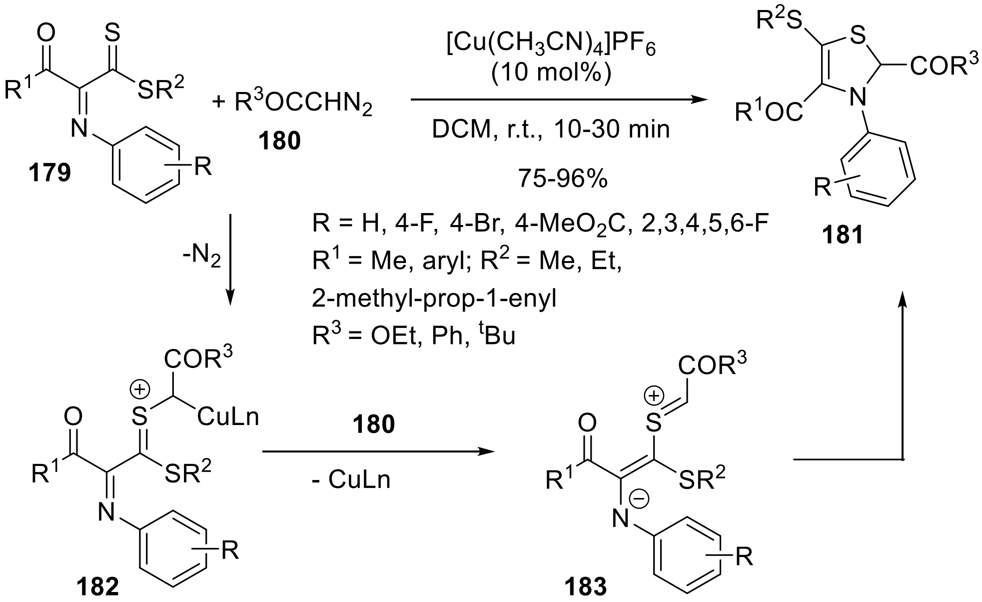
Scheme 50

Cheng and coworkers have reported a wonderful example of dirhodium(II)-catalyzed reaction between two diazocarbonyl compounds, an enoldiazoacetamide and a 2-diazoketone, resulting into annulation of enoldiazoacetamides **173** with 2-diazoketones **174**.[98] This annulation reaction allows the efficient construction of donor–acceptor cyclopropane-fused benzoxa-[3.2.1]octane **175** scaffold with excellent chemo-, regio-, and diastereoselectivity under mild conditions. The study of substrate scope of this reaction revealed that enoldiazoacetamides **173** bearing dialkylamino, and cyclic amino moieties were all ideal reagents for this reaction. For 2-diazoketones **174**, changing the ester group or introducing substituents onto the phenyl ring didn't affect the efficiency of this process. Mechanistically, enoldiazoacetamides **173** generate donor-acceptor cyclopropenes **176** in the presence of Rh_2(pfb) that undergo [3+2]-cycloaddition with carbonyl ylides **178**, generated from intramolecular reaction of rhodium-carbenoid **177** with carbonyl group in α-diazoketones **174** (Scheme 51). The use of $Rh_2(pfb)_4$ and enoldiazoacetamides was crucial for achieving compatible reactivity and controllable selectivity in this reaction.



