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Recent studies on the reactions of α-diazocarbonyl compounds

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1. Introduction

The chemistry of diazo compounds has a long history. It has attracted attention because of their various useful applications in organic synthesis. In particular, they have been used extensively as precursors of metal carbenes. Usually, α-diazocarbonyl compounds

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are easy to prepare and can be handled without difficulty in the laboratory. On the other hand, α-diazocarbonyl compounds have a diverse reactivity. Particularly, they can be decomposed by transition metal complexes to generate Fischer-type metal carbene intermediates, which can subsequently undergo diverse transformations, including X–H (X=C, O, S, N, etc.) insertion, cyclopropanation, ylide formation, and 1,2-migration. Recently, olefination and polymerization of α-diazocarbonyl compounds have also been reported, demonstrating new possible applications. In addition to these transition metal-catalyzed transformations, α-diazocarbonyl compounds undergo various reactions under thermolytic and photolytic conditions. They can be used as nucleophiles in nucleophilic addition reactions. The rich chemistry of diazo compounds has been investigated and explored extensively over the past decades. Those studies have been summarized in several excellent and comprehensive reviews.[1] This report will focus on the most recent advances in this area, which primarily covers the literature published since 2003. Because of their close relation with α-diazocarbonyl compounds, some reactions with alkyl or aryl diazo compounds are also covered in this report.

2. New developments in the preparation and in situ generation of diazo compounds

Since the first synthesis of ethyl diazoacetate in 1883 from glycine through diazotization, various methodologies have been developed and there are now several well-established procedures for preparing different types of diazocarbonyl compounds. Some recent advances are reviewed in this report.

Acylation of diazomethane by reaction of diazomethane with acyl halides or anhydrides and diazo transfer of an azide reagent to the carbon adjacent to a carbonyl group are two basic methods to synthesize diazocarbonyl compounds. Despite the hazardous nature of diazomethane, the former remains the single most important route to acyclic terminal α-diazoketones. Efforts have been made to activate the acids under milder reaction conditions.[2] Addition of NBS to triphenylphosphine and carboxylic acids can generate an acylphosphonium salt, which reacts with diazomethane to afford α-diazoketones (Scheme 1).[3] The reaction conditions are mild and various functional groups are tolerated.

Scheme 1.
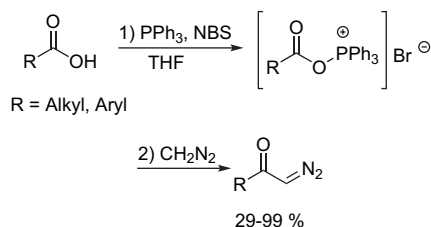
New diazo group transfer reagents and procedures have been developed recently. Charette and co-workers used the highly electron-deficient trifluoromethanesulfonyl azide **1** in the preparation of α-nitro-α-diazocarbonyl compounds, α-cyano-α-diazocarbonyl compounds, and α-sulfonyl-α-diazocarbonyl compounds.[4] Since diazo compounds are relatively unstable, it is desirable to improve the work-up procedure after diazo transfer. For this purpose, a polymer-bound sulfonyl azide has been employed as diazo transfer reagent. Flynn and Hanson have reported the development of a high-load, soluble oligomeric benzenesulfonyl azide **2**.[5] The diazo transfer is efficient and the insoluble sulfonamide byproduct can be completely removed by a single filtration through a silica gel SPE cartridge. This method is particularly valuable when highly unstable α-diazocarbonyl compounds have to be prepared.
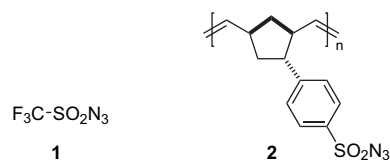
Bräse and Schroen designed and synthesized various polymer-bound diazonium salts. These diazonium salts were used for directly converting α-amino esters into α-diazoacetic esters (Scheme 2).[6]

Scheme 2.
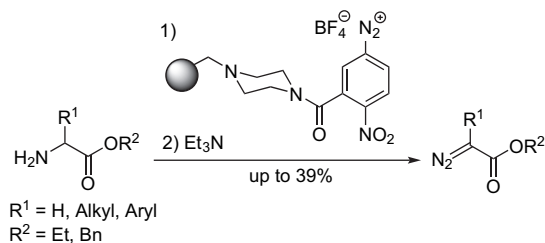
Direct diazo transfer to the methylene group that is only activated by a single carbonyl group usually requires strong base such as LDA to deprotonate. An indirect method is to convert the ester or ketone into the corresponding α-formylated carbonyl compounds, followed by a deformylating diazo transfer. α-Benzoylation and α-trifluoroacetylation are also utilized in this transformation. Recently, Taber and co-workers have modified their α-benzoylation-based diazo transfer process by using a TiCl$_4$-mediated benzoylation of an ester. The diazo transfer can be carried out to the crude benzoylated ester (Scheme 3).[7]

Scheme 3.
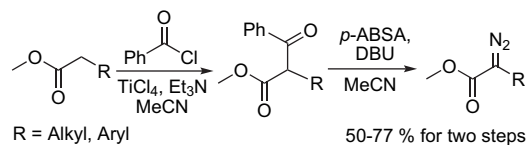
When the diazo group is not stabilized by an adjacent carbonyl group, the corresponding diazo compounds are usually not stable. In such cases, an in situ diazo generation strategy has to be applied. Based on the Bamford–Stevens tosylhydrazone decomposition, tosylhydrazone salts have been successfully used for the generation of diazo compounds under mild conditions. The diazo compounds thus generated in situ can be coupled with various reactions, including transition metal-catalyzed reactions (Scheme 4).[8]
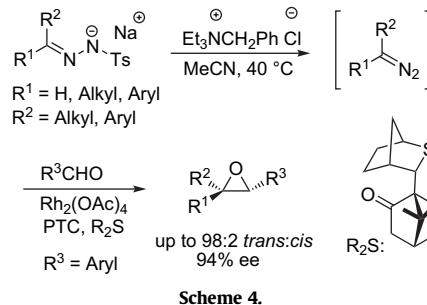
Scheme 4.

Diazo compounds can also be generated in situ from precursors other than tosylhydrazone salts. Stoltz and May reported a highly stereoselective tandem rhodium-catalyzed Bamford–Stevens/Claisen reaction of *N*-aziridinylimines (Scheme 5).[9] The diazo

compound generated in situ by thermal reaction of N-aziridinylimines was catalyzed by Rh2(OAc)4 to generate Rh(II) carbene intermediates, which were followed by a 1,2-hydrogen shift to afford Z-enol ethers. Further thermal Claisen rearrangement occurred from allylic enol ethers.
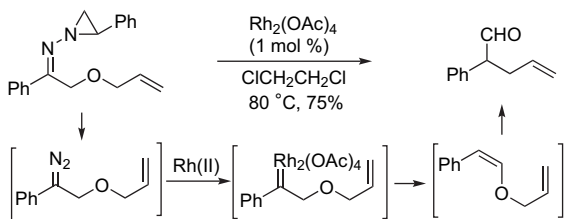
Scheme 5.

Myers and Furrow developed a general procedure for the esterification of carboxylic acids with diazoalkanes. The diazoalkanes were generated in situ by the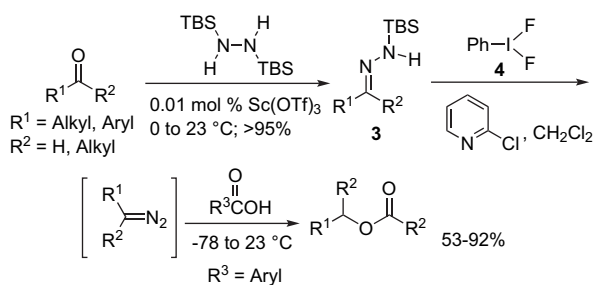 oxidation of N-tert-butyldimethylsilylhydrazones **3**, which were easily generated from aldehydes, by reaction with (difluoroiodo)benzene **4** (Scheme 6).[10] The procedure can be applied to a wide range of diazo precursors and carboxylic substrates.
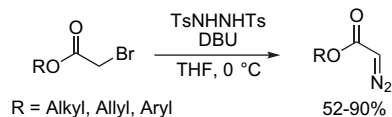

Scheme 6.

Cuevas-Yañez and co-workers have reported the N-alkylation of 1H-imidazole by a Cu(acac)2-mediated reaction of diazoalkanes generated in situ from the corresponding p-toluenesulfonate hydrazones (Scheme 7).[11] Very recently, Fukuyama and co-workers described a novel synthetic method for the preparation of diazoacetates from the corresponding bromoacetates by treatment with N,N′-ditosylhydrazine and DBU (Scheme 8).[12]

A deacylative oxidation strategy for the introduction of an alkoxy or amino group into the α-position relative to a carbonyl group was developed by Brodsky and Du Bois. The trifluoroacetyl-substituted carbonyl compounds were used as the precursors for
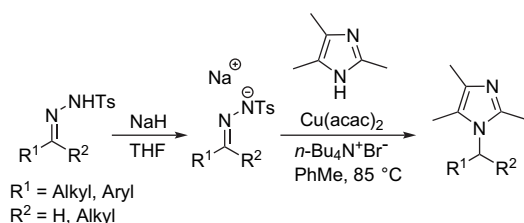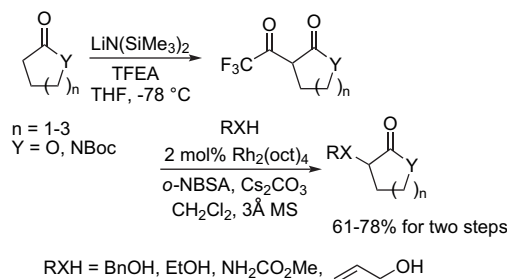

Scheme 7.

Scheme 8.

the generation of diazo compounds. Diazotization with o-nitrobenzenesulfonyl azide (o-NBSA) by using Cs2CO3 as base generated the corresponding α-diazocarbonyl compounds, which were catalyzed by rhodium(II) octanoate [Rh2(oct)4] in situ in the presence of an alcohol or amine (Scheme 9).[13]

Scheme 9.

3. Developments of new transition metal catalysts

Catalyst design remains the central issue in the transition metal-catalyzed reactions of α-diazo compounds. Although Cu(I) and Rh(II) complexes are the two most efficient types of catalysts, other transition metals are also effective in diazo decomposition. Ruthenium,[14,15] cobalt,[16] chromium,[17] and iron[18] complexes have been extensively exploited in cyclopropanation with diazo compounds. As an example, a ruthenium porphyrin complex [Ru^{II}(TDCPP)(CO)] **5** can efficiently catalyze a three-component coupling reaction of an α-diazo ester with a series of N-benzylidene imines and alkenes to form functionalized pyrrolidines **6** in excellent diastereoselectivity (Scheme 10).[15a]
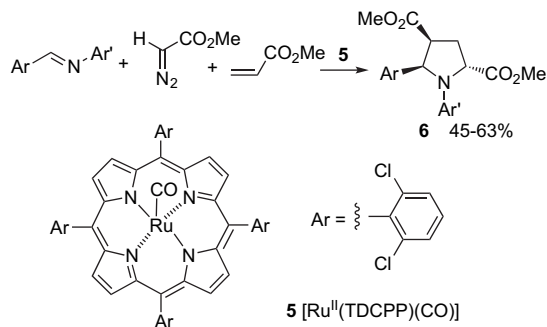
Scheme 10.

Very recently, Xiao and Wang have found that the easily available [RuCl2(p-cymene)]2 can catalyze the reaction of aryl α-diazoacetates with allyl sulfides. The [2,3]-sigmatropic rearrangement of sulfonium ylides generated from α-diazocarbonyl compounds and sulfides affords the homo allyl sulfide products **7** in moderate to good yields (Scheme 11).[15j]
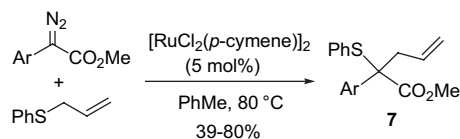
Scheme 11.

Iron-based complexes have also been utilized in the catalytic N–H insertion reaction of α-diazocarbonyl compounds. Aviv and Gross have reported the synthesis of non-protected amino acid esters

from ammonia and diazoacetates with an iron porphyrin catalyst **8** (Scheme 12).[18d]
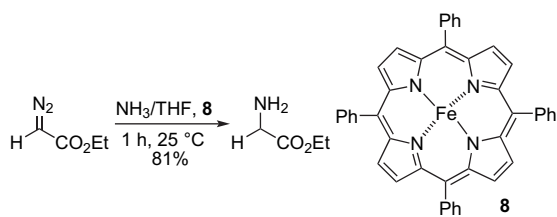
Scheme 12.

Silver(I) catalysts have been previously used in the decomposition of α-diazocarbonyl compounds. The Ag(I)-catalyzed reaction usually follows a Wolff rearrangement pathway.[19] Recently, an Ag(I)-catalyzed reaction of α-diazocarbonyl compounds has been found to follow other pathways. Dias and co-workers have reported a silver-catalyzed activation of alkyl halides, which involves silver-carbene intermediates.[20a] Besides, AgSbF₆ has been found an effective catalyst for the cyclopropanation in the reaction with donor/acceptor-substituted carbenoids (Scheme 13).[20b] The Ag(I)-catalyzed reaction yielded the cyclopropanation product **9**, which showed a different reaction profile from the Rh(II)-catalyzed reaction. In the latter case, C–H insertion to give **10** is usually dominant.

cat.	yield (%)	ratio (**9** : **10**)	de (%)
AgSbF₆	80	>20 : 1	94
Rh₂(OAc)₄	4	1 : >20	

Scheme 13.

Gold complexes as soft Lewis acids have attracted considerable attention recently.[21] Au(I) complexes are normally not effective in diazo decompositions. However, a recent report demonstrated that the Au(I) complex **11** with an N-heterocyclic carbene 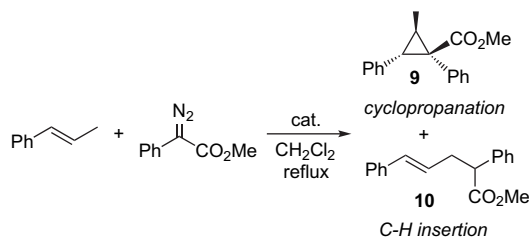ligand could catalyze the diazo decomposition of ethyl diazoacetate. The cyclopropanation of olefins as well as insertion into N–H and O–H bonds were achieved in this reaction (Scheme 14).[22]

Palladium complexes are very important transition metal catalysts for various transformations in organic chemistry, but their applications in the catalytic reactions of diazo compounds have been limited. However, there is growing interest in this field recently.[23] Bröring and co-workers have shown that palladium-carbene complexes are generated from a Pd-catalyzed reaction of diazo compounds.[23a] Van Vranken and Devine have reported a palladium-catalyzed three-component coupling of vinyl halides, trimethylsilyldiazomethane, and amines, which afforded allyl-amines **12** as the products (Scheme 15). The mechanism of this novel Pd-catalyzed reaction is suggested to involve the formation of a palladium-carbene intermediate **13** that undergoes migration of the vinyl ligand to the empty p-orbital of the carbene ligand. The resulting η¹-allylpalladium species is subsequently converted to the η³-allylpalladium intermediate **14** that is trapped by the amine nucleophile.[23b]
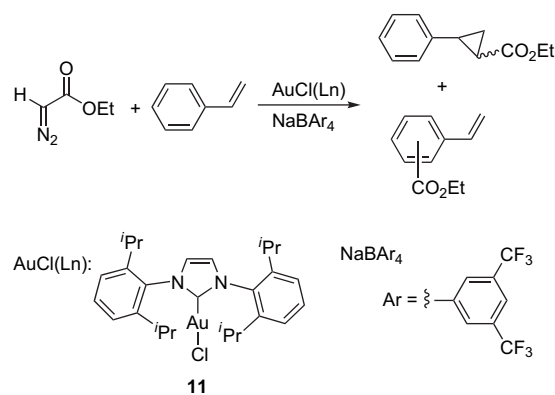
Scheme 14.
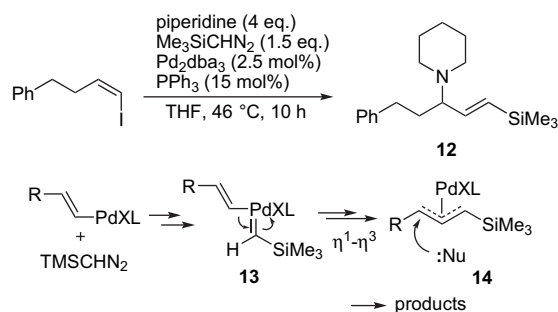
Scheme 15.

Wang and co-workers have observed an efficient Pd-catalyzed cross-coupling of iodides with ethyl diazoacetate (Scheme 16). Remarkably, the diazo moiety remained intact in the reaction. The reaction afforded the cross-coupling products in moderate to good yields, thus providing a new way to introduce a diazo functionality into organic compounds.[23d]
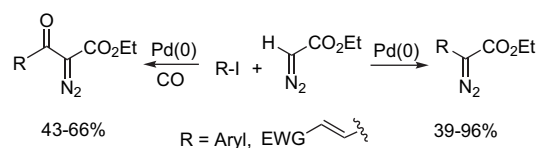
Scheme 16.

