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Synthetic Methods

New Syntheses of Diazo Compounds

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azides · diazo compounds · group transfer · nitrogen groups · synthetic methods

***D**iazo compounds ($R^1R^2C{=}N_2$) are known as versatile and useful substrates for an array of chemical transformations and, therefore, diazo chemistry is still far from losing anything of its long-standing fascination. In addition to many studies on the subsequent chemistry of the diazo group, the inventory of methods for the preparation of diazo compounds is continuously supplemented by new methods and novel variations of established procedures. Several of these synthetic approaches take into account the lability and remarkable chemical reactivity of certain classes of diazo compounds, and environmentally more benign procedures also continue to be developed.*

1. Introduction

Diazo compounds are remarkably versatile building blocks in organic synthesis. Thermally or photochemically induced expulsion of molecular nitrogen provides access to carbene chemistry,[1] and transition-metal-catalyzed dediazoniation typically generates short-lived metal–carbene complexes, which can give rise to a wide array of carbenoid reactions that often feature a remarkable degree of chemo-, regio-, and stereoselectivity (e.g. cyclopropanation of alkenes, C–H, O–H, and N–H insertion, formation of ylides and formal carbene dimers).[2,3] Exposure to protons leads to the formation of aliphatic diazonium ions: in this sense, diazo compounds can be considered as precursors or synthetic equivalents of carbocations.[1] With conservation of the CN_2 moiety, diazo compounds are known to take part in 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles.[4]

For all these reasons, it is not surprising to observe that the long-standing interest in the chemistry of diazo compounds has been continuous.[5] Notably, more than 100 years after the syntheses of the first diazo compounds (ethyl diazoacetate[6a] and diazomethane[6b]) and after the invention of a considerable number of effective and versatile synthetic methods, new methods and novel variations of known procedures for the synthesis of diazo compounds continue to be published in the contemporary literature. Some of the recent studies appear to have been governed by the motivation to diminish the potential safety hazards originating in the thermal lability and chemical reactivity of various classes of diazo compounds and/or of reagents used in the preparation of them (e.g. organoazides).

For diazo compounds, their thermal stability and lability toward acids strongly depend on the electronic character of the substituents at the diazo carbon atom: the reactivity scale ranges from the less stable simple diazoalkanes and aryl-substituted diazomethane derivatives to well-behaved diazo compounds bearing two acceptor groups such as carbonyl, phosphoryl, and sulfonyl substitutents.[1] Nevertheless, it is wise to be particularly careful when working with any kind of diazo compound. The potential safety risk is certainly one reason why only a few diazo compounds are commercially available.[7] Diazo compounds are generally perceived as being potentially explosive, and indeed, some unexpected incidents of explosions have been reported (e.g. see Ref. [74]). For diazomethane ($CH_2{=}N_2$) and ethyl diazoacetate (EDA), which are without doubt the two most synthetically useful diazo compounds, studies of their detonation properties have been published,[8,9] and the thermal stability of EDA has also been investigated.[10] Diazomethane has been valued by generations of synthetic chemists as a methylating reagent (in particular for the direct conversion of carboxylic acids into their methyl ester derivatives under mild reaction conditions, as well as for the O-methylation of phenols), but among all the commonly used diazo compounds, diazomethane is also the most hazardous.[11] Therefore, reactions involving diazomethane are generally performed with appropriate precautions, including a submolar reaction scale, glass vessels without ground-glass joints and other sharp surfaces, dilute ethereal solution or by gas-phase transport in an atmosphere of diethyl ether or argon.[12] Commercially available (trime-

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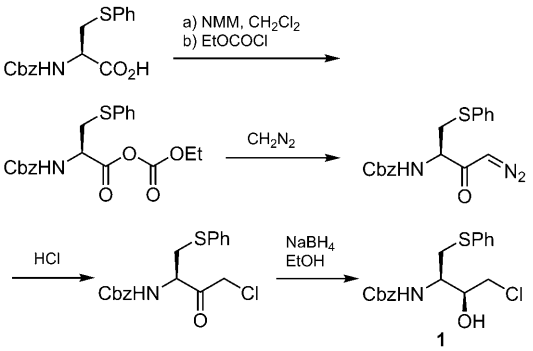
thylsilyl)diazomethane ($Me_3SiCH{=}N_2$, b.p. 96 °C), which is much more thermally stable than diazomethane, can act as a substitute for the latter in a wide range of applications.[13] However, because of its price and likely also because of its limited purity, it has not yet found general acceptance as a safe substitute for diazomethane.

