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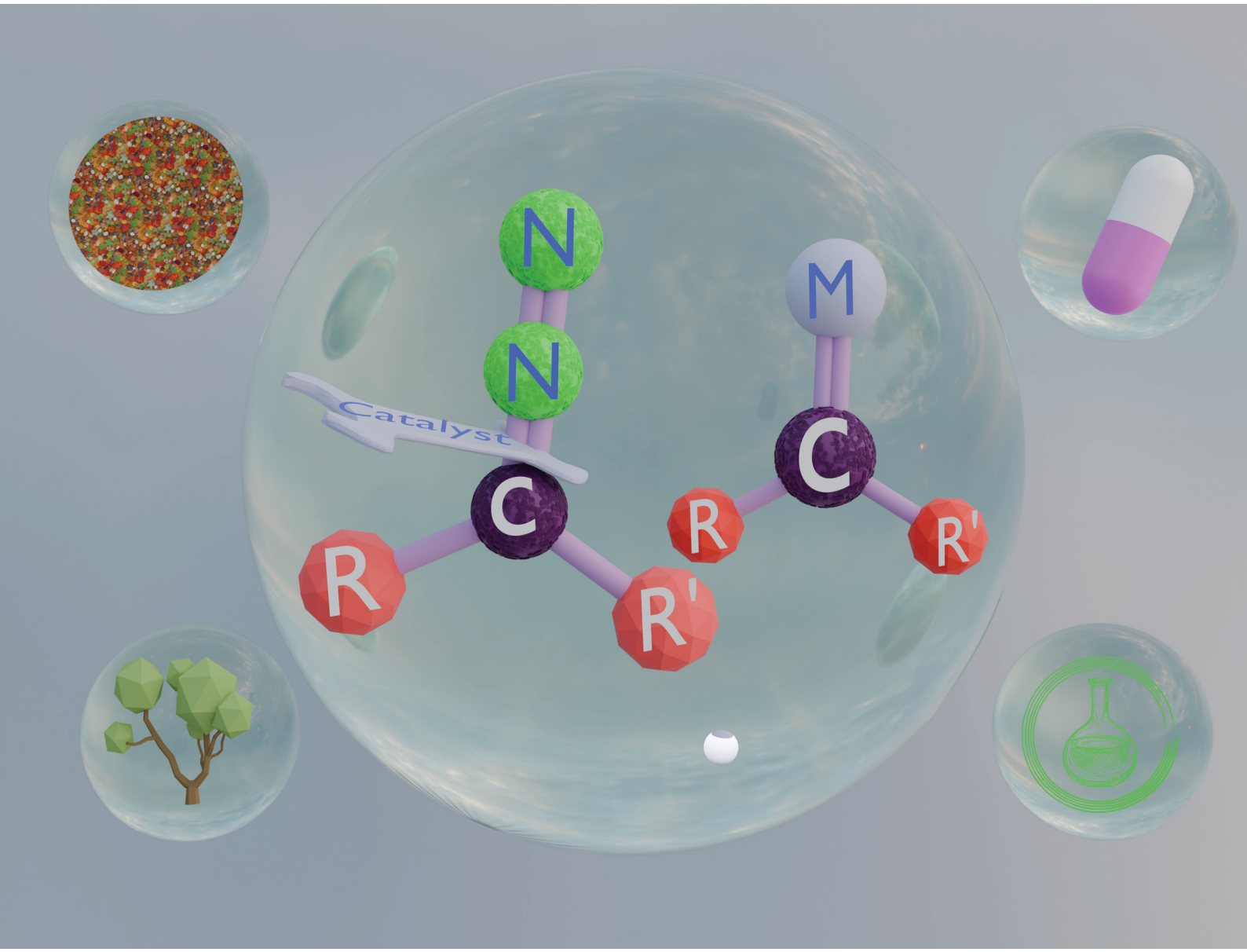

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REVIEW ARTICLE
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REVIEW

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Diazo compounds: synthesis, carbene generation and reactivity

Hilal Ahmad Khan, [a] Michal Szostak *[b] and Chinnappan Sivasankar *[a]

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Diazo compounds are among the most popular intermediates in organic synthesis owing to the ease and versatility of generation of metal–carbenes. In this manuscript, we present an overview of recent methods for the synthesis of diazo compound precursors and the reactivity of metal–carbenes generated from diazo compounds. Synthetic methods, such as diazotization, nitrosoamide fragmentation, Bamford–Stevens reaction, oxidation of hydrazones, Förster reaction, Regitz diazo transfer, and retention of diazo functionality to synthesise complex diazo compounds are discussed. Reactivity of metal–carbenes with respect to X–H insertions, including C–H, O–H and N–H bonds are discussed with a focus on Cu, Rh and Pd catalysis. Furthermore, recent advances in the synthesis of ketenes by a direct carbonylation of diazo carbenes and cyclopropanation reactions are discussed. Finally, the expanding applications of diazo chemistry in various disciplines and future prospects that underscore its enduring relevance and transformative potential in synthetic methodology are discussed.

1. Introduction – structure, characterization and stability of diazo compounds

Diazo compounds are versatile building blocks in organic synthesis and are readily used in academia for the preparation of complex molecules by generation of metal–carbenes. Historically, ethyl diazo acetate was the first diazo compound reported by Curtius in 1883.[1] However, the structural puzzle

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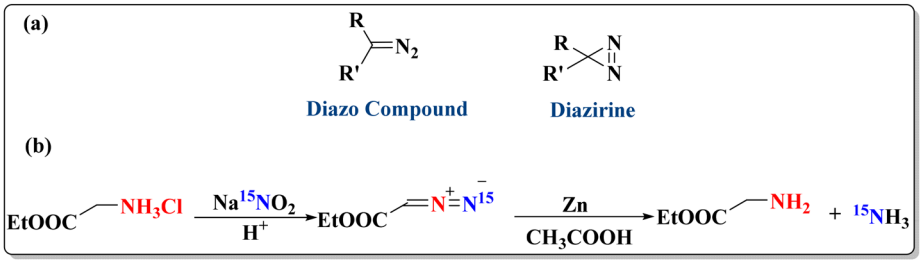
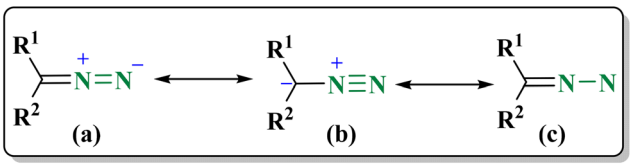


Scheme 1 (a) Structures of diazo compounds and diazirines. (b) Experimental evidence for the linear structure of ethyl diazoacetate.

(linear *versus* cyclic – Scheme 1a) was solved only in 1957 by isotopic labelled experiments (Scheme 1b). In this experiment, the terminal ^{15}N-labelled ethyl diazo acetate was obtained from diazotisation of ethyl glycinate using ^{15}N-labeled sodium nitrite. The reductive cleavage of corresponding labelled ethyl diazoacetate to unlabelled glycine and $^{15}NH_3$ established that diazo compounds have linear form and that cyclic structure (diazirines) could be excluded, as no scrambling of the label was observed.[2]

The overall structure of simple diazoalkanes with general formula R_2N_2 can be represented by two main canonical structures (Scheme 2). Diazo compounds can be thought of as C(sp^2)–N(sp)–N(sp) hybridized molecules because of planarity of structure and substantial delocalization of the charges. Electron withdrawing group substituted diazoalkanes can further delocalize the negative charge into the additional group, thus, it is considered that diazoalkanes having substituted electron withdrawing groups resemble the resonance structure (a) given in Scheme 2.

Diazo compounds absorb in the visible region of the electromagnetic spectrum and are, thus, usually yellow to red in colour. The UV/VIS spectra of diazo compounds show two maxima,[3] the strong one around 270 nm^{-1} and the weaker one at around 410–460 nm^{-1}. The so-called "diazo band", which corresponds to the stretching of the N–N triple bond, is a prominent feature in the IR spectrum, giving off a strong signal between 1950 cm^{-1} and 2300 cm^{-1} depending on the substituents.[4]



Scheme 2 Resonance structures of diazo compounds.

The high reactivity and high nitrogen content of diazo compounds makes them potentially explosive compounds.[4] Furthermore, the potential toxicity of diazo compounds is the other consideration that should be taken into account.[5] The propensity for protonation, which results in the formation of highly electrophilic alkyl diazoniums that can break down into free carbocations, is likely the cause of the potential toxicity of diazo compounds. The subsequent alkylation of nucleophilic macromolecules like DNA by these species might cause irreparable harm. It is thus a current recommendation to handle these versatile reagents with care.

Irrespective of their high reactivity and potential toxicity, diazo compounds have emerged to be one of the most valuable classes of reagents in synthetic chemistry. Many characteristics are responsible for their widespread use: (1) they function as easily accessible precursors to free carbenes, metal–carbenes and carbocations; (2) they are economically viable and easily accessible *via* several methods, (3) N_2 is the sole by-product of their decomposition.[6]

1.1. Electronic-stabilization of diazo compounds

Owing to the synthetic relevance and diverse uses, an increasing number of diazo compounds have been synthesized and used over the past decades. To modify the reactivity and applicability of diazo compounds, functional groups of varying electronic nature are introduced on the diazo carbon atom which either increase or stabilise the reactivity of the resultant metal–carbenes during the reaction (Scheme 3).[7] For instance, diazo

Chinnappan Sivasankar

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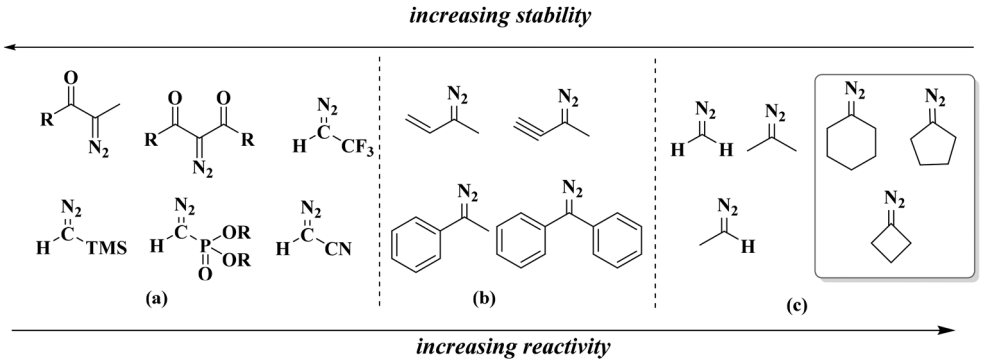


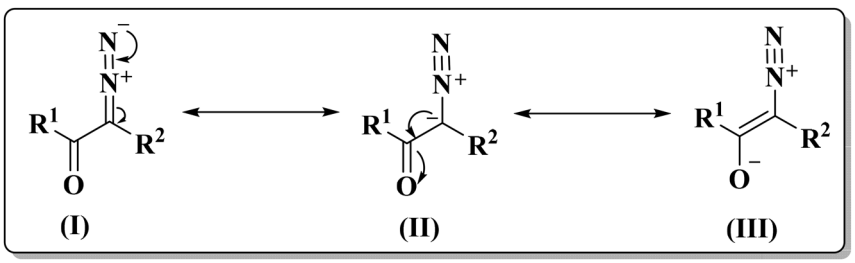
Scheme 3 Electron acceptor substituents increase the stability of the diazo compounds, (a) stable diazo compounds, (b) semi-stable diazo compounds and (c) unstable diazo compounds.

functionality has been added to carbonyl compounds,[8] phosphonates,[9] nitriles[10] and alkanes.[4a] Diazo compounds flanked with electron withdrawing groups on either or both the sides of the diazo carbon are stabilised (Scheme 3a) due to the delocalisation of the negative charge to the substituted group such as aromatic, sulfonyl, phosphoryl and carbonyl substituents (Scheme 4). Many of these stabilised diazo compounds are tolerant to mild organic acids like CH_3COOH and also can be purified using silica gel column chromatography. Due to their easy accessibility, diazoacetates and diazoketones are the most often used diazo species in contemporary organic chemistry among stabilised diazo compounds.

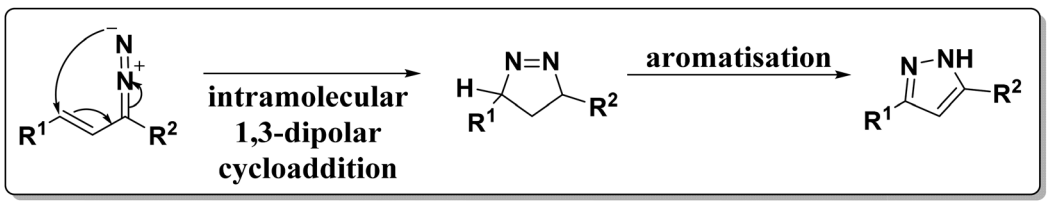
An adjacent aromatic ring,[11] acetylenic group[12] or vinylic group[13] can also stabilise the diazo compounds by partial stabilisation of negative charge, although the effect is less prominent when compared to electron-withdrawing groups (Scheme 3b). The members of this class of diazo compounds act as more powerful nucleophiles and are, thus, acid labile which prevents their purification by silica gel column chromatography. Furthermore, the complexities in their synthesis limit the applicability of such diazo compounds and are mostly generated *in situ* from stable precursors. Due to their propensity to cyclize into pyrazoles, vinylic diazo compounds present an extra challenge (Scheme 5).[13]

Diazo compounds are often described in terms of their nucleophilic resonance contributors **a** and **b** (Scheme 2), however, they also possess a latent electrophilic nature that becomes evident in reactions with strong nucleophiles. This duality can be rationalized from the nitrene-type resonance structure **c** (Scheme 2), which emphasizes the electrophilic character of the diazo carbon.[14a] This electrophilicity manifests particularly in reactions with nucleophilic heterocyclic carbenes (NHCs), where diazo species act as electrophiles to form azine-type adducts or ylide intermediates.

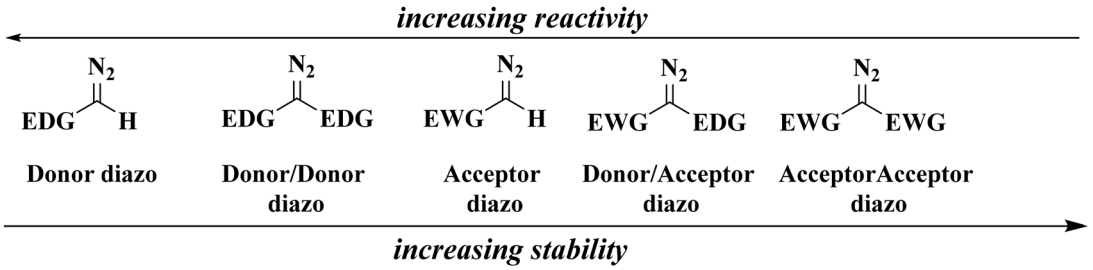
Hopkins *et al.* demonstrated that 1,3-dimesitylimidazol-2-ylidene reacts with diphenyldiazomethane or diazofluorene to afford stable azines, underscoring the electrophilic reactivity of diazoalkanes towards NHCs.[14a] Similarly, Korotkikh and co-



Scheme 4 Delocalisation of negative charge in α-diazocarbonyl compounds.



Scheme 5 Intramolecular isomerization of vinyl diazo compounds to pyrazoles.



Scheme 6 Classification of diazocompounds based on the nature of α-substituents.

workers observed that 1,2,4-triazol-5-ylidenes undergo addition to diphenyldiazomethane, yielding azine derivatives through carbene–diazo coupling,[14b] and extended these findings to bis-carbene systems where diazo compounds and sulfur act as electrophilic partners.[14c] These studies demonstrate that diazo compounds can behave as electrophiles in the presence of potent nucleophiles such as NHCs, forming C–N bonded intermediates *via* attack at the diazo carbon. Thus, the overall reactivity profile of diazo compounds is amphiphilic and their dominant behaviour during any reaction depends on the nature of the reaction partner and the electronic environment around the diazo group.

Based on the nature of the α-substituents-donor (D) or acceptor (A), diazo compounds are also classified as donor/donor (D/D), donor/acceptor (D/A), or acceptor/acceptor (A/A) (Scheme 6), each exhibiting distinct reactivity profiles.[15a] Typical acceptor groups include keto, nitro, cyano, phosphonyl, and sulfonyl moieties, while donor groups commonly comprise vinyl, aryl, and heteroaryl units. Metal carbenoids generally exhibit electrophilic character; thus, the presence of acceptor groups tends to enhance reactivity but reduce selectivity, whereas donor groups moderate reactivity and improve selectivity.[15b] Although significant progress has been made in diazo-derived carbene chemistry over the past century, research has predominantly focused on acceptor-, donor/acceptor-, and acceptor/acceptor-carbenes due to their relatively favorable stability profiles. In contrast, donor- and donor/donor-carbenes remain less explored, largely due to safety concerns (*e.g.*, potential explosiveness) and practical limitations such as facile dimerization. Notably, donor–acceptor diazo compounds strike a valuable compromise between reactivity and stability: the donor group tempers the electrophilicity imparted by the acceptor, enabling controlled carbene generation while maintaining sufficient thermal stability for practical use.[15c]

1.2. Stability of alkyl diazo compounds

Simple alkyl diazo compounds, such as diazomethane and diazoethane, are highly unstable as the ability of alkyl groups to donate electron density to the diazo carbon through hyperconjugation increases the negative charge on the carbon atom linked to the diazo group.[4a] This increases their nucleophilicity, acid-lability and instability, thus making this class of diazo compounds highly challenging to prepare and utilise. Therefore, their use in organic synthesis is limited as they tend to decompose before being added to the reaction mixture. This family also includes diazo compounds containing diazo group in a strained ring (Scheme 3c).[16] In general, these compounds are too reactive to readily handle and decompose even at low temperatures, however, some *in situ* procedures for aryl-alkyl cross-couplings implicate that they act as intermediates in such reactions.[17] This stability trend of diazo compounds is also supported by IR observations which show that increasing electron accepting nature of the substituents on the diazo carbon results in a strong N≡N bond. Recently, Bull's group of Imperial College London in association with scientists at GlaxoSmithKline studied the stability of 44 diazo compounds with a wide range of substituents at the diazo carbon and found that not all diazo compounds are explosive in nature, and their stability depends on the nature of their substituents.[18]

2. Synthesis of diazo compounds

Owing to the distinct stability of diazo compounds, various complementary synthetic approaches have been developed to synthesise stabilised, semi-stabilised and non-stabilised diazo compounds.[4a,19] Synthesis of diazo compounds *via* functional group modifications of alkyl amines involve two methods, namely (1) diazotisation and (2) base-mediated cleavage of *N*-alkyl-*N*-nitroso sulfonamides/fragmentation of nitrosoamide compounds, while manipulations from aldehydes and ketones to yield diazo compounds include (1) Forster reaction, (2) oxidation of hydrazones, (3) base-mediated fragmentation of sulfonylhydrazones, and (4) photolysis of 1,3,4-oxadiazolines. Furthermore, Regitz diazo transfer reaction enables diazo installation onto activated methylene groups of carbonyl compounds. This method is performed through deprotonation followed by azide intercepted diazo transfer to the resulting enolate ion.

In the following section, the most relevant methods for the synthesis of diazo compounds are discussed with a focus on their synthetic versatility, limitations and common use.

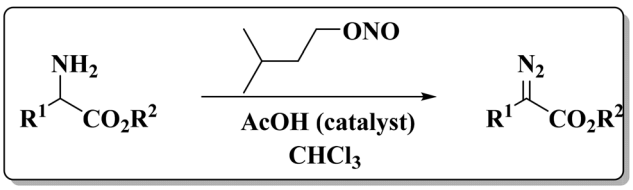
2.1. Diazotisation

Diazotisation is one of the most commonly used methods for the preparation of diazo compounds from readily available aliphatic amines activated by an electron-withdrawing group ($-CF_3$, –COOEt, $-P(O)(OEt)_2$ or $-NO_2$) on the α-carbon. However,

alternative methods like hydrazone oxidation, Bamford–Stevens reaction or nitroso decomposition, should be employed for the synthesis of alkyl or phenyl substituted, electron-rich diazo compounds. This method is also the standard procedure for the synthesis of diazonium salts from anilines, and sometimes is being used for the synthesis of specific azides from the respective hydrazines (Scheme 7).[19]

In the standard protocol, sodium nitrite is added portion wise to an acidic aqueous solution of an amine salt at low temperature (0 °C or below). Mechanistically, the *in situ* generated active reagent, HNO_2 produces *N*-nitroso intermediate from the amine that yields an aliphatic diazonium upon dehydration. The resultant diazonium salt may either form the diazo compound by the elimination of acidic proton or may lose dinitrogen to form carbocation leading to several by-products. Deprotonation at the α-carbon is feasible where electron-withdrawing groups are attached to stabilize the aliphatic diazonium intermediate. In the absence of stabilizing electron-accepting groups, solvolysis and rearrangements lead to the thermodynamically favourable extrusion of dinitrogen gas (Scheme 8). Thus, stability of the diazonium intermediate is a major drawback of this method which limits its use for the synthesis of semi-stable and non-stable diazo compounds.

In case of water-sensitive derivatives, diazotisation can be performed in organic media using alkyl nitrite reagents and suitable Brønsted or Lewis acids (*e.g.*, CH_3COOH or $BF_3{\cdot}Et_2O$) (Scheme 9). For example, refluxing α-amino acid esters with

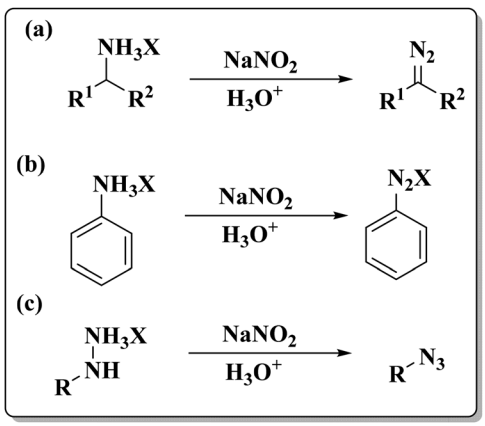


Scheme 9 Isoamyl nitrite promoted diazotisation of substituted amino esters.