Scheme 51

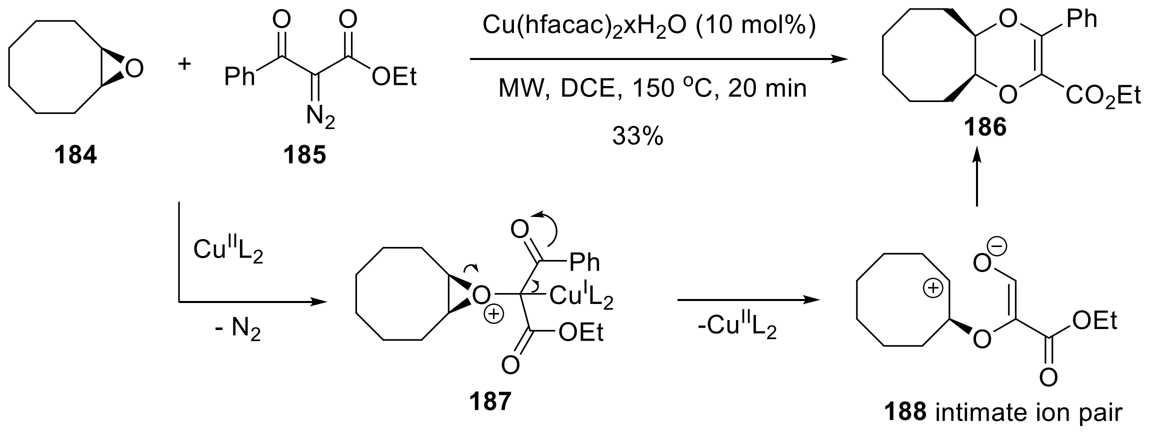
The copper-catalyzed reaction of α-diazocarbonyl compounds **180** with α-(*N*-aryl)imino-β-oxodithioesters **179** results into [4+1]-heterocyclization furnishing 2,3-dihydrothiazoles **181** in good yields (Scheme 52).[99] When nitrogen atom was bearing a hydroxyl group instead of an aryl group, the reaction afforded functionalized thiazoles. A wide variety of substituents are tolerated in the reaction. Mechanistically, the copper-carbenoid reacts with C=S bond in preference to C=O and C=N bonds generating the thiocarbonyl ylide **182**. After losing the catalyst, the ylide is converted into a zwitterion **183** that cyclizes to give the 2,3-dihydrothiazole products. In the case of N-OH substrates, dehydration led to aromatization forming thiazoles.



Scheme 52

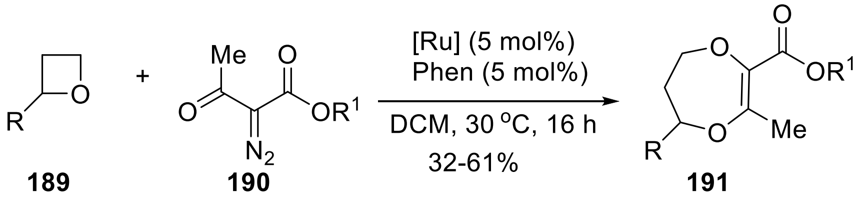
5. Reactions via Ylides from C-N, C-O, and C-S Bonds

The reactions of metal-carbenoids with heteroatoms generating yildes and subsequent transformations have wide applications in organic synthesis.[2] Recently, some interesting applications of this protocol have been reported by metal-catalyzed reactions of α-diazocarbonyls with small-ring heterocyclic motifs such as oxiranes, azetidines, and thiiranes. A microwave-assisted ring expansion reaction of oxirane **184** with α–diazo-β–ketoester **185** using copper hexafluoroacetylacetonate as a catalyst giving rise to 2-acyl-5,6-dihydro-1,4-dioxines **186** has been developed (Scheme 53).[100] 1,2-Disubstituted *cis*-oxiranes afforded *cis*-3-acyl-5,6-dihydro-1,4-dioxines as stereospecific products. The yields of the products in all cases were below 50%. The stereochemical outcome in case of oxiranes was explained by formation of the final product via an intimate ion-pair **188**, generated after the elimination of copper-complex from the ylide **187**. Similar reactions of aziridines with these α-diazocarbonyl compounds to synthesize 3-acyl-5,6-dihydro-1,4-oxazines were investigated in different solvents under catalysis of different transition metal catalysts used in the reactions of oxiranes and thiiranes, but the reactions did not yield the desired products.