The preceding statements could create the impression that the potential risk associated with diazo compounds prevents their use in the industrial manufacture of chemicals, however, this is not the case. A recent patent describes the generation and in-situ consumption of diazomethane in a multimolar batch process (cleavage of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald) in a two-phase system containing a phase-transfer catalyst).[14] Continuous processes with minimized risks have also been described.[8,15] An example is provided by the cost-effective multistep synthesis of the chiral 1-chloro-2-butanol derivative **1** (Scheme 1), which is a key intermediate



Scheme 1. Use of diazomethane in an industrial synthesis of building block **1** (Phoenix Chemicals Ltd., Merseyside, UK).[8] Cbz = benzyloxycarbonyl, NMM = *N*-methylmorpholine.

in the synthesis of the HIV protease inhibitor nelfinavir.[8] In this process, diazomethane is generated (Diazald/DMSO, aq KOH) and consumed continuously: with a maximum production rate of 50–60 tons per year, less than 80 grams of diazomethane is present in the production unit at any one time.

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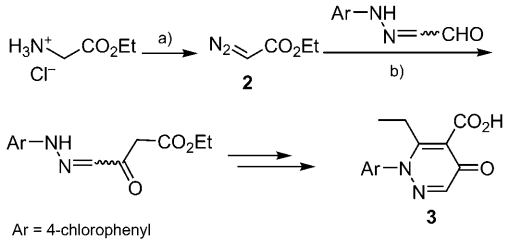
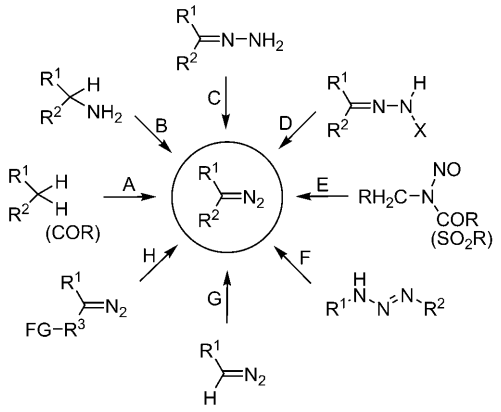
Safe procedures for the industrial production of ethyl diazoacetate have also been published.[16,17] For a synthesis of pyridazinonecarboxylic acid **3**, the potassium salt of which is a registered plant growth regulator (clofencet or Genesis (Monsanto)), ethyl diazoacetate was generated as a 10.9% toluene solution on a 160 mol scale and was used directly (Scheme 2).[17] In another process, a toluene solution of EDA was applied on a 100 kilogram scale to the ruthenium-catalyzed enantioselective cyclopropanation of a styrene derivative.[18]



Scheme 2. Preparation of ethyl diazoacetate (**2**) and subsequent transformation into pyridazinone **3** (Monsanto Co., St. Louis, USA).[17] Reaction conditions: a) 1. aq NaOAc, HCl, toluene; 2. aq $NaNO_2$, 15 °C; 3. phase separation, 90% yield; b) toluene, $SnCl_4$ (6.5 mol%), −5 → 15 °C.

2. Syntheses

The major routes for the synthesis of diazo compounds are as follows (Scheme 3):[1,2,19] A) diazo-group transfer onto activated methylene or methine compounds, B) diazotization



Scheme 3. Major synthetic routes to diazo compounds. FG = functional group.

of α-acceptor-substituted primary aliphatic amines, C) dehydrogenation of hydrazones, D) base treatment of sulfonylhydrazones, E) alkaline cleavage of *N*-alkyl-*N*-nitroso sulfonamides, carboxamides, ureas, and urethanes, F) triazene fragmentation (rare), G) electrophilic substitution at diazomethyl compounds, H) substituent modification of an existing diazo compound.