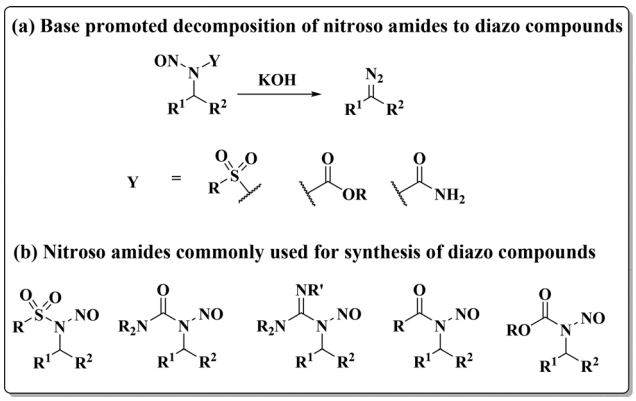
isoamyl nitrite in chloroform or benzene in the presence of a small amount of organic acid has been employed for the direct synthesis of substituted diazoesters from amino acids, a reaction that was not feasible using aqueous HNO_2.[20]

2.2. Base-mediated fragmentation of nitrosoamides

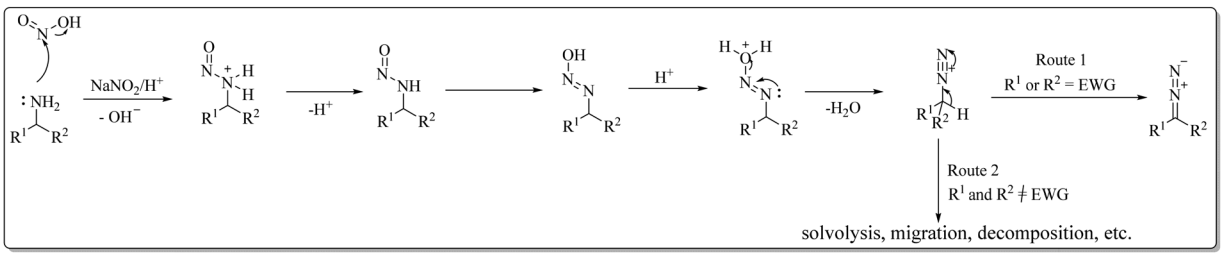
The problem posed by the diazonium intermediate in the diazotisation of amines not bearing any electron-accepting groups can be circumvented by transforming amines to nitrosoamide derivatives. Various derivatives of nitrosoamides, such as amides sulfonamides, ureas, guanidines and carbamates, undergo base mediated cleavage resulting in the formation of diazo compounds (Scheme 10).[19] Historically, this method can be traced back to 1894, when von Pechman first reported evolution of yellow gas, diazomethane on treatment of nitrosomethyl carbamates with alkali.[5c] At present, this method remains the preferred route for the preparation of diazo-



Scheme 7 Diazotisation of (a) amines, (b) anilines and (c) hydrazines.



Scheme 10 (a) Decomposition of nitroso amides to diazo compounds, (b) nitroso amides commonly used for diazo synthesis.



Scheme 8 Mechanism of diazotisation.

methane starting from the commercially available sulfonamide-based, Diazald.[21] Other non-stabilised diazo compounds, such as phenyl diazomethane, can also be synthesised using this method, however, due to the carcinogenic nature of the precursors used and low yield of alkyl diazo with longer alkyl chain lengths,[22] the method is less preferred and other methods, such as direct oxidation of hydrazones and Bamford–Stevens reaction, are preferred for the synthesis of higher diazoalkanes.

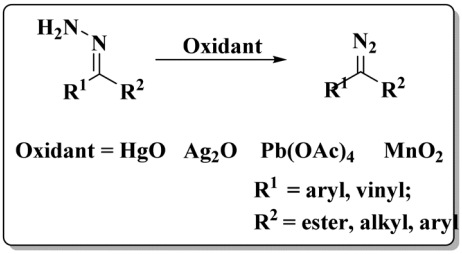
2.3. Base-mediated fragmentation of sulfonylhydrazones (Bamford–Stevens reaction)

When heated in basic medium, sulfonylhydrazones (prepared by the condensation of ketones or aldehydes with sulfonyl hydrazides) can be deprotonated at nitrogen followed by sulfinate elimination to yield diazo compounds (Scheme 11). As the process is carried out at temperatures above 70 °C, semi-stable and unstable diazo compounds prepared by this protocol are intercepted *in situ* with suitable substrates, while unstable diazoalkanes are more frequently prepared by oxidation of hydrazones.[19,23]

2.4. Oxidation of hydrazones

The method is similar to the Bamford–Stevens reaction, however, the method involves the oxidation of hydrazones using an external oxidant (Scheme 12). The method has an advantage of providing access to temperature sensitive diazo compounds as the reaction is performed at lower temperatures.[4a] A wide variety of metal-based oxidants, such as a MnO_2, Ag_2O, HgO, $Pb(OAc)_4$, have been used to effect this dehydrogenation of hydrazones to diazo compounds and recent advancements utilising organic oxidants for converting hydrazones to diazo compounds have also been reported.[4a,24] Despite being less toxic than its mercury and lead based counterparts, a major drawback associated with the activated MnO_2 is the need of large excess of the oxidant to convert hydrazone to the diazo compound. The excess oxidant causes the decomposition of diazo compounds to the corresponding azines, aldehydes, ketones and benzyl alcohols, thereby lowering the efficiency of the overall process. In practice, activated MnO_2 is generally used for the oxidation of arylhydrazones and vinylhydrazones to corresponding semi-stable diazo compounds.[19]

In a useful variation of this method, Javed and Brewer reported the modified Swern protocol for the dehydrogenation

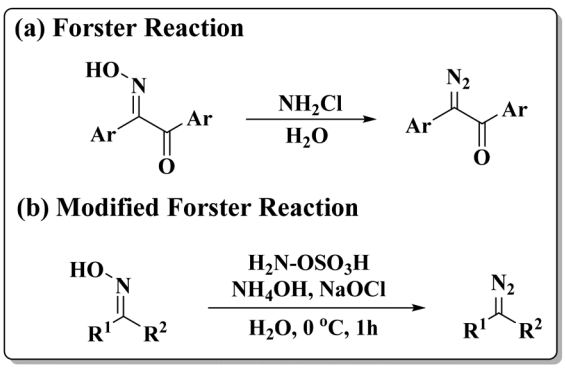


Scheme 12 Oxidation of hydrazones using metal oxidants.

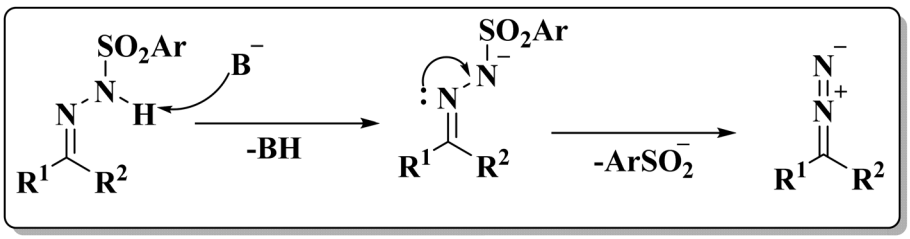
of hydrazones utilizing metal-free organic oxidants and a wide variety of sensitive diazoalkanes as solutions in THF were obtained in good yields. The products could be easily separated from the insoluble by-product, triethylammonium chloride salt, by simple filtration.[25] Furthermore, Furrow and Myers used difluoroiodobenzene as an organic oxidant for *in situ* production of diazoalkanes from TBS-protected hydrazones, which were directly quenched using carboxylic acids to form corresponding esters. However, sensitivity to water and limited availability impact the synthetic utility of this method.[26]

2.5. Forster reaction

First reported in 1915 by Forster, the reaction of oximes with chloramine, which is generated from sodium hypochlorite and ammonia, produces α-diazoketones (Scheme 13a).[27] This reaction is sometimes used for the preparation of a small selection of α-diazoketones. The method is less tolerant to a variety of



Scheme 13 Synthesis of diazo compounds using (a) Förster reaction, (b) modified Förster reaction.



Scheme 11 Bamford–Stevens reaction.

functional groups because of strong oxidising nature of chloramine, which has been a limitation of attempts to generalize this method for the development of unstable aliphatic diazo compounds. A modification to this method involves the use of hydroxylamine *o*-sulfonic acid as an alternative to chloramine (Scheme 13b).[28] However, this modification also lacks generality as efforts to synthesize diazo compounds from oximes of benzaldehyde and acetophenone typically afford products in low yields (Fluorenone oxime yielded diazofluorene in 60%, benzophenone oxime gave diphenyldiazomethane (30%) while oximes of acetophenone and benzaldehyde resulted in small amounts of diphenyldiazomethane and phenyldiazomethane).

2.6. Regitz diazo transfer

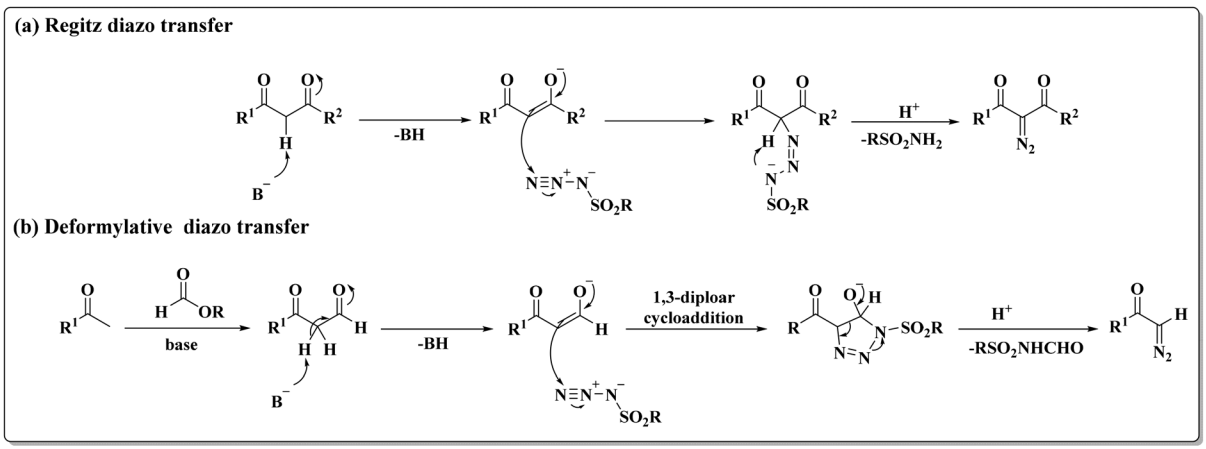
In this popular method, a diazo group from an organoazide (usually a sulfonyl azide, such as trifluoromethanesulfonyl azide, mesyl azide, tosyl azide, or commercially available 4-acetamidobenzenesulfonyl azide) is transferred onto the compounds containing activated methylene groups. The doubly activated methylene group of 1,3-dicarbonyl compounds can be easily deprotonated by a mild base and the resulting enolate ion is diazotised by sulfonyl azide (Scheme 14a). However, in case of simple ketones and esters having only one electron accepting group, the substrate is further activated by introducing formyl or trifluoroacetyl group that is lost in the process of diazo transfer (Scheme 14b). The method is widely used for the synthesis of various α-diazoketones and α-diazoesters. However, it is worth noting that the method is not as atom economic as large sulfonyl azides are used as diazo transfer agents.[29]

Over the past few decades, diazo transfer chemistry has undergone a substantial revolution. What began as a relatively niche, somewhat temperamental transformation has grown into a powerful and reliable method for building complex molecules. Key to this evolution has been the development of safer, more selective, and operationally simple protocols, driven by a better understanding of the underlying mechanism and smart reagent design.

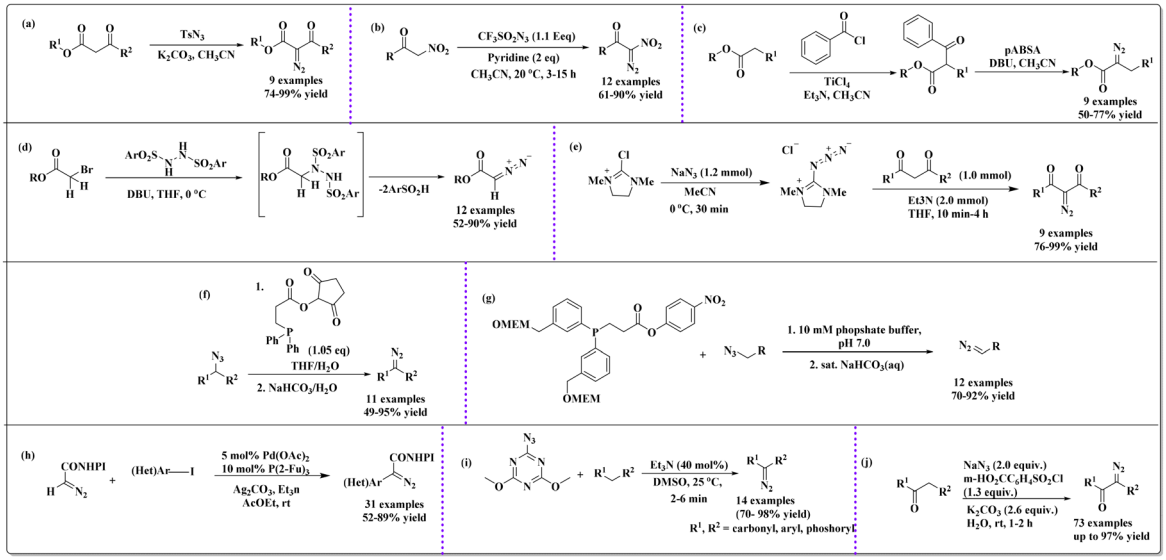
Koskinen and Muñoz showed that potassium carbonate in acetonitrile could efficiently mediate diazo transfer to active methylene substrates using sulfonyl azides (Scheme 15a). The reaction not only proceeded cleanly and rapidly, but also eliminated the need for harsh purification representing a notable improvement over the classical Regitz-type conditions.[30a] This work set the stage for broader synthetic adoption of diazo transfer reactions, particularly in the construction of α-diazo carbonyl compounds. Charette and coworkers introduced trifluoromethanesulfonyl azide to diazotize α-nitrocarbonyl compounds without forming unwanted triazenes, thus, expanding the utility of diazo transfer (Scheme 15b). The method avoided side reactions common to earlier reagents and provided high-yielding access to α-nitro-α-diazo derivatives. This seminal work not only refined the Regitz logic but laid the foundation for selective diazo installation onto electron-deficient substrates, which had previously been challenging.[30b] Taber *et al.* designed a practical two-step approach involving $TiCl_4$-mediated benzoylation followed by diazo transfer using pABSA (Scheme 15c). This strategy offered excellent substrate tolerance and proved highly scalable, ideal for accessing α-diazo esters from readily available esters.[30c]

The field took a major conceptual shift with Fukuyama's development of *N*,*N*′-ditosylhydrazine-crystalline, bench-stable reagent. It enabled diazoacetate formation from bromoacetates under mild, base-promoted conditions, avoiding acidic or oxidative activations (Scheme 15d).[30d] This method was not only efficient but applicable to a wide variety of cyclic and sterically hindered alcohols and it has a broader design principle that not just reaction conditions but reagent design could also drive the evolution of diazo transfer.

The introduction of 2-azido-1,3-dimethylimidazolinium chloride by Kitamura *et al.* further simplified diazo transfer reaction (Scheme 15e). The reagent's *in situ* formation, clean byproducts, and performed especially well with 1,3-dicarbonyl substrates. These made it especially useful in library synthesis and process-friendly routes. Azidoimidazolinium salt was also used for the synthesis of Ohira-Bestmann reagent and was obtained in 76% by the reaction with diethyl (2-oxopropyl)



Scheme 14 Mechanism of (a) Regitz diazo transfer, (b) deformylative diazo transfer.



Scheme 15 Advances in diazo transfer reactions.

phosphonate.[30e] Meanwhile, a novel direction was taken by Myers and Raines who bypassed traditional diazo transfer altogether. Drawing inspiration from Staudinger ligation, they developed a phosphine-mediated route that used phosphinoesters to trap azides and form acyl triazenes (Scheme 15f). These intermediates then fragmented cleanly to give diazo compounds. The method offered chemoselectivity, functional group compatibility, mechanistic novelty-avoiding direct diazo transfer and instead leveraging intramolecular acylation and controlled fragmentation. It expanded the synthetic relevance of diazo chemistry beyond enolate-based pathways and offered a complementary route for azide-rich substrates.[30f] Chou and Raines extended phosphine-based approach to bioorthogonal application, with a refined phosphinoester reagent that enabled azide-to-diazo conversion in aqueous buffers at room temperature (Scheme 15g). This approach allowed diazo installation on biomolecules under physiological conditions harnessing pK_a-controlled selectivity and enabling applications in molecular labeling and probe design.[30g]

As the synthetic scope expanded, so did the complexity of the targets. A notable advancement in the synthesis of redox-active diazo compounds was reported by Mendoza and co-workers, who developed a strategy to access aryldiazoacetates through the Pd-catalyzed C–H arylation of *N*-hydroxyphthalimide diazoacetate. By leveraging Pd-catalyzed C–H arylation of *N*-hydroxyphthalimide diazoacetates, they managed to overcome the instability issues typically associated with diazo compounds under palladium catalysis. Careful tuning of catalysts and additives with a Pd(II)/tris(2-furyl)phosphine catalyst, Ag_2CO_3 as an iodide scavenger, and triethylamine as base yielded a protocol that delivered aryldiazoacetates bearing a wide variety of substituents, including bioactive fragments (Scheme 15h).[30h] These diazo compounds served as versatile precursors for enantioselective carbene-transfer reactions, notably in the synthesis of congested cyclopropanes, thus enabling the stereoselective synthesis of congested quaternary carbon centers from simple aryl iodides and olefins.

Ma and coworkers introduced ADT (2-azido-4,6-dimethoxy-1,3,5-triazine) as an intrinsically safe, shelf-stable, and fast-reacting diazo-transfer reagent that works with inorganic bases at room temperature (Scheme 15i). ADT achieved rapid diazo transfer to enolizable substrates with broad scope and excellent safety profiles making it a promising diazo-transfer reagent for quick preparation of diazo compounds.[30i] More recently, Krasavin *et al.* demonstrated SAFE (sulfonyl-azide-free) protocol for the diazo transfer in aqueous media without explosive sulfonyl azides. Capable of transforming 73 active diverse methylene compounds substrates to produce respective diazo compounds-22 of them newly reported-the SAFE method supports array synthesis and scaffold diversification, and its adaptability to continuous-flow systems signals its value in both research and production settings (Scheme 15j).[30j]

These advances illustrate the transformation of diazo-transfer chemistry from mechanistically constrained, azide-heavy protocols into a vibrant landscape of tailored reagents, each offering operational ease, safety, and broad synthetic utility. They retain the foundational logic of the Regitz mechanism but embraces a diversity of routes that including non-classical reagents, mild aqueous systems, and bioorthogonal platforms. Through strategic design-whether by tuning leaving group pK_a, eliminating hazardous intermediates, or engineering water solubility-diazo chemistry has evolved from a niche transformation into a central tool for modern molecular synthesis.

2.7 Synthetic modularity in diazophoshonate and diazoamide construction

The Regitz diazo transfer reaction has been successfully employed for the synthesis of different kinds of diazo compounds such as aryldiazoacetates, diazoketones, 2-diazo-1,3-dicarbonyl compounds, α-arylsulfonylcarboxylates,

α-phosphonoacetates, and α-phosphonoketones. However, isolated examples for the synthesis of aryldiazophosphonates with low yields using this method are reported in the literature.

α-Aryl-α-diazophosphonates are traditionally synthesised typically either using Arbuzov protocol-where acyl chlorides react with trialkyl phosphites to yield α-ketophosphonates, which are then converted into tosylhydrazone derivatives and decomposed with base (Scheme 16a);[31a] or using Pd(0)-catalyzed cross-coupling of aryl iodides with α-diazomethylphosphonate[31b] (Scheme 16b) or alternatively through deacylative cross-coupling of aryl iodides with diazophosphonoacetone (Scheme 16c).[31c] However, these traditional techniques often suffer from low overall yields and require lengthy reaction times, making them less efficient. More recently, Titanyuk *et al.* reported a straightforward and practical method for synthesizing α-aryldiazophosphonates using a diazo transfer reaction. This process involves transferring a diazo group from tosyl azide (TsN_3) to benzylphosphonates in the presence of potassium *tert*-butoxide (KO*t*Bu), yielding the desired diazophosphonates in up to 79% yield. This route is advantageous because it uses readily available reagents, offers broad functional group tolerance, operates under mild conditions, and can be performed on a multi-gram scale (Scheme 16d).[31d]

Rastogi *et al.* introduced a versatile and mild synthetic route for the synthesis of α-diazo-β-keto esters, phosphonates, and sulfones *via* acylation of diazomethyl anions with *N*-acylbenzotriazoles (Scheme 16e).[31e] This approach avoids harsh conditions, is broadly tolerant of different substrates, and produces diazo compounds with excellent yields. Notably, when *N*-*o*-amino benzoylbenzotriazoles react with DAMP (dimethyl (diazomethyl)phosphonate), an unprecedented migration of the phosphonate group from carbon to nitrogen occurs, leading to the formation of novel diazoacetyl phenylphosphoramidates; a unique transformation not observed in more conventional pathways.