On the other hand, it has been well documented that the reactivity of metal carbene intermediates is greatly affected by the catalyst ligands. Therefore, new ligands have been designed and applied to the classic Cu(I) and Rh(II) catalysts. Pérez and co-workers investigated the catalytic behavior of Cu(I) catalysts in the diazo decomposition of ethyl diazoacetate with N-heterocyclic carbene ligands. It was found that [IPrCuCl] (IPr=1,3-bis(diisopropylphenyl)imidazol-2-ylidene) was an effective catalyst for the transfer of carbene from ethyl diazoacetate through cyclopropanation, and O–H and N–H insertion. The homocoupling of diazo compounds, the common drawback for transition metal-catalyzed reactions of diazo compounds, could be largely avoided with this catalyst.[24]

Rh(II) complexes have proved to be excellent catalysts for diazo compound-based carbene-transfer reactions. Recently, Corey and co-workers synthesized a series of unsymmetrical dirhodium(II) catalysts [Rh₂(RCO₂)ₙ(L*₄₋ₙ)]. Some of them, such as Rh₂(OAc)(DPTI)₃ (**15**) and Rh₂(t-BuCO₂)₂(DPTI)₂ (**16**), are more effective for [2+1]-cyclopropanation reactions, especially in cyclopropenation.[25]

However, the high price of rhodium impedes its wide use in organic synthesis. Efforts have been made in the past few years to

15 **16**

Scheme 18.
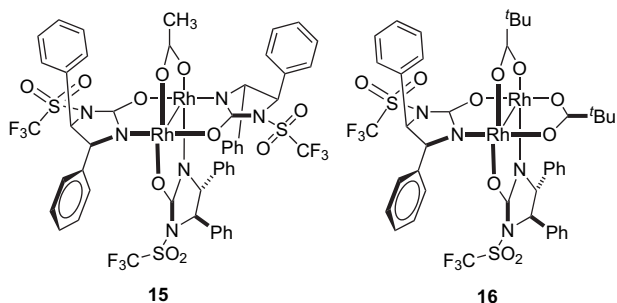
recycle the Rh(II) catalysts.[26] Biffis and co-workers developed a fluorous chiral dirhodium(II) catalyst **17**, which was efficient in cyclopropanation reactions. The catalyst could be easily separated from the reaction mixture and was recyclable. Furthermore, it enabled the use of a reaction protocol without organic solvents besides the reagents and a tiny amount of fluorous solvent.[26a]

a strategy to immobilize the Rh(II) catalyst by using highly cross-linked macroporous polystyrene resins with a pyridine attachment. The immobilized catalysts display a similar reactivity and stereoselectivity to their homogeneous counterparts and can be effectively recycled with limited loss in stereoselectivity (Scheme 19).[26d–f]

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Doyle's rhodium(II) carboxamidate complexes are effective chiral catalysts in asymmetric carbenoid transfer reactions. The immobilized chiral Rh(II) carboxamidate complexes **18** have been prepared by the attachment of the ester moiety of the ligand to a polymer backbone (Scheme 17). It was observed that the immobilization of Rh(II) catalysts with mixed ligands had significant influence on the reactivity and stereoselectivity of the Rh(II) carbene in C–H bond insertion and cyclopropanation.[26b]

R* = prolinate ligand

Scheme 19.

4. Insertion reactions

4.1. Catalytic X–H (X=C, Si, O, S, N, etc.) insertion

Together with cyclopropanation, X–H bond (X=C, O, S, N, Si, etc.) insertion is characteristic for metal carbenes. In particular, unfunctionalized C–H bond insertion by metal carbenes provides a very important approach for C–H bond activation (Scheme 20).[27] X–H bond insertion of metal carbenes has been extensively investigated and some of these reactions have been used in the total synthesis of complex molecules.[28] Several excellent reviews that summarize metal carbene C–H insertion have already appeared.[1,27] In this section, the most recent selected advances are reviewed.

18

Scheme 17.

Forbes and co-workers have synthesized an ionic liquid metal-conjugate **19** (Scheme 18).[26c] The ligand exchange of acetate with an imidazolium group tethered to a carboxylic acid afforded the Rh(II) carboxylate that covalently bonded to an organic salt. This modified Rh(II) catalyst can be used in ionic liquids as an effective catalyst for the cyclopropanation of styrene using ethyl diazoacetate.

Another strategy to immobilize Rh(II) catalysts is to coordinate the solid support to the axial empty site of the Rh(II) complex. A dirhodium complex has two axial bonding positions. While one axial empty orbital interacts with the diazo carbon to bring dinitrogen extrusion and generation of the Rh(II) carbene, the other axial bonding site may interact with the solvent or a ligand. Pyridine has been known to strongly bond with rhodium. Taking into account these advantages, Davies and co-workers have developed

Scheme 20.

Intramolecular C–H activation reactions permit remote functionalization through C–C bond formation. This type of reaction presents a general approach for the synthesis of a variety of carbocyclic and heterocyclic structures in a regio- and stereoc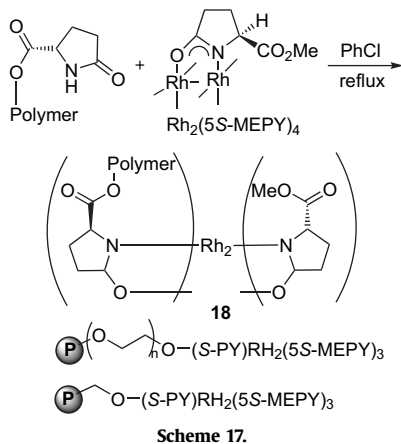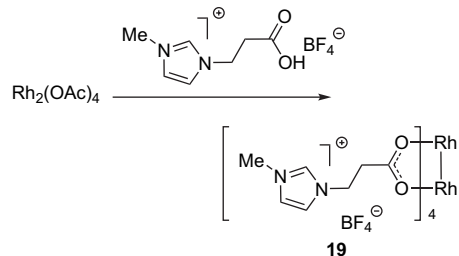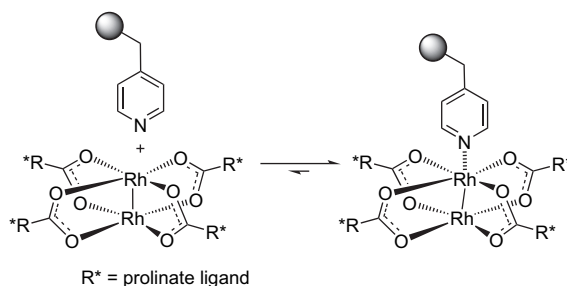ontrolled manner. It has been well documented that the reactivity of the C–H bond is remarkably affected by electronic and steric factors. In most cases, the formation of a five-membered ring is overwhelmingly predominant. The regio- and stereoselective C–H bond insertion has been employed for the construction of cyclopentanones,[28a,29] dihydrofuranones,[30] γ-lactones,[31] γ-lactams,[32] tetrahydrofurans,[33] and tetrahydrothiophenes[34] (Scheme 21).

cyclopentanone: X = CH$_2$; Z = H, COR, PO(OR)$_2$
γ-lactone: X = O, Z = H, COR
γ-lactam: X = N, Z = H, COR

tetrahydrofuran: X = O
tetrahydrothiphene: X = S
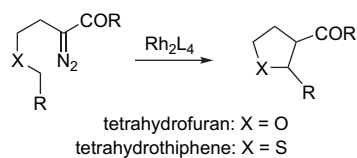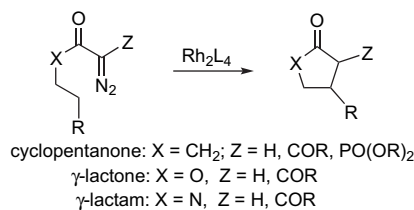
Scheme 21.

Although intramolecular 1,5-C–H insertion is overwhelmingly predominant, due to the entropically favorable six-membered transition state, steric or electronic factors may override this entropic preference. 1,4 C–H insertion occurs when the C–H bond is activated by a neighboring heteroatom, in most cases oxygen or nitrogen.[35,36] And 1,6 C–H insertion has been reported for some structurally rigid systems.[28c,37] Recently, Wang and co-workers have reported the first example of 1,3 C–H insertion in the Rh(II)-mediated reactions of β-tosyl α-diazocarbonyl compounds **20** (Scheme 22).[38] This study further demonstrates the dramatic effect of neighboring groups on Rh(II) carbene reactions.

R^1 = Me, Et, etc.
R^2 = OEt, Me, Ph
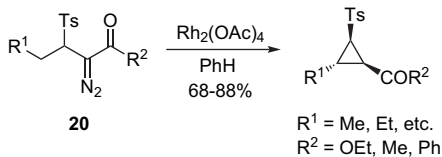
Scheme 22.

Although rhodium(II) complexes have been proved the most effective catalysts for carbenoid C–H insertion, other metal complexes can also be effective, such as copper or ruthenium complexes. In one example, Yu and Che reported the intramolecular C–H insertion via ruthenium porphyrin or RuCl$_2$-(p-cymene)$_2$ catalysis.[39]

Another important development for intramolecular C–H insertion is the application of 'green' solvents. The Rh(II) carbene-mediated C–H insertion usually uses less coordinative solvents, such as dichloromethane or 1,2-dichloroethane. Afonso and co-workers demonstrated that Rh(II)-catalyzed intramolecular C–H insertion on α-diazo-acetamides could be achieved effectively in ionic liquids or in water.[40] The use of water as the solvent in Rh(II) carbene C–H insertion allows a simple work-up of the reaction and recycling of the catalyst. The fact that the highly feasible O–H insertion into water cannot compete with C–H insertion in this case implies that the reaction might actually occur 'on water', rather than 'in water'.

For a long time, the intermolecular reaction has been considered to be of little synthetic utility, because of the poor chemoselectivity. In the past few years, the situation has changed to some extent with the development of the new catalytic systems and the donor/acceptor-substituted carbenoids.[1j]

Although dirhodium tetracarboxylates are widely used in intramolecular C–H insertion, they are usually less effective in the intermolecular C–H insertion of acceptor-substituted carbenoids. The reaction displays very poor regioselectivity, and carbene dimerization dominates, unless the diazo compound is added very slowly. Even when the target C–H bond is activated by an adjacent phenyl group, vinyl group or heteroatom, the selectivity is still poor.

To avoid carbene dimerization, one strategy is to increase the bulk of the catalyst ligand. Recently, higher yields in intermolecular C–H insertion using bulky copper catalysts have been reported by Pérez and co-workers.[41] In the reaction between ethyl diazoacetate and tetrahydrofuran, the yield of the C–H activation product could be improved to 98% with catalyst **21** (Scheme 23).[41a] The C–H insertion of alkanes catalyzed by this catalyst also demonstrated a high chemoselectivity, as shown by the reaction with catalyst **22**.[41b] The main advantage of these catalysts appears to be their extremely bulky nature, yet the catalytic activity still remains. In addition, Pérez and co-workers discovered silver(I) scorpionate[42] and (NHC)CuCl (NHC=N-heterocyclic carbene)[43] catalyst systems for the intermolecular C–H insertion of ethyl diazoacetate.

21 Tp^{Ms} : R = 2,4,6-Me$_3$C$_6$H$_2$
22 Tp^{Br3} : R = Br
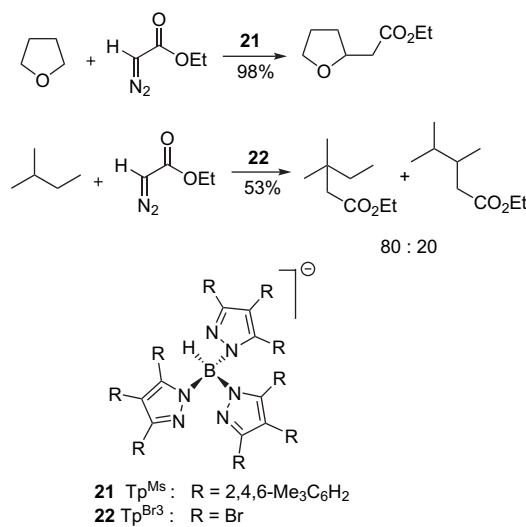
Scheme 23.

Donor/acceptor-substituted carbenoids have proved to be superior for intermolecular C–H insertion in terms of chemo-, regio-, and stereoselectivity. Metal carbenes derived from aryldiazoacetates and vinyldiazoacetates have been extensively studied by Davies and co-workers.[1j,n] Due to the enhanced stability of donor/acceptor-substituted carbenoids, they are far less susceptible to dimer formation. A recent example is the rhodium-catalyzed C–H insertion reaction of ethyl phenyldiazoacetate **23** into dihydroaromatic compound **24** (Scheme 24). The reaction was highly regioselective and gave a polyfunctionalized aromatic compound **25** after oxidation by DDQ.[44]

25
74% yield
single regioisomer
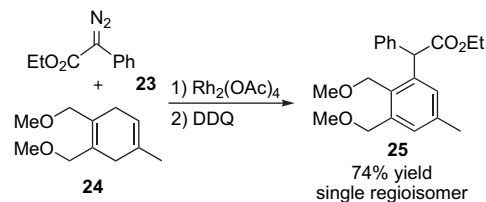
Scheme 24.

In addition to C–H insertion, there have been some new developments in metal carbene heteroatom–H insertion. Catalytic O–H insertion provides a direct entry to C–O bond formation, which can be a useful route to cyclic ethers.[45] Transition metal-catalyzed O–H insertion is generally considered as a stepwise process via an initial oxonium ylide formation followed by a rapid 1,2-hydrogen shift. However, Hammett correlation data for the electronic effects on Rh(II) carbene O–H insertion favor a concerted reaction

pathway.[46] Recently, an interesting example of Rh(II)-catalyzed three-component reactions of aryldiazoacetates, alcohols, and aldehydes/imines, reported by Hu and co-workers, provided evidence of oxonium ylide formation for O–H insertion (Scheme 25).[47] In this case, the proposed oxonium ylide intermediate **26** can be trapped by aldehyde or imine before the 1,2-H shift to generate formal O–H insertion products **27**. The three-component reaction gave **28** or **29** in high yield, and excellent diastereoselectivity was achieved in this reaction very recently.[47b]

Scheme 25.
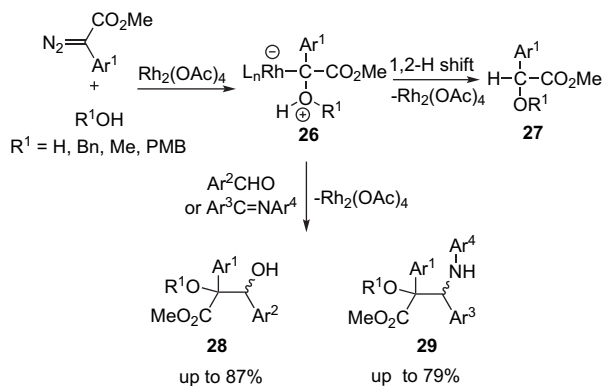
Besides rhodium complexes, O–H insertion can also be catalyzed by other metal complexes. Recently, diruthenium(II)tetrakis(acetate)[48] and Tp^{x}Cu[49] have been reported as effective catalysts for O–H insertion. Tp^{x}Cu has also been found to be an effective catalyst for N–H insertion.[50]

The S–H insertion of diazocarbonyl compounds with thiols is a synthetically useful reaction that can introduce a sulfur-containing substituent adjacent to the carbonyl group of ketones or esters. The reactions of thioacetic S-acid with α-diazocarbonyl compounds under conditions of Rh$_2$(OAc)$_4$ or BF$_3$·OEt$_2$ catalysis have been investigated (Scheme 26).[51] Interestingly, the formation of a C–S or C–O bond is dependent on the catalysts. Catalytic asymmetric S–H insertion reactions of carbenoids were studied, but the enantioselectivity was poor.[52]

Scheme 26.
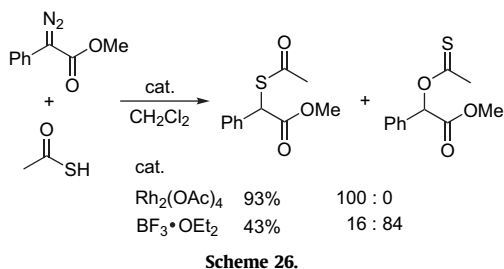
Catalytic N–H insertion is a useful strategy to build a C–N bond, and the mechanism of N–H insertion is probably similar to the mechanism of O–H insertion. Intramolecular N–H insertion is among the most efficient and direct methods yet devised for synthesizing nitrogen heterocycles. A five-membered ring is usually favored in intramolecular N–H insertion, providing pyrrolidine derivatives in good yields.[53] On the other hand, there are also examples of metal carbene insertion into 1,4-, 1,6- and 1,7-N–H bonds, which affords four-,[54] six-,[55] and seven-[56] membered nitrogen-containing rings, respectively.

Largely due to the high reactivity of the N–H bond to the metal carbene, intermolecular N–H insertion is usually chemoselective and highly selective over other possible metal carbene processes, such as C–H insertion and dimerization. Thus, this type of metal carbene insertion is useful in organic synthesis. As an example, Moody and co-workers have reported a new variation of the Robinson–Gabriel synthesis of oxazoles **31**, thiazoles **32**, and 1,3-azoles **33**. In this synthesis, the key intermediate of the 1,4-dicarbonyl compound **30** is obtained by an intermolecular rhodium carbene N–H insertion reaction (Scheme 27).[57]

Scheme 27.
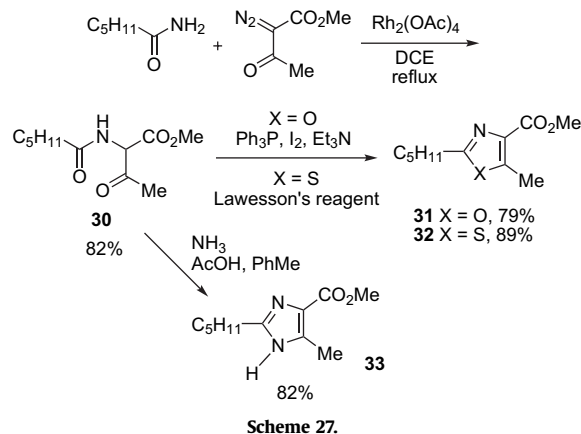
This approach has been utilized for the synthesis of amino acid-derived oxazole building blocks of the natural products, diazonamide A[58] and amythiamicin D.[59] Janda and co-workers have further developed a solid-phase variant of these reactions.[60] The synthesis of indoles in a similar strategy has also been reported.[61] Furthermore, this reaction sequence is an effective method to synthesize oxazolones and other heterocycles when α-diazo-β-ketoesters are used as substrates.[62]

4.2. Asymmetric catalysis in X–H insertion

Asymmetric catalysis in metal carbene X–H insertion continues to be the major focus in this field in the past few years. The three major chiral rhodium(II) catalysts developed in the 1990s,[1j] namely chiral rhodium(II) carboxamidates **34** introduced by Doyle,[63] proline-based chiral rhodium(II) carboxylates **35** developed by the groups of McKervey and Davies,[64] and phthalimide derivatives of amino acid-based chiral rhodium(II) carboxylates **36** developed by Hashimoto,[65] have found further applications in asymmetric C–H insertion. Although further elaboration of these well-established catalysts to reach a higher level of reactivity and selectivity continues to be an important part of research activities, more attention has been directed to the application of these catalysts in organic synthesis. Issues such as expanding the substrate scope, application to total synthesis, and development of new synthetic methodologies in connection with other reactions (tandem processes) have been the major focus recently.
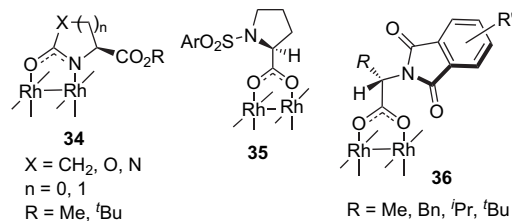
Doyle's chiral Rh(II) carboxamidate complexes have been the most successful for the asymmetric intramolecular C–H insertion of acceptor-substituted carbenoids. These catalysts have been extensively used in the asymmetric synthesis of lactones[63d,g] and lactams.[63b,c,e,f] An example is the total synthesis of (+)-imperanene

38 via the asymmetric synthesis of γ-butyrolactone **37** by intramolecular C–H insertion catalyzed by Rh₂(4S-MPPIM)₄ (Scheme 28).[63a]
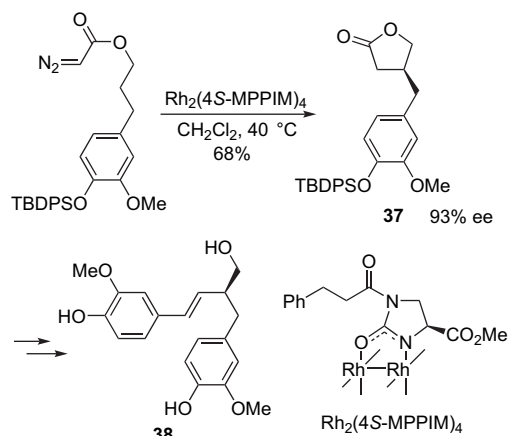
Scheme 28.