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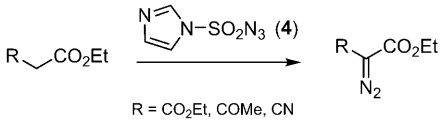
2.1. Diazo-Group Transfer onto Activated Methylene Compounds

Several sulfonyl azides and a few other electron-deficient organoazide derivatives are suited for the base-assisted diazo-group transfer onto activated methylene compounds.[19c] The search for alternatives to *p*-tosyl azide, which has been the favored reagent for many years, aimed to identify an azide which a) is less likely to explode, and b) is transformed (during the reaction) into a sulfonamide derivative that can be separated from the diazo compound more conveniently and efficiently than is *p*-tosyl amide. There is still no ideal diazo-transfer reagent, but the dominating role of *p*-tosyl azide has recently been challenged by methanesulfonyl azide (mesyl azide)[20] and *p*-acetamidobenzenesulfonyl azide.[21] A systematic comparison[22] of the explosion risks of different sulfonyl azides (ΔH_{decomp}, approximate T_{decomp}, impact sensitivity) points to the advantages of *p*-dodecylbenzenesulfonyl azide[23] (mixture of positional isomers), which has the additional benefit of furnishing a liquid sulfonamide compound that can be conveniently separated from crystalline diazo compounds. Nevertheless, this azide is not yet generally used in the laboratory.[24] Polystyrene-supported benzenesulfonyl azide has recently been proposed as a safe-to-handle diazo-transfer reagent.[25] Furthermore, an oligomer-bound benzenesulfonyl azide has been developed, which is converted into an insoluble sulfonamide that can be easily removed.[26]

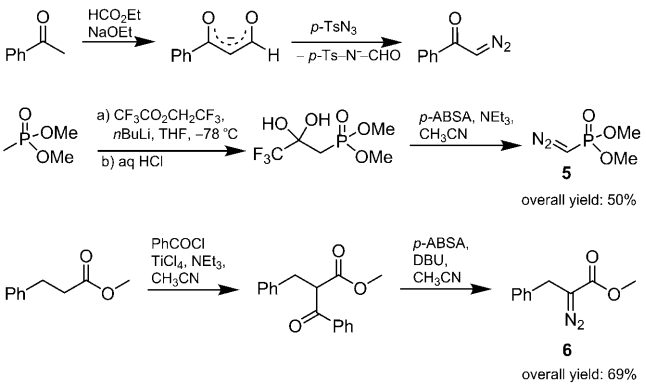
Imidazole-1-sulfonylazide (**4**) is the most recently developed among the diazo-transfer reagents.[27] It can easily be prepared from sodium azide, sulfuryl chloride, and imidazole. It has a long shelf-life—however, violent decomposition occurs above 150 °C—and can be handled conveniently in the form of its crystalline hydrochloride salt. Effective diazo-group transfer with **4** was achieved for malonic esters, β-ketoesters, and cyanoacetates, but failed for (phenylsulfonyl)- and (diethoxyphosphoryl)acetates (Scheme 4).



Scheme 4. Diazo-group transfer with sulfonyl azide **4**. Reaction conditions: pyridine or K_2CO_3, RT, 9–16 h, 59–65% yield.

The diazo-group transfer reaction from an appropriate azide onto a methylene group succeeds not only when the latter bears two strong acceptor substituents (acyl, cyano, nitro, sulfonyl, phosphoryl), but also for aryl-,[21,28] heteroaryl-,[28] and vinylacetate substituents.[29] The combination of *p*-acetamidobenzenesulfonyl azide and DBU has emerged as the method of choice for these applications. The combination of a sulfonyl azide and DBU can also be used to prepare α-aryl-α-diazoketones: however, depending on the electronic nature of the aryl substituent, the yield is strongly influenced by the azide, the amount of base, and the solvent.[30]

In general, (diazomethyl)ketone and α-diazocarboxylate derivatives are not accessible by direct diazo-group transfer onto simple enolizable ketones and carboxylic esters. These substrates must first be activated by the introduction of an additional electron-withdrawing group, which is removed in the course of the diazo-transfer reaction (Scheme 5). To this