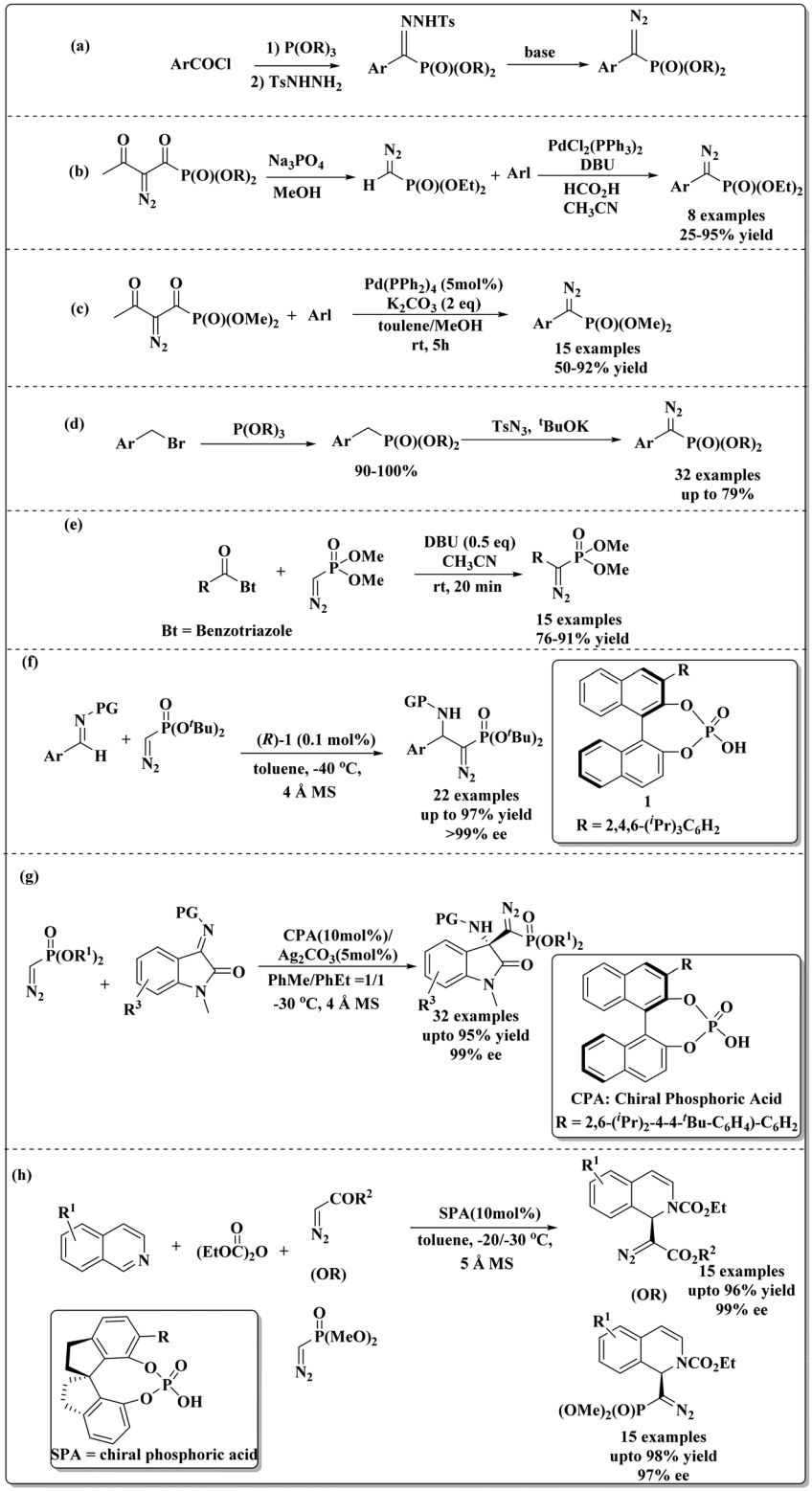
In their seminal work, Peng *et al.* utilized *N*-carbamoyl imines as nucleophiles in an organocatalyzed Mannich reaction with dialkyl α-diazomethylphosphonates in asymmetric reactions to yield dialkyl-substituted β-amino phosphonates under organocatalysis.[31f] The approach leveraged hydrogen bonding to direct the stereochemical outcome, producing β-amino phosphonates with three contiguous stereocenters (Scheme 16f). The same group also reported an elegant asymmetric Mannich reaction employing α-diazomethylphosphonates and isatin-derived ketimines. Using a chiral silver phosphate catalyst, the transformation achieved high yields and excellent stereoselectivity. The reaction exhibits excellent stereoselectivity and yields dual chiral centred β-amino phosphonates valuable intermediates in drug design (Scheme 16g).[31g] Pushing further the boundaries of the approach, Peng *et al.* recently reported a spiro-fused CPA-catalyzed acyl-Mannich reaction of isoquinolineDEPC adducts with diazoacetates and diazomethylphosphonates. The combination of acylative electrophile formation and rigid chiral catalysis yielded α-diazo-β-isoquinoline phosphonate and carbonates derivatives in excellent yields (up to 98%) with up to 99% ee. The protocol demonstrated broad scope and scalability, with derivatizations including hydrazone formation and Pd-catalyzed hydrogenation (Scheme 16h).[31h]

The construction of α-diazoamides has also seen significant advances through strategically distinct synthetic approaches aimed at maximizing functional group compatibility, operational simplicity, and biological relevance. Nelson and coworkers developed a versatile toolkit of synthetic routes that enabled access to a broad array of α-diazoamide scaffolds. Among the three key strategies they explored, the first one-pot protocol involved a classic acylation-elimination sequence. The glyoxylic acids were transformed into tosylhydrazones and then converted into acid chlorides and subsequently coupled with a wide range of amines, including primary, secondary, and aromatic varieties, followed by base-promoted elimination to furnish the desired diazoamides in good yields (Scheme 17a). The second route utilized a palladium-catalyzed α-arylation of preformed diazoacetamides using $Pd(PPh_3)_4$ and Ag_2CO_3 in toluene. This strategy allowed the introduction of aryl substituents at the α-position, although it was more effective with aryl iodides than bromides and showed limited success with electron-rich aryl groups (Scheme 17b). The third strategy employed diazo transfer using the safer sulfonyl azide *p*-acetamidobenzenesulfonyl azide (*p*-ABSA), which enabled direct diazo installation onto β-ketoamides, 1,3-dicarbonyl compounds, and other electron-deficient substrates. This route was especially valuable for accessing β-keto diazoamides, which are synthetically challenging by other means, and demonstrated compatibility with a variety of nitrogen nucleophiles (Scheme 17c).[32a]

While Nelson's contributions laid a robust foundation for the synthesis and diversification of α-diazoamides, a subsequent refinement came from Jun and Raines and colleagues who reimagined diazoamide synthesis with a focus on modularity, scalability, and compatibility with biological systems. Their method relied on a concise two-step sequence beginning with commercially available *N*-succinimidyl 2-diazoacetate. In the first step, a mild palladium-catalyzed C–H arylation was carried out using $Pd(OAc)_2$ and tris(2-furyl)phosphine, allowing for the direct coupling of aryl iodides to the diazoacetate scaffold. In contrast to Nelson's arylation protocols, which often failed with electron-rich arenes, this method operated at room temperature and tolerated a broad array of functionalized aryl groups, including azido, alkynyl, and fluoro substituents. The second step involved aminolysis of the resulting *N*-succinimidyl esters with primary or secondary amines in the presence of triethylamine. This reaction proceeded efficiently under mild conditions, delivering both *N*-monosubstituted and *N*,*N*-disubstituted α-diazoamides. Attempts to apply similar conditions to *N*-phthalimidoyl esters were unsuccessful, underscoring the superior reactivity and flexibility of the succinimidyl platform (Scheme 17d).[32b]

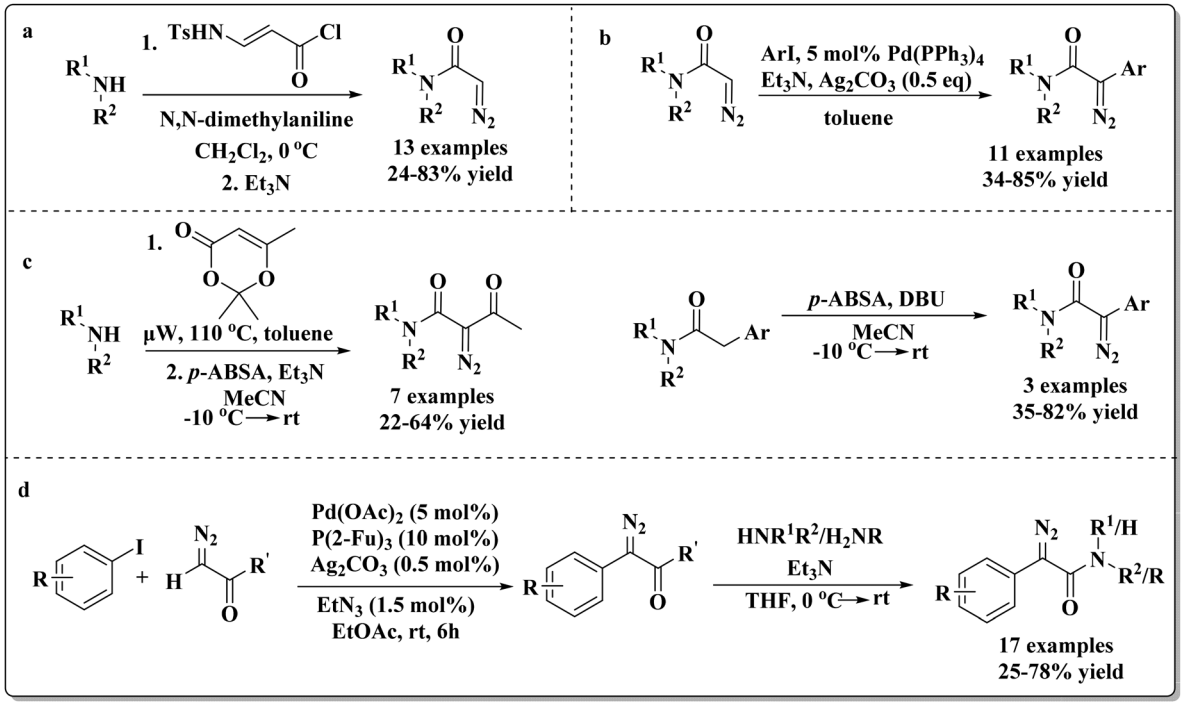
2.8 Synthesis of complex diazo compounds through retention of diazo functionality

Historically derived through diazotization and sulfonyl-mediated routes, diazo compounds were initially prized for



Scheme 16 Approaches for the synthesis of diazophoshonates.

their role in cyclopropanation, insertion reactions, and the synthesis of dyes and polymers. While the traditional approaches for the synthesis of these versatile intermediates have proven robust, their reliance on preinstalled reactive handles can limit scaffold diversity, functional group tolerance, and synthetic efficiency. The modern landscape reveals a profound conceptual expansion: chemists now exploit diazo compounds not merely as reactive intermediates, but as stra-



Scheme 17 Approaches for the synthesis of diazoamides.

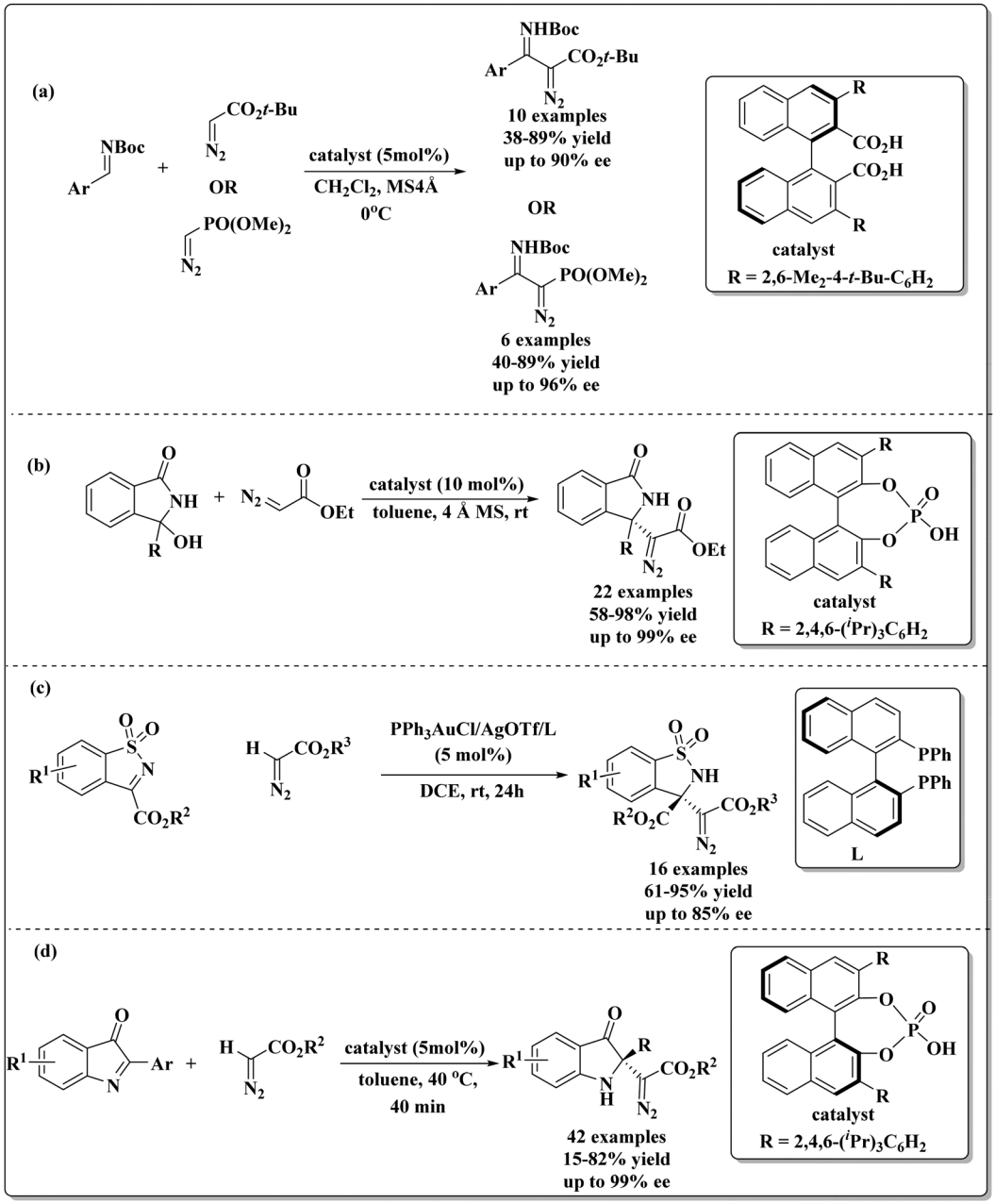
tegic substrates for constructing complexity in a controlled and modular fashion. A new generation of synthetic strategies has emerged, capable of constructing complex diazo scaffolds from simple, readily available precursors. These approaches capitalize on the reactivity of nucleophiles and electrophiles in addition reactions, harness the modularity of cross-coupling techniques, and exploit multicomponent, flow, and photochemical platforms to build molecular complexity with precision and control. This section of this review article explores how these modern tactics; especially those rooted in carbon-carbon and carbon-heteroatom bond formation; unlock diazo architectures that were previously inaccessible or synthetically impractical.

Based on the CPA-catalyzed Mannich methodolgy developed by Peng *et al.* for the synthesis of diazophoshonates,[31f] Hashimoto and Maruoka developed an asymmetric Mannich reaction between α-diazo esters and *N*-Boc imines, catalyzed by novel axially chiral 3,3′-disubstituted BINOL-derived dicarboxylic acid.[33a] The bulky aryl substituents created a rigid chiral pocket, enabling highly enantioselective access to α-amino-α-diazo esters bearing quaternary stereocenters (up to 90% ee). This design proved general across a range of arylaldehyde-derived imines, and was also extended to ketimine and phosphonate analogues, broadening the scope of stereodefined diazo-functionalized amines (Scheme 18a).

Singh *et al.* established asymmetric Mannich-type reaction of α-diazo esters with *in situ* generated *N*-acyl ketimines derived from 3-hydroxyisoindolinones in the presence of a chiral Brønsted acid under ambient conditions for the first time.[33b] A variety of isoindolinone-based α-amino diazo esters were utilized to access biologically interesting chiral isoindolinone-based α-amino diazo esters with remarkably high enantioselectivities (up to 99% ee). The enantioselective construction of chiral diazo compounds comprising a quaternary stereogenic center is one of the salient features of this exciting chemistry. The synthetic utility of this protocol has also been demonstrated by the hydrogenation of the diazo moiety of the product (Scheme 18b). Around the same time, Wang *et al.* implemented Au(I)–BINAP complex catalysis for the Mannich reaction of diazo esters with *N*-sulfonyl cyclic ketimines.[33c] In this study, contrary to Brønsted acid strategy of Singh *et al.*, metal-mediated electrophilic activation enabled a unique route to β-amino diazo esters bearing quaternary stereocenters. Operando IR and NMR analysis affirmed the role of gold(I) in enolate formation and carbene suppression, while chiral ligand geometry modulated enantioselectivity (Scheme 18c).

Zhao *et al.* expanded this strategy by exploring reactions of 2-aryl-3*H*-indol-3-ones with α-diazo derivatives. Catalyzed by chiral phosphoric acids, these reactions afforded 2,2-disubstituted indolin-3-ones bearing a quaternary stereocenter and containing diazo groups in the C2 substituents in excellent yield (up to 82%) with outstanding enantioselectivity (up to 99% ee).[33d] Substrate tolerance extended to fused rings and heteroaromatic donors, with mechanistic insights provided *via* DFT-calculated transition states. The study also reinforced the importance of diazo groups as synthetic handles through downstream transformations (hydroxylation, aziridination) (Scheme 18d).

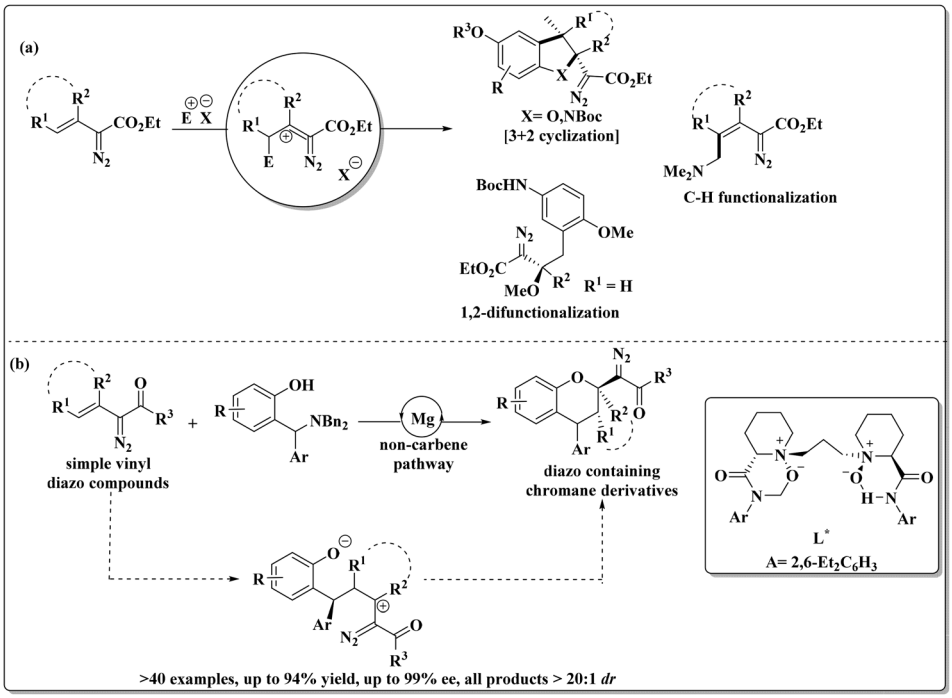
The reactivity of vinyl diazo compounds towards electrophilic partners opens avenues for cascade reactions, dearomative



Scheme 18 Mannich reaction-based synthesis of complex diazo compounds.

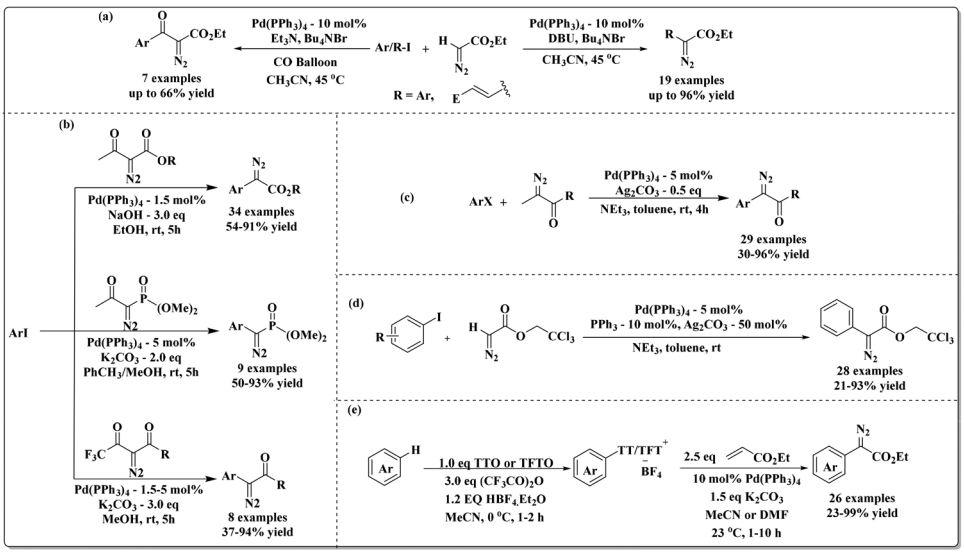
cyclizations, and functional group installation. Doyle *et al.* reported a diverse array of vinyl diazo couplings with quinone-based electrophiles, proceeding *via in situ* generation of vinyl diazonium intermediates.[34a] These transformations encompass [3 + 2] cyclizations, 1,2-difunctionalizations, and C–H functionalizations, producing polycyclic architectures with controlled regioselectivity and versatile functional handles amenable to downstream diversification. The study highlights non-carbene reactivity pathways that complement classical diazo carbene chemistry, and can be leveraged under Brønsted acid or metal catalysis (Scheme 19a). Liu and co-workers contributed a novel perspective by demonstrating stereocontrolled cyclizations of vinyl diazo compounds with phenols using chiral magnesium complex as catalyst, which acts as Lewis acid to bond with the two carbonyl oxygens of reactants. Operating *via* nucleophilic addition rather than carbene formation, this pathway furnishes enantioenriched chromane derivatives with excellent diastereocontrol, and unveils a new strategy for accessing the valuable optically pure chiral diazo compound from simple vinyl diazo material (Scheme 19b).[34b]

Palladium-catalyzed cross-coupling has been a cornerstone for constructing C–C bonds, with advances expanding its scope to carbon nucleophiles from methylene compounds, ketones, esters, amides, and nitriles. Diazo carbon compounds



Scheme 19 Non-carbene pathways for retention of diazo functionality utilising vinyl diazo compounds.

bear a partial negative charge and thus have considerable nucleophilicity; and have been directly used as partners in Pd-catalysed cross-coupling reactions, particularly to retaining the diazo functionality under transition-metal catalysis. Wang *et al.* applied palladium catalysis to couple aryl or vinyl iodides with ethyl diazoacetates. The process yielded tetrasubstituted olefins bearing diazo moieties from vinyl iodides and aryl substituted diazo esters from aryl iodides. Moreover, it was observed that carbonylation occurs prior to the coupling if the reaction is carried out under an atmosphere of CO, expanding utility in molecular electronics and bioresponsive materials. The reaction proceeds with stereospecific control, illustrating the compatibility of diazo groups with oxidative Pd cycles. The method underscore the compatibility of diazo scaffolds with transition-metal coupling systems, affording chemoselective modifications without sacrificing diazo integrity (Scheme 20a).[35a] The same group introduced a palladium(0)-catalyzed deacylative cross-coupling method for efficient synthesis of aryldiazoa-



Scheme 20 Cross coupling reactions for retention of diazo functionality.

cetates/aryldiazophosphate from aryl iodides and acyldiazoacetates/acyldiazophosphate under mild reaction conditions. The strategy is compatible with various electronically diverse aryl iodides, allowing for a wide substrate scope. Mechanistically, the process involves palladium(0)-mediated oxidative addition, transmetalation, and reductive elimination, resulting in the formation of valuable C–C bonds (Scheme 20b).[35b] Wang *et al.* also reported palladium-catalyzed C–H functionalization of acyldiazomethanes with aryl iodides. This transformation proceeds *via* Ag_2CO_3-assisted deprotonation, favoring diazo retention over dediazoniation, as supported by DFT studies. The authors further developed a tandem protocol combining C–H activation and Pd–carbene migratory insertion, enabling efficient synthesis of α,α-diaryl esters with broad substrate scope(Scheme 20c).[35c] Complementing Wang's work, Davies *et al.* introduced palladium-catalyzed cross-coupling strategy for the synthesis of 2,2,2-trichloroethyl (TCE) aryl- and vinyldiazoacetates from aryl and vinyl iodides. Addition of further phosphine ligand to the reaction mixture was required to avoid decomposition of the diazo product. The method circumvents limitations of diazo-transfer reactions, particularly for electron-rich or sterically hindered substrates, and demonstrates excellent functional group tolerance. Notably, the resulting TCE diazo compounds exhibit high reactivity and enantioselectivity in rhodium-catalyzed cyclopropanation reactions (Scheme 20d).[35d] A recent contribution by Ritter and coworkers introduces a general and regioselective method for late-stage diazoester installation *via* palladium-catalyzed cross-coupling of arylthianthrenium salts with diazoacetates. This two-step protocol begins with site-selective C–H thianthrenation of arenes, followed by rapid oxidative addition of the resulting arylthianthrenium salts to Pd(0), enabling diazo group incorporation into densely functionalized arenes. The installed diazo functionality remains amenable to diverse downstream transformations, including cyclopropanation, aziridination, and X–H insertion reactions. Notably, this strategy circumvents limitations associated with aryl halides and diazo-transfer reactions, offering access to aryl diazoacetates that are otherwise synthetically inaccessible. The method tolerates a wide range of functional groups and avoids the instability typically associated with electron-rich diazoalkanes, positioning it as a versatile platform for late-stage functionalization in complex molecule synthesis (Scheme 20e).[35e]