The chiral Rh(II) carboxamidate complexes are also found to influence the chemoselectivity and regioselectivity of the C–H insertion reactions.[63d] An interesting observation made by Doyle and co-workers is the Rh₂(4S-MEOX)₄-catalyzed asymmetric C–H insertion of diazoamide, which contains a bis(trimethylsilyl)methyl protective group (Scheme 29).[63c] This is an unusual example in which the chiral catalysts of opposite configuration induce different outcomes with the same achiral substrate. The barrier to equilibrate between the diastereomeric conformations is attributed to this result.
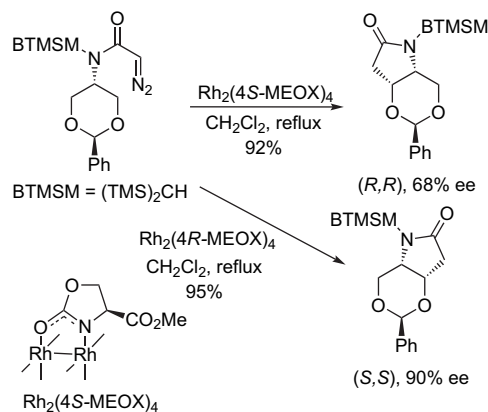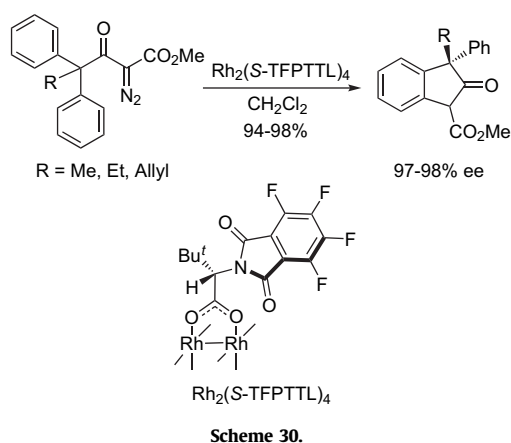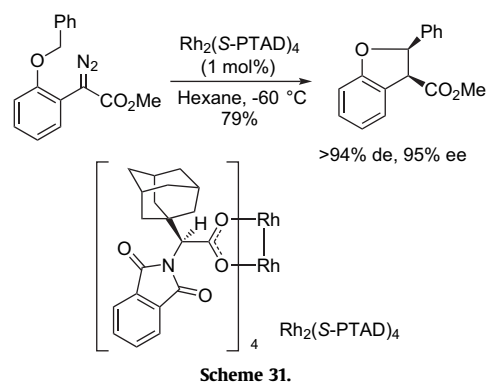

Scheme 29.

The performance of chiral Rh(II) catalysts may be dramatically modified by the change of electronic properties of the chiral ligands. Hashimoto and co-workers have introduced fluorine into their phthalimide derivatives of amino acid-based chiral rhodium(II) carboxylates. Both the reactivity and enantioselectivity are dramatically enhanced with the fluorinated Rh(II) catalyst, Rh₂[(S)-TFPTTL]₄ dirhodium(II) tetrakis[N-tetrafluorophthaloyl-(S)-tert-leucinate]. This catalyst has achieved a very high turnover number (up to 98,000; when R=Me) with only a 0.001 mol% amount, without compromising the yield or enantioselectivity of the process (Scheme 30).[65b]

Davies and co-workers have recently prepared an adamantylglycine-derived dirhodium tetracarboxylate, Rh₂(S-PTAD)₄. This Rh(II) catalyst was found to be very effective for carbenoid reactions and a high asymmetric induction was obtained in intermolecular cyclopropanation (99% ee), intermolecular C–H insertion (92% ee), and intramolecular C–H insertion (95% ee)

Scheme 30.

(Scheme 31). Interestingly, the chiral ligand, adamantylglycine, itself was synthesized from an Rh₂(S-DOSP)₄-catalyzed C–H insertion reaction of the vinyldiazoacetate with adamantane.[65e]

Scheme 31.

Intermolecular C–H insertion by carbenoids is generally more challenging in terms of regio-, chemo-, and stereoselectivity. Moreover, as mentioned earlier, dimerization of the diazo substrate is normally a serious side reaction. In particular, for acceptor-substituted carbenoids, this problem has, so far, not been solved.

Significant success has been gained in asymmetric catalysis of intermolecular C–H insertion with the introduction of donor/acceptor-substituted carbenoids. Davies's group has extensively exploited the asymmetric catalytic reactions with aryldiazoacetates and vinyldiazoacetates.[1i,j,64] The Rh(II) carbenes derived from aryldiazoacetates and vinyldiazoacetates are generally highly selective in intermolecular C–H insertion reactions. C–H insertion prefers to occur at the α-position of oxygen[64b,e] or nitrogen[64a,f,i,j,l] functionalities, which can be used as surrogates of classic Aldol, Michael, and Mannich reactions.

A recent example is the enantioselective synthesis of β-amino esters **40** with Rh₂(S-DOSP)₄-catalyzed C–H insertion reactions of the bis-silylmethylamine **39** with various aryldiazoacetates (Scheme 32).[64l]

C–H insertion is also favored for allylic and benzylic sites, and the carbenoid derived from aryldiazoacetate is far more prone toward C–H insertion than cyclopropanation. Asymmetric allylic C–H insertion of alkenes via metal-catalyzed diazoacetate decomposition offers a unique approach to γ,δ-unsaturated esters **41**, which contain two stereocenters. This type of compounds is classically synthesized through a Claisen rearrangement (Scheme 33).[64k] Asymmetric benzylic C–H insertion has also been developed by Davies and co-workers.[64d]

Vinylcarbenoids are also used in asymmetric intermolecular C–H insertion, and the introduction of substrates with a directing
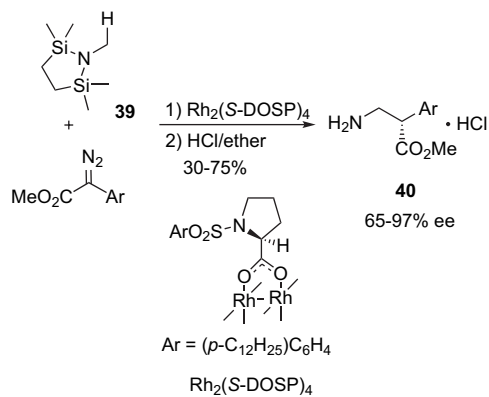
Scheme 32.
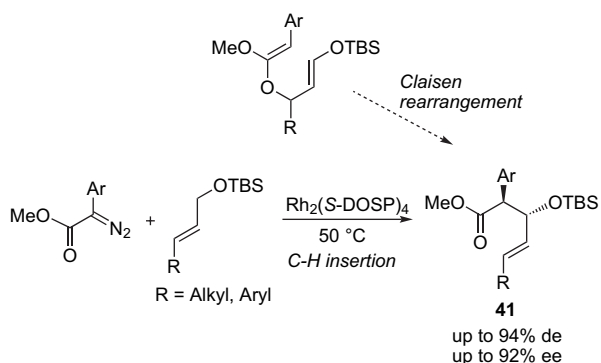
Scheme 33.

functionality adds to the diversity and widespread synthetic utility of this chemistry. The Rh$_2$(S-DOSP)$_4$-mediated reactions of vinyl-carbenoids with allylic substrates resulted in a very unusual chemistry.[64g,h] The reaction underwent a C–H activation/Cope rearrangement, as demonstrated by the reaction with vinyl-diazoacetate **42**. The vinylcarbenoid generated from **42** activated the allylic C–H bond of **43**, which was followed by a Cope rearrangement to yield **45**. The C–H activation product **44** was also detected (Scheme 34).[64g] Since this process is highly efficient and stereoselective, it has been successfully utilized in the total synthesis of the natural products, (−)-colombiasin A and (−)-elisapterosin B.[28i]
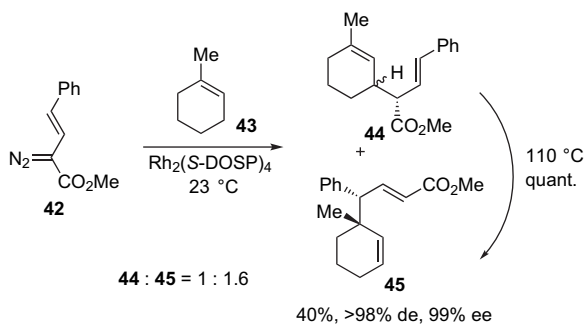
Scheme 34.

Vinyldiazolactone **46** as a vinylcarbene precursor has also been investigated recently. The Rh(II) carbene generated from this type of diazo compound is more favorably disposed toward intermolecular C–H insertion than cyclopropanation (**47**/**48**=9:1). A moderately high level of enantioselectivity has been achieved with Doyle's chiral Rh(II) carboxamidate catalyst **49** (Scheme 35).[63h]

Scheme 35.

Although the major research activity on the asymmetric catalysis of X–H insertion has been concentrated on the C–H bond, some significant developments have been recently reported on Si–H, O–H, and N–H bond insertion. Si–H insertion is considered to be similar to C–H in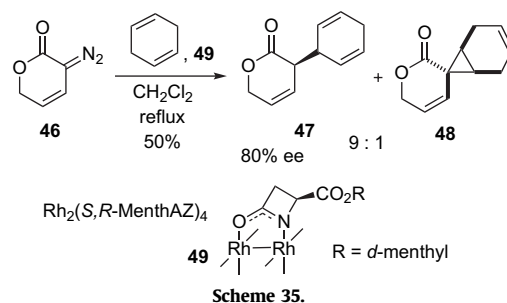sertion in its reaction mechanism. Moody and co-workers have screened a series of chiral rhodium(II) catalysts based on α-hydroxy acids and N-arenesulfonyl α-amino acids for asymmetric Si–H insertion by a parallel synthesis technique. However, the enantioselectivity remains only low to moderate for all of the chiral Rh(II) catalysts.[66] Recently, Corey and co-workers have obtained a high level of enantioselectivity with diazo-2-cyclohexenone by using a fluorinated proline-based chiral Rh(II) catalyst **50** (Scheme 36).[67]
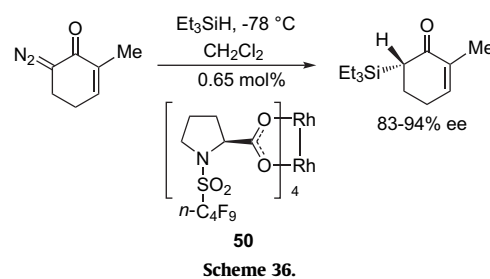
Scheme 36.

Metal carbene O–H insertion and N–H insertion are believed to follow a ylide generation/1,2-proton shift mechanism, which is different from that of the corresponding C–H and Si–H insertions. In contrast to C–H insertion, asymmetric catalytic O–H insertion and N–H insertion have been essentially unsuccessful until very recently, when a breakthrough in O–H insertion was made by Fu's group. With Cu(OTf)$_2$/bisazaferrocene (+)-**51** as the chiral catalyst and 2-trimethylsilylethanol as the O–H bond donor, a high level of enantioselectivity was obtained with a series of methyl aryldiazoacetates (Scheme 37).[68]

On the other hand, Zhou and co-workers have made a breakthrough in Cu(I)-catalyzed asymmetric N–H insertion by using their chiral spirobisoxazoline **54** as ligand. For ethyl 2-diazopropionate **52a**, generally a high level of enantioselectivity has
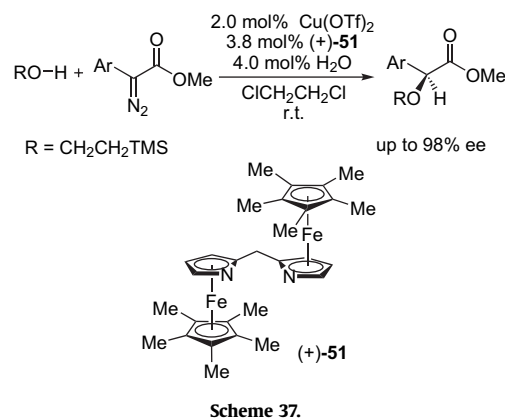
Scheme 37.

been obtained (Scheme 38).[69] However, for ethyl phenyl-diazoacetate **52b**, only a low enantioselectivity could be observed.
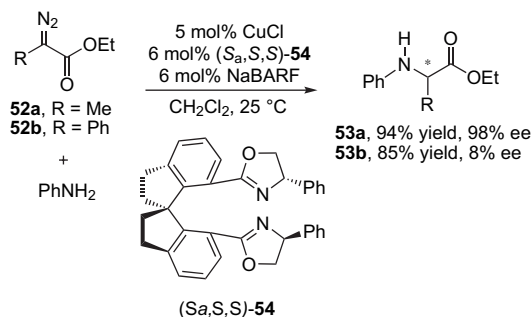
Scheme 38.

5. Cyclopropanation and related reactions

Along with C–H insertion, cyclopropanation is typical for transition metal-catalyzed reactions of α-diazocarbonyl compounds (Scheme 39).[1a,d] Three-membered ring products are very important, because they occur as structural subunits in biologically active natural/unnatural products and synthetic intermediates.[70,71] Transition metal-catalyzed reactions of diazocarbonyl compounds with olefins and alkynes are powerful methods for the synthesis of cyclopropanes and cyclopropenes. Although the transition metal-catalyzed cyclopropanation of diazocarbonyl compounds has been extensively investigated in the past decades, there have still been some new developments at the present time, especially in asymmetric catalysis.
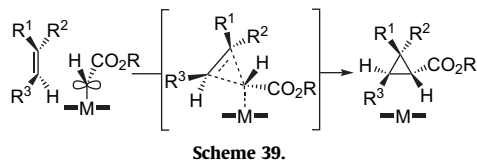
Scheme 39.

5.1. Catalytic cyclopropanation

An interesting development seen in the past few years is the combination of transition metal-catalyzed cyclopropanation with other types of reactions in single or cascade operations. Owing to the high strain of the three-membered ring system, there are varieties of possible pathways for the ring opening of cyclopropanation products. On the other hand, it is now understood that many functional groups can be tolerated in the transition metal-catalyzed reactions of α-diazo compounds. Consequently, it is possible to design a diazo substrate bearing the necessary functional groups for further transformation after cyclopropanation.

Charette and co-workers used the α-nitro-α-diazoesters **55** (X=N$_2$) as carbene precursors in Rh(II)-catalyzed cyclopropanation. Through the combination of the cyclopropanation with reduction, a series of cyclopropane α-amino acids and amines could be synthesized.[72a,b] On the other hand, with subsequent ring opening of the cyclopropanation products **56** by amine, followed by DDQ oxidation, a series of polysubstituted pyrroles **57** could be obtained (Scheme 40).[72c]

Cyclopropane rings bearing both electron-donating and electron-withdrawing groups are prone to undergo ring opening.[73] As an example, Rh(II)-catalyzed reaction of α-diazoketones with vinyl ethers afforded the cyclopropanation products **58**, which carried an electron-withdrawing carbonyl group and an electron-donating
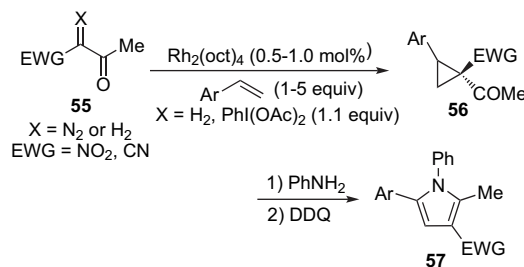
alkoxy group. This type of cyclopropane derivatives was found to undergo ring opening in the presence of Rh$_2$(OAc)$_4$ affording the 1,4-diketones **59**. The Rh$_2$(OAc)$_4$-assisted ring opening is presumably due to the coordination of the Rh(II) complex with the carbonyl oxygen (Scheme 41).[74]
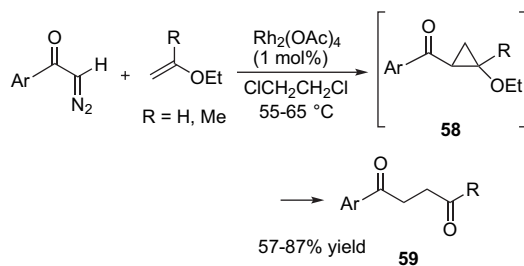
Scheme 40.

Scheme 41.