Scheme 53

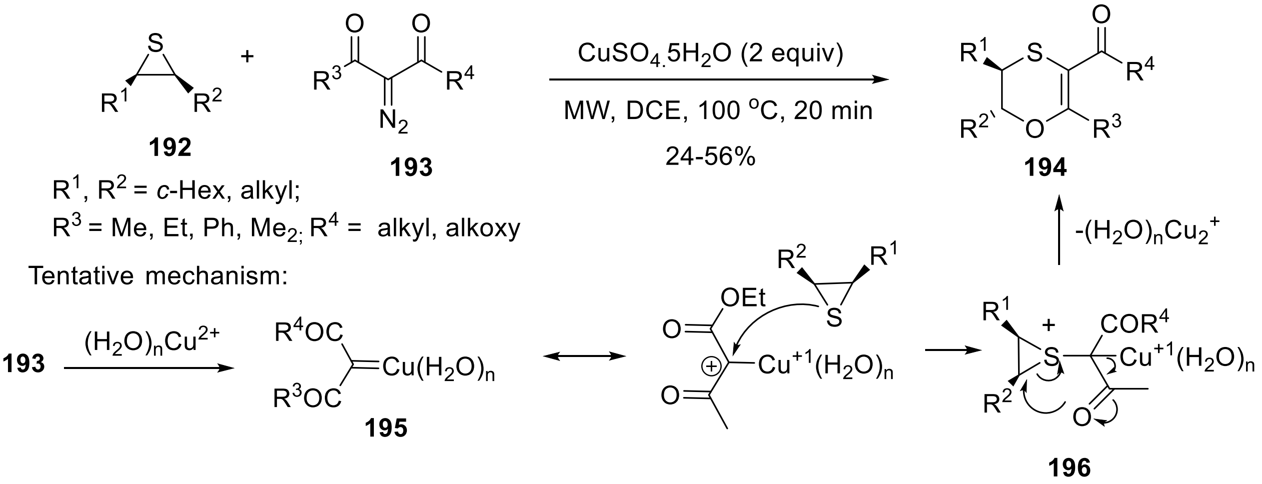
Egger and coworkers have reported the reaction α-diazo-β-ketoesters **190** with α-aryloxitanes **189** in the presence of $[CpRu(CH_3CN)_3][BArF]$ and 1,10-phenanthroline.[101] The products dioxepines **191** are obtained in moderated yields (Scheme 54) but with a good enantiospecificity by regioselective [4+3]-insertion that follows S_N1-like transformation, as determined by vibrational circular dichroism and X-ray diffraction analyses. The preferential formation of dioxepines 4 vs. furan 5 was explained by applying the Baldwin's rules for the ring closure. Furans, products of [4+1] insertions, were only observed as traces in this protocol.



R = naphthyl, 4-MeC_6H_4, 4-ClC_6H_4, 4-FC_6H_4,
2,4,6-$Me_3C_6H_2$
R^1 = Et, CH_2CH_2OMe, CH_2CCl_3, ^tBu