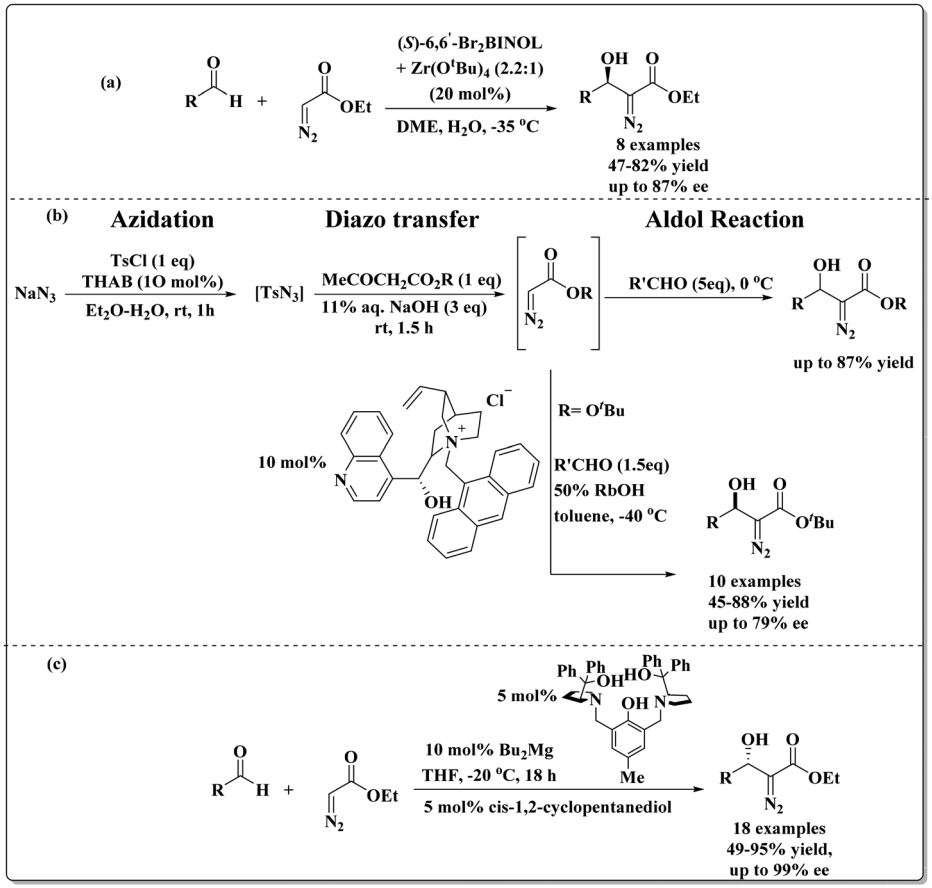
Recent advances in diazo synthesis have significantly expanded the repertoire of catalytic strategies for constructing α-diazo carbonyl architectures, one such strategy is the direct C–C bond formation with aldehydes. Early work by Yao and Wang demonstrated that BINOL-Zr(O*t*Bu)$_4$ catalysis enables direct aldol-type reactions between aldehydes and ethyl diazoacetate, affording β-hydroxy-α-diazoesters with moderately high enantioselectivity (53–87% ee) under mild conditions. This Lewis acid-mediated approach established the diazoester as a competent nucleophile, with the diazo functionality retained for downstream transformations (Scheme 21a).[36a] On similar lines, Nishida *et al.* developed a one-pot protocol in which sodium azide, acetoacetates, and aldehydes combine to furnish α-diazo-β-hydroxyesters under phase-transfer catalysis (PTC). The use of cinchonidinium-based chiral PTCs enabled moderate enantioselectivity (up to 79% ee) while avoiding the isolation of unstable intermediates (Scheme 21b).[36b] Further refinements by the same group, expanded the scope of the phase transfer catalysis to the catalytic asymmetric aldol reaction. The PTC-catalyzed asymmetric aldol-type reaction afforded α-diazo-β-hydroxyesters with up to 81% ee, and subsequent SmI_2-mediated N–N bond cleavage enabled conversion to α-amino-β-hydroxyesters, underscoring the synthetic versatility of diazo intermediates.[36c] Complementary to these PTC and Lewis acid strategies, Trost and coworkers developed a dinuclear magnesium-catalyzed aldol reaction using ProPhenol ligands and Bu_2Mg. This system achieved exceptional enantioselectivity (up to 98% ee) and scalability, with the resulting diazo products amenable to oxidation and alkylation, yielding 1,2-diols with high stereocontrol (Scheme 21c).[36d]

These studies underscore the diversity and adaptability of diazo compound synthesis and offer a glimpse of how diazo synthesis has transformed over the years, evolving from foundational transformations to sophisticated, highly selective methodologies. In this context, the comprehensive review by Wang *et al.* provides an in-depth account of reactions where diazo compounds undergo nitrogen-retaining transformations, rather than the more common nitrogen-eliminating carbene pathways.[36e] The authors classify these processes into six categories, including reactions where diazo compounds act as nucleophiles, electrophiles, or 1,3-dipoles, as well as reductions and intramolecular rearrangements. Through examples such as enantioselective aldol and Mannich-type reactions, and cycloadditions yielding pyrazolines and pyrazoles, the review highlights how retaining the diazo group enhances synthetic versatility and enables efficient access to diverse nitrogen-containing architectures with high selectivity and precision.

3. Reactivity of carbenes

One of the main applications of diazo compounds is that they act as facile and readily accessible precursors to metal–carbenes. In this section, we briefly introduce the reactivity and properties of metal–carbenes.

In general, carbenes are neutral molecules with a divalent carbon atom that has just six valence electrons.[37a,b] Depending on their electronic state, carbenes can be classified as singlet in which two non-bonding electrons are located in same orbital or triplet in which two non-bonding electrons are distributed between two orbitals (Fig. 1). The electronic structure and substituents on carbene carbon, define their electrophilic or nucleophilic character or a combination of both. Thus, carbenes are better described as *amphiphilic* species. For instance, singlet carbenes stabilized by heteroatoms or π-donor substituents (such as N-heterocyclic carbenes) are pre-



Scheme 21 Aldol type condensation for retention of diazo functionality.

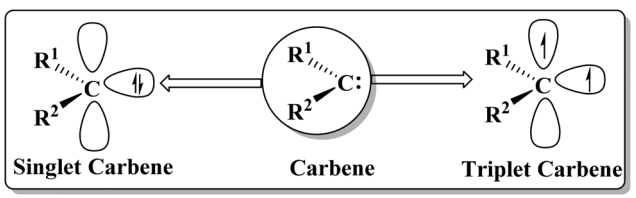


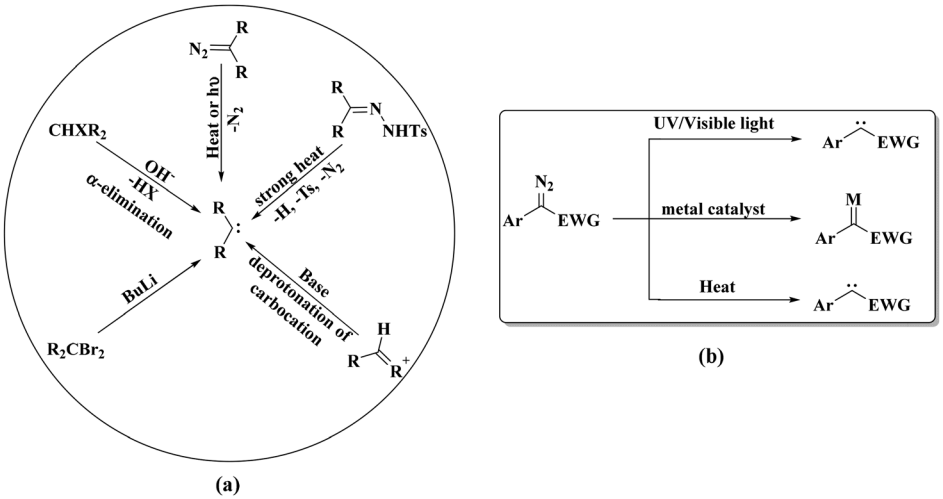
Fig. 1 Carbenes: singlet and triplet carbenes.

dominantly nucleophilic, whereas alkyl- or aryl-substituted carbenes often display electrophilic reactivity.[37c,d] Recent theoretical analyses of philicity indices by Korotkikh *et al*. revealed that nucleophilic carbenes such as N-heterocyclic, diamino-, and ylidic types possess low electronegativities ($\chi \approx 1.5$–3.9 eV) and small global electrophilicities ($\omega \approx 0.1$–1.1 eV), whereas typical electrophilic carbenes, including alkyl-, aryl-, and difluoro-carbenes, exhibit higher χ (≈4.7–7.1 eV) and ω (≈1.4–4.9 eV) values.[37e] The study also introduced new donor-acceptor philicity indices (I^e, P^H), demonstrating that nucleophilic carbenes such as diaminocarbenes and ylidic carbenes reach $I^{eH} \approx 10$–12 eV, while strongly electrophilic carbenes like dicyano- or bis(trifluoromethyl)carbenes show near-zero or negative I^{eH}, underscoring the wide electronic diversity and amphiphilic nature of this class of molecules.

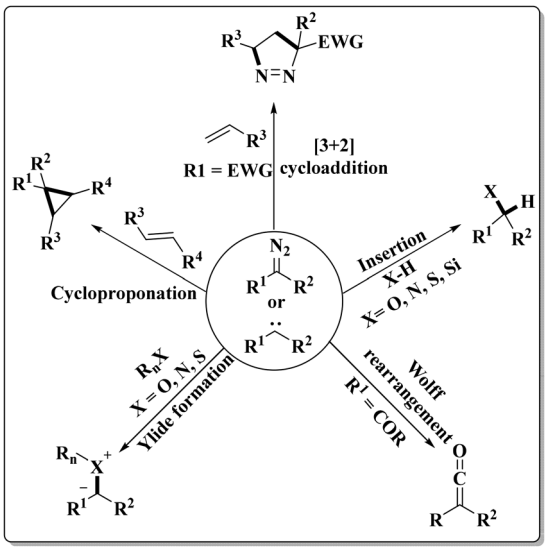
Carbenes were initially produced *via* the photochemical or thermal breakdown of diazo or diazirine compounds, deprotonation of chloroform with a strong base or deprotonation of carbocations (Scheme 22a).[38] However, these early carbene reactions were somewhat sporadic due to the high reactivity of carbenes and thus showed limited selectivity. These intriguing species became a powerful tool for synthetic applications when Fischer introduced transition metals to produce metal–carbenes in 1964.[39] Since then, metal–carbenes have been widely used in numerous synthetic reactions of great impact.

3.1. Diazo compounds as carbene precursors

At present, diazo compounds are the most important class of carbene precursors. There are three main methods to generate these reactive intermediates from diazo compounds, namely thermal, photochemical or by using transition metals (Scheme 22b).[40] Thermal methods have the disadvantage of limited applicability due to harsh reaction conditions. Thus, transition metal bound carbenes generated from diazo compounds provided an important alternative to the thermal reactions. In some cases, these metal–carbenes have similar reactivity to free carbenes, while typically the choice of metal has a major impact on the reactivity of metal–carbenes.



Scheme 22 (a) Traditional methods for carbene generation, (b) generation of carbene from diazo.



Scheme 23 General reactivity of metal carbenes/diazo compounds.

Many late transition metals, including copper, iron, rhodium and ruthenium decompose diazo compounds to generate their respective metal–carbene complexes.[41] In the context of sustainability, some of these transition metals have high cost, are toxic to the environment and their traces are difficult to eliminate, which represents a problem for industrial applications.[40] Thus, in quest for economical and more environmentally-friendly strategies, photochemical methods evolved. However, utilisation of highly energetic ultraviolet light greatly affects the selectivity of these processes.[40,42] Alternatively, a number of other precursors which generate diazo compounds *in situ* are utilised as carbene precursors (Fig. 2).[43] Ylides, such as sulfonium ylides, iodonium ylides, sulfoxonium ylides, and phosphonium ylides have been explored as stable carbene precursors and their properties are similar to that of carbenes derived from diazo compounds.[44] Furthermore, ring-chain isomerization of *N*-sulfonyl-1,2,3-triazoles exposes diazo group and studies suggest that a comparatively low amount of potentially explosive diazo com-

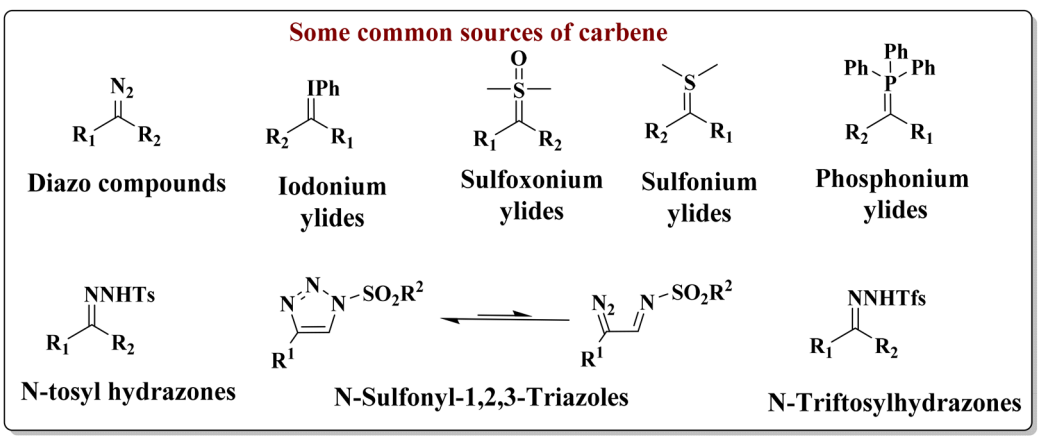


Fig. 2 Common sources of carbenes.

pounds are present in the reaction at any given time, which can be intercepted by metal to form metal–carbene complex.[45] More recently, *N*-triftosylhydrazones have been utilised as effective diazo surrogates that decompose at temperatures as low as −40 °C, which enabled to carry out a number of synthetically challenging transformations and widened the scope of some more established reactions.[46]

3.2. Fischer and Schrock carbenes

After the discovery of stabilisation of free carbenes by metal-to-carbon double bonds with transition metals, some of these carbenes have been isolated as metal–carbene complexes. The donation of d-orbital electrons from the metal to the electron-deficient carbene carbon improves the stability of the carbene. When this d-electron donation is weak, the carbenes continue to have electrophilic nature and are known as Fischer carbenes.[47] These carbenes are stabilized through π-backdonation from the metal and π-donation from heteroatom substituents and are most common for late transition metals in low oxidation states like Cu(I), Rh(I), Au(I), and Pd(II) with strong π-acceptor ligands such as CO or phosphines. However, the carbenes become nucleophilic in their reactivity when the electron donation from the metal to the carbene carbon is strong and are known as Schrock carbenes (Fig. 3). In these, carbene carbon is bound to early transition metals in high oxidation states such as in the early transition metals in high oxidation state like Mo(VI), W(VI), and Ta(V), stabilized by strongly σ-donating ligands such as alkoxides, amides, or alkyl groups.[48]

These metal–carbene complexes have been utilised as reagents in a number of organic transformations including C–H/X–H (X = O, N, S, or B) insertions, cyclopropanation, ylide synthesis, and rearrangements, permitting the synthesis of highly functionalized molecules (Scheme 23).[49]

4. Reactivity of metal–carbenes from diazo compounds

One of the main applications of diazo compounds is that they act as facile and readily accessible precursors to carbenes through thermal, photochemical or transition metal decomposition. In this context, diazo compounds are readily available reagents that permit a wide range of organic transformations by the intermediacy of metal–carbenes. While the vast majority of the reactions involving diazo compounds are based on carbene generation (Scheme 23), it should be noted that some useful transformations without carbene formation also exist and readers are directed to ref. 50 for further details.[50]

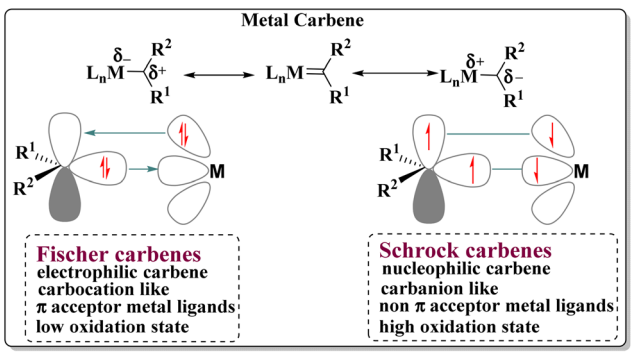


Fig. 3 Fischer and Schrock carbenes.

While the present review mainly focuses on insertion reactions, ketene chemistry, nucleophilic reactions and cyclopropanation reactions of diazo compounds, the chemistry of diazo reagents stretches significantly beyond these domains. The complementary or emerging facets of diazo-compound chemistry, are discussed in numerous comprehensive review articles.

For catalytic carbene/alkyne metathesis (CAM) involving diazo compounds (particularly α-carbonyl diazo precursors) and alkynes, Xu *et al.* provide a detailed review explaining how these diazo-derived carbenes engage alkynes to form vinyl carbene intermediates and trigger cascade transformations, a trajectory rarely addressed in conventional carbene–alkene/cyclopropanation discussions.[51a] In a related context, Saá *et al.* presented a comprehensive review on ruthenium-catalyzed CAM transformations, detailing the mechanistic intricacies and synthetic scope of these vinylcarbene-mediated cascades.[51b] The articles highlight the expanding frontiers of diazo chemistry, bridging conventional cyclopropanation reactivity with newer metathetic and cascade pathways enabled by transition-metal catalysis. For coupling and functionalization reactions of copper-carbene (from diazo compounds) with terminal alkynes and related systems, Dong, Liu and Xu highlight how diazo compounds; when used with copper catalysts; enable cross-coupling, cyclopropenation and allene formation *via* carbene/alkyne reactivity-again broadening beyond classical insertion/cyclopropanation themes.[51c] Complementing this, Xu *et al.* reviewed stepwise carbene-transfer reactions of diazo-derived metal carbenes with alkenes, which go beyond classical cyclopropanation.[51d] The review demonstrates that diazo chemistry encompasses direct addition of alkenes to metal carbenes, migratory insertion and C–H activation sequences, as well as radical-coupling pathways, illustrating the broader scope of diazo reactivity. Recent review article by Xu *et al.* demonstrates how diazo-derived carbenes can be employed in metal-catalyzed asymmetric transformations to construct chiral all-carbon quaternary centers, highlighting the capacity of diazo chemistry to generate complex, enantioenriched structures of relevance to pharmaceuticals and natural products.[51e] Reisman, Nani, and Levin provide a comprehensive review of the Buchner reaction and related arene cyclopropanation processes, with a focus on applications in natural product total synthesis.[51f] The Buchner reaction, originally reported by Buchner and Curtius in 1885, involves the generation of carbenes from diazo compounds, which undergo cyclopropanation of aromatic rings. Subsequent ring expansion yields bicyclic intermediates, such as norcaradienes and cycloheptatrienes, which serve as versatile building blocks in organic synthesis. The review highlights the reaction mechanism, sub-

strate scope, and synthetic applications, illustrating the evolution and enduring relevance of arene cyclopropanation in modern synthetic strategies.

Visible-light-mediated carbene generation from diazo compounds has emerged as a mild and sustainable alternative to traditional thermal methods, which often require high temperatures, and harsh reagents. Under visible-light irradiation, diazo compounds undergo photolysis either through direct excitation or through photosensitization, leading to nitrogen extrusion and the formation of reactive singlet or triplet carbenes. This approach offers greater functional group tolerance and temporal control over carbene release, enabling selective transformations such as cyclopropanations, C–H insertions, ylide formations, and heterocycle synthesis under ambient conditions. Moreover, the use of visible light-rather than UV-enhances safety and compatibility with sensitive functional groups and complex molecular architectures. Recent advances have also leveraged photocatalysts, including transition metal complexes and organic dyes, to facilitate energy transfer or electron transfer processes that promote diazo activation under ambient conditions. Since this review article is primarily focused on the transition metal catalysed carbene generation and the reactions therein, we recommend readers to read comprehensive review articles dedicated to visible-light-mediated carbene generation.[52]

These reviews underscore the remarkable versatility of diazo compounds, demonstrating that their chemistry spans from classical insertions and cyclopropanations to sophisticated transformations such as cascade carbene/alkyne metathesis, stepwise carbene transfer, asymmetric catalysis, and aromatic cyclopropanation. This expanding landscape not only broadens the fundamental understanding of diazo reactivity but also provides powerful tools for constructing complex and enantioenriched molecular architectures in modern synthetic chemistry.

In the following section, we present an overview of the recent studies on the application of metal–carbene complexes generated from diazo compounds with respect to X–H insertions, including C–H, O–H and N–H bonds with a focus on Cu, Rh and Pd catalysis. Furthermore, recent advances in the synthesis of ketenes by a direct carbonylation of diazo carbenes and cyclopropanation reactions will be discussed.