The capability of donor–acceptor metal carbenes derived from vinyldiazoacetates to undergo cyclopropanation of dienes with the predominant formation of cis-1,2-divinyl compounds makes possible a subsequent Cope rearrangement to afford the bicyclic dienes. This tandem cyclopropanation/Cope rearrangement has been extensively studied by Davies and co-workers.[75] In one example, a 6-azabicyclo[3.2.2]nonane ring system **60** can be constructed by the Rh(II)-catalyzed reaction of vinyldiazoacetates with 1,2-dihydropyridines (Scheme 42).[75b] Asymmetric induction is possible by using dirhodium tetraprolinates as chiral catalysts in this reaction with moderately high levels of enantioselectivity.
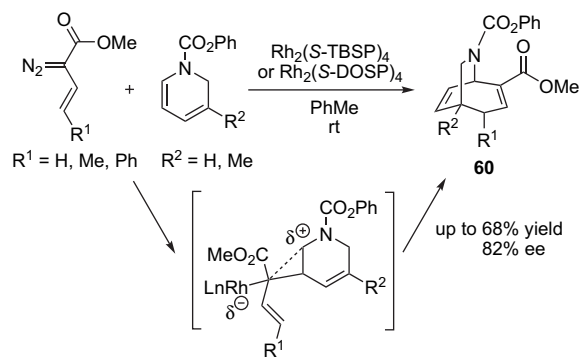
Scheme 42.

The sequential catalytic process involving cyclopropanation can be developed by connection with other well-established transition metal-catalyzed reactions, such as Pd-catalyzed cross-coupling reactions and Ru-catalyzed olefin metathesis.[76] The substrates used in the Pd-catalyzed cross-coupling reactions are organohalides and triflates, organoborons, and organostannanes. Although Rh(II) complexes are highly reactive in the decomposition of diazo compounds, they do not normally react with these functional groups. A demonstration of the usefulness of this strategy is the combination of the Rh(II)-catalyzed cyclopropanation and C–H insertion with

a subsequent palladium(II)-catalyzed Suzuki coupling, which offers a novel method for diversity synthesis (Scheme 43).[76b]
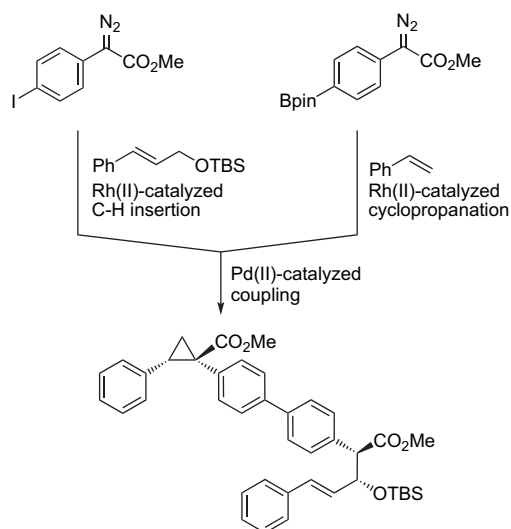
Scheme 43.

Cyclopropanation can also be designed to be incorporated into a tandem catalytic process. A recent example is the tandem enyne metathesis/cyclopropanation catalyzed by Grubbs' ruthenium catalyst **61**. With single Grubbs' ruthenium catalyst, a variety of diazo compounds participate successfully in a regioselective cyclopropanation of 1,3-dienes, generated in situ from various enynes (Scheme 44).[77]
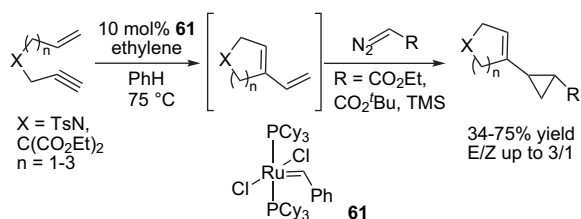
Scheme 44.

Other developments in intermolecular cyclopropanation involve the use of $Bu_3SnC(=N_2)CO_2R$ as the carbene precursor,[78] Rh(II)-catalyzed cyclopropanation in aqueous media,[72a] etc.

When both functionalities, the diazo unit and the alkene, are situated in the same molecule, intramolecular cyclopropanation is possible in the presence of the appropriate catalyst. Actually, intramolecular cyclopropanation is a powerful tool to construct bicyclic systems. Chemoselectivity is a commonly encountered problem in transition metal-catalyzed intramolecular cyclopropanation via metal carbenes. In most cases, intramolecular C–H insertion is the major competing pathway, although other competing pathways such as sigmatropic rearrangement are also possible. The factors that influence the selectivity for these reactions are quite complicated. Doyle and co-workers have developed a novel strategy to build macrocycles by using intramolecular cyclopropanation.[79] They also systematically studied various factors that may influence the chemoselectivity. As shown in Scheme 45, both the transition metals and the ligands can exert a significant influence on the ratio of cyclopropanation/[2,3]-sigmatropic rearrangement.[80]

Similar to intermolecular cyclopropanation, intramolecular cyclopropanation can also undergo a tandem process, which may be useful in organic synthesis.[81] An example is the enantioselective synthesis of bicyclo[6.1.0]nonane-9-carboxylic acids **62** via Rh(II)-catalyzed intramolecular cyclopropanation followed by Me_2AlOTf-

promoted intramolecular Friedel–Crafts alkylation of the aromatic nucleophile with the γ-lactone moiety in bicyclic products (Scheme 46).[81a]
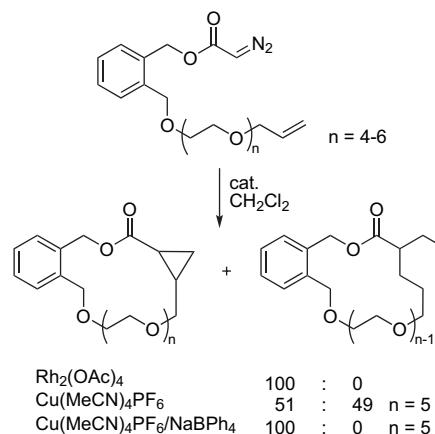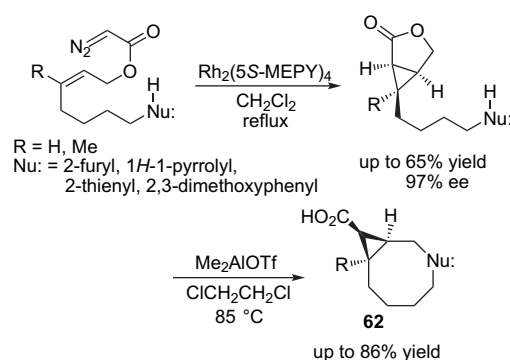
Scheme 45.

Scheme 46.

Cyclopropanation of metal carbenes to aromatic double bonds normally follows subsequent rearrangement, such as a Büchner reaction. As an example, Rh(II)-catalyzed reaction of diazo compounds **63** affords the intramolecular cyclopropanation products **65**, which is followed by a six-electron electrocyclic ring opening to give the substituted azulenes **64** as the final product (Scheme 47).[82]
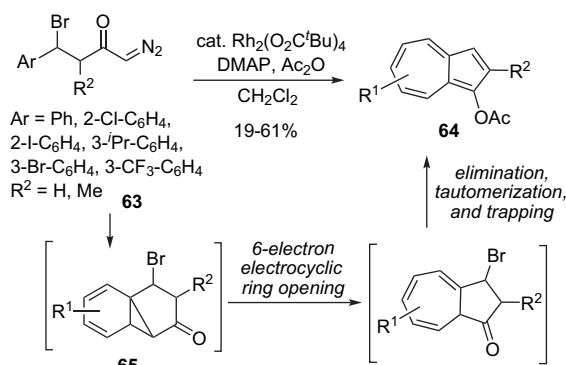
Scheme 47.

Cyclopropanation also occurs by the reactions of metal carbenes with furan and pyrrole. In the case of furan, the initial cyclopropanation product **66** will be followed by a consecutive ring opening process, eventually leading to the ring opening of furan.[83] This reaction has been recently utilized in the construction of central seven-membered ring of guanacastepene (Scheme 48).[83c]
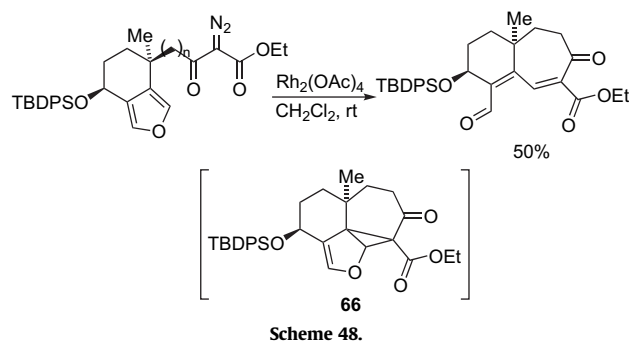
Scheme 48.

Unlike furan, the cyclopropanation products from pyrrole undergo a rearrangement that leads to the formal C–H insertion products. The formal C–H insertion gives a mixture of 2- and 3-regioisomers (Scheme 49).[84]

Scheme 49.
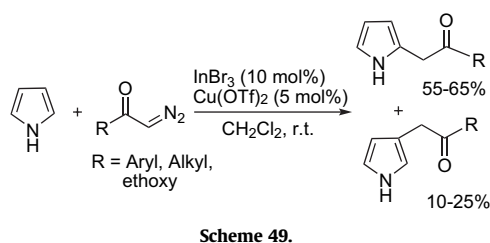
Cyclopropanation of other aromatic compounds includes activated quinolines, isoquinolines,[85] and benzopyrylium triflates.[86] In these cases, cyclopropanation is followed by ring enlargement that is similar to the Büchner reaction.

Reaction of alkynes with metal carbenes affords cyclopropenation products, which are potentially valuable synthetic intermediates for the construction of carbocyclic and heterocyclic compounds. A recent example of the Rh(II)-catalyzed chemoselective cyclopropenation was reported by Fox and Panne. By changing the ligands of the Rh(II) complexes **67**, it is possible to switch between cyclopropenation and alkyne insertion (Scheme 50).[87]

Scheme 50.
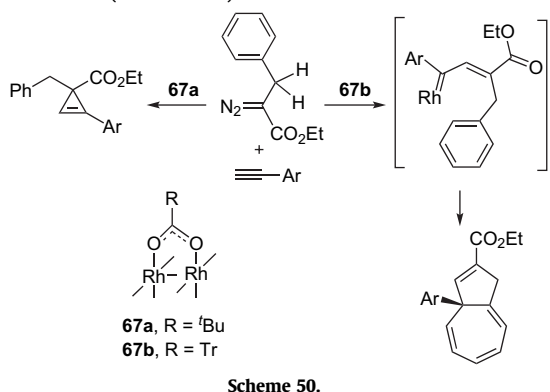
5.2. Asymmetric catalysis in cyclopropanation

Although asymmetric catalytic cyclopropanation via metal carbene-transfer has a long history, it still attracts attention and there have been new developments in the past three years. New chiral catalysts and catalytic systems have been designed in order to reach a high enantioselectivity and reactivity. Rh(II) and Cu(I) complexes are the two most commonly used chiral catalysts in asymmetric cyclopropanation.

The prolinate chiral rhodium catalysts developed by McKervey's group and Davies's group have been very successful for asymmetric

C–H insertion with donor/acceptor-substituted diazo compounds. These catalytic systems are also successful for cyclopropanation and cyclopropenation. As an example, Davies and co-workers have demonstrated that Rh₂(S-DOSP)₄ is an effective chiral catalyst for the enantioselective cyclopropenation of alkynes by methyl aryldiazoacetates.[88]

A bridged dirhodium tetraprolinate Rh₂(S-biTISP)₂ has been designed and was found to be an excellent catalyst in asymmetric cyclopropanation. It can be used for α-diazophosphonates and affords a high level of diastereocontrol and a moderate to good level of enantiocontrol (Scheme 51).[89] This catalyst also has a high turnover number and turnover frequency.[90] Moreover, this catalyst is also immobilized by highly cross-linked macroporous polystyrene resins with a pyridine attachment.[26d–f]

Scheme 51.
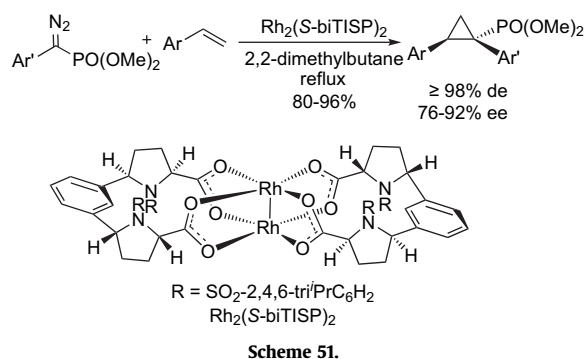
Doyle's rhodium(II) carboxamidate complexes are also effective chiral catalysts in cyclopropanation reactions, particularly in intramolecular cyclopropanation reactions. Recently, diastereoselectivity in the dirhodium(II) carboxamidate-catalyzed intramolecular cyclopropanation was evaluated with diazoacetates bearing a chiral linker to the remote double bond.[91]

Cyclopropanation of substituted double bonds by metal carbenes usually favors the formation of trans-substituted cyclopropanes. To obtain a high selectivity for the cis-isomer remains a challenge. To tackle this problem, Doyle and co-workers have developed a new azetidine-ligated dirhodium(II) catalyst **69** that possesses an L-menthyl ester attachment. This Rh(II) catalyst provides significant diastereocontrol and high enantiocontrol for the formation of cis-cyclopropane products from the reactions of substituted styrenes with diazoesters. The usefulness of this reaction has been demonstrated by a total synthesis of a cyclopropane-configured phenylethylthiazoylthiourea (PETT) analogue **68** (Scheme 52).[92]

Scheme 52.
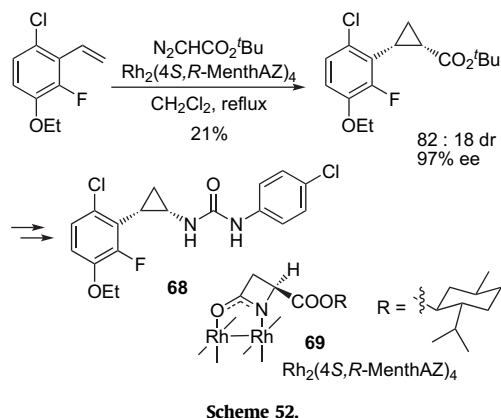
Charette and co-workers have focused on the transition metal-catalyzed reaction with diazo compounds bearing an adjacent nitro

or cyano group. A new azetidine-based dirhodium(II) catalyst Rh$_2$[4S-(4′)-FBNAZ]$_4$ **71** was prepared and found to be effective in the intramolecular cyclopropanation of substituted allylic cyano-diazoacetates **70** with up to 91% ee (Scheme 53).[93]

Scheme 53.
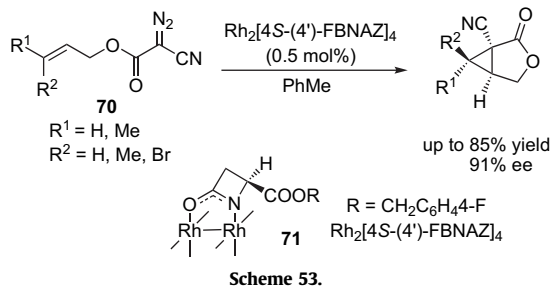
The most commonly applied chiral Rh(II) catalysts in the reaction of α-diazocarbonyl compounds to date have been Rh$_2$-bridged dimers having four identical chiral ligands. Corey and co-workers have designed and synthesized a series of mixed dirhodium(II) catalysts [Rh$_2$(RCO$_2$)$_n$(L$_{*4-n}$)].[25] Especially, Rh$_2$(OAc) (DPTI)$_3$ **15** and Rh$_2$(O$_2$C-t-Bu)$_2$(DPTI)$_2$ **16** are very effective in asymmetric cyclopropanation (Scheme 54). The reaction mechanism of the Rh(II)-catalyzed reaction was discussed based on the experimental data obtained with the mixed Rh(II) complexes.[25,94]

Scheme 54.

In addition to the Rh(II) catalysts, Cu(I) complexes are also efficient catalysts for cyclopropanation in carbene-transfer reactions, especially in asymmetric cyclopropanation.[95] A recent mechanistic investigation indicates that the selectivity-determining step in the copper-catalyzed cyclopropanation proceeds by a concerted, but very asynchronous, addition of a metallacarbene to the alkene.[96]

C_2 Symmetric bisoxazoline copper complexes have proved to be very effective chiral catalysts for cyclopropanation. Modification to these chiral ligands has been one of the main areas of interest in recent years. Heterogeneous bisoxazolines have been tested with the employment of various immobilization and recycling methods.[97] Immobilization of the chiral ligands by a fluorous-phase approach has also been examined for bisoxazoline ligands. As an example, fluorous bisoxazoline ligands **72** were tested in the Cu(I)-catalyzed cyclopropanation of styrene with various α-diazo-acetates.[98] The catalyst can be easily separated from the products by simple precipitation using hexane and can be recycled without any loss of diastereo- and enantioselectivity.

On the other hand, the structure of bisoxazolines may be tuned through modification of their steric and electronic features, e.g., 3,3′-bithiophene backbone **73** has been studied and tested in 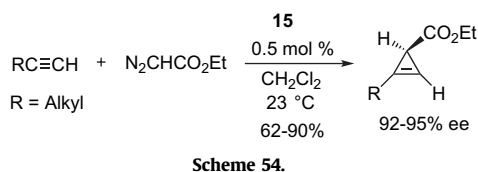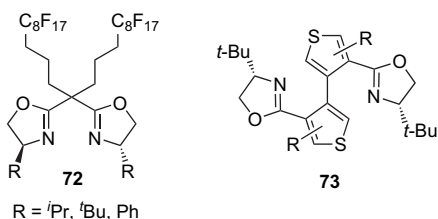asymmetric cyclopropanation.[99] This investigation suggests that steric factors and catalyst geometrical features are more important than the electronic properties of the chiral ligands.

Itagaki and co-workers prepared some new bisoxazoline ligands with an aryl group at the 4-position and a gem-dimethyl group at the 5-position on the oxazoline ring (Scheme 55).[100] Enhancement of the trans selectivity (trans/cis 87/13) and the enantioselectivity (96% ee for the trans product) was demonstrated for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene by tert-butyl diazoacetate with CuOTf/**74**.