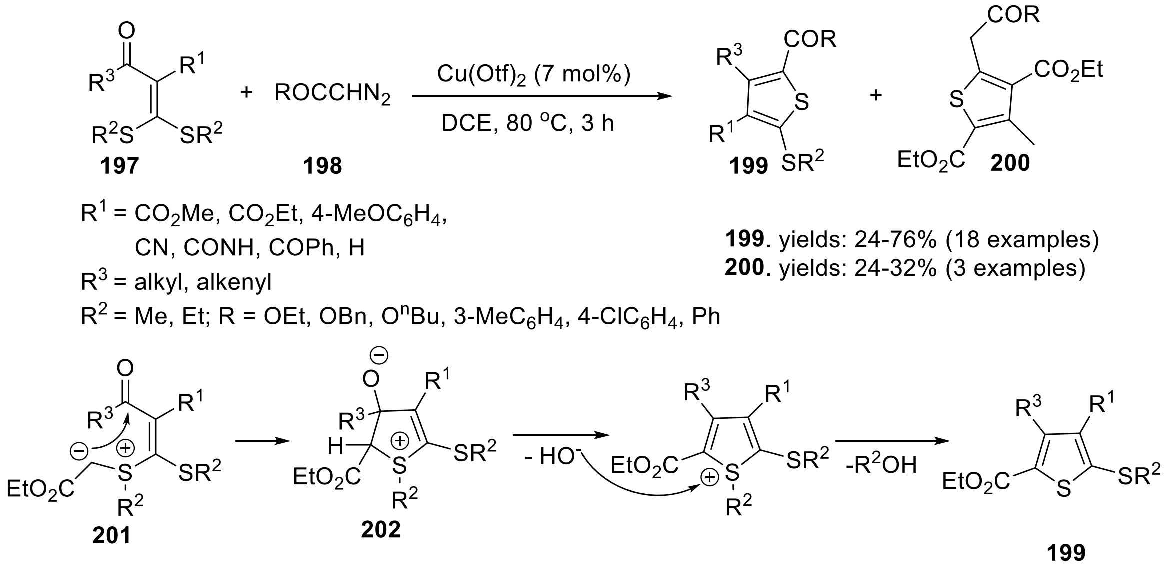
Scheme 54

A simple method for the synthesis of 3-acyl-5,6-dihydro-1,4-oxathiienes **194** has been developed by employing the chemistry of α-dizaocarbonyl compounds in microwave.[102] The reaction between α–diazo-β–1,3-dicarbonyl compounds **193** and thiiranes **192** under microwave and copper sulfate assistance, yields 3-acyl-5,6-dihydro-1,4-oxathiines. The *cis*-1,2-disubstituted thiiranes yielded *trans*-3-acyl-5,6-dihydro-1,4-oxathiines (opposite stereochemistry to that of oxiranes) in moderate yields (Scheme 55). The study on scope of the method indicated that the yields with monosubstituted thiiranes were generally lower than those with disubstituted thiiranes, and the longer the alkyl chain, the lower was the yield. The reaction is also sensitive to steric factors. The proposed mechanism in this case involves nucleophilic reaction of thiirane **192** with copper-carbenoid **195**, formed from the reaction of copper salt with keto-carbene generated *in situ* by decomposition of diazocarbonyl compound **193**. This reaction generates a metal-sulfonium ylide **196** that isomerizes to an enolate with elimination of copper moiety. The enolate attacks the thiiranium ring from back side to yield the 1,4-oxathiienes.



Scheme 55

Sun and coworkers have reported a novel copper(II)-catalyzed domino reaction between the alkyl diazoacetates **198** and acyclic ketene-(S,S)-acetals **197**.[103] This reaction offered a simple and convenient approach to a range of poly-substituted thiophenes **199** and **200**. A diverse range of acyclic ketene-(S,S)-acetals are tolerated in the protocol (Scheme 56). The reaction proceeds via a copper-catalyzed tandem process involving the generation of sulfur ylides **201** followed by the nucleophilic attack of carbanion in the ylide on the carbonyl carbon forming a five-membered ring **202** and leading to a cleavage sequence furnishing product **199**. The product **200** was obtained together with **199** when R^1 was CO_2Me, CO_2Et, and 4-$MeOC_6H_4$ by the reaction of second mol of the metal-carbenoid at SR^2 of product **199**. Regarding the scope of α-diazocarbonyls, if H was replaced with Ph, COPh, Ac, CO_2Et, the reaction did not proceed probably due to steric factors.



Scheme 56

6. Concluding Remarks

The insertion and addition reactions of metal-carbenoids, generated from α-diazocarbonyl compounds, constitute easy and straight forward methods for construction of carbon-carbon, and carbon-heteroatom bonds. The last decade has witnessed enormous growth in application of these reactions in the construction of complex molecular structures. The present review paper reveals the design and development of several novel α-diazocarbonyl compounds, and their applications in organic synthesis. Among C-H insertion reactions, several novel intramolecular S(sp3)-H insertion and C(sp2)-H insertion reactions are notable developments. The C-H activation and annulation has furnished some biologically relevant scaffolds. The catalytic system has been diversified too. Besides copper and rhodium, iron, silver, cobalt, gold, and scandium have been employed for the purpose. Among heteroatom-H insertion, insertion into N-H and O-H bonds of ammonia and water, respectively, are significant developments as well. Interestingly, most of these protocols report insertion reactions in a highly chemoselective manner. In a few reactions, cooperative catalysis has also been employed. A three-component reaction of vinyl diazoacetate, alcohols, and amines has been reported resulting into a 1,3-difunctionalization of the vinyl carbene in highly regio, diastereo- and enantioselective manner. Although copper, and rhodium complexes have been employed for cyclopropanation ruthenium complexes appear the catalysts of choice for the purpose. The dependence of reactions on steric and electronic factors on substrates, catalytic systems, and conditions, have been excellently demonstrated by preparation of five different scaffolds from a single indole-tethered diazocarbonyl compound. A novel reaction between two diazocarbonyl compounds, both reacting selectively in different manner – one generating a cyclopropene and other generating carbonyl ylide, and then [3+2]-cycloaddition between the cyclopropene and carbonyl ylide, has been reported. The reactions of metal-carbenoids with compounds containing carbon-heteroatom double bonds have been published furnishing 1,2-dihydropyrimidine-2-carboxylates, multifunctional pyrroles, 5,9-epoxycyclohepta[b]pyran-2(3*H*)-ones, and 2,3-dihydrothiazoles, etc. The ylides, generated from the reaction of metal-carbenoids with oxygen atom of oxiranes and oxetanes, and with sulfur atom of thiirane have resulted into cleavage and annulation forming 1,4-dioxines, dioxepines, and 1,4-oxathiienes, respectively. Thus, there has been highly encouraging progress in this area of organic chemistry during last couple of years and many more interesting developments are anticipated.

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