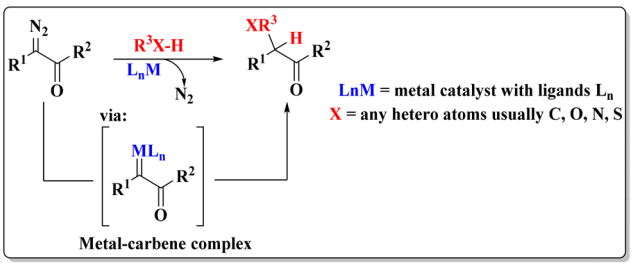
4.1. Transition metal-catalysed carbene insertion into X–H (X = C, O, N, S) bonds

A wide range of synthetic opportunities for the preparation of functionalised molecules provided by the ubiquitous presence of carbon–hydrogen and heteroatom–hydrogen bonds in organic molecules can be attained by X–H activation (X = C, O, N, S).[53] In this direction, transition metals, such as Rh, Cu, Ru, Co and Fe have been extensively employed in the decomposition of diazo compounds to yield metal–carbenes.[54]

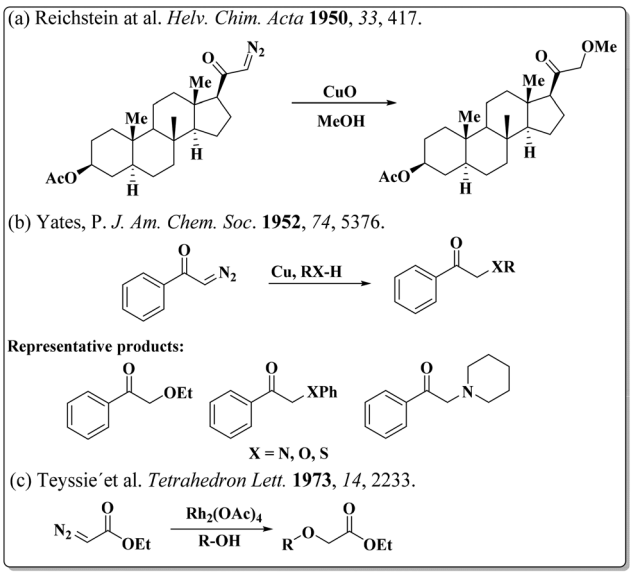
Metal–carbene promoted X–H insertions for carbon–heteroatom transformations have undergone significant development in recent years. In these reactions, metal–carbene complex is generated from the diazo compound, which then reacts with X–H bonds to yield the insertion product either in concerted or stepwise fashion (Scheme 24).[55] Typically, these Rh, Cu, Ru and Fe catalysed insertion reactions are tolerant to a wide variety of functional groups as well as reaction conditions.

Historically, the 1950 report of copper(I) oxide catalysed conversion of α-diazo ketone pregnenolone derivative into an unexpected α-methoxy ketone product instead of normal Wolf rearrangement product in methanol stimulated the progress of transition metal-catalysed X–H insertion reactions (Scheme 25a).[56] Subsequently, Yates reported the first detailed study of X–H insertion of aniline, ethanol, thiophenol and piperidine employing α-diazoketones as carbene precursor and copper as a catalyst (Scheme 25b).[57] The pioneering work of Nozaki, Noyori and coworkers on asymmetric catalysis highlighted the possibility of formation of chiral copper-stabilized carbene complexes.[58] Teyssie reported that $Rh_2(OAc)_4$ is the best catalyst for the carbene insertion into O–H bonds with remarkable reactivity and high turnover numbers (approximately 600 turnovers) (Scheme 25c).[59]

Other milestones in metal–carbenes from diazo compounds include highly efficient Merck synthesis of antibiotic thiena-



Scheme 24 General scheme for X–H insertion reactions.



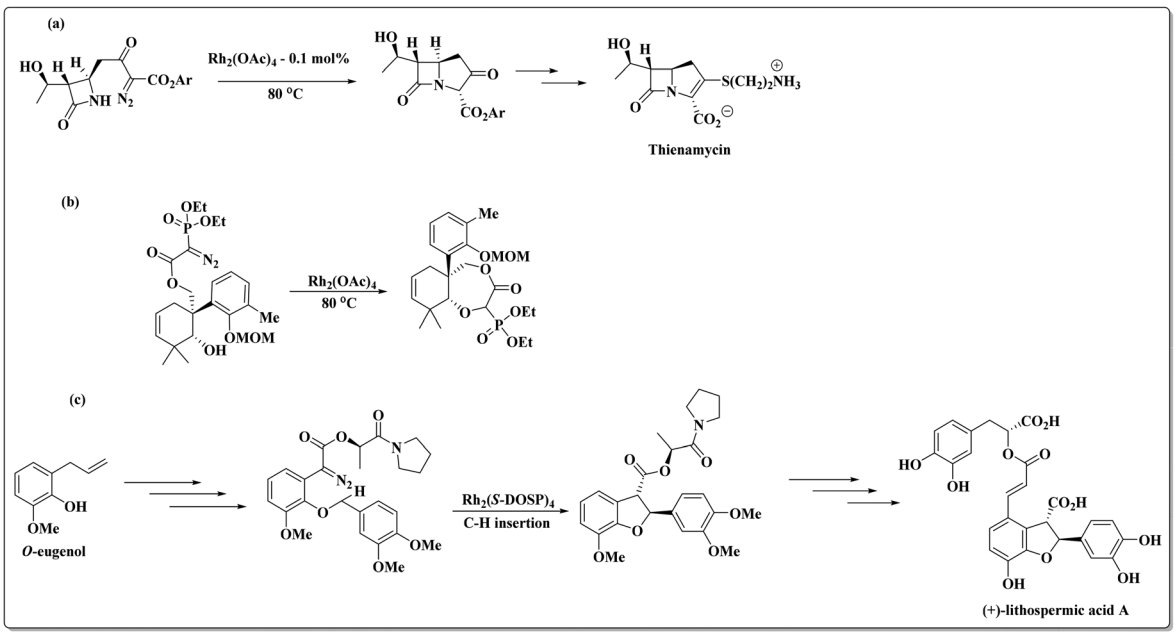
Scheme 25 Seminal observations regarding carbene insertion into X–H bonds.

mycin involving N–H insertion as a key step even in the presence of strained molecules such as β-lactams, demonstrating the utility of Rh–carbene chemistry in practical applications (Scheme 26a).[60] In their remarkable total synthesis of Maoecrystal V, Yang's group demonstrated intramolecular O–H insertion catalyzed by $Rh_2(OAc)_4$ as a straightforward and elegant method for late-stage carbon-heteroatom transformations (Scheme 26b).[61] In another example, Yu and Wang reported the total synthesis of (+)-lithospermic acid in 12 steps from *o*-eugenol involving Rh-catalyzed asymmetric benzylic C–H insertion (Scheme 26c).[62]

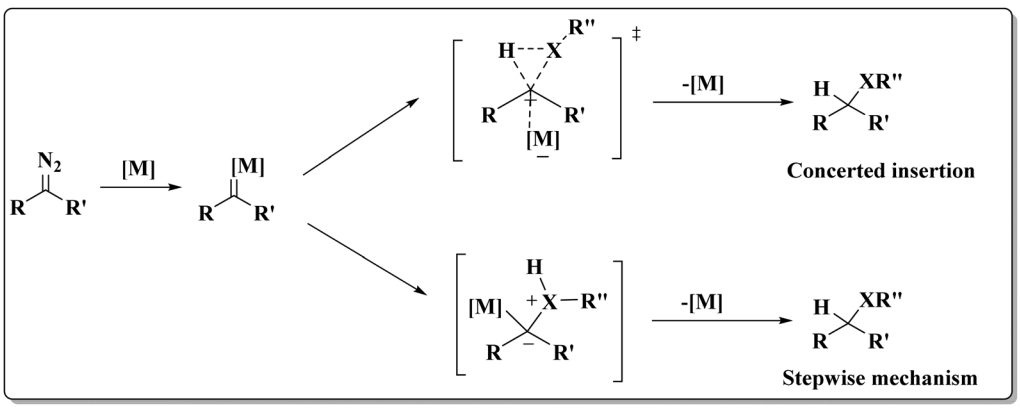
Mechanistically, for the insertion reactions, the formation of metal–carbene complex follows the concerted reaction mechanism *via* three center transition state in case of non-polar bonds (*e.g.*, C–H, Si–H)[63] or the reaction proceeds *via* stepwise mechanism involving ylide formation followed by proton transfer for polar bonds (*e.g.*, N–H, O–H) (Scheme 27).[64] In the former case, the formation of C–X or C–H bonds is accompanied by the simultaneous cleavage of the metal catalyst from the carbene carbon; thus, the enantioselectivity of the reaction is anticipated to be affected by the chiral ligands. Conversely, asymmetric carbene insertion into polar bonds has developed very slowly, even though carbene insertion into polar bonds has long been well-known.[65]

4.2. Palladium catalysed cross-coupling reactions of diazo compounds

In the last decade, diazo compounds have been used as indispensable reaction partners in transition metal-catalysed cross-coupling reactions.[66] In general, a new chemical bond is formed between a nucleophilic (an organometallic compound) and an electrophilic (an organic halide or pseudohalide) coup-



Scheme 26 Practical applications of X–H insertion reactions.



Scheme 27 Proposed mechanisms for carbene insertion reactions.

ling partners during any coupling reaction in the presence of a transition metal catalyst.[67] The exploration of new cross coupling partners has remained one of the major research interests among organic synthesis community and significant advancements have been made in this field. In this context, palladium-catalysed metal–carbene migratory insertion has evolved as an efficient methodology for carbon–carbon bond formation since the ground-breaking work of Van Vranken.[66,68] These cross-coupling reactions are mechanistically different from the standard palladium-catalysed cross-coupling reactions (Scheme 28).[43a]

The oxidative addition intermediate reacts with the diazo compound to form Pd carbene species (Scheme 28; Cycle B), contrary to the traditional cross-coupling reactions in which oxidative addition intermediate follows the ligand-exchange reductive elimination (Scheme 28; Cycle A). The Pd–carbene complex subsequently undergoes migratory insertion followed by β-hydride elimination to generate the final product. The migratory insertion step has been found to be general in terms of the different functional groups, including cyclopropyl, alkynyl, allenyl, propargyl, vinyl, benzyl, acyl and aryl.[43a]

In 2001, Van Vranken and co-workers reported the first palladium-catalysed cross-coupling reaction involving benzyl halides as electrophiles and trimethylsilyldiazomethane ($TMSCHN_2$) as the carbene precursor.[68a] The reaction furnished substituted styrenes in moderate yields (Scheme 29a). Since Van Vranken's pioneering work, a number of palladium-catalyzed carbene coupling reactions have been reported. The same group reported that ethyl diazoacetate (EDA) also reacted with benzyl bromides under similar reaction conditions to afford cinnamates in moderate yields. Electron-withdrawing substituted benzyl halides resulted in desired products in good yields, while electron-neutral and electron-donating substituted benzyl halides provided the products in lower yields (Scheme 29b).[69]

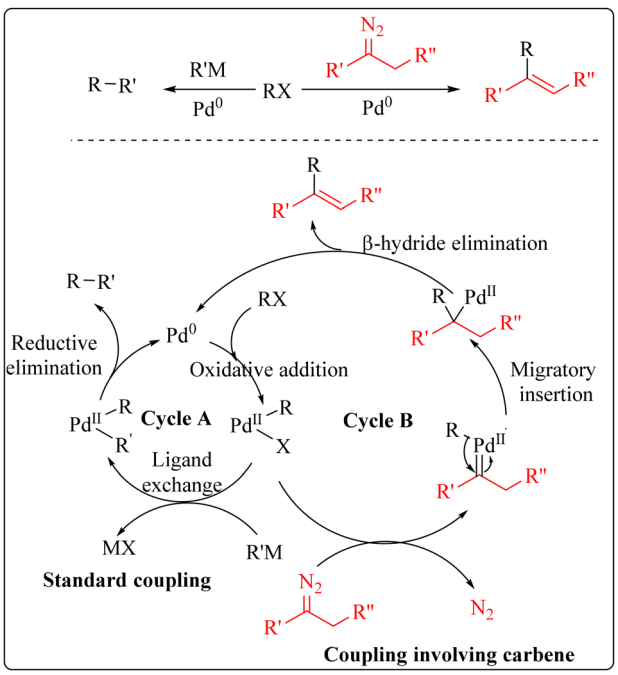
In 2009, Chan and co-workers expanded the scope of diazo coupling partners to more stable α-aryl-α-diazoesters, affording α,β-diaryl acrylates with excellent *E*-selectivity. The authors also used stoichiometric amount of a well-characterised Pd-complex, an intermediate that could be formed from palladium and benzyl halide, directly and isolated the desired product in good yield in support of migratory insertion mechanism (Scheme 29c).[70] In another development, Wang and co-workers used α-trifluoromethyl diazo compounds and α-diazo phosphonates as coupling partners with benzyl halides and the reactions afforded corresponding olefins in good yields and excellent *E*-selectivity (Scheme 29d and e).[71]

More recently, Sivasankar and co-workers reported the synthesis of 1,1,3,4-tertasubstituted dienes using Baylis-Hillman allyl bromides as coupling partners with α-diazoesters. The reaction afforded the polyfunctionalized products in moderate to good yields (Scheme 29f).[72] In addition to benzyl halides, allylic halides have also been used as suitable electrophilic coupling partners in palladium-catalysed cross-coupling reactions with diazo compounds. The readers are encouraged to a recent review for additional examples of cross-coupling reactions of diazo compounds.[73]

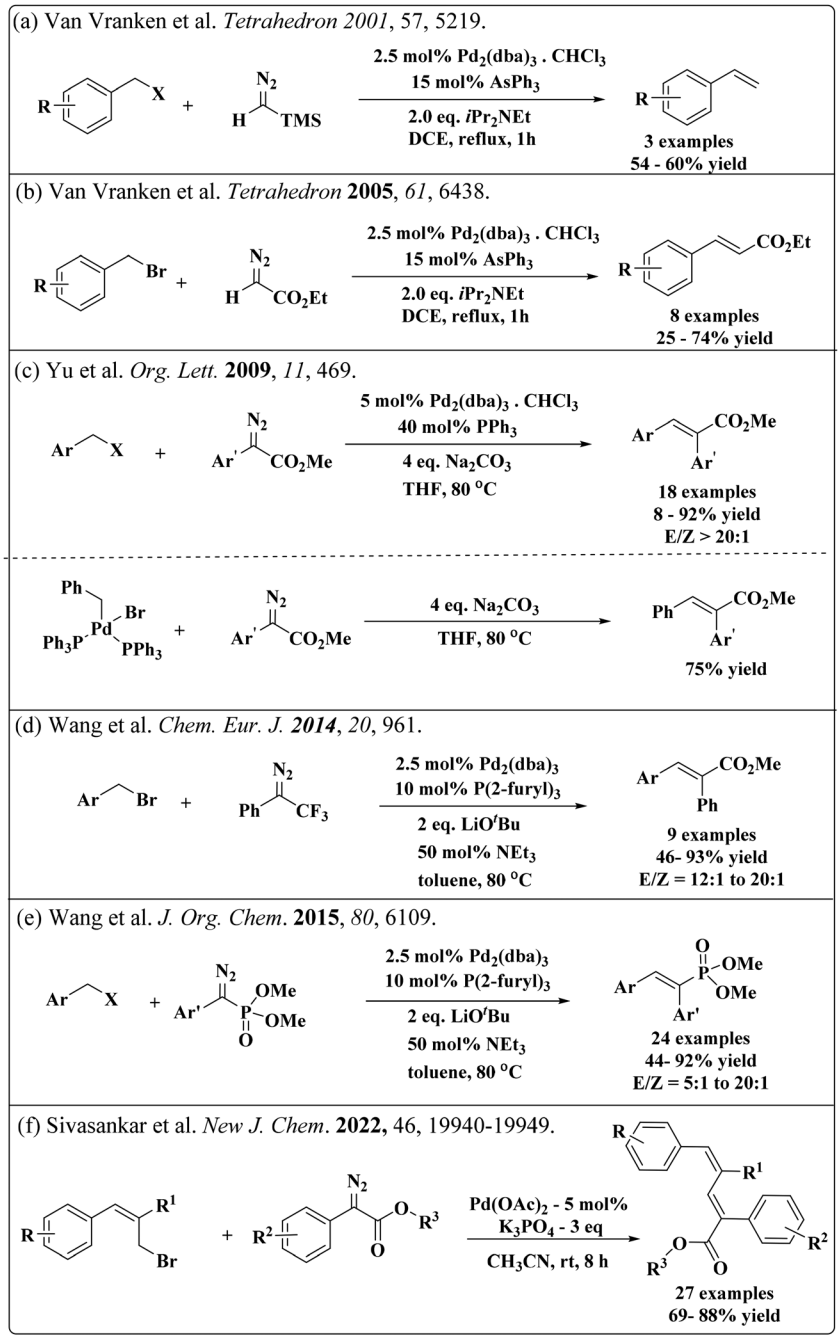
4.3. Ketene formation reactions from diazo compounds

4.3.1. Ketenes and diazo compounds. Ketenes are an important class of reactive intermediates which may be considered as the derivatives of allenes in which a terminal carbon atom is replaced by an oxygen atom. Thus, the central carbon is bonded to an oxygen atom and to a carbon atom through double bonds, and is therefore sp hybridized. The presence of highly reactive alkenyl and carbonyl groups make ketenes highly valuable organic reactive intermediates as various transformations of one or both of these groups are possible.

In 1901, Wedekind reported the formation of $^{n}Pr_3NHCl$ (**3**) from the reaction of diphenylacetyl chloride (**1**) with $^{n}Pr_3N$.[74] They proposed that the reaction proceeds *via* the formation of intermediate (**2**) which is similar to ketene but the intermediate was not isolated or characterised (Scheme 30a). Wedekind noted: "Herewith is made the hypothesis that the atomic grouping $(R_1{\cdot}R_2){\cdot}C_2O^{\bullet}$ is temporarily capable of existence in solution". Later in 1905, Staudinger isolated an unexpected new reactive intermediate diphenylketene (**5**) as a low-melting solid while studying the reaction of chlorodiphenylacetyl chloride (**4**) with zinc (Scheme 30b).[75] Soon dimethylketene (**8**) was also discovered and was found to dimerise into symmetrical cyclobutanedione (**9**)[76] while diphenylketene yielded β-lactam (**6**) with imines (**7**) (Staudinger reaction) (Scheme 30b and c).[77] Since then, cycloadditions have remained the most characteristic feature of ketene chemistry.

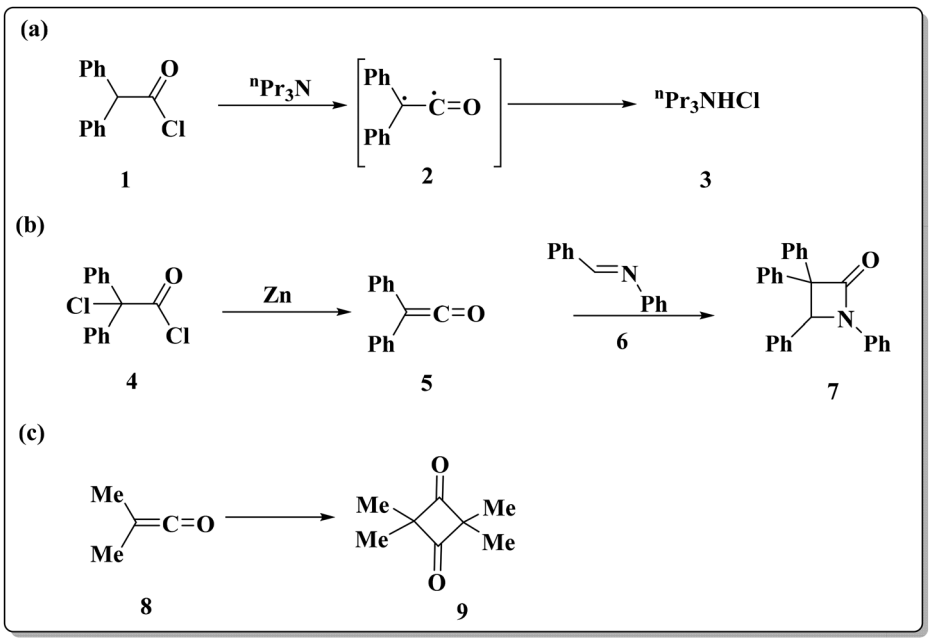


Scheme 28 Mechanism of standard coupling reactions and carbene coupling reaction.

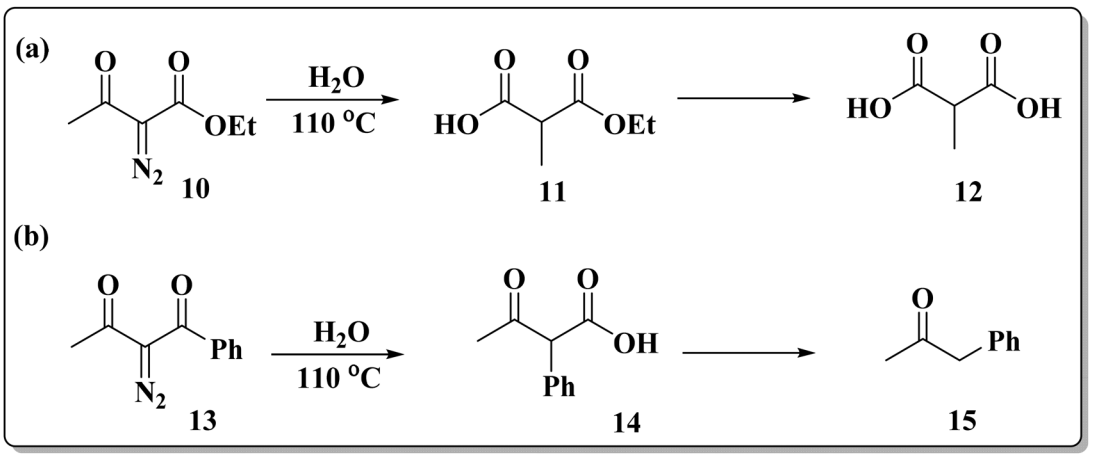


Scheme 29 Palladium-catalysed cross-coupling of benzyl halides with diazo compounds.

In 1902, Wolff reported that heating ethyl-2-diazo-3-oxobutyrate (**10**) with water afforded ethane-1,1-dicarboxylic acid (isosuccinic acid) (**12**) by way of the ethyl ester (**11**) (Scheme 31).[78] Under similar conditions 1-phenylpropan-2-one (**15**) was obtained from 2-diazo-1-phenylbutane-1,3-dione (**13**). However, Wolff did not foresee the mechanism underlying these modifications at the time. The discovery of ketene intermediates in 1905 by Staudinger suggested that ketenes are a necessary intermediate in the production of carboxylic acids in "aqueous" Wolff rearrangements.[75–77] Wolff adopted this mechanism in a paper wherein he also described Ag(I)-catalysed rearrangements of α-diazo ketones.[79] Since then, Wolff rearrangement has been used as a main synthetic route for the generation of various reactive ketenes and the products derived from diazo compounds. A comprehensive review article marking the century since the discovery of the Wolff rearrangement (1902–2002) by W. Kirmse delves into the historical developments, mechanistic understanding, and synthetic applications of the reaction, which converts α-diazocarbonyl compounds into ketenes.[80]



Scheme 30 (a) Wedekind's work, (b) first example of ketene formation and Staudinger reaction, (c) dimerization of dimethylketene.