Scheme 55.
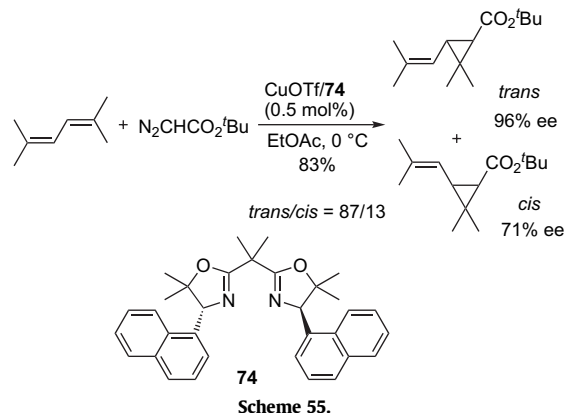
Modification of the backbone of the bisoxazoline ligands has been studied by several groups. Zhang and co-workers have introduced a biaryl backbone into the bisoxazoline ligands.[101] Heteroatoms have also been introduced into the backbone. In one example, Pfaltz and co-workers developed a new class of anionic, boron-bridged analogues of the chiral bisoxazoline ligands **75a** and **75b**. The interesting feature of this new type of bisoxazoline ligands is that the negative charge is located in the backbone. The Cu(I)-catalyzed asymmetric cyclopropanation with these ligands gives promising results (Scheme 56).[102]

Scheme 56.
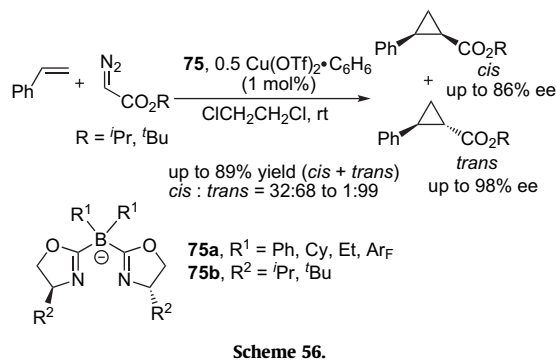
The C_2 symmetric bisoxazoline ligands are mostly used in Cu(I)-catalyzed intermolecular cyclopropanation. A recent example reported by Nakada and co-workers on the asymmetric cyclopropanation of α-diazo-β-keto sulfones demonstrates the successful application of C_2 symmetric bisoxazoline ligands **76** in intramolecular cyclopropanation (Scheme 57).[103] This example is the first highly enantioselective cyclopropanation for α-diazo-β-keto sulfones.

Some other C_2 symmetric ligands have also been explored recently.[104] Wilson and co-workers have reported a new chiral bipyridyl ligand **77** (Scheme 58).[104a] This ligand was evaluated in the asymmetric Cu(I)-catalyzed cyclopropanation reactions of a series of alkenes and diazoesters. High diastereoselectivity and enantioselectivity were observed (>95:5 dr and up to 99% ee).

In addition to the C_2 symmetric ligands, C_1 symmetric ligands,[105] C_3 symmetric ligands,[106] and multidentate N-donor ligands[107] have been developed for copper-catalyzed asymmetric cyclopropanation. Moreover, other chiral transition metal
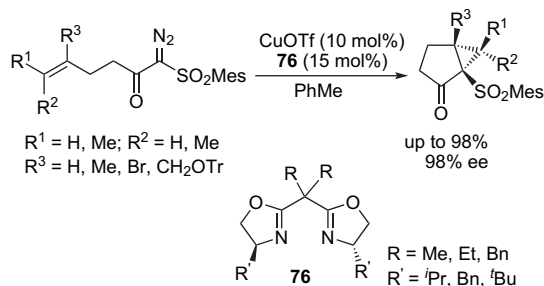
Scheme 57.
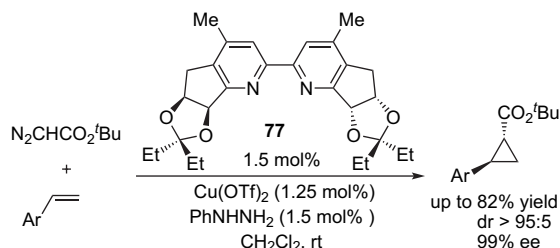
Scheme 58.

complexes, such as those of ruthenium,[108] iron,[109] cobalt,[110] and chromium,[111] have also been investigated in asymmetric cyclopropanation.

6. Ylide formation and related reactions

The interaction of the electron-deficient carbenic carbon of the metal carbene intermediate with a pair of non-bonding electrons contributed by a Lewis base (B:) generates a metal complex-associated ylide or a free ylide. The ylide intermediate thus generated is usually highly reactive and undergoes further reactions to give stable products (Scheme 59).
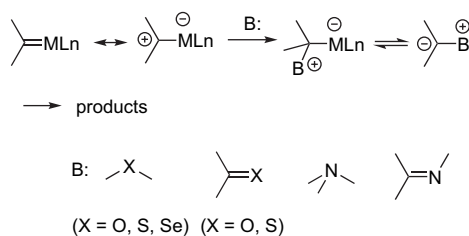
Scheme 59.

The common Lewis bases that are utilized to generate ylides include ethers, sulfides, amines, carbonyl compounds, and imines. The typical reactions of the ylides include: (1) [2,3]-sigmatropic rearrangement of allylic, propargylic, and allenic ylides; (2) 1,2-shift (Stevens rearrangement); (3) 1,3-dipolar cycloaddition of the ylides generated from carbonyl compounds or imines with dipolarophiles, usually C=C or C≡C bonds; and (4) nucleophilic addition/elimination, leading to the formation of epoxides or cyclopropanes.

The diverse reactivities of ylides make these intermediates valuable in organic synthesis. The ylide formation from a metal carbene and the subsequent reactions can occur in either an inter- or intramolecular manner. With these cascade transformations, it is possible to rapidly assemble organic compounds with considerable complexity from relatively simple starting materials. Besides, some of these reactions show excellent chemo-, regio-, and stereo-selectivity. Recent advances in asymmetric catalysis in this field add further merit to these transformations. Since this chemistry has been reviewed by us very recently,[112] in order to avoid repetition,

only the literature mainly published in the past two years will be surveyed here.

6.1. Sulfonium ylides

Sulfide groups are easy to interact with metal carbenes to generate the corresponding ylides. Useful reactions of the sulfonium ylides fall into two main classes: [2,3]-sigmatropic rearrangements and 1,2-shifts.

Sulfonium ylides generated from the reaction of metal carbene complexes and allylic, propargylic, or allenic sulfides readily undergo [2,3]-sigmatropic rearrangement. This type of rearrangement, known as the Doyle–Kirmse reaction, represents one of the most versatile bond reorganization processes in organic chemistry. Crich and co-workers have used this rearrangement as tool for amino acid and peptide modification (Scheme 60).[113] It is worthy of note that, even though there are many potential sites, such as N–H bonds and carbonyl groups, in both the allyl sulfide **78** and the diazo substrate **79**, which may interact with Rh(II) carbene, the sulfur ylide [2,3]-sigmatropic rearrangement product **80** is still formed in reasonable yield.
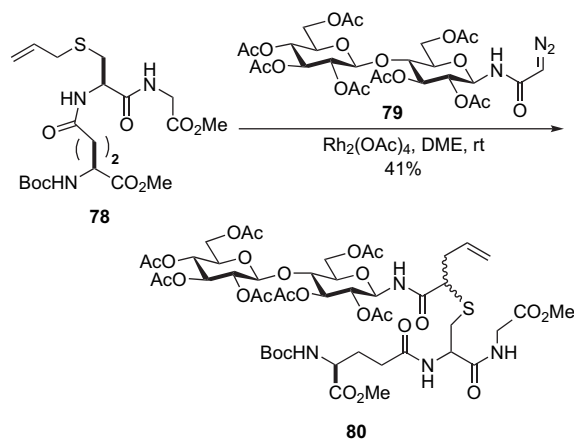
Scheme 60.

The Doyle–Kirmse reaction is usually performed in an anhydrous organic solvent under an inert atmosphere. However, it has been demonstrated that [2,3]-sigmatropic rearrangement of sulfur ylides derived from Rh(II) carbene and sulfides can be efficiently carried out in water. No O–H insertion product can be identified.[114] Again, this might be another example of an 'on water' reaction.

The allenyl sufides **81**, obtained from the [2,3]-sigmatropic rearrangement of sulfonium ylides generated from Rh(II) carbene and propargyl sulfide, can be further catalyzed by a Ru(II) catalyst to afford the furan derivatives **83** through a 1,4 migration of the sulfanyl group and generation of Ru carbene intermediates **82**. This discovery leads to a one-pot sequential catalytic transformation of α-diazocarbonyl compounds to furan derivatives (Scheme 61).[115]

Asymmetric catalysis in sulfonium ylide [2,3]-sigmatropic rearrangement reactions has progressed slowly in the past few years. Recently high stereoselectivity has been achieved using a double asymmetric induction approach with diazo substrates **84** bearing a chiral auxiliary, as shown in Scheme 62. With either chiral diimine ligand **85** or achiral ligand **86**, comparable enantioselectivities were obtained. It is noted in this reaction that the sense of the asymmetric induction is dictated by the chiral camphorsultam auxiliary, rather than by the chiral catalyst.[116]

The other major reaction pathway for sulfonium ylides is a 1,2-shift (Stevens rearrangement). This reaction has been extensively investigated by West and co-workers.[117] Such rearrangements may occur via a homolysis–recombination mechanism. The 1,2-shift is
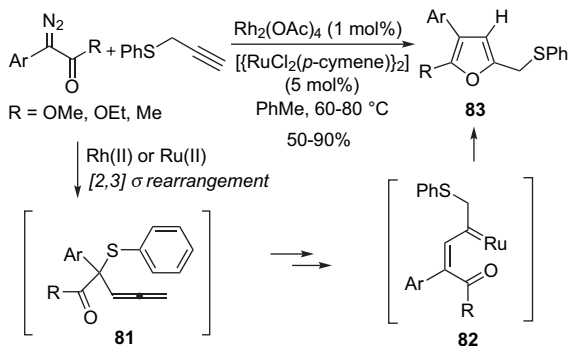
Scheme 61.
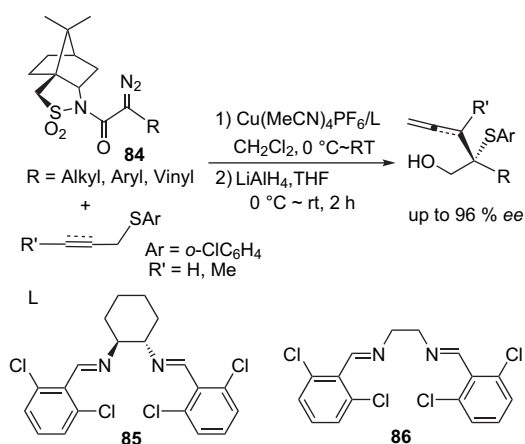
Scheme 62.

a useful methodology for carbene insertion into a C–S bond. This reaction is particularly useful in the synthesis of cyclic thioethers.[118] A recent example is a macrocyclic ring expansion by a double Stevens rearrangement (Scheme 63).[118b]

(R = H, 51%; R = Me, 42%)
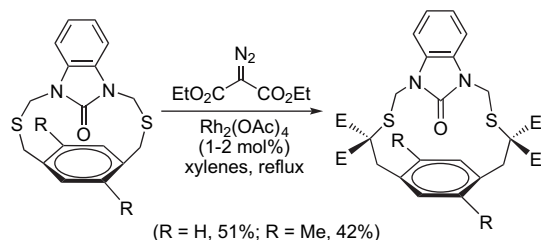
Scheme 63.

Nucleophilic addition of sulfonium ylides to a C=O or C=N bond is a route to produce epoxides or aziridines, with the release of sulfides. Aggarwal and co-workers have developed a catalytic cycle to achieve asymmetric epoxidation with a sulfonium ylide as a reactive intermediate.[119] Recent advances in this direction are the generation of diazo compounds in situ through a Bamford–Stevens reaction of tosylhydrazone salts, as shown in Scheme 4.[8]

6.2. Oxonium ylides

The oxygen heteroatom in ethers is a weak to moderate Lewis base. Nevertheless, a highly reactive metal carbene complex, such as Rh(II) carbene or Cu(I) carbene complex, can interact with the oxygen to generate an oxygen ylide. Similar to those of the sulfonium ylides, the major reaction pathways for oxonium ylides generated from metal carbene complexes are also [2,3]-sigmatropic rearrangements and 1,2-shifts.

A recent advance in [2,3]-sigmatropic rearrangements of oxonium ylides is the utilization of iodonium ylides as diazoketone surrogates for the generation of onium ylide intermediates and the subsequent rearrangement. The one-step procedure proceeds in comparable yields relative to the corresponding two-step route employing diazoketone intermediates (Scheme 64).[120]
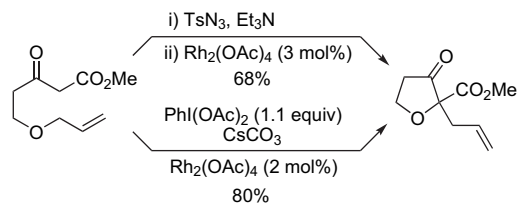
Scheme 64.

Stereoselective [2,3]-sigmatropic rearrangement of oxonium ylides has found applications in organic synthesis. A recent example is the synthesis of the fungal metabolite, (+)-decarestrictine L **89**. Tandem oxonium ylide formation and rearrangement are used to construct the tetrahydropyranyl core of this natural product (Scheme 65).[121] With Cu(tfacac)$_2$ as the catalyst, the reaction of **87** afforded the tetrahydropyrane **88** with good diastereoselectivity.
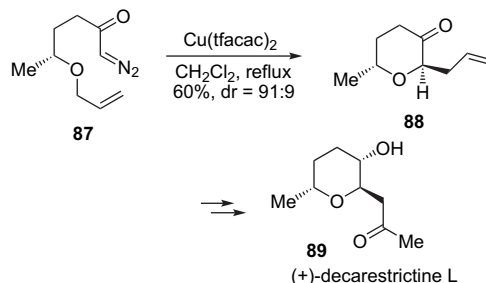
Scheme 65.

Besides [2,3]-sigmatropic rearrangement and 1,2-shift reactions, the oxonium ylide intermediate can be trapped by a nucleophile or proceed through other pathways. A recent example is a multicomponent reaction of the diazoketone **90** with an alcohol and aldehyde. This reaction involves a tricyclooxonium ylide intermediate **91** (Scheme 66).[122] The rearrangement of **91** results in the separation of positive and negative charges to give **92**. Subsequent trapping of the positive charge by the alcohol and the negative charge by the aldehyde gave **93**.
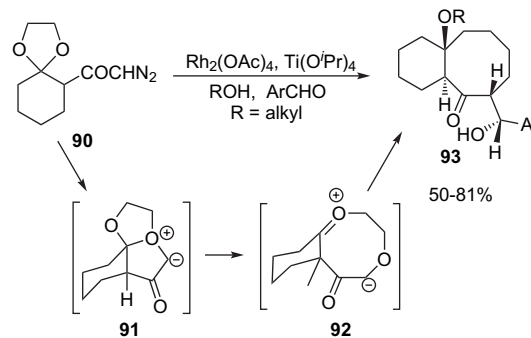
Scheme 66.

6.3. Ammonium ylides

Ammonium ylides can be generated from a metal carbene and an amine. These ylides undergo a 1,2-shift or a [2,3]-sigmatropic rearrangement in a manner similar to that of the corresponding

oxonium and sulfonium ylides.[123] A recent development was reported by Vanecko and West, who have utilized a ring expansion reaction of spiro azetidinium ylide **94** in the synthesis of pyrrolizidine alkaloids (Scheme 67).[123b]

Scheme 67.
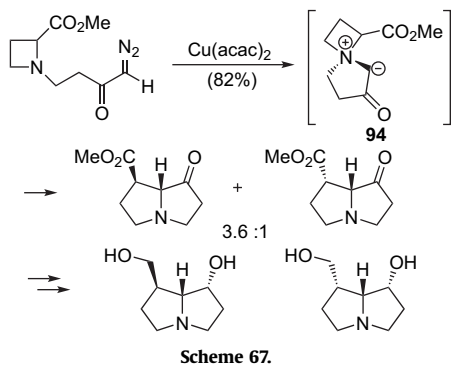
An interesting feature of ammonium ylides is that they can function as nucleophiles to add to imines and arylaldehydes. This chemistry has been studied extensively by Doyle and Hu.[124] Recently, this nucleophilic addition reaction has been extended to azo compounds. As shown in Scheme 68, the ammonium ylides **95** adds to diethyl azodicarboxylate (DEAD) to give **96** in moderate to good yields.[124c]

Scheme 68.
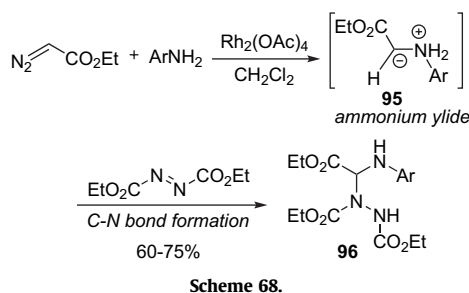
6.4. Carbonyl and azomethine ylides

The oxygen lone-pair electrons in a carbonyl group can react with the electron-deficient carbonic carbon of a metal carbene complex to generate the carbonyl ylide. Unlike an oxonium ylide, a positive charge in such a carbonyl ylide is mainly localized at the carbonyl carbon. Consequently, carbonyl ylides behave like 1,3-dipolar species (Scheme 69).

Scheme 69.
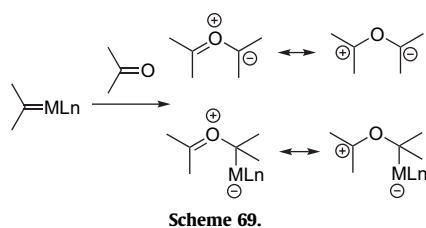
Carbonyl ylides possess versatile reactivities, among which the 1,3-dipolar cycloaddition is the most common and important reaction. The reaction sequence of ylide formation and then 1,3-dipolar cycloaddition can occur in either an inter- or intramolecular manner. Furthermore, the carbonyl ylides generated from metal carbenes can add not only to alkenes and alkynes but also to C=O and C=N bonds.