Scheme 5. Deformylating and deacylating diazo-group-transfer reactions. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, *p*-ABSA = *p*-acetamidobenzenesulfonyl azide, THF = tetrahydrofuran, Ts = *p*-toluenesulfonyl.

end, Regitz and co-workers originally developed the so-called "deformylating diazo-group-transfer" strategy.[31] It was later supplemented by a more efficient activation with the trifluoroacetyl group (reaction of the enolizable carbonyl compound with LiHMDS/$CF_3CO_2CH_2CF_3$) by Danheiser and co-workers.[24,32] A short synthesis of dimethyl (diazomethyl)-phosphonate (**5**) illustrates the use of the method developed by Danheiser (Scheme 5):[33] compound **5**, now known as the Seyferth–Gilbert reagent, is useful for the conversion of aldehydes into 1-alkynes. Taber et al. have developed a simpler and less costly benzoylation method, which has grown in elegance and scope by a $TiCl_4$-mediated benzoylation variant, and allows the efficient preparation of various α-diazocarboxylate compounds such as **6**.[34]

Diazo-group-transfer reactions in ionic liquids, which are based on 1-butyl-3-methylimidazolium (bmim) salts, have recently been reported.[35] With [bmim]X (X = BF_4, OH, Br) as solvent, numerous acyclic and cyclic 1,3-diketone and β-ketoester derivatives were rapidly and efficiently converted into the corresponding 2-diazo-1,3-dicarbonyl compounds. The reactions were performed with *p*-tosyl or mesyl azide in the absence of an external base—the ionic liquid is likely to play the role of a base—but addition of catalytic quantities of an amine base such as 4-dimethylaminopyridine (DMAP) resulted in a slightly enhanced reaction rate. Extraction of the diazo compound from the ionic liquid was most effective in the case of [bmim]Br. Debenzoylating diazo-group transfer onto 2-substituted 3-oxo-3-phenylpropionates was also achieved in good yield ([bmim]Br, 4-nitrobenzenesulfonyl azide (2 equiv), DBU (1 equiv), 25 °C, 2 h). The ionic liquid can be recycled and reused, but as happens so often when ionic liquids are used as reaction media, this advantage is lost when the organic reaction products need to be extracted from the ionic liquid with a much larger volume of an organic solvent.

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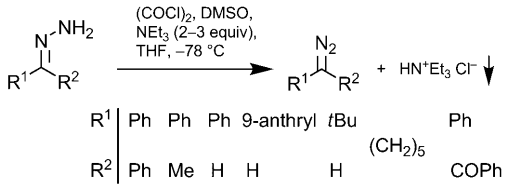
2.2. Diazo Compounds from Hydrazones

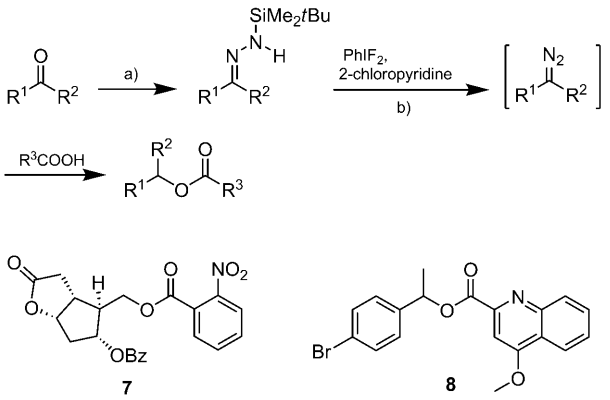
The synthesis of diazo compounds by dehydrogenation of hydrazones (Scheme 3, path C) can be achieved with numerous oxidizing reagents,[36] but heavy-metal-based oxidants—mainly yellow mercury oxide, manganese dioxide, silver(I) oxide, and lead tetraacetate—are by far the preferred reagents. A new metal-free alternative is offered by chlorodimethylsulfonium chloride (Swern reagent), which is generated in situ from DMSO and oxalyl chloride in the presence of triethylamine.[37] This reagent allows the preparation of 2-diazo-1,2-diphenylethanone and various aryl- or alkyl-substituted derivatives of diazomethane in mostly good yield: even the rather unstable diazocyclohexane was obtained in moderate yield (Scheme 6). By using the appropriate solvent



Scheme 6. Synthesis of diazo compounds by metal-free dehydrogenation of hydrazones. DMSO = dimethyl sulfoxide.

system (diethyl ether/dichloromethane 9:1 instead of THF) for the esterification of carboxylic acids, unstable diazoalkanes can subsequently be used without isolation.