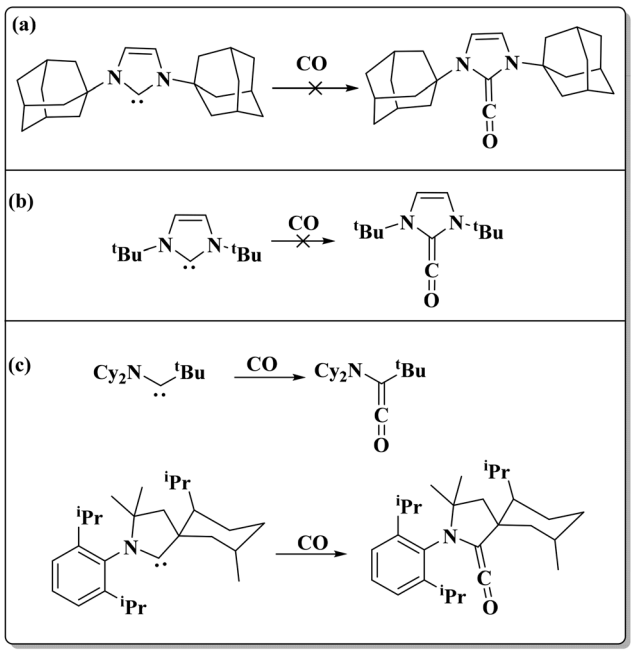


Scheme 31 First examples of Wolff rearrangement.

4.3.2. Direct carbonylation of carbenes. Recent advancements have confirmed the close relationship between carbenes and ketenes. The direct carbonylation of carbenes to form ketenes using metal carbonyls or the carbonylation of carbenes using CO gas in presence of metal complexes as catalysts afford β-lactams in the presence of imines, formally derived from ketenes (Scheme 32). Various ketenes, RR′C═C═O, have been produced by carbonylation of carbenes afforded *in situ* through decomposition of diazo compounds, RR′C═N_2, as precursors. The discovery of stable carbenes by Bertrand with the isolation of phosphanylcarbenes[81] as well as the development of N-heterocyclic carbenes (NHCs) by Arduengo[82] offered new opportunities for carbonylation of carbenes to synthesise ketenes.

Lyashchuk and Skrypnik described that the addition of CO to IAd (an NHC with *N*-adamantyl wingtips) yields a stable ketene (Scheme 32a).[83] However, these results could not be verified by Arduengo and co-workers, who reported that carbonylation of the parent NHC only produces a weakly linked van der Waals complex.[84] The observations were consistent with the experimental result that I*t*Bu was unreactive with CO (Scheme 32b).[85] Subsequently, Bertrand and co-workers reported that acyclic and cyclic (alkyl)(amino)carbenes (CAACs) easily combine with CO to form ketenes that could be separated and identified by X-ray analysis (Scheme 32c).[86]

Ungváry and co-workers carefully explored ketene formation by $Co_2(CO)_8$-catalyzed carbonylation of diazo compounds[87] under 50–70 bar pressure of CO, which reacted further with



Scheme 32 (a) *N*-Adamantyl substituented NHC does not yield Ketene with CO. (b) *t*Bu substituted NHC does not react with CO. (c) Acyclic and cyclic alkylaminocarbenes yield ketenes on reacting with CO.

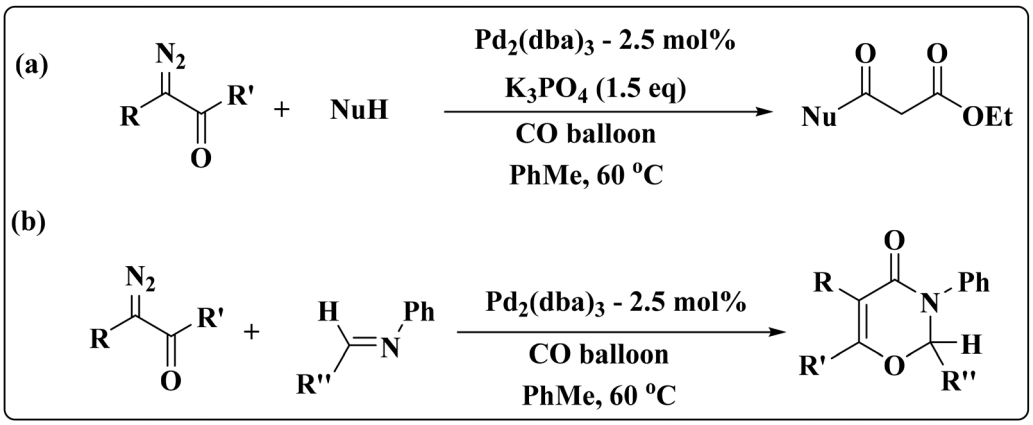
alcohols[87a] and imines to yield 1,3-dicarbonyl compounds and β-lactams, respectively.[87b] The reports by Ungváry suggested that carbonylation of diazo compounds utilising transition-metal-catalysts was feasible. However, despite their importance, the scope of these studies was limited since only ethyl diazoacetate was used in most of their studies and harsh reaction conditions, including high reaction temperatures and high CO pressure, further limited their potential widespread application in synthetic chemistry. Subsequently, Wang and co-workers reported Pd-catalyzed carbonylation of α-diazo carbonyl compounds and *N*-tosylhydrazones with CO at atmospheric pressure and moderate temperature (Scheme 33).[88] The authors reported tandem reactions of ketenes with nucleophiles and ketones and demonstrated that the [4 + 2] cycloaddition reaction of acylketenes with imines yielded 1,3-oxazin-4-one derivatives in good yields. Nevertheless, due to the toxicity and the need of cautious handling of gaseous carbon monoxide, numerous attempts have been made to use safe sources of CO, such as metal carbonyls, as the solid CO surrogates for the carbonylation of carbenes.

In this context, Sivasankar and co-workers in a series of reports, described carbonylation of carbenes generated from diazo compounds using $Co_2(CO)_8$ as a solid CO source.[89] The *in situ* generated ketene was detected using IR spectroscopy. The subsequent reaction of ketenes with aniline derivates afforded synthetically valuable amidoesters and amidophosphonates, while [2 + 2] cycloaddition reaction with imines yielded β-lactams, and the annulation of amides from 2-aminophenol resulted in the formation of benzooxazoles (Scheme 34).

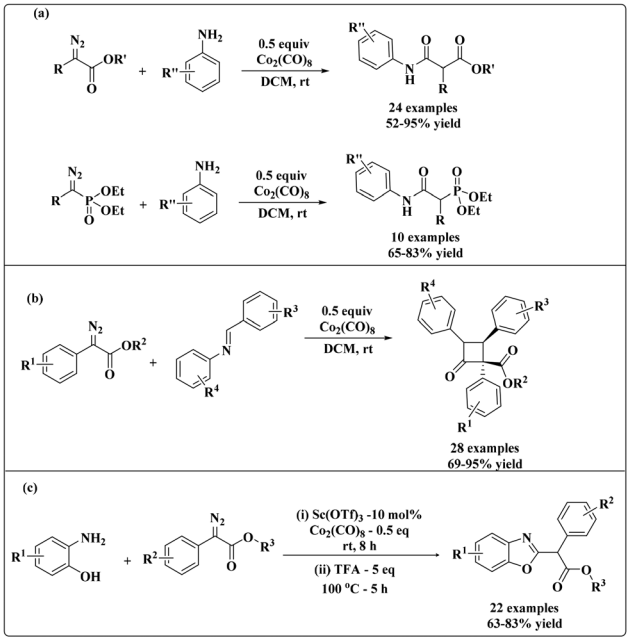
Recently, Xu *et al.* documented a comprehensive review of recent advances in catalytic asymmetric reactions of ketenes. The authors describe how ketenes can be converted into valuable chiral products under the influence of stereochemically defined catalysts.[90] The review focuses on three major reaction classes: hydrofunctionalization, difunctionalization, and cycloaddition. In hydrofunctionalization, catalysts such as chiral N-heterocyclic carbenes, phosphoric acids, and iridium complexes enable the enantioselective formation of esters, amides, and alpha-functionalized carbonyl compounds. Difunctionalization strategies facilitate the sequential introduction of distinct substituents at the alpha- and beta-positions, while asymmetric cycloaddition reactions allow for the construction of complex cyclic and polycyclic architectures with high stereocontrol.

4.4. Cyclopropanation reactions of diazo compounds

Cyclopropanation reaction is among the most explored reactions of diazo compounds.[91] The broad interest in cyclopropanes arises from their significant ring strain,[92a] the presence in a wide variety of natural products,[92b] and their interesting physical properties and bonding characteristics[92c] that



Scheme 33 (a) Reaction of EDA with CO and different nucleophiles. (b) [4 + 2] cycloaddition reaction of acylketenes with imines.



Scheme 34 (a) Synthesis of amido esters and amido phosphonates *via* ketene intermediate. (b) [2 + 2] cycloaddition reaction of ketenes with imines afford β-lactam. (c) Synthesis of benzoxazoles from *via* ketene formation.

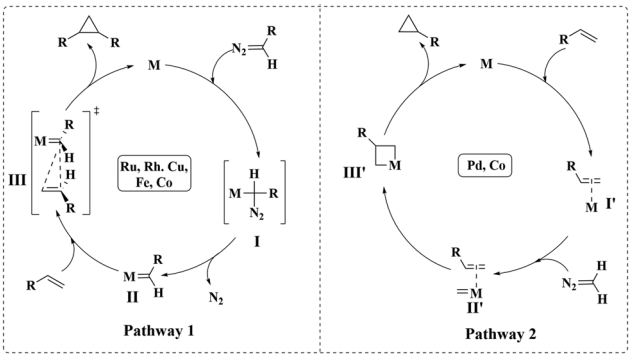


Fig. 4 Two proposed pathways for the cylcopropanation of olefins using diazo compounds.

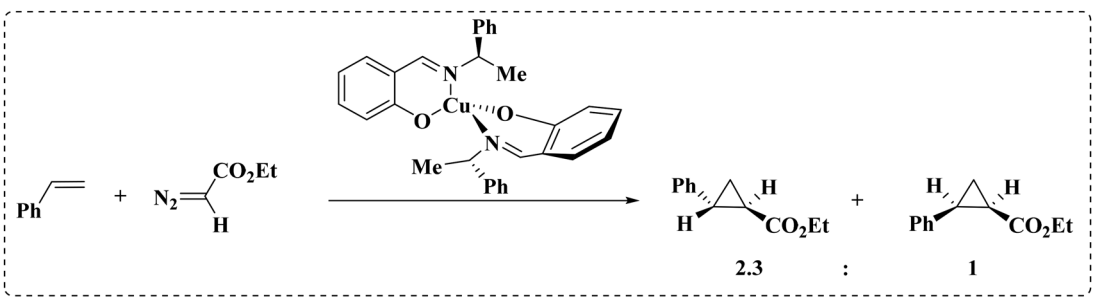
altogether make these compounds of high interest to synthetic chemists.

Cyclopropanation is usually achieved in a selective manner by Simons–Smith cyclopropanation[93] or by metal-catalysed decomposition of diazo compounds. The metal-catalysed cyclopropanation of alkenes using diazo compounds is proposed to follow either of the two pathways shown in Fig. 4.

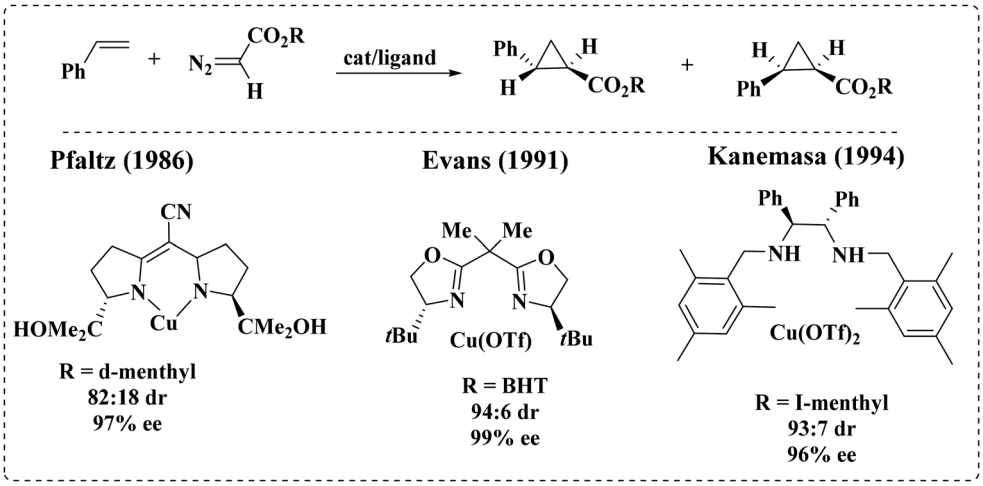
Pathway 1 is the more common mechanism followed by metal–carbenoids for cyclopropanation in which nucleophilic diazo compound coordinates with the metal-center to form metal–carbenoid intermediate **I**, which after extrusion of N_2 generates the metal carbene complex **II**. The metal carbene complex reacts in a concerted [2 + 1] addition with the alkene to generate the intermediate **III** from which the product cyclopropane is released with the regeneration of the catalyst.[94] Pathway 2 is limited to select metals, such as palladium. In this mechanistic pathway, alkene coordinates to the metal centre prior to the complexation of carbene to generate the intermediate **I′**, which then reacts with the carbene generated from the diazo compound to give the intermediate **II′**. A formal [2 + 2] addition results in the formation of the metallocyclobutane intermediate **III′** from which product cyclopropane is formed after reductive elimination and the catalyst is regenerated.[95]

Cyclopropanation using diazo compounds has been reported with different types of metal catalysts. In 1966, Nozaki, Noyori and co-workers demonstrated the first copper-catalysed enantioselective cyclopropanation of styrene with ethyl diazoacetate in 6% ee (Scheme 35),[96] which subsequently led to the synthesis of a wide variety of asymmetric copper catalysts (Scheme 36).[97] Salomon and Kochi published a seminal mechanistic study that had significant impact on the understanding of copper catalysis in the decomposition of diazo compounds (Scheme 37).[98a] The study demonstrated that the diazo compound reduces Cu(II) to Cu(I) during cyclopropanation, and the *in situ* generated Cu(I) catalyst is involved in the process of diazo decomposition and cyclopropanation. However, due to lower stability of air-sensitive Cu(I) complexes, Cu(II) complexes are extensively used as pre-catalysts for the *in situ* generation of Cu(I) active catalysts.[98b,c]

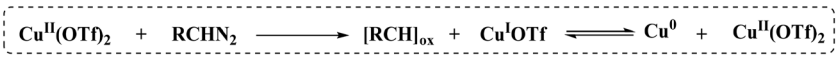
At present, a wide range of transition metals, such as Co, Pd, Ru, Fe and Ir have been reported to catalyse cyclopropanation reactions with diazo compounds.[99] Copper and cobalt are



Scheme 35 First report of enantioselective olefin cyclopropanation using diazo compound.



Scheme 36 Selected chiral copper catalysts for olefin cyclopropanation.



Scheme 37 Reduction of Cu(II) to Cu(I) with diazo compounds.

more suitable for *trans* and enantioselective cyclopropanations.[100] However, as a supplement to conventional catalysts, select ruthenium[101] and iridium[102] catalysts provide high *cis*-selectivity. Typically, rhodium complexes are very active and enantiodiscriminating.[103] Iron[104] and palladium[68a,105] are also common catalysts for cyclopropanations; the former is employed with electron-poor alkenes, while the latter is used with electron-efficient alkenes. For readers interested in gaining a deeper and more comprehensive understanding of cyclopropanation reactions mediated by diazo compounds, it is recommended to consult detailed reviews such as those by G. Maas,[106a] Qian and Zhang,[106b] Allouche and Charette,[106c] and Ferreira *et al.*[106d] These articles provide in-depth insights into the evolution, scope, and asymmetric variants of cyclopropanation reactions employing diazo compounds, offering valuable insights into the evolution and scope of diazo-based cyclopropanation chemistry.

5. Application of diazo compounds and future prospects

Diazo compounds have garnered considerable attention beyond traditional synthetic methodologies and are increasingly recognized for their utility across disciplines particularly due to their unique capacity to generate reactive carbenes under mild conditions. This reactivity has been harnessed in diverse fields and has found innovative applications ranging from chemical biology to materials science. Although the applications of diazo compounds across different fields merit a fully dedicated review article in their own right, we have briefly provided an overview to give readers insight into how diazo chemistry has revolutionized diverse scientific domains in recent years. This panoramic perspective underscores the interdisciplinary relevance and transformative potential of diazo compounds. Readers can also explore Raines *et al.*'s "Diazo Compounds: Versatile Tools for Chemical Biology",[107a] Jianbo Wang's 'Diazo compounds: Recent applications in synthetic organic chemistry and beyond"[107b] and Davies and Denton's "Application of donor/acceptor-carbenoids to the synthesis of natural products"[15b] for broader understanding of the field.

5.1. Applications in chemical biology

In the early half of the 1960s, diazo chemistry embarked on a transformative journey from dynamic sensing of protein conformational changes to the molecular dissection of enzymatic function. Through four landmark studies, researchers progressed from visualizing protein rearrangements to identifying active-site residues and irreversibly inactivating enzymes *via* targeted carbene insertion. Grossberg and Pressman introduced an arylated diazo probe capable of sensing antibody conformational shifts upon hapten binding.[108a] Upon nitrogen extrusion, the probe generated an aryl carbene that reversibly inserted into surface residues, transforming a covalent label into a dynamic structural sensor. By monitoring changes in these carbene adducts, they visualized real-time protein dynamics-marking the debut of diazo-derived carbenes as molecular reporters and laying the groundwork for covalent probes in biological sensing. Doscher and Wilcox advanced the field by demonstrating that diazoacetamides preferentially esterify protein carboxylates over simpler acids. Their compari-

son of reactivity between α-chymotrypsinogen and small-molecule carboxylates showed that diazo compounds could selectively engage functionally relevant residues in complex biological environments.[108b] This pivotal insight introduced a conceptual "chemical handle" for selective biomolecular tagging and catalyzed the evolution of bioorthogonal labelling strategies, where electronic tuning of diazo reagents enables site-specific conjugation under physiological conditions. Building on the previous work, Riehm and Scheraga elevated diazo-based protein interrogation from broad chemoselectivity to pinpoint structural mapping. Using a diazomethyl ketone to generate an electrophilic α-oxo carbene, they selectively labeled a catalytic aspartate within the active site of ribonuclease.[108c] This covalent "foot printing" provided high-resolution identification of functional residues, establishing diazo probes as precision tools for mechanistic dissection of proteins. In a defining contribution to enzymology later that year, Delpierre and Fruton demonstrated that diphenyldiazomethane irreversibly inactivates pepsin by inserting into histidine residues at its active site.[108d] By generating diphenylcarbene *in situ*, they achieved direct covalent capture of catalytic residues-solidifying diazo compounds as powerful mechanistic probes capable of mapping enzymatic function through selective inactivation.

Collectively, the pioneering studies from 1960 to 1965 established a remarkable trajectory-from reversible sensing and chemoselective labelling, to catalytic foot printing and targeted inactivation-laying the conceptual and technical foundation for modern diazo-based probes and bioorthogonal platforms. This era crystallized the diazo → carbene → covalent insertion sequence as a versatile biochemical strategy, where judicious substituent design enabled reactivity tuning and site-specificity. That foundational arc continues to resonate in contemporary chemical biology, where stabilized diazoacetamides are employed for selective conjugation within living systems. By finely adjusting reagent basicity and electronic properties, modern probes favour O–H or N–H insertion over hydrolysis, enabling residue-specific labelling under physiological conditions.

The potent reactivity of diazo and diazonium species, while carefully controlled for selective protein modification, is also leveraged in the realm of nucleic acid chemistry for DNA cleavage. A comprehensive book chapter by Dev P. Arya outlines the mechanisms by which certain diazo and diazonium compounds, including those derived from natural products like kinamycins, can induce DNA damage and strand scission. These agents typically generate highly reactive intermediates (*e.g.*, carbenes, radicals, or electrophilic diazonium cations) that react with DNA bases or the phosphodiester backbone, leading to cytotoxic effects.[109] It provides critical mechanistic background on how diazo substituents and their decomposition pathways can dictate highly diverse reaction outcomes, from precise insertion to destructive cleavage, thus informing the rational design of both therapeutic agents and targeted chemical biology probes.

Beyond permanent labeling, diazo chemistry has remarkably been harnessed for the bioreversible modification of proteins, opening avenues for dynamic control over protein function. McGrath and co-workers demonstrated this innovative application by utilizing stabilized diazo compounds to achieve transient esterification of protein carboxyl groups.[110] This strategy leverages the controlled reactivity of the diazo-derived carbene to form an ester linkage that is designed to be susceptible to enzymatic hydrolysis *in vivo*. This approach effectively allows for the "masking" or "unmasking" of protein functionalities, akin to a protein prodrug, highlighting the versatility of diazo chemistry not just for stable tagging, but for transient, stimuli-responsive modulation of biological systems. This represents a significant departure from traditional stable bioconjugation, underscoring the nuanced control achievable over carbene reactivity for diverse biological outcomes.

While diazo compounds themselves can act as direct labeling agents, their utility also extends to serving as modular, bioorthogonal handles for subsequent transformations. Bernardim and colleagues exemplified this by developing a novel diazocarbonylacrylic reagent that facilitates the precise and site-specific installation of a diazo functionality onto proteins, particularly *via* thiol-Michael addition to cysteine residues.[111] This method provides a "diazo-tagged" protein, where the newly introduced diazo group can then be leveraged for further bioorthogonal conjugations, such as 1,3-dipolar cycloadditions with strained alkynes. This strategy offers a versatile platform for multi-step protein modification, allowing for the introduction of various tags (*e.g.*, fluorophores or affinity labels) onto specific protein sites. The work underscores the adaptability of diazo chemistry, where the diazo moiety itself functions as a crucial intermediate handle, enabling advanced and controlled bioconjugation strategies.

Recent advancements continue to push the boundaries of diazo chemistry for protein modification, exemplified by the work of Raines *et al.* on a novel modular diazo compound for late-stage protein modification.[112] This research focuses on developing highly efficient and specific reagents that can react with proteins that are already folded or part of complex biological assemblies, without compromising their native structure or function. The "modular" design implies that the diazo reactive unit can be readily combined with various recognition elements or reporter tags, facilitating diverse applications from labeling to activity probing. This study represents a significant step forward in optimizing diazo probe design, showcasing improved selectivity and broader applicability for modifying proteins in complex biological settings. It reinforces the ongoing efforts to precisely control carbene reactivity, making diazo chemistry an even more robust and adaptable tool for sophisticated chemical biology endeavors.