Cyclic carbonyl ylides can be generated through an intramolecular reaction of a metal carbene complex with a pendant carbonyl group. The ylide is then trapped by a dipolarophile to give

an oxygen-bridged bicyclic product. This tandem ylide formation/1,3-dipolar cycloaddition sequence has been extensively explored in organic synthesis by Padwa,[1c,f,125] Hashimoto,[126] Hodgson,[1h,127] and by many other groups.[128]

Padwa and co-workers have established an isomünchnone dipole, a push–pull carbonyl ylide, as an important intermediate in organic synthesis. The isomünchnone dipole can be trapped efficiently by various dipolarophiles to give the nitrogen-containing polycyclic compounds. A recent report by Padwa and co-workers describes the concise total synthesis of (±)-aspidophytine **98** by a Rh(II)-catalyzed carbenoid cyclization/cycloaddition cascade of a suitably substituted α-diazoimide **97** as the key step (Scheme 70).[125d]

Scheme 70.
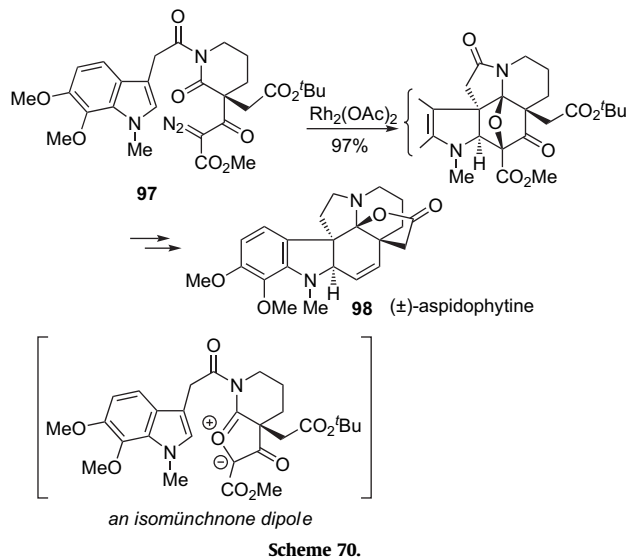
Hashimoto and co-workers have focused on the application of an ylide formation/1,3-dipolar cycloaddition cascade in the total synthesis of zaragozic acids, a family of polyketide natural products. Recently, they have achieved the total synthesis of zaragozic acid A **101** and C **102** (Scheme 71).[126b] The key step in their synthesis was the generation of a carbonyl ylide (a 1,3-dipole) from the Rh₂(OAc)₄-catalyzed reaction of diazo ester **99**, which was reacted with an electron-deficient triple bond to give **100** containing the core structure of zaragozic acid.

In addition to alkenes and alkynes, aldehydes, ketones, and imines can additionally act as dipolarophiles to react with carbonyl ylide dipoles. Various electron-deficient multiple bonds, such as N=N, N=O, C≡C bonds, and singlet oxygen, are also found to react with carbonyl ylides. These cycloaddition reactions provide efficient routes to various heterocycles.[129]

The 1,3-dipolar intermediates may follow pathways other than cycloaddition to double bonds. These pathways include rearrangement, ring closure to give epoxides, and nucleophilic addition.[112] An interesting recent report is the addition of nucleophiles to the carbonyl ylides. As shown in Scheme 72, the Rh₂(OAc)₄-catalyzed reaction of diazoketone **103** generates the carbonyl ylide intermediate **104**, which is attacked by nucleophiles, such as alcohols or amines, to afford the bicyclic products **105**.[130]

Asymmetric catalysis of the cascade carbonyl ylide formation–cycloaddition with chiral Rh(II) catalysts has been extensively investigated by Hashimoto, Hodgson, and by other groups.[112] Most of these investigations have used chiral metal complexes, mostly Rh(II) complexes, to generate chiral metal carbenes from diazocarbonyl compounds. An alternative and interesting approach, developed by Suga and co-workers, is to achieve the asymmetric induction by using an achiral Rh(II) catalyst to generate the

Scheme 71.

Scheme 72.
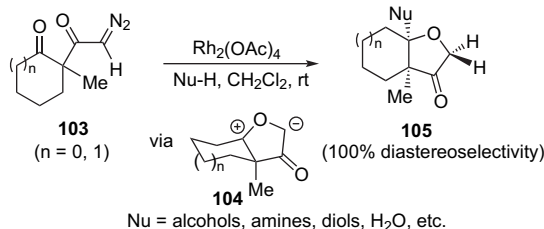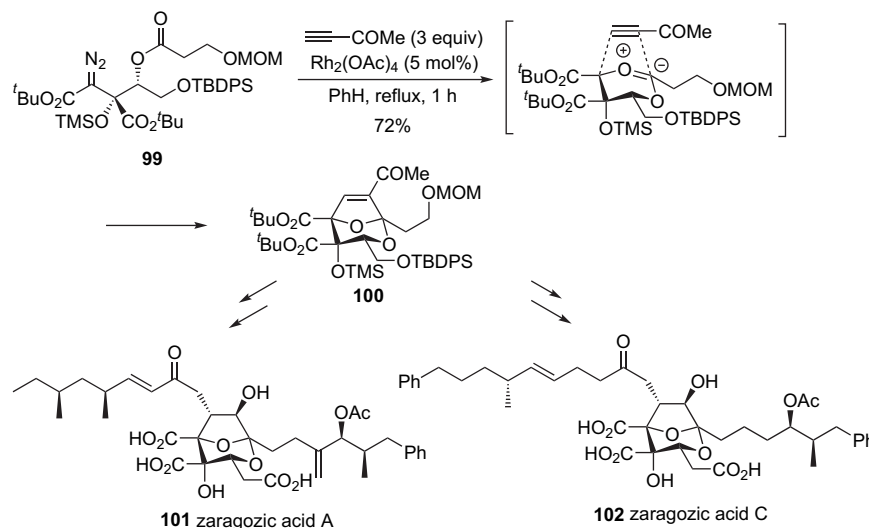
carbonyl ylide and a chiral Lewis acid to activate the C=O bond. High levels of enantioselectivity can be obtained by this approach with the chiral Lewis acids, Sc(III)-Pybox-^{i}Pr and Yb(III)-Pybox-Ph.[131]

Other developments in stereoselective 1,3-dipole cycloaddition include a chiral auxiliary approach by using dipolarophiles bearing chiral sulfinyl groups reported by Ruano and co-workers. A moderately high level of diastereoselectivity was observed.[132]

Very recently, Fu described the first examples of diastereo- and enantioselective copper-catalyzed asymmetric [4+1] cycloadditions of enones with diazo compounds through the use of a planar-chiral bipyridine ligand (−)-bpy 107. The carbonyl ylide intermediate 106 was considered as a reactive intermediate in this reaction (Scheme 73).[133]

Similar to the reaction with carbonyl compounds, a metal carbene reacts with imines readily to generate the corresponding azomethine ylides. The major reaction pathways of azomethine

Scheme 73.
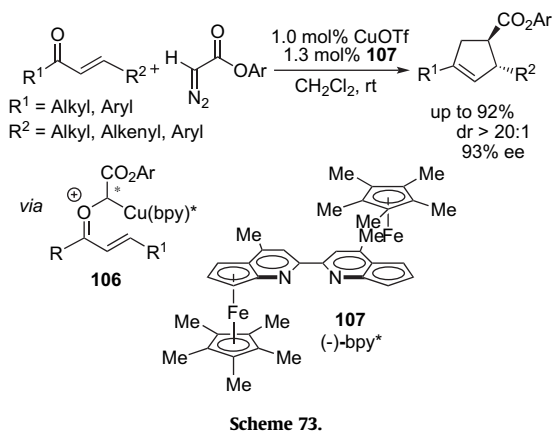
ylides are ring closure and 1,3-dipolar addition, which afford aziridines and pyrrolidines, respectively.[112] Transition metal complex-catalyzed three-component reactions, which include an imine, a diazo compound, and a dipolarophile, have been extensively studied in recent years.[134]

Che and co-workers have recently studied the stereoselective ruthenium porphyrin-catalyzed three-component coupling reaction of α-diazoesters with a series of N-benzylidene imines and alkenes, alkynes or azodicarboxylates to form the corresponding functionalized pyrrolidines, pyrrolines or 1,2,4-triazolidines (Scheme 10).[15a,134a,b]

6.5. Halonium ylides

Transfer of a metal carbene moiety from a metal carbene complex to a halogen is possible to generate a halonium ylide. The halonium ylides may follow similar pathways to other heteroatom (S, O, N, etc.) counterparts. One such example was very recently reported by Dias and co-workers. Silver(I) tris(pyrazolyl)borate 108-catalyzed reaction of diazoacetate in the presence of primary allylic or propargylic halides affords the [2,3]-sigmatropic rearrangement products in good yields (Scheme 74).[135]

Scheme 74.
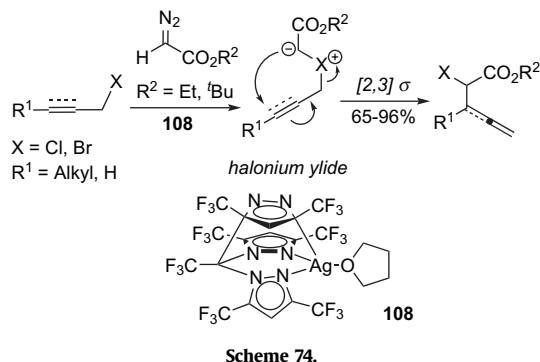
7. 1,2-Migration and Wolff rearrangement

7.1. 1,2-Migration

1,2-Migration is commonly encountered in transition metal-catalyzed reactions of α-diazocarbonyl compounds. Although 1,2-migration is usually considered as a side reaction that competes

with other typical metal carbene reactions such as X–H insertion and cyclopropanation, it has some useful applications in synthesis, e.g., Rh(II)-catalyzed reaction of β-hydroxy-α-diazocarbonyl compounds is a useful method to synthesize 1,3-dicarbonyl compounds.

When there are different migrating groups adjacent to the carbene center, the question arises as to which group will migrate preferentially (Scheme 75). Previous experimental data have clearly indicated that 1,2-H migration is a highly favorable process. Normally, no other group can compete with hydrogen in metal carbene 1,2-migration if there is a hydrogen present in the β-position. A phenyl group is easier to migrate, while an alkyl group is the most difficult to migrate.
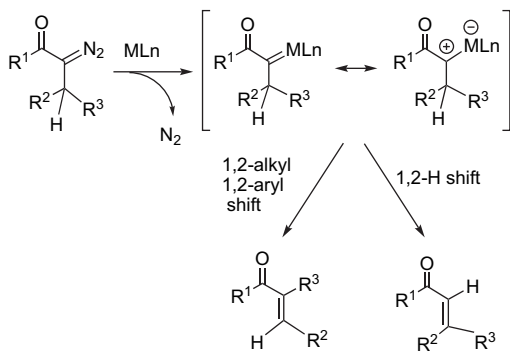
Scheme 75.

Recent studies by Wang and co-workers have demonstrated that this 1,2-migratory aptitude is significantly affected by the electronic and steric effects of the non-migrating substituents (bystander groups).[136] As shown by the examples in Scheme 76, 1,2-phenyl migration becomes predominant over 1,2-H migration when the bystander group is changed from a hydroxyl group to a tosylamino group and to a trichloroacetylamino group. This change of migratory aptitude is rationalized by the stabilizing effect of the partial positive charge developed in the transition state **109** by the protected amino group (Scheme 76).[136a,c] From the results of theoretical calculations on the 1,2-migration of singlet carbene, it is assumed that the 1,2-hydrogen migration can be viewed as largely resembling a hydride shift with significant charge separation in the transition state, while the 1,2-phenyl migration proceeds with less charge separation in the transition state.
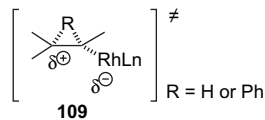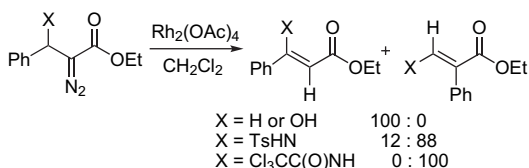
Scheme 76.

A similar change of migratory aptitude can also be seen in the case of 1,2-H versus 1,2-vinyl or 1,2-acetylenyl migration (Scheme 77).[136c]

The steric effect also plays an important role in affecting the migratory aptitude. A sterically bulkier group in the migrating origin obviously favors a large group, such as phenyl, to migrate, because the steric hindrance can thus be relieved. On the other hand, when there is a bulkier group attached to the carbene carbon, a small group (H) will migrate in order to relieve steric congestion

| X = OH | 100 : 0 |
| X = Cl$_3$CC(O)NH | 0 : 100 |
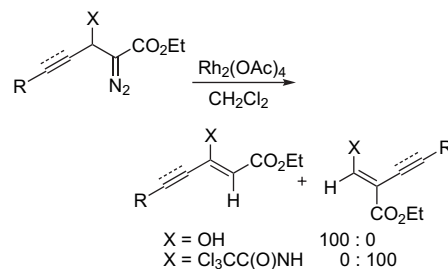
Scheme 77.

in the product. This trend can be clearly seen in the examples shown in Scheme 78.[136d]

| R = Me | 100 : 0 |
| R = ^{t}Bu | 0 : 100 |
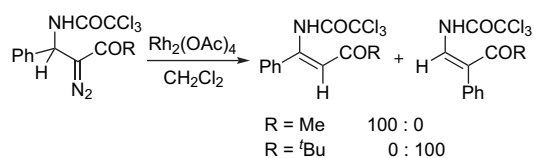
Scheme 78.

The ligands of Rh(II) catalysts have been known to change the reaction pathway of Rh(II) carbenes. Recently, Aggarwal and co-workers have showed that, by tuning the ligands on Rh(II) from acetate to trifluoroacetate, the normally very facile 1,2-H migration process could be completely reversed to favor 1,2-alkyl migration in the reaction with **110** (Scheme 79).[137] This is the first example in which 1,2-alkyl migration overrides 1,2-H migration.

R = PhCH$_2$CH$_2$

110

| Rh$_2$(OAc)$_4$ / PhMe, reflux | 91 : 9 |
| Rh$_2$(tfa)$_4$ / PhMe, rt | 0 : 100 |
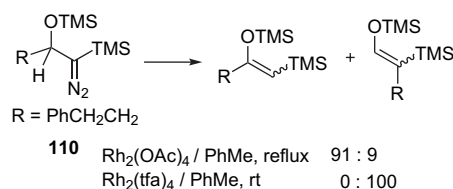
Scheme 79.

Wang and co-workers have also observed that a thio group has a higher migratory aptitude over hydrogen in the Rh$_2$(OAc)$_4$-catalyzed reactions of diazo compounds **111** (Scheme 80).[138]

111

R^1 = Et, *n*-hexyl, Ph, *p*-PhC$_6$H$_4$, *p*-MeOPh
R^2 = OEt, Me, Ph
R^3 = Ph, Bn, 2-naphthyl
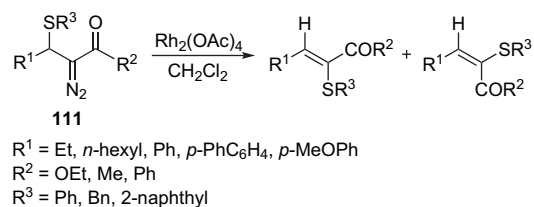
Scheme 80.

In a related investigation, the same group has observed a 2,3-migration in Rh(II)-catalyzed reactions of α-trifluoroacetamido β-diazocarbonyl compounds. The migration presumably proceeds through a five-centered transition state.[139]

7.2. Wolff rearrangement and related reactions

The Wolff rearrangement of α-diazocarbonyl compounds generate a short-lived ketene intermediate that may undergo further reactions such as cycloaddition or attack by nucleophiles (Scheme 81).[19] The Wolff rearrangement has been widely used in organic synthesis for the homologation of carboxylic acids (Arndt–Eistert reaction) and for ring contraction, leading to strained cyclic

systems. The Wolff rearrangement can be carried out under either photochemical or transition metal-catalyzed conditions.
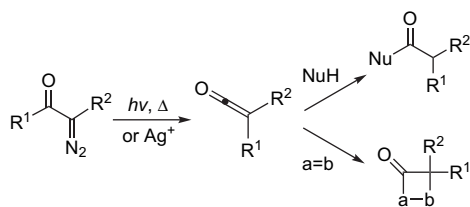
Scheme 81.

As a well-established synthetic methodology, the Wolff rearrangement continues to find application in organic synthesis in the past few years.[140] A remarkable example of a Wolff rearrangement-based ring contraction in synthesis was reported by Mascitti and Corey in the total synthesis of pentacycloanammoxic acid **116**, a highly unusual fatty acid with rigid ladder structure. To construct the unusual fused four-membered ring system, ring contraction by the Wolff rearrangement was repeated two times from **112** to **113** and from **114** to **115** (Scheme 82).[140d,e]
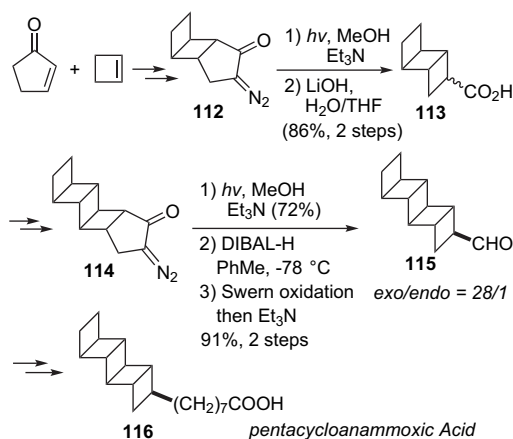
Scheme 82.

Several new synthetic methodologies based on the Wolff rearrangement have been reported recently. Stoltz and co-workers have developed an efficient method for the construction of a highly functionalized cycloheptadienone **118** and a vinylcyclopentenone **119** by a tandem Wolff/Cope rearrangement sequence with vinyl cyclopropyl diazoketone **117**. The interesting feature is that, under Ag(I)-catalyzed conditions, the tandem reaction affords the cycloheptadienone derivative **118**, while under photochemical conditions it gives the vinylcyclopentenone **119** (Scheme 83).[141] The formation of **119** is due to a secondary photochemical reaction of the primary product **118**.