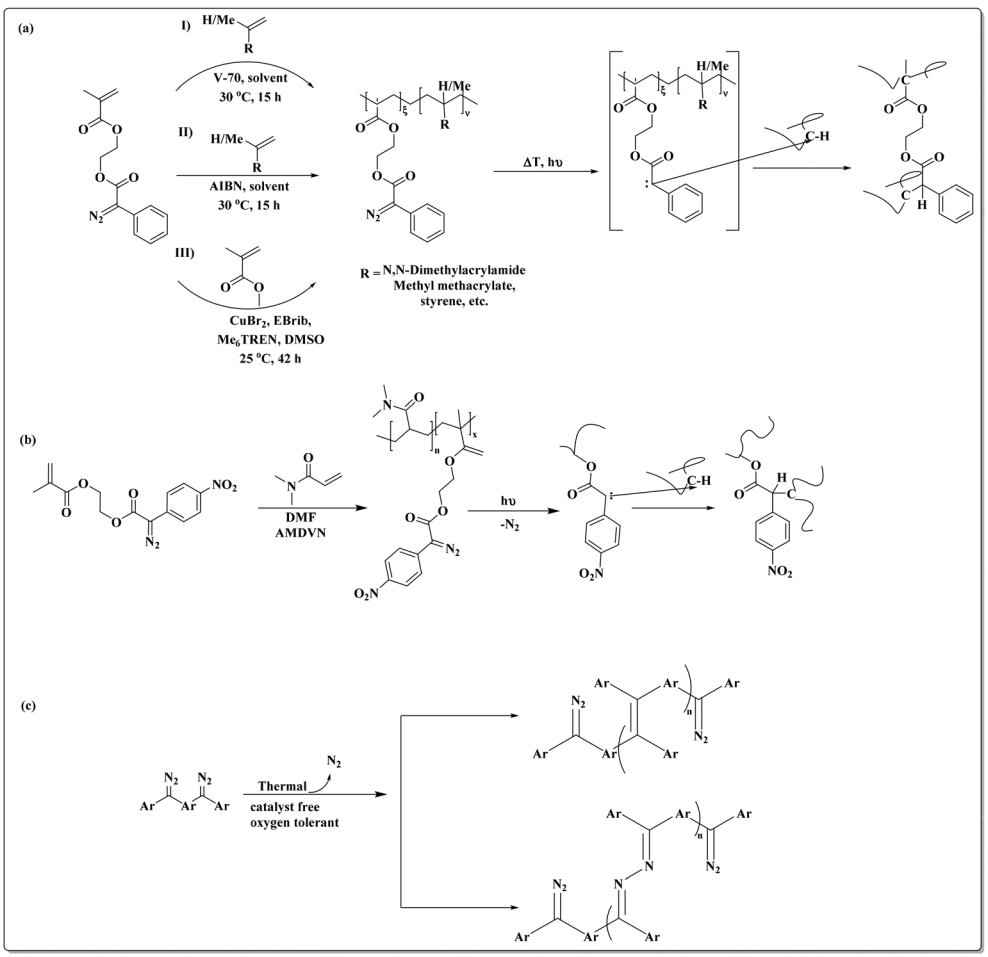
5.2. Applications in polymer chemistry

Besides biological applications, diazo chemistry has found significant applications in material sciences, prominently in enhancing the properties of traditional materials. One of the earliest applications of diazo chemistry in materials science is its critical role in photoresist technology for microfabrication. Diazonaphthoquinone (DNQ) derivatives have been extensively

used as photoactive compounds in positive photoresists. On exposure to UV irradiation, these diazo compounds undergo a Wolff rearrangement to form a highly reactive ketene, which then reacts with ambient water to yield carboxylic acid This photochemical transformation makes the exposed regions soluble in alkaline developers, allowing for the precise patterning of thin polymer films.[113] Although the mechanism involves a ketene rather than a direct carbene insertion for dissolution, the underlying principle of photo-induced reactivity of diazo compounds to alter polymer properties for high-resolution patterning has been a cornerstone of the semiconductor industry.

The thermal decomposition of diazo compounds has been widely explored for the cross-linking of polymeric materials, especially for thermosetting resins and coatings. The thermally generated carbenes can insert into various C–H, O–H, or N–H bonds present in the polymer matrix, leading to the formation of a rigid, insoluble network. This method offers advantages in applications where precise thermal control is feasible, allowing for the formation of materials with enhanced mechanical strength, chemical resistance, and thermal stability.

Rühe *et al.* demonstrated that diazo-functionalized copolymers can undergo C–H insertion cross-linking (CHic) under mild thermal conditions (typically below 100 °C), enabling the fabrication of surface-attached polymer networks directly from solution-processed films, yielding coatings with excellent solvent resistance, adhesion, and long-term durability. The mild activation conditions are compatible with sensitive substrates, expanding the utility of CHic chemistry beyond high-temperature industrial settings (Scheme 38a).[114a] Rusitov *et al.* advanced CHic chemistry by designing a nitrophenyl diazo ester (nitroPEDAz) cross-linker that absorbs strongly in the long-wavelength UV and visible regions, enabling rapid carbene generation under low-energy UV, filtered UV, or even direct sunlight (Scheme 38b). Incorporating nitroPEDAz into polymer backbones allowed for network formation and simultaneous surface attachment at extremely low light doses. The push–pull electronic design, achieved by para-nitro substitution, red-shifted absorption and improved photoreactivity by more than 300-fold compared to unsubstituted analogues. This strategy enables photolithographic patterning, large-area curing, and functional surface fabrication-such as protein-repellent hydrogel microstructures—on diverse substrates, including polyethylene, polystyrene, and PEEK, without additional photoinitiators or high-intensity light sources.[114b]



Scheme 38 Polymer network formation using carbene mediated C–H insertion (CHic) based crosslinking.

In a related direction, Liu and co-workers showcased the design of fluorinated bis-diazo cross-linkers that combine C–H insertion chemistry with enhanced hydrophobicity and low-surface-energy characteristics (Scheme 38c). Upon controlled activation, these bisdiazo monomers can undergo sequential or simultaneous carbene generation and insertion reactions, leading to the formation of cross-linked polymer networks or even linear chains depending on the reaction conditions and the nature of the monomers. The perfluoroalkyl substitution not only improves solubility in fluoropolymer-compatible systems but also imparts anti-fouling and non-stick properties to the resulting cross-linked materials. These cross-linkers demonstrated efficient network formation in both thermal and photochemical activation modes, and their strong affinity for low-energy surfaces such as PTFE and FEP enables direct surface functionalization without primers.[114c]

Bas de Bruin *et al*. employed diazo-based cross-linkers to cure acrylic systems *via* either thermal or blue light activation, offering energy-efficient alternatives to conventional UV-curing technologies while maintaining comparable mechanical performance.[115] Upon exposure to blue light, the diazo groups generate highly reactive carbene intermediates which then undergo insertion reactions into the polymer backbone, generating a cross-linked network with mechanical and barrier properties comparable to UV-cured analogues. The use of blue light is particularly advantageous as it is less energetic and safer than UV light, allowing for curing processes that are more compatible with sensitive substrates and broader industrial application.

Moreover, diazo copolymers have been successfully applied to cellulose-based substrates, such as paper, where thermally induced carbene insertion significantly improves wet strength and dimensional stability. Schölch and co-workers demonstrated this by developing diazo-based copolymers for improving the wet strength of paper.[116] Upon thermal activation, the carbenes insert into the abundant C–H and O–H bonds of cellulose, forming a covalently cross-linked fiber network. This catalyst-free process yields a substantial increase in wet mechanical strength and dimensional stability, offering a sustainable alternative to formaldehyde-based wet-strength resins.

Extending beyond specific substrates, Yang *et al.* proposed a general strategy for carbene-mediated polymer cross-linking *via* C–H activation and insertion. By synthesizing multi-diazo cross-linkers through modular esterification and Regitz diazo transfer, they achieved efficient cross-linking across diverse polymer matrices, including poly(vinyl acetate), polyethylene, and elastomers. Structural optimization from monodiazo to tridiazo systems significantly enhanced cross-linking efficiency, reducing the required loadings and broadening applicability.[117] This work underscores the versatility of diazo chemistry as a platform for advanced material design, surface adhesion, and functional network fabrication.

5.3. Applications in other fields

Diazo compounds have become indispensable in drug discovery, enabling key transformations such as cyclopropanation, C–H insertion, and heterocycle formation. One of the most impactful contributions of diazo chemistry to medicinal chemistry is the construction of nitrogen-containing heterocycles, which are prevalent in therapeutic agents. For example, diazo compounds have been employed in the synthesis of piperidines, pyrazoles, and isoquinolines-scaffolds that serve as pharmacophores in numerous drugs.[118] The use of metalloradical catalysis, particularly with cobalt(II) porphyrins, has enabled efficient ring-closing reactions starting from linear precursors, offering robust access to these heterocycles under mild conditions.[119]

Diazo compounds also facilitate the synthesis of fluorinated building blocks, which are highly valued in pharmaceuticals for their metabolic stability and bioavailability. Trifluorodiazoethane, for instance, has emerged as a key reagent for introducing fluorine atoms into drug-like molecules *via* cyclopropanation and C–H insertion reactions.[120] These transformations are not only atom-economical but also compatible with complex substrates, making them attractive for late-stage functionalization in drug development.

Recent advances have also highlighted the potential of diazo compounds in multicomponent reactions, which are particularly useful for generating compound libraries in early-stage drug discovery. These reactions allow for the rapid assembly of diverse molecular architectures from simple starting materials, often under metal-free or photochemical conditions.[121] Such approaches align well with the principles of green chemistry and high-throughput synthesis, further enhancing the appeal of diazo chemistry in pharmaceutical research.

These developments underscore the growing importance of diazo compounds in drug discovery, not only as synthetic tools but also as functional reagents for probing biological systems. Their unique reactivity profile, tunable selectivity, and compatibility with complex molecules position them as indispensable assets in the design and development of next-generation therapeutics.

Diazo chemistry has also played a foundational role in the dye industry, particularly through its central role in the synthesis of azo dyes-a class that dominates the coloration of textiles, paper, food, and cosmetics.[122] The remarkable adaptability of diazo chemistry is exemplified in its use to tune dye properties such as color brightness, fastness, and solubility through substituent variation and molecular design.[123] The formation of heterocyclic azo dyes, for instance, offers improved lightfastness and photostability, making them highly suitable for demanding textile applications such as polyester and nylon. These dyes often incorporate heteroatoms that enhance interaction with polymer fibers and improve environmental resilience.[124]

Modern developments have further refined the diazotization and coupling methodology, enabling controlled and efficient synthesis of disazo dyes, which feature two azo linkages and offer enhanced depth of color and molecular symmetry. Nitrothiazole-based disazo dyes, as explored by several researchers, demonstrate improved wet fastness and thermal

stability, underscoring the potential of diazo chemistry to produce dyes tailored for high-performance textile finishes.[125]

In addition to textile applications, diazo chemistry has found a role in photochromic dyes and digital imaging media, where diazo-based compounds respond to light stimuli to create dynamic color changes. These applications leverage the reversible and photochemically active nature of diazo groups, further cementing their importance in modern dye technology.[126]

These applications demonstrate the enduring significance of diazo chemistry in the dye industry, from its roots in classical synthetic organic chemistry to its evolving role in color science and materials engineering.

From their historical origins in classical synthetic transformations to their modern roles in chemical biology, materials science, dye technology, and pharmaceutical research, diazo compounds have demonstrated remarkable versatility and impact. The unifying diazo → carbene → insertion paradigm has underpinned groundbreaking advances in molecular sensing, selective bioconjugation, ambient polymer cross-linking, color science, and drug design. Yet, the breadth of these applications-spanning mechanistic chemistry, bioengineering, industrial processing, and therapeutic innovation-suggests that the current discourse merely scratches the surface. Indeed, the full potential of diazo chemistry extends far beyond the fields reviewed here. Its role in green synthesis, nanotechnology, environmental science, and photodynamic therapy remains underexplored in mainstream literature. Given this vast and growing interdisciplinary relevance, a broader and more comprehensive review is warranted to fully capture the dynamic evolution and future trajectory of diazo compounds across the chemical sciences.

5.4. Future prospects

As the chemical sciences continue to converge with biology, materials engineering, and environmental innovation, diazo chemistry stands poised to serve as a unifying platform for transformative discovery.[8b,107a] Its modularity, tunable reactivity, and compatibility with mild conditions make it uniquely suited for interdisciplinary integration-from programmable biomolecular tools[107a] and responsive smart materials[127a] to eco-conscious synthetic methodologies.[127b] The next frontier will likely see diazo compounds embedded in hybrid systems: nanostructures for targeted therapy,[127c] adaptive polymers for wearable electronics,[127d] and catalytic frameworks for sustainable manufacturing.[127e] With advances in computational design, photochemical control, and bioorthogonal reactivity, diazo chemistry may evolve into a cornerstone of precision science where molecular design meets functional utility across scales and disciplines.

6. Conclusions

Discovered over 130 years ago, diazo chemistry has been most productive since the dawn of the 21st century. Recent developments in chemical synthesis have enabled the facile preparation of stabilized, semi-stabilised and non-stabilised diazo compounds. The potential to tune the reactivity of diazo compounds by delocalisation of the electrons on the α-carbon renders diazo compounds as attractive reagents in synthetic chemistry. The driving force for the recent developments has been the ability of these diazo compounds to react rapidly and selectively with various transition metals to generate metal–carbenes, which show excellent functional group tolerance, while the advent of new catalysts in parallel has increased ease of access to these versatile reagents. This is exemplified by X–H insertion reactions, cross-coupling reactions, cyclopropanations and applications of ketenes derived from carbenes in new and significant synthetic areas. Chemists are now better equipped to target more complex molecules employing diazo compounds.

Author contributions

Hilal Ahmad Khan: writing original draft. Chinnappan Sivasankar: supervision, writing, reviewing & editing. Michal Szostak: supervision, writing, reviewing & editing.

Conflicts of interest

The authors declare that there is no conflict of interest.

Data availability

There is no supporting data available for this review article.

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References

1 T. Curtius, *Chem. Ber.*, 1883, **16**, 2330.
2 K. Clusius and U. Lüthi, *Helv. Chim. Acta*, 1957, **40**, 445.
3 (*a*) E. Heilbronner and H.-D. Martin, *Chem. Ber.*, 1973, **106**, 3376; (*b*) J. Bastide and J. P. Maier, *Chem. Phys.*, 1976, **12**, 177.
4 (*a*) M. Regitz and G. Maas, *Diazo Compounds-Properties and Synthesis*, Academic Press, Orlando, 1986; (*b*) T. J. de Boer and H. J. Backer, *Org. Synth.*, 1956, **36**, 16.
5 (*a*) R. Schoental, *Nature*, 1960, **188**, 420; (*b*) E. B. LeWinn, *Am. J. Med. Sci.*, 1949, **218**, 556; (*c*) H. V. Pechmann, *Chem.*

Ber., 1894, **27**, 1888; (*d*) H. V. Pechmann, *Chem. Ber.*, 1895, **28**, 855.
6 M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, 1998.
7 Y. He, Z. Huang;, K. Wu, J. Ma, Y. G. Zhou and Z. Yu, *Chem. Soc. Rev.*, 2022, **51**, 2759.
8 (*a*) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, **94**, 1091; (*b*) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire and M. A. McKervey, *Chem. Rev.*, 2015, **115**, 9981.
9 R. S. Marmor and D. Seyferth, *J. Org. Chem.*, 1971, **36**, 128.
10 T. Curtius, *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 2489.
11 D. C. Moebius, V. L. Redina and J. S. Kingsbury, *Top. Curr. Chem.*, 2014, **346**, 111.
12 H. Reimlinger, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 216.
13 D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 1935, 286–289.
14 (*a*) J. M. Hopkins, M. Bowdridge, K. N. Robertson, T. S. Cameron, H. A. Jenkins and J. A. C. Clyburne, *J. Org. Chem.*, 2001, **66**(17), 5713; (*b*) N. I. Korotkikh, N. V. Glinyanaya, A. H. Cowley, J. A. Moore, A. V. Knishevitsky, T. M. Pekhtereva and O. P. Shvaikaa, *ARKIVOC*, 2007, (XVI), 156; (*c*) A. V. Kiselyov, N. I. Korotkikh, A. H. Cowley, J. A. Moore, M. A. Findlater, T. M. Pekhtereva and O. P. Shvaika, *ARKIVOC*, 2008, **XV**, 329.
15 (*a*) H. M. L. Davies and R. E. J. Beckwith, *Chem. Rev.*, 2003, **103**, 2861; (*b*) H. M. L. Davies and J. R. Denton, *Chem. Soc. Rev.*, 2009, **38**, 3061; (*c*) D. Zhu, J. Ma, K. Luo, H. Fu, L. Zhang and S. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 8452.
16 D. E. Applequist and D. E. McGreer, *J. Am. Chem. Soc.*, 1960, **82**, 1965.
17 D. M. Allwood, D. C. Blakemore, A. D. Brown and S. V. Ley, *J. Org. Chem.*, 2014, **79**, 328.
18 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67.
19 H. Zollinger, *Diazo Chemistry II*, Wiley-WCH, Weinheim, 1995.
20 N. Takamura, T. Mizoguchi, K. Koga and S. Yamada, *Tetrahedron*, 1975, **31**, 227.
21 T. J. de Boer and H. J. Backer, *Org. Synth.*, 1963, **4**, 250.
22 U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, *Reports on Carcinogen*, 12th edn, 2011, vol. 316.
23 W. R. Bamford and T. S. M. Stevens, *J. Chem. Soc.*, 1952, 4735.
24 (*a*) T. Curtius, *Chem. Ber.*, 1889, **22**, 2161; (*b*) T. L. Holton and H. Schechter, *J. Org. Chem.*, 1995, **60**, 4725.
25 M. I. Javed and M. Brewer, *Org. Lett.*, 2007, **9**, 1789.
26 M. E. Furrow and A. G. Myers, *J. Am. Chem. Soc.*, 2004, **126**, 12222.
27 M. O. Forster, *J. Chem. Soc.*, 1915, **107**, 260.
28 J. Meinwald, P. G. Gassman and E. G. Miller, *J. Am. Chem. Soc.*, 1959, **81**, 4751.
29 L. Kürti and B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, 2005, pp. 376–377.
30 (*a*) A. M. P. Koskinen and L. Muñoz, *J. Chem. Soc., Chem. Commun.*, 1990, 652–653; (*b*) A. B. Charette, R. P. Wurz and T. Ollevier, *J. Org. Chem.*, 2000, **65**, 9252; (*c*) D. F. Taber, R. B. Sheth and P. V. Joshi, *J. Org. Chem.*, 2005, **70**, 2851; (*d*) T. Toma, J. Shimokawa and T. Fukuyama, *Org. Lett.*, 2007, **9**, 3195; (*e*) M. Kitamura, N. Tashiro and T. Okauchi, *Synlett*, 2009, 2943; (*f*) E. L. Myers and R. T. Raines, *Angew. Chem., Int. Ed.*, 2009, **48**, 2359; (*g*) H.-H. Chou and R. T. Raines, *J. Am. Chem. Soc.*, 2013, **135**, 14936; (*h*) Z. Yu and A. Mendoza, *ACS Catal.*, 2019, **9**, 7870; (*i*) S. Xie, Z. Yan, Y. Li, Q. Song and M. Ma, *J. Org. Chem.*, 2018, **83**, 10916; (*j*) D. Dar'in, G. Kantin and M. Krasavin, *Chem. Commun.*, 2019, **55**, 5239.
31 (*a*) D. Seyferth, P. Hilbert and R. S. Marmor, *J. Am. Chem. Soc.*, 1967, **89**, 4811; (*b*) M. D. Kosobokov, I. D. Titanyuk and I. P. Beletskaya, *Tetrahedron Lett.*, 2014, **55**, 6791; (*c*) F. Ye, C. Wang, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 11625; (*d*) I. P. Beletskaya and I. D. Titanyuk, *J. Org. Chem.*, 2022, **87**, 2748; (*e*) M. M. D. Pramanik and N. Rastogi, *Org. Biomol. Chem.*, 2016, **14**, 1239; (*f*) H. Zhang, X. Wen, L. Gan and Y. Peng, *Org. Lett.*, 2012, **14**(8), 2126; (*g*) J. Cheng, X. Wen, Y. Wang, F. Du, L. Cai and Y. Peng, *Org. Lett.*, 2016, **18**, 4336; (*h*) W. Wu, Y. Wang, J. Guo, L. Cai, Y. Chen, Y. Huang and Y. Peng, *Chem. Commun.*, 2020, **56**, 11235.
32 (*a*) S. Chow, A. I. Greena, C. Artera, S. Livera, A. Leggotta, L. Traska, G. Karageorgis, S. Warrinera and A. Nelson, *Synthesis*, 2020, **52**(11), 1695; (*b*) J. V. Jun and R. T. Raines, *Org. Lett.*, 2021, **23**, 3110.
33 (*a*) T. Hashimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2007, **129**, 10054; (*b*) R. A. Unhale, M. M. Sadhu, S. K. Ray, R. G. Biswas and V. K. Singh, *Chem. Commun.*, 2018, **54**, 3516; (*c*) M. Zhou, Q. Su, Y. Addepalli, Y. He and Z. Wang, *Org. Biomol. Chem.*, 2018, **16**, 2923; (*d*) C. Lin, J.-H. He, M.-L. Rao, G.-P. Yang, W.-J. Li, M. Zhou, C. Zhao, X.-Z. Fu, B. He and Y.-L. Zhao, *Org. Lett.*, 2025, **27**(12), 3048.
34 (*a*) H. Zheng, K. Wang, I. Faghihi, W. P. Griffith, H. Arman and M. P. Doyle, *ACS Catal.*, 2021, **11**, 9869; (*b*) Q. Jiang, Y.-Q. Deng, X.-L. Luo, Z.-H. Dong, Y. Zhou, Y. Liu, W.-D. Chu, C.-Y. He, S. Luo and Q.-Z. Liu, *ACS Catal.*, 2024, **14**, 10964.
35 (*a*) C. Peng, J. Cheng and J. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 8708; (*b*) F. Ye, C. Wang, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 11625; (*c*) F. Ye, S. Qu, L. Zhou, C. Peng, C. Wang, J. Cheng, M. L. Hossain, Yu Liu, Y. Zhang, Z.-X. Wang and J. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 4435; (*d*) L. Fu, J. D. Mighion, E. A. Voight and H. M. L. Davies, *Chem. – Eur. J.*, 2017, **23**, 3272; (*e*) L. Li, S. Müller, R. Petzold and T. Ritter, *Angew. Chem., Int. Ed.*, 2025, **64**, e202419931.
36 (*a*) W. Yao and J. Wang, *Org. Lett.*, 2003, **5**, 1527; (*b*) S. Arai, K. Hasegawa and A. Nishida, *Tetrahedron Lett.*, 2004, **45**, 1023; (*c*) K. Hasegawa, S. Arai and A. Nishida,

Tetrahedron, 2006, **62**, 1390; (*d*) B. M. Trost, S. Malhotra, P. Koschker and P. Ellerbrock, *J. Am. Chem. Soc.*, 2012, **134**, 2075; (*e*) D. Qiu, M. Qiu, R. Ma, Y. Zhang and J. Wang, *Acta Chim. Sin.*, 2016, **74**, 472.

37 (*a*) W. V. E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, 1956, **78**, 4947; (*b*) H. Meerwein, H. Rathjen and H. Werner, *Ber. dtsch. Chem. Ges. A/B*, 1942, **75**, 1610; (*c*) J.-L. Mieusset and U. H. Brinker, *J. Org. Chem.*, 2008, **73**(4), 1553–1558; (*d*) D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.*, 2000, **100**(1), 39–92; (*e*) N. I. Korotkikh, G. F. Rayenkob, V. S. Saberova, V. I. Yenyaa, L. M. Vakhitovab and A. V. Kiselyov, *Comput. Theor. Chem.*, 2024, **1238**, 114728.

38 (*a*) A. P. Marchand and N. M. Brockeway, *Chem. Rev.*, 1974, **74**, 431; (*b*) A historical review: A. J. Arduengo III and R. Krafczyk, *Chem. Unserer Zeit*, 1998, **32**, 6.

39 E. O. Fischer and A. Maasböl, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 580.

40 J. Durka, J. Turkowska and D. Gryko, *ACS Sustainable Chem. Eng.*, 2021, **9**, 8895.

41 (*a*) T. M. Bott, J. A. Vanecko and F. G. West, *J. Org. Chem.*, 2009, **74**, 2832; (*b*) J. R. Wolf, C. G. Hamaker, J. P. Djukic, T. Kodadek and L. K. Woo, *J. Am. Chem. Soc.*, 1995, **117**, 9194; (*c*) H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park and K. Itoh, *J. Am. Chem. Soc.*, 1994, **116**, 2223.

42 (*a*) Ł. W. Ciszewski, K. Rybicka-Jasińska and D. Gryko, *Org. Biomol. Chem.*, 2019, **17**, 432; (*b*) Z. Yang, M. L. Stivanin, I. D. Jurberg and R. M. Koenigs, *Chem. Soc. Rev.*, 2020, **49**, 6833.

43 (*a*) Y. Xiaa and J. Wang, *Chem. Soc. Rev.*, 2017, **46**, 2306; (*b*) Y. Xia and J. Wang, *J. Am. Chem. Soc.*, 2020, **142**, 10592.

44 (*a*) G. K. Murphy and F. G. West, *Org. Lett.*, 2006, **8**, 4359; (*b*) P. Müller, D. Fernandez, P. Nury and J.-C. Rossier, *J. Phys. Org. Chem.*, 1998, **11**, 321; (*c*) I. K. Mangion, I. K. Nwamba, M. Shevlin and M. A. Huffman, *Org. Lett.*, 2009, **11**, 3566; (*d*) D. V. Griffiths and J. C. Tebby, *J. Chem. Soc., Chem. Commun.*, 1986, 817.

45 (*a*) H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151; (*b*) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972; (*c*) M. Zibinsky and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2013, **52**, 1507.

46 Z. Liu, P. Sivaguru, G. Zanoni and X. Bi, *Acc. Chem. Res.*, 2022, **55**, 1763.

47 (*a*) E. O. Fischer and A. Maasboel, *Angew. Chem., Int. Ed. Engl.*, 1964, **76**, 645; (*b*) H. D. Karl and J. Stendel, *Chem. Rev.*, 2009, **109**, 3227; (*c*) D. J. Cardin, B. Çetinkaya, M. J. Doyle and M. F. Lappert, *Chem. Soc. Rev.*, 1973, **2**, 99.

48 (*a*) R. R. Schrock, *J. Am. Chem. Soc.*, 1974, **96**, 6796; (*b*) R. R. Schrock, *Angew. Chem., Int. Ed.*, 2006, **45**, 3748.

49 (*a*) F. J. Lombard and M. J. Coster, *Org. Biomol. Chem.*, 2015, **13**, 6419; (*b*) D. Gillingham and N. Fei, *Chem. Soc. Rev.*, 2013, **42**, 4918; (*c*) M. Yu and B. L. Pagenkopf, *Tetrahedron*, 2005, **61**, 321; (*d*) X. Guo and W. Hu, *Acc. Chem. Res.*, 2013, **46**, 2427; (*e*) F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, **51**, 7986.

50 (*a*) R. Kumar, D. Nair and I. N. N. Namboothiri, *Tetrahedron*, 2014, **70**, 1794; (*b*) T. V. Baiju and I. N. N. Namboothiri, *Chem. Rec.*, 2017, **17**, 939; (*c*) Z.-W. Qu, H. Zhu and S. Grimme, *Eur. J. Org. Chem.*, 2022, e202200408; (*d*) Y. Hussain, C. Empel, R. M. Koenigs and P. Chauhan, *Angew. Chem., Int. Ed.*, 2023, **62**, e202309184.

51 (*a*) C. Pei, C. Zhang, Yu Qian and X. Xu, *Org. Biomol. Chem.*, 2018, **16**, 8677; (*b*) D. Padín, J. s A. Varela and C. Saá, *Synlett*, 2020, **31**, 1147; (*c*) K. Dong, M. Liu and X. Xu, *Molecules*, 2022, **27**, 3088; (*d*) M. Yao, S. Dong, A. Yusuf and X. Xu, *Synthesis*, 2024, **56**, 2886–2898; (*e*) M. Yao, S. Dong and X. Xu, *Chem. – Eur. J.*, 2024, **30**, e202304299; (*f*) S. E. Reisman, R. R. Nani and S. Levin, *Synlett*, 2011, 2437.

52 (*a*) Z. Zhang and V. Gevorgyan, *Chem. Rev.*, 2024, **124**, 7214; (*b*) Ł. W. Ciszewski, K. Rybicka-Jasińska and D. Gryko, *Org. Biomol. Chem.*, 2019, **17**, 432; (*c*) R. D. C. Gallo, G. Cariello, T. A. C. Goulart and I. D. Jurberg, *Chem. Commun.*, 2023, **59**, 7346; (*d*) Z. Yang, M. L. Stivanin, I. D. Jurberg and R. M. Koenigs, *Chem. Soc. Rev.*, 2020, **49**, 6833; (*e*) J. Durka, J. Turkowska and D. Gryko, *ACS Sustainable Chem. Eng.*, 2021, **9**(27), 8895.

53 S.-F. Zhu and Q.-L. Zhou, *Acc. Chem. Res.*, 2012, **45**(8), 1365.

54 (*a*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*b*) B. D. Bergstrom, L. A. Nickerson, J. T. Shaw and L. W. Souza, *Angew. Chem., Int. Ed.*, 2021, **60**, 6864; (*c*) Y. Park, Y. Kim and S. Chang, *Chem. Rev.*, 2017, **117**, 9247; (*d*) D. Zhu, L.-F. Chen, H.-L. Fan, Q.-L. Yao and S.-F. Zhu, *Chem. Soc. Rev.*, 2020, **49**, 908.

55 D. Gillingham and N. Fei, *Chem. Soc. Rev.*, 2013, **42**, 4918.

56 R. Casanova and T. Reichstein, *Helv. Chim. Acta*, 1950, **33**, 417.

57 P. Yates, *J. Am. Chem. Soc.*, 1952, **74**, 5376.

58 H. Nozaki, H. Takaya, S. Moriuti and R. Noyori, *Tetrahedron*, 1968, **24**, 3655.

59 R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert and P. Teyssie, *Tetrahedron Lett.*, 1973, **14**, 2233.

60 T. N. Salzmann, R. W. Radcliffe, B. G. Christensen and F. A. Bouffard, *J. Am. Chem. Soc.*, 1980, **102**, 6161.

61 J. X. Gong, G. A. Lin, W. B. Sun, C. C. Li and Z. Yang, *J. Am. Chem. Soc.*, 2010, **132**, 16745.

62 D.-H. Wang and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 5767.

63 M. C. Pirrung, H. Liu and A. T. Morehead, *J. Am. Chem. Soc.*, 2002, **124**, 1014.

64 Y. Liang, H. Zhoum and Z.-X. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 17783.

65 S. Gutiérrez, M. Tomas-Gamasa and J. L. Mascareñas, *Chem. Sci.*, 2022, **13**, 6478.

66 (*a*) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, **46**, 236; (*b*) Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810.

67 (*a*) A. Suzuki, *Angew. Chem., Int. Ed.*, 2011, **50**, 6722; (*b*) R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*,

2011, **111**, 1417; (*c*) C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062.

68 (*a*) K. L. Greenman, D. S. Carter and D. L. V. Vranken, *Tetrahedron*, 2001, **57**, 5219; (*b*) Y. Zhang and J. Wang, *Eur. J. Org. Chem.*, 2011, 1015; (*c*) J. Barluenga and C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **50**, 7486; (*d*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560.

69 K. L. Greenman and D. L. V. Vranken, *Tetrahedron*, 2005, **61**, 6438.

70 W. Y. Yu, Y. T. Tsoi, Z. Zhou and A. S. C. Chan, *Org. Lett.*, 2009, **11**, 469.

71 (*a*) X. Wang, Y. Xu, Y. Deng, Y. Zhou, J. Feng, G. Ji, Y. Zhang and J. Wang, *Chem. – Eur. J.*, 2014, **20**, 961; (*b*) Y. Zhou, F. Ye, X. Wang, S. Xu, Y. Zhang and J. Wang, *J. Org. Chem.*, 2015, **80**, 6109.

72 H. A. Khan, V. Wotsa, J. Lavanya and C. Sivasankar, *New J. Chem.*, 2022, **46**, 19940.

73 Y. Xia, D. Qiu and J. Wang, *Chem. Rev.*, 2017, **117**, 13810–13889.

74 (*a*) E. Wedekind, *Ber. Dtsch. Chem. Ges.*, 1901, **34**, 2070; (*b*) E. Wedekind, *Justus Liebigs Ann. Chem.*, 1902, **323**, 246.

75 H. Staudinger, *Ber. Dtsch. Chem. Ges.*, 1905, **38**, 1735.

76 H. Staudinger and H. Klever, *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 968.

77 H. Staudinger, *Justus Liebigs Ann. Chem.*, 1907, **356**, 51.

78 L. Wolff, *Justus Liebigs Ann. Chem.*, 1902, **325**, 129.

79 L. Wolff, *Justus Liebigs Ann. Chem.*, 1912, **394**, 23.

80 W. Kirmse, *Eur. J. Org. Chem.*, 2002, 2193.

81 A. Igau, H. Grutzmacher, A. Baceiredo and G. Bertrand, *J. Am. Chem. Soc.*, 1988, **110**, 6463.

82 A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361.

83 S. N. Lyashchuk and Y. G. Skrypnik, *Tetrahedron Lett.*, 1994, **35**, 5271.

84 D. A. Dixon, A. J. Arduengo, K. D. Dobbs and D. V. Khasnis, *Tetrahedron Lett.*, 1995, **36**, 645.

85 M. K. Denk, J. M. Rodezno, S. Gupta and A. J. Lough, *J. Organomet. Chem.*, 2001, **617–618**, 242.

86 G. D. Frey, V. Lavallo, B. Donnadieu, W. W. Schoeller and G. Bertrand, *Science*, 2007, **316**, 439.

87 (*a*) R. Tuba and F. Ungváry, *J. Mol. Catal. A: Chem.*, 2003, **203**, 59; (*b*) E. Fördös, R. Tuba, L. Párkányi, T. Kégl and F. Ungváry, *Eur. J. Org. Chem.*, 2009, 1994; (*c*) N. Ungvári, T. Kégl and F. Ungváry, *J. Mol. Catal. A: Chem.*, 2004, **219**, 7; (*d*) R. Tuba, E. Fördös and F. Ungváry, *J. Mol. Catal. A: Chem.*, 2005, **236**, 113; (*e*) N. Ungváry, E. Fördös, T. Kégl and F. Ungváry, *Inorg. Chim. Acta*, 2009, **362**, 1333; (*f*) T. Kégl and F. Ungváry, *J. Organomet. Chem.*, 2007, **692**, 1825; (*g*) N. Ungváry, E. Fördös, T. Kégl and F. Ungváry, *Inorg. Chim. Acta*, 2010, **363**, 2016.

88 Z. Zhang, Y. Liu, L. Ling, Y. Li, Y. Dong, M. Gong, X. Zhao, Y. Zhang and J. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 4330.

89 (*a*) K. Ramakrishna and C. Sivasankar, *Eur. J. Org. Chem.*, 2017, 4035; (*b*) P. K. Madarasi and C. Sivasankar, *New J. Chem.*, 2020, **44**, 8718; (*c*) F. F. Koothradan, A. Jayarani and C. Sivasankar, *J. Org. Chem.*, 2024, **89**, 4294; (*d*) H. A. Khan, S. Sarkar, M. Shobana and C. Sivasankar, *Adv. Synth. Catal.*, 2023, **365**, 4616.

90 C. Li, X. Zhang and X. Xu, *Eur. J. Org. Chem.*, 2025, e202500434.

91 (*a*) H. Lebel, J. F. Marcoux, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977; (*b*) H. Pellissier, *Tetrahedron*, 2008, **64**, 7041.

92 (*a*) Z. Rapoport, *The Chemistry of the Cyclopopyl Group*, John Wiley and Sons, 1987; (*b*) K. B. Wiberg, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 312; (*c*) W. A. Donaldson, *Tetrahedron*, 2001, **57**, 8589.

93 (*a*) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1958, **80**, 5323; (*b*) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, 1959, **81**, 4256.

94 (*a*) M. P. Doyle, J. H. Griffin, V. Bagheri and R. L. Dorow, *Organometallics*, 1984, **3**, 53; (*b*) Y. Li, J. S. Huang, Z. Y. Zhou, C. M. Che and X. Z. You, *J. Am. Chem. Soc.*, 2002, **124**, 13185; (*c*) C. M. Che, J. S. Huang, F. W. Lee, Y. Li, T. S. Lai, H. L. Kwong, P. F. Teng, W. S. Lee, W. C. Lo, S. M. Peng and Z. Y. Zhou, *J. Am. Chem. Soc.*, 2001, **123**, 4119; (*d*) X. L. Dai and T. H. Warren, *J. Am. Chem. Soc.*, 2004, **126**, 10085.

95 (*a*) B. F. Straub, *J. Am. Chem. Soc.*, 2002, **124**, 14195; (*b*) G. Berthon-Gelloz, M. Marchant, B. F. Straub and I. E. Marko, *Chem. – Eur. J.*, 2009, **15**, 2923.

96 H. Nozaki, S. Moriuti, H. Takaya and R. Noyori, *Tetrahedron Lett.*, 1966, **7**, 5239.

97 (*a*) H. Fritschi, U. Leutenegger and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1005; (*b*) D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726; (*c*) S. Kanemasa, S. Hamura, E. Harada and H. Yamamoto, *Tetrahedron Lett.*, 1994, **35**, 7985.

98 (*a*) R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, 1973, **95**, 3300; (*b*) R. G. Salomon and J. K. Kochi, *J. Am. Chem. Soc.*, 1973, **95**, 1889; (*c*) R. G. Salomon, M. F. Salomon and T. R. Heyne, *J. Org. Chem.*, 1975, **40**, 756.

99 G. Bartoli, G. Bencivenni and R. Dalpozz, *Synthesis*, 2014, **46**, 0979.

100 (*a*) X. Zhao, Y. Zhang and J. Wang, *Chem. Commun.*, 2012, **48**, 10162; (*b*) Y. Chen, J. V. Ruppel and X. P. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 12074; (*c*) T. Rasmussen, J. F. Jensen, N. Østergaard, D. Tanner, T. Ziegler and P.-O. Norrby, *Chem. – Eur. J.*, 2002, **8**, 177; (*d*) A. Nakamura, A. Konishi, Y. Tatsuno and S. Otsuka, *J. Am. Chem. Soc.*, 1978, **100**, 3443; (*e*) X. Xu, S. Zhu, X. Cui, L. Wojtas and X. P. Zhang, *Angew. Chem.*, 2013, **125**, 12073.

101 (*a*) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; (*b*) H. Nishiyama, Cyclopropanation with Ruthenium Catalysts, in C. Bruneau and P. H. Dixneuf, *Ruthenium Catalysts and Fine Chemistry, Topics in Organometallic Chemistry*, Springer, Berlin, Heidelberg, 2004, vol. 11.

102 (*a*) S. Kanchiku, H. Suematsu, K. Matsumoto, T. Uchida and T. Katsuki, *Angew. Chem.*, 2007, **119**, 3963, (*Angew.*

Chem., Int. Ed., 2007, **46**, 3889); (*b*) H. Suematsu, S. Kanchiku, T. Uchida and T. Katsuki, *J. Am. Chem. Soc.*, 2008, **130**, 10327; (*c*) M. Ichinose, H. Suematsu and T. Katsuki, *Angew. Chem.*, 2009, **121**, 3167, (*Angew. Chem., Int. Ed.*, 2009, **48**, 3121).

103 D. Intrieri, A. Caselli and E. Gallo, *Eur. J. Inorg. Chem.*, 2011, **2011**, 5071.

104 S.-F. Zhu and Q.-L. Zhou, *Natl. Sci. Rev.*, 2014, **1**, 580.

105 (*a*) S. Chen, J. Ma and J. Wang, *Tetrahedron Lett.*, 2008, **49**, 6781; (*b*) E. V. Guseva, N. V. Volchkov, Y. V. Tomilov and O. M. Nefedov, *Eur. J. Org. Chem.*, 2004, 3136.

106 (*a*) G. Maas, *Chem. Soc. Rev.*, 2004, **33**, 183; (*b*) D. Qian and J. Zhang, *Chem. Soc. Rev.*, 2015, **44**, 677; (*c*) E. M. D. Allouche and A. B. Charette, *Synthesis*, 2019, **51**, 3947; (*d*) M. M. Q. Simões, J. A. S. Cavaleiro and V. F. Ferreira, *Molecules*, 2023, **28**, 6683.

107 (*a*) K. A. Mix, M. R. Aronoff and R. T. Raines, *ACS Chem. Biol.*, 2016, **11**, 3233; (*b*) J. Wang, *Tetrahedron Lett.*, 2022, **108**, 154135.

108 (*a*) A. L. Grossberg and D. Pressman, *J. Am. Chem. Soc.*, 1960, **82**, 5478; (*b*) M. S. Doscher and P. E. Wilcox, *J. Biol. Chem.*, 1961, **236**, 1328; (*c*) J. P. Riehm and H. A. Scheraga, *Biochemistry*, 1965, **4**, 772; (*d*) G. R. Delpierre and J. S. Fruton, *Proc. Natl. Acad. Sci. U. S. A.*, 1965, **54**, 1161.

109 D. P. Arya, *Top. Heterocycl. Chem.*, 2006, **2**, 129.

110 N. A. McGrath, K. A. Andersen, A. K. F. Davis, J. E. Lomax and R. T. Raines, *Chem. Sci.*, 2015, **6**, 752.

111 B. Bernardim, L. Dunsmore, H. Li, B. Hocking, R. Nuñez-Franco, C. D. Navo, G. Jiménez-Osés, A. C. B. Burtoloso and G. J. L. Bernardes, *Bioconjugate Chem.*, 2020, **31**, 1604.

112 J. V. Jun, Y. D. Petri, L. W. Erickson and R. T. Raines, *J. Am. Chem. Soc.*, 2023, **145**, 6615.

113 (*a*) N. C. de Lucas, J. C. Netto-Ferreira, J. Andraos and J. C. Scaiano, *J. Org. Chem.*, 2001, **66**, 5016–5021; (*b*) J. J. M. Vleggaar, A. H. Huizer, P. A. Kraakman, W. P. M. Nijssen, R. J. Visser and C. A. G. O. Varma, *J. Am. Chem. Soc.*, 1994, **116**(26), 11754; (*c*) A. Reiser, J. P. Huang, X. He, T. F. Yeh, S. Jha, H. Y. Shih, M. S. Kim, Y. K. Han and K. Yan, *Eur. Polym. J.*, 2002, **38**, 619; (*d*) G. Kim, S.-E. Kang, D. H. Kim, J.-In Won, Y. Ku, J. Son, J.-K. Lee and B. J. Jung, *Molecules*, 2023, **28**, 6784.

114 (*a*) J. Kost, A. Bleiziffer, D. Rusitov and J. Rühe, *J. Am. Chem. Soc.*, 2021, **143**, 10108; (*b*) D. Rusitov, F. Deussen and J. Rühe, *Adv. Mater. Interfaces*, 2023, **10**, 2300316; (*c*) X. Liu, M. G. Moloney and K. Okuda, *Polym. Chem.*, 2025, **16**, 2480.

115 F. J. de Zwart, L. A. Wolzak, P. C. M. Laan, S. Mathew, J. Flapper, K. J. van den Berg, J. N. H. Reek and B. de Bruin, *Macromol. Rapid Commun.*, 2023, e2300380.

116 S. Schölch, J.-L. Schäfer, T. Meckel, T. Brandstetter, M. Biesalski and J. Rühe, *Biomacromolecules*, 2021, **22**, 2864.

117 S. Yang, S. Yi, J. Yun, N. Li, Y. Jiang, Z. Huang, C. Xu, C. He and X. Pan, *Macromolecules*, 2022, **55**, 1598.

118 (*a*) J. Liu, R. Liang, Q. Yan, L. Zheng, Z.-Q. Liu and S. Pu, *Org. Chem. Front.*, 2025, **12**, 3065; (*b*) F. Doraghi, P. Baghershahi, M. Ghasemi, M. Mahdavi and A. Al-Harrasi, *RSC Adv.*, 2024, **14**, 39337.

119 (*a*) Y. Wang, X. Wen, X. Cui, L. Wojtas and X. P. Zhang, *J. Am. Chem. Soc.*, 2017, **139**, 1049; (*b*) M. Lankelma, A. M. Olivares and B. de Bruin, *Chem. – Eur. J.*, 2019, **25**, 5658; (*c*) S. Roy, S. K. Das and B. Chattopadhyay, *Angew. Chem., Int. Ed.*, 2018, **57**, 2238.

120 Y. Wang, C. Zhang, S. Li, L. Liu, X. Feng and Z. Liu, *Eur. J. Org. Chem.*, 2024, e202400304.

121 O. Bakulina, A. Inyutina, D. Dar'in and M. Krasavin, *Molecules*, 2021, **26**, 6563.

122 F. Eltaboni, N. Bader, R. El-Kailany, N. El Sharif and A. Ahmida, *J. Chem. Rev.*, 2022, **4**, 313.

123 (*a*) H. Zollinger, *Azo Dyes and Pigments*, Academic Press, 2003; (*b*) K. Hunger, *Industrial Dyes: Chemistry, Properties, Applications*, Wiley-VCH, Weinheim, 2003.

124 Vinodkumar, J. Keshavayya, I. Pushpavathi, C. T. Keerthikumar, M. R. Maliyappa and B. N. Ravi, *Struct. Chem.*, 2020, **31**, 1317.

125 J. O. Otutu, E. Osabohien and E. M. Efurhievwe, *Orient. J. Chem.*, 2010, **26**, 31–38.

126 A. Natansohn, *Chemical Reviews*, 2002, **102**(11), 4139.

127 (*a*) N. Ding, Q. Sun, C. Zhao, W. Zhang, S. Li and S. Pang, *Mater. Chem. Front.*, 2022, **6**, 2670; (*b*) S. Guha, S. Sen and L. Gremaud, *RSC Mechanochem.*, 2025, **2**, 45; (*c*) G. G. Arzoumanidis, *Fine Chem. Eng.*, 2022, **3**, 20; (*d*) Y. Chen, X. Zhangb and C. Lu, *Chem. Sci.*, 2024, **15**, 16436; (*e*) M. M. Q. Simões, J. A. S. Cavaleiro and V. F. Ferreira, *Molecules*, 2023, **28**, 6683.