The ketene intermediates generated from the Wolff rearrangement undergo [2+2] cycloaddition reactions with alkenes, alkynes, and imines. These cycloaddition reactions provide efficient tools for constructing four-membered ring structures. In particular, the reaction with imines (Staudinger reaction) is an important procedure to synthesize β-lactam derivatives. Xu and co-workers have studied this reaction in some detail.[142] By using ethoxycarbonyl(phenylthio)ketene **121**, which is generated by a thia-Wolff rearrangement in a Rh₂(OAc)₄-catalyzed reaction of 3-phenylthio-2-diazo-3-oxopropionate **120**, a new synthesis of 3-alkoxycarbonyl β-lactam derivatives **122** has been developed (Scheme 84).[142a]

Besides the [2+2] cycloaddition reaction, ketenes can also undergo other cycloaddition reactions, such as [2+1], [2+4], and [4+1] cycloadditions. Danheiser and co-workers have extensively investigated the [4+1] cycloaddition. A recent example is a new
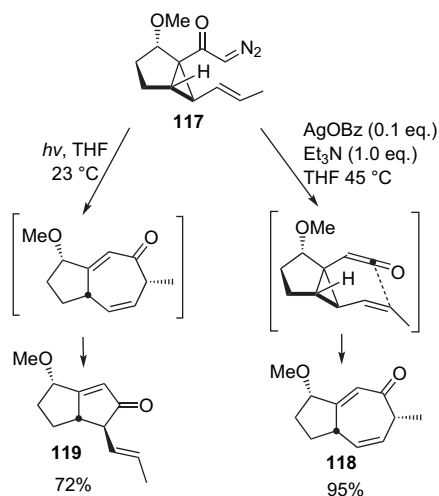
Scheme 83.
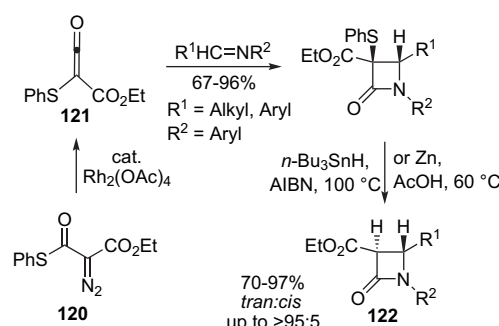
Scheme 84.

[4+1] annulation route to cyclopentenones **125** via the reactions of (trialkylsilyl)arylketenes **124**, which are generated photochemically from **123** (Scheme 85).[143]
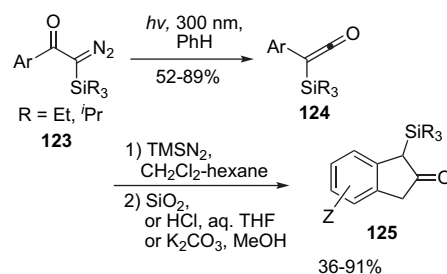
Scheme 85.

A [4+2] 6π-electrocyclization route to highly substituted aromatic compounds **128** has also been developed by the same group (Scheme 86).[144] The reaction is proceeded from the initial C-acylation of the ynolates **127** by the vinylketene intermediates **126**.

Other important developments in the Wolff rearrangement include novel catalytic systems such as in situ generated silver
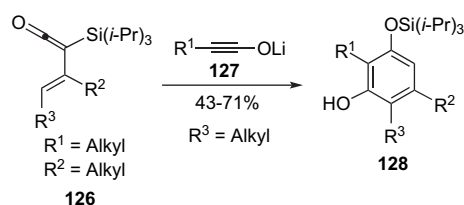
Scheme 86.

nanoclusters,[145] mechanistic studies,[146] applications of the Wolff rearrangement in processes for the patterning of polymers,[147] and for the synthesis of UV light-sensitive micelles.[148]

8. Reactions with α-diazocarbonyl compounds as nucleophiles

Although diazo compounds are highly unstable under acidic conditions, they are generally stable under basic conditions. Acyldiazomethane can be deprotonated to generate an anion, which can function as a carbon nucleophile. Moreover, since the carbon attached to the dinitrogen is negatively polarized, the diazo compound itself can be a nucleophile (Scheme 87).[1d,149] Mayr and co-workers have showed that diazomethane, phenyldiazomethane, and trimethylsilyldiazomethane are comparable in nucleophilicity to ketene acetals, while the less reactive compounds, diphenyldiazomethane, ethyl diazoacetate, and diazoacetone, are comparable to typical silyl enol ethers and activated allylsilanes, and the nucleophilicity of diethyl diazomalonate corresponds to that of 1,1-dialkylethylenes or styrenes.[150] These nucleophiles bearing a diazo functionality can add to C=O or C=N double bonds to afford diazo compounds with various functional groups.
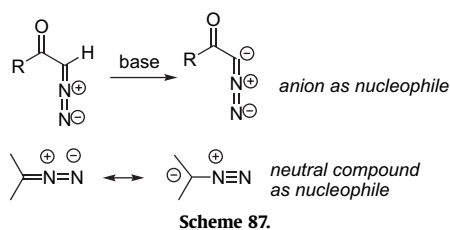
Scheme 87.

On the other hand, α-diazo β-keto compounds **129** can be enolized to generate enolates, which can function as nucleophiles (Scheme 88). The most common procedure to enolize these diazo compounds is to convert them into boron or Ti(IV) enolates or into silyl enol ethers **130**. Similar to the common enolates, nucleophilic additions to C=O or C=N bonds are possible with **130**.
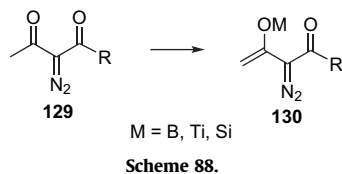
Scheme 88.

Although the sensitivity of the diazo functionality to the strong acids and bases has limited the potential widespread use of these diazo group-containing nucleophiles, some useful synthetic methodologies have been developed based on these nucleophiles, and there have been some new developments in recent years.

Nucleophilic addition of an acyldiazomethane to an aldehyde or ketone under strongly basic conditions has been known for some time.[149] The α-hydroxy β-diazocarbonyl compounds thus obtained can be catalyzed by transition metal complexes to give β-keto carbonyl compounds through 1,2-migration. This transformation has potential utility in organic synthesis (Scheme 89).

A reaction using mild condition for promoting the condensation of acyldiazomethanes with aldehydes or imines involves the application of DBU in catalytic amounts.[151] This reaction can also be carried out in water (Scheme 90).[151b] In addition, phase-transfer catalyst quaternary ammonium salts have been introduced into these reactions.[152] The condensation can also be carried out under Lewis acid-catalyzed conditions.[153]

B = n-BuLi, LDA, NaH, KOH, NaOH, KHMDS

Scheme 89.

R = Me, Aryl, PhC≡C, C₅H₁₁C≡C
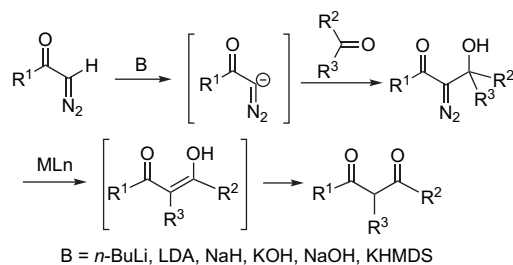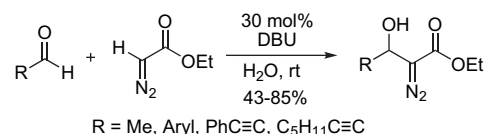
Scheme 90.

A further extension of this chemistry is the catalytic asymmetric aldol-type reactions of aldehydes with diazoesters. Yao and Wang have reported that, with a chiral complex of (S)-6,6′-Br₂BINOL-Zr(O^{t}Bu)₄, asymmetric induction is possible with moderate enantioselectivities (Scheme 91).[154]

R = Aryl, PhCH=CH, n-C₃H₇   53-87% ee
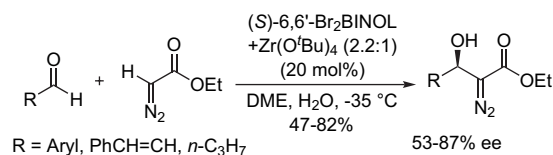
Scheme 91.

A similar level of enantioselectivity has been reported by Nishida and co-workers in the condensation of aldehydes with *tert*-butyl diazoacetate catalyzed by a phase-transfer catalyst, cinchonidinium salt **131** (Scheme 92).[152a,b]
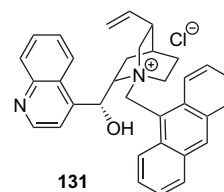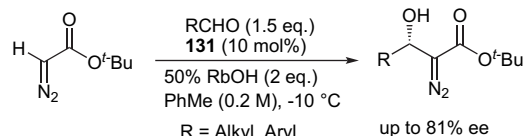
Scheme 92.

As imines are generally thought to be less active than aldehydes, the corresponding addition of the diazo compounds to imines has not been studied in detail. An investigation by Wang and co-workers demonstrated that the condensation of acyldiazomethanes could be carried out similarly to that with aldehydes.[155] A recent example is the nucleophilic addition of ethyl diazoacetate (EDA) derived anions to N-tert-butylsulfonyl cycloketimines **132**. The addition products **133** can be converted into cyclic enamines **134** via Rh₂(OAc)₄-catalyzed ring expansion (Scheme 93).[155d] Meanwhile, a Lewis acid-catalyzed nucleophilic addition of diazoacetate to iminium ion has also been reported.[156]

In a further study, Wang and co-workers have developed a stereoselective C=N addition of diazo group-containing anions
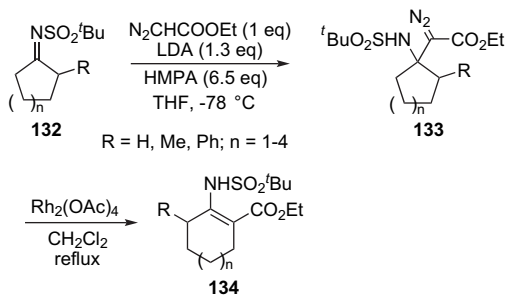
Scheme 93.

with a chiral auxiliary approach (Scheme 94).[157] Thus, the anion derived from the diazoamide **135**, which was bonded to Evans' chiral oxazolidinone auxiliary, added to N-tosylimine with high diastereoselectivity. In the optimized reaction conditions, high diastereoselectivity could be achieved for a series of imine substrates. The chiral auxiliary could be removed and the products were converted into syn- or anti-α-hydroxy-β-amino acid derivatives **136** or **137**.
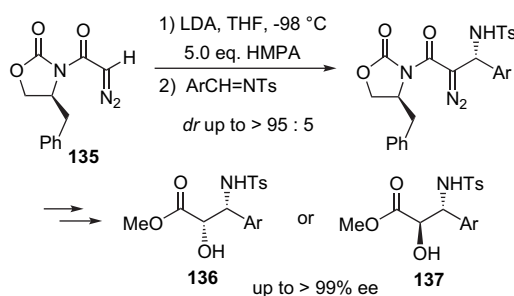
Scheme 94.

An asymmetric catalytic version of this C=N bond addition has been recently achieved by Terada and co-workers with a chiral binaphthol monophosphoric acid **138**,[158] and by Maruoka and co-workers by using a chiral dicarboxylic acid **139** (Scheme 95).[159]
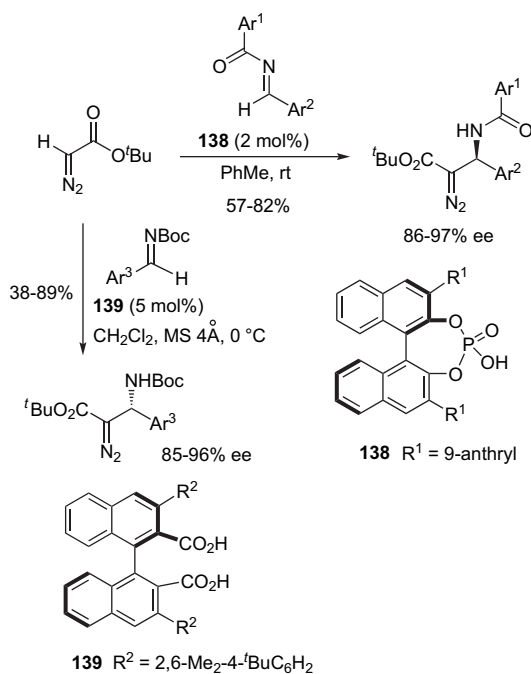
Scheme 95.

The nucleophilic addition to C=O or C=N bonds by the enolates derived from β-keto α-diazocarbonyl compounds can also be achieved similarly. These nucleophilic additions have been incorporated as key steps in the synthetic methods for heterocycles.

Ti(IV) enolates **140** derived from α-diazo β-ketoesters react efficiently with aldehydes, but the reaction becomes sluggish when ketones are used as substrates. To activate the C=O group, Ti(O^{i}Pr)$_4$ was used as Lewis acid in the reaction. In this way, the corresponding nucleophilic addition occurred to various ketones. The addition products **141** were further converted into cyclic compounds **142** or **143** through a photoinduced Wolff rearrangement or Rh(II)-catalyzed insertion reactions (Scheme 96).[160] A similar addition reaction was also carried out with tosylimines and the addition products were similarly converted into γ-lactams or pyrroles.[161]
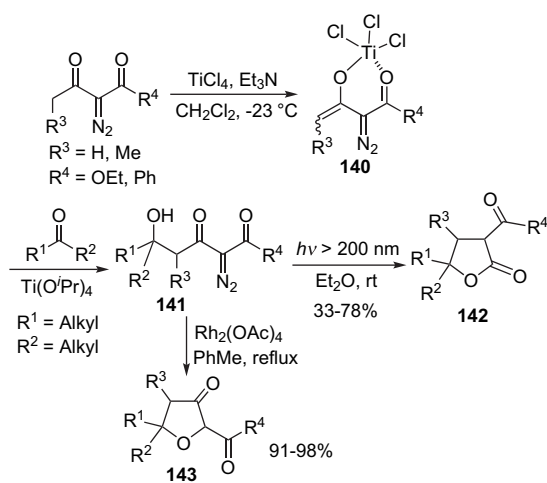
Scheme 96.

Padwa and co-workers have investigated the DABCO-promoted aldol-type reactions of the azido diazo dicarbonyl compounds **144** with aldehydes. The products, γ-azido-α-diazo-δ-hydroxy-β-keto esters **145** can be further converted into different compounds such as **146** and **147** (Scheme 97).[162]
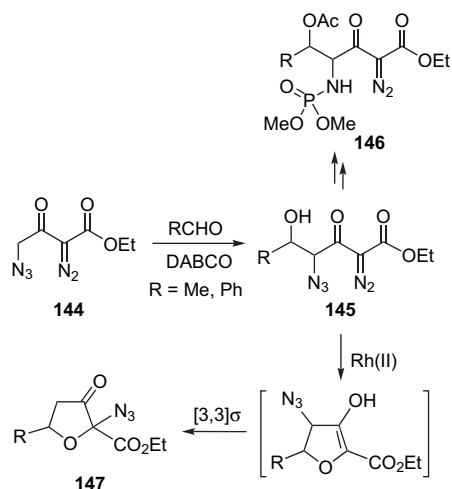
Scheme 97.

A further extension of this chemistry would be asymmetric catalysis in the above nucleophilic addition. It is conceivable that the Mukaiyama aldol addition with silyl enol ethers may be similarly applied.[163] Doyle and co-workers have explored such a possibility with enol ether **148** by using AgF/(R)-BINAP as a chiral catalyst.

A moderately high level of enantioselectivity has been achieved (Scheme 98).[163b]

Scheme 98.
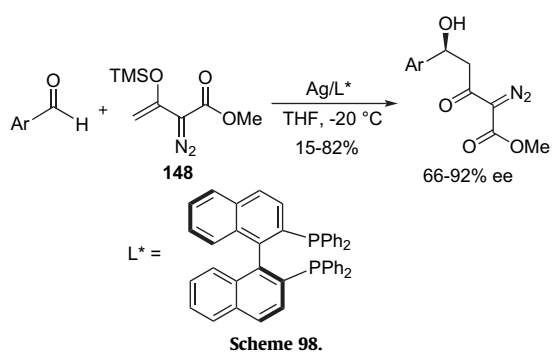
On the other hand, there are other types of reactions that are related to diazo group-containing nucleophiles. The most notable is the addition of the anion derived from a diazophosphonate to aldehydes, which is the key step in the synthesis of terminal alkynes from aldehydes (Scheme 99).
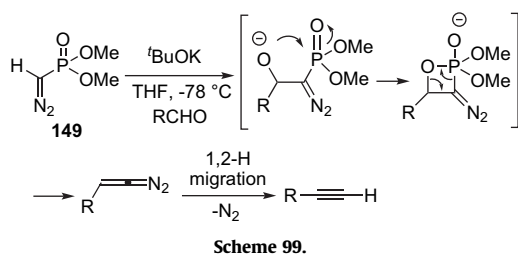
Scheme 99.

A valuable modification of the original procedure, which utilizes dimethyl diazomethylphosphonate **149**, as shown in Scheme 99, is the use of more stable dimethyl-2-oxopropylphosphonate **150**.[164] More recently, the use of ROMPgel-supported ethyl 1-diazo-2-oxopropylphosphonate **151** has been reported.[165] In these cases, the diazophosphonate anion is generated by base-promoted deacetylation. These diazo reagents have proved to be useful in natural product synthesis.[166] As a further extension, Taylor and co-workers have reported a one-pot conversion of activated alcohols into terminal alkynes using manganese dioxide in combination with **150**.[167]
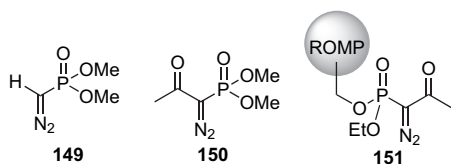
Ethyl diazoacetate has also been reported to undergo a Michael addition-type reaction to add to the β-carbon of α,β-unsaturated aldehydes **152**. The reaction was catalyzed by acid and gave cyclopropane derivatives **153** as the final products (Scheme 100).[168]

9. Miscellaneous reactions

9.1. Diazocarbonyl compounds as 1,3-dipoles in [3+2] cycloaddition

The diazo group itself can act as a 1,3-dipole to add to a dipolarophile with retention of the nitrogen moiety. The cycloaddition reactions with electron-deficient olefins can occur in the absence of a catalyst in purely thermal conditions. This reaction has been an efficient procedure to synthesize pyrazolines (Scheme 101).[169]

Scheme 100.

Scheme 101.
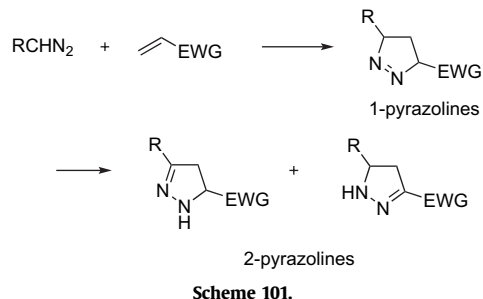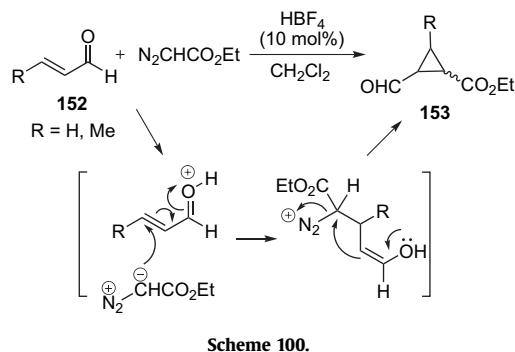
Recent studies on this type of 1,3-dipolar cycloaddition have focused on the development of stereoselective reactions. A chiral auxiliary-based approach has been reported by using dipolarophiles bearing chiral substituents. García Ruano and co-workers utilized chiral vinyl sulfoxide **154** as dipolarophile in 1,3-dipolar cycloadditions.[170] It was demonstrated that the chiral sulfinyl group was able to completely control the π-facial selectivity to give **155** in very high diastereoselectivity. Interestingly, the diastereoselectivity could be inverted in the presence of Lewis acids, with Yb(OTf)₃ being the most efficient. Chelation of the Yb(OTf)₃ with carbonyl oxygen and sulfinyl oxygen was considered to be responsible for the inversion of facial selectivity (Scheme 102).[170d]

Scheme 102.
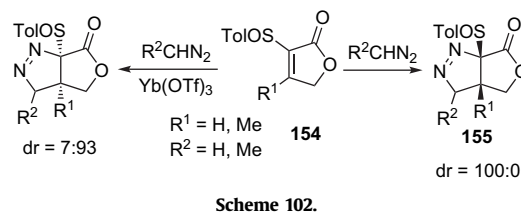
An asymmetric catalytic variant of this transformation has been a challenging problem, but progress has been made recently by Maruoka and co-workers. With catalytic chiral titanium BINOLate Lewis acids, (S)-BINOL/Ti(O^{i}Pr)$_4$ (2:1) and bis{((S)-binaphthoxy)-(isopropoxy)titanium}oxide, high enantioselectivities were achieved in 1,3-dipolar cycloadditions between diazoacetate and α-substituted acroleins (Scheme 103).[171]

Electron-deficient alkynes also react with electron-rich diazo compounds such as diazomethane under mild conditions. This is an important method to prepare pyrazole derivatives. However, the reaction of less electron-rich α-diazocarbonyl compounds with electron-deficient alkynes usually requires activation by Lewis
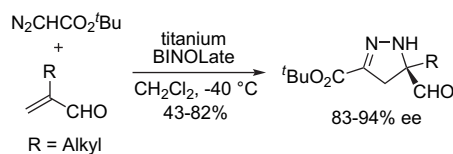
Scheme 103.

acids. Jiang and Li have recently reported an intermolecular 1,3-dipolar cycloaddition of diazocarbonyl compounds with alkynes by using an $InCl_3$-catalyzed cycloaddition in water (Scheme 104).[172] The alkynes bearing a carbonyl group at the neighboring position reacted smoothly with ethyl diazoacetate (EDA) to give the pyrazole products **156** and **157** in good yields. However, phenylacetylene failed to react under the same conditions. This suggests that $InCl_3$ activates the alkynes by coordinating the carbonyl group and thus lowers the LUMO of the alkyne moiety.
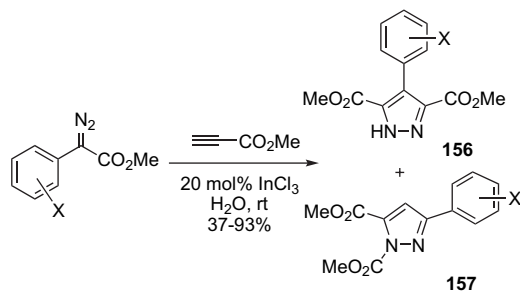
Scheme 104.

For simple alkyl or aryl alkynes, the reaction with α-diazocarbonyl compounds usually fails and Lewis acid activation cannot be applied in such cases. An alternative mode of activation by raising the HOMO level of the alkyne was reported by Qi and Ready very recently.[173] Thus, the alkyne was converted into the copper(I) acetylide, which was then reacted with diazoacetate. The cycloaddition occurred smoothly to afford the pyrazole derivatives **158** in moderate to good yields (Scheme 105). The copper is suggested as an electron-donating group to raise the HOMO of the alkyne. The cycloaddition thus involves the LUMO level of the diazo compound. This is a rare example of an inverse electron demand cycloaddition.
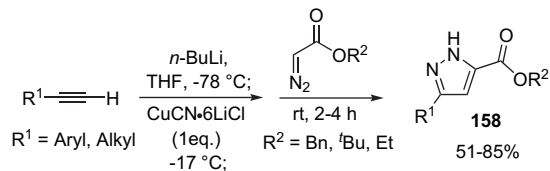
Scheme 105.

Other developments in the reactions of diazo compounds as 1,3-dipoles include the reactions of 1,3-dipolarophiles with trimethylsilyldiazomethane,[174] or with in situ generated aryldiazomethanes,[175] the reactions of conjugated nitroalkenes with the anion of diethyl 1-diazomethylphosphonate, generated in situ from diethyl 1-diazo-2-oxopropylphosphonate (Bestmann-Ohira reagent),[176] and a three-component reaction of in situ generated N-fluoropyridinium fluoride with isonitrile and diazo compound.[177]

Arynes have also been used in the 1,3-dipolar cycloaddition with diazo compounds. The reaction affords indazole derivatives that are pharmaceutically important compounds.[178] Recently, Jin and Yamamoto have developed a [3+2] cycloaddition of various diazomethane derivatives with arynes generated from silylaryl triflates **159** by treatment with KF or CsF (Scheme 106).[179] When only 0.5 equiv of diazo compounds were used in this reaction, the 1,3-dipolar addition product further reacted with arynes to yield **160**.

9.2. Dimerization, olefination, and oligomerization and polymerization of diazocarbonyl compounds

9.2.1. Dimerization of diazocarbonyl compounds

Although dimerization is normally regarded as an unwanted side reaction in transition metal-catalyzed reactions of diazocarbonyl compounds, it can be a quite useful and efficient route to
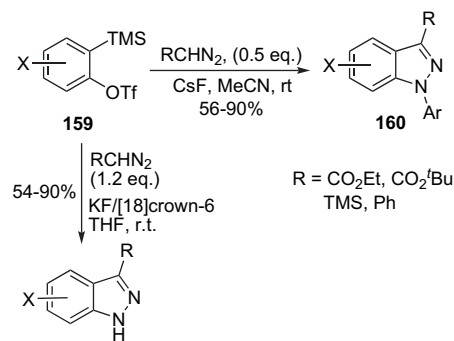
Scheme 106.

olefins. Many transition metal complexes, such as nickel, copper, iridium, osmium, tantalum, rhenium, and chromium complexes, have been shown to catalyze the generation of olefins from diazo compounds. When this reaction is used as a synthetic method for olefins, the cis/trans selectivity becomes a crucial issue.[180] Generally, the thermodynamically more stable trans isomer is predominant. Recently, Hodgson and co-workers have demonstrated that the highly cis selective heterocoupling of α-diazoacetates can be achieved by Grubbs' second-generation catalyst (Scheme 107).[181]
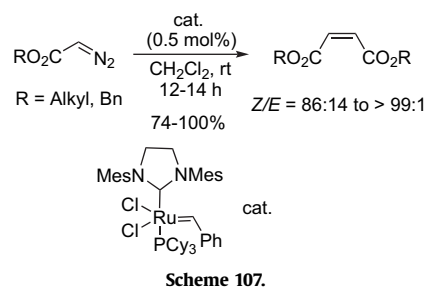
Scheme 107.

Li and Che have also obtained high cis selectivity in the coupling reactions of α-diazoacetates with their ruthenium porphyrin catalyst. This catalytic system was especially efficient in the synthesis of macrocyclic compounds bearing a cis-alkene motif, as demonstrated by a one-step synthesis of paulolide A **162** and B **163** from the corresponding bisdiazo compound **161** (Scheme 108).[182]

9.2.2. Olefination of diazocarbonyl compounds

The olefination of aldehydes or ketones with diazo compounds is another important approach for constructing carbon–carbon double bonds, which avoids the need for stepwise generation of ylide precursors under basic conditions in a traditional Wittig reaction. The reaction is usually carried out in the presence of a phosphine, in most cases Ph_3P. When aldehydes are used as substrates, the olefins are usually produced with high selectivity for
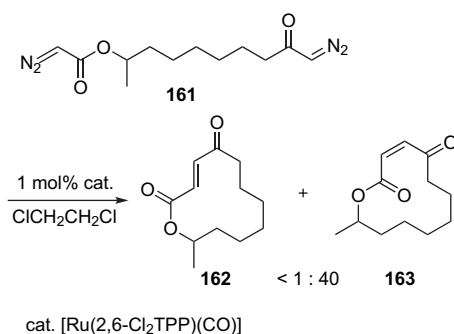
Scheme 108.

the *E*-geometry. Since the first report by Herrmann and co-workers with MeReO$_3$ (methylrhenium trioxide, MTO) in 1991,[183a] this area has been extensively studied and efficient catalytic olefination reactions with good stereoselectivity have been reported based on Re,[183,184] Ru,[185] Rh,[186] Fe,[187] Cu,[188] and Co[189] complexes.

Depending on the metal complex, there are two different mechanistic pathways proposed for the olefination of aldehydes with diazo compounds (Scheme 109). In the first place, the metal carbene reacts with the carbonyl compound to form a metal oxo species, which is then reduced by the phosphorus reagent followed by the reaction with EDA to generate the metal carbene **165**, which reacts with aldehyde in a manner similar to olefin metathesis to afford the olefination product **166**, with regeneration of the metal oxo species **164** (Path A). Alternatively, the metal carbene is first generated by the reaction of the metal complex with EDA. The phosphorus reagent attacks the metal carbene, forming a phosphorus ylide species **167** that reacts with carbonyl derivatives by a Wittig reaction (Path B). With electron spray mass spectrometry, NMR, and other spectroscopic methods, evidence to support both mechanisms has been obtained. It has been suggested that, in the reaction with methylrhenium trioxide (MTO) and similar rhenium oxides as catalysts, the reaction follows Path A, with a metal-laoxetane as intermediate,[183,184] while in the reaction with iron and cobalt porphyrin, or Ru complexes as catalysts, Path B is followed, with generation of the phosphorus ylide.[185,187,189] On the other hand, in the methylation of aldehyde by TMSCHN$_2$ with ClRh(PPh$_3$)$_3$ as catalyst, a different mechanism for the generation of the phosphorus ylide that does not involve a metal carbene is proposed.[186b]

Scheme 109.
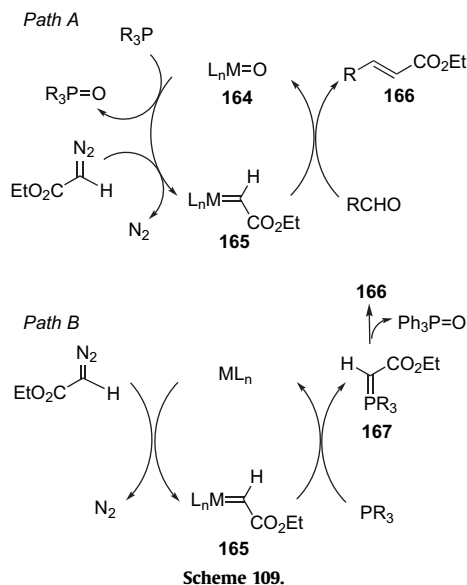
A recent development is that reported by Tang, Zhou and co-workers on the olefination of ketenes with ethyl diazoacetate catalyzed by tetra(*p*-chlorophenyl)porphyrin iron chloride [Fe(TCP)Cl].[187h] This reaction could serve as an efficient synthesis of allenes. Moreover, when a chiral phosphine **168** was used instead of Ph$_3$P, the olefination occurred with high enantioselectivity (Scheme 110). This result confirmed that the mechanism involves ylide olefination.

Another recent observation is that, with ruthenium-based olefin metathesis catalysts, α,β-unsaturated aldehydes can be olefinated with diazoacetates in the presence of triphenylphosphine. Based on this result, a cross-metathesis/olefination tandem transformation of terminal olefins into 1,3-dienoic esters has been developed using a single ruthenium carbene complex **169** (Scheme 111).[185d]

Scheme 110.

Scheme 111.
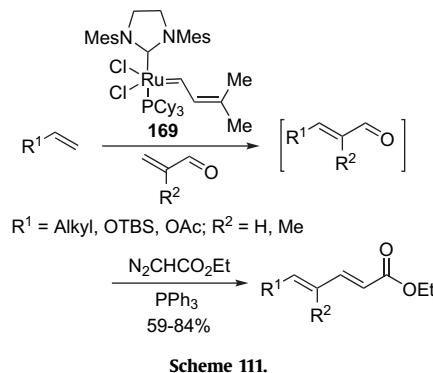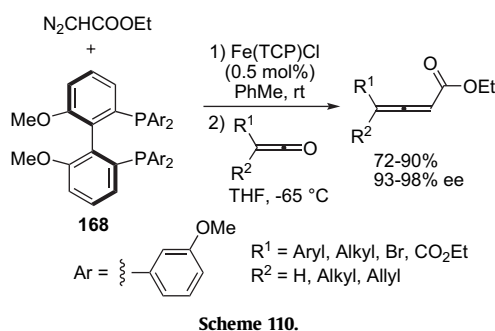
9.2.3. Oligomerization and polymerization of diazocarbonyl compounds

Polymerization with diazo compounds will generate polymers that contain polymer backbones consisting of one-carbon units. This is fundamentally different from the traditional vinyl polymerization, which generally produces polymers that contain carbon–carbon single bond units (Scheme 112). Although polymerization of diazoalkanes has been known for a long time, the polymerization of the more stable α-diazocarbonyl compounds has not been reported until very recently.

Scheme 112.
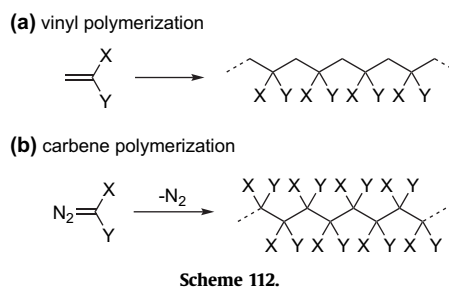
Ihara, Inoue and co-workers have investigated the palladium-mediated oligomerization of diazoacetates and related diazocarbonyl compounds. However, the viscous oils obtained with Pd-catalyzed polymerization with alkyl diazoacetates generally have low molecular weight and low selectivity (average degree of polymerization up to about ca. 100). A mechanism has been proposed for the polymerization process.[190] Oligomerization of alkyl diazoacetates with copper powder has also been reported.[191]

A recent breakthrough in this field is the report of an unprecedented stereoregular polymerization of ethyl diazoacetate, which gives a high molecular weight poly(ethyl 2-ylidene acetate) (120–165 kDa) (Scheme 113).[192] The reaction is catalyzed by a series of new rhodium(I) complexes **170**. These new polymers with unique structure are expected to show special material properties.

Finally, Shea and co-workers have very recently investigated the polymerization of ethyl diazoacetate with BH$_3$. The polymerization
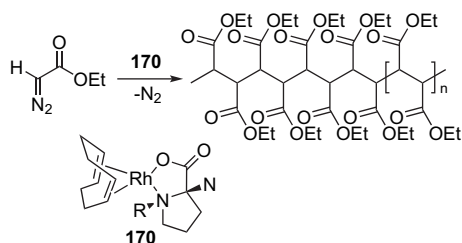
Scheme 113.

proceeds with the formation of an unusual homologated *C*-boron enolate.[193]

10. Concluding remarks

Although α-diazocarbonyl compounds have been studied for many years, it is clear from the various new developments published since 2003 that there is still much exciting undiscovered chemistry can be expected from this type of compounds. As transition metal carbene precursors, α-diazocarbonyl compounds continue to find application in organic synthesis, especially in asymmetric catalysis. Chiral Cu(I) and Rh(II) complexes developed in the past decades have been further proved to be effective in enantioselective carbene-transfer reactions, especially C–H insertion and cyclopropanation. As exemplified by the total synthesis of natural products in this review, these highly enantioselective reactions have reached the stage where they can serve as powerful tools in synthetic organic chemists' arsenal for constructing complex molecules. Asymmetric catalysis has also seen progress in other metal carbene-transfer reactions, such as ylide reactions, and O–H and N–H insertions. In addition, the tandem processes incorporating metal carbene-transfer reactions have been developed and have found applications in constructing complex structures from relatively simple starting materials by a single catalytic operation.

The search for new catalysts continues to be important in this field and several new catalysts have been found to be effective in the reactions with α-diazocarbonyl compounds. For the well-established catalysts, such as Rh(II) complexes, the design of novel ligands and the catalyst immobilization have been the major focus of attention in the past few years.

Noteworthy developments have been seen in areas other than those of the above-mentioned typical reactions for diazo compounds (insertion, cyclopropanation, ylide generation, etc.). These include polymerization, olefination, and the reactions in which diazo compounds serve as nucleophiles. These developments open new possibilities in this field.

Given the various achievements that have been made in the past few years, there is enough reason to expect more imaginative new applications of α-diazocarbonyl compounds to be forthcoming in the near future.

Acknowledgements

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