Another novel metal-free diazoalkane synthesis is represented by the oxidation of *N*-(*tert*-butyldimethylsilyl)hydrazones of aldehydes or ketones with (difluoroiodo)benzene[38] (Scheme 7). When a carboxylic acid is present during the oxidation step, the generated diazoalkane is immediately consumed upon the formation of the carboxylic ester. Thus, the moderate atom economy of this method is compensated by the advantage of keeping the concentration of the unstable

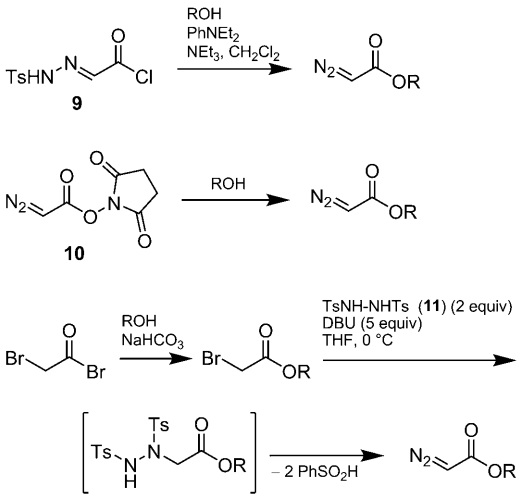


Scheme 7. Esterification of diazoalkanes generated in situ by oxidation of *N*-silylhydrazones with (difluoriodo)benzene. Reaction conditions: a) (tBuMe$_2$Si)NH-NH(SiMe$_2$$t$Bu), Sc(OTf)$_3$ (0.01 mol%), 0→23 °C; b) standard conditions for oxidation/esterification: hydrazone (1.5 equiv), PhIF$_2$ (2.3 equiv), 2-chloropyridine (5 equiv), carboxylic acid (1 equiv), CH_2Cl_2, −78→23 °C. Bz = benzoyl.

diazoalkane very low throughout the course of the reaction. In addition, the mild and approximately neutral reaction conditions of the esterification step are tolerated by numerous functional groups on the diazoalkane and the carboxylic acid, so that even unusual carboxylic esters such as **7** and **8** can be obtained in high yield.

2.3. Diazoacetylation of Alcohols

α-Diazoacetate derivatives can be prepared conveniently by several different routes, in particular by diazotization of esters of glycine (see Scheme 2), by alkaline cleavage of 2-diazo-3-oxocarboxylates and by diazoacetylation of alcohols. The activated carboxylic acid derivatives **9**[39] and **10**[40] (Scheme 8) are frequently used for the latter strategy. Fukuyama and co-workers[41] have recently introduced a



Scheme 8. Synthesis of α-diazoacetates by diazoacetylation of alcohols.

novel diazoacetylation method: an α-diazoacetate is formed in one step starting with an α-bromoacetate and *N*,*N*′-ditosylhydrazine (**11**; a crystalline, thermally stable, shelf-stable reagent) in the presence of a base (Scheme 8). A notable mechanistic aspect of this reaction is the facile two-fold elimination of toluenesulfinic acid from the initially formed α-hydrazinoacetic ester. Primary and secondary, saturated and unsaturated alcohols can be employed. This method also allows the conversion of α-bromoketones into α-diazoketones, as demonstrated with the synthesis of 2-diazo-1-phenyl-1-ethanone (ω-diazoacetophenone).

2.4. Diazo Compounds from Triazenes

In certain cases triazenes, which are available by coupling of aromatic diazonium salts with primary amines, can serve as precursors to diazo compounds (Scheme 3, path F). For example, triazene **12** and the analogous Merrifield resin-bound triazenes **13** undergo fragmentation to yield an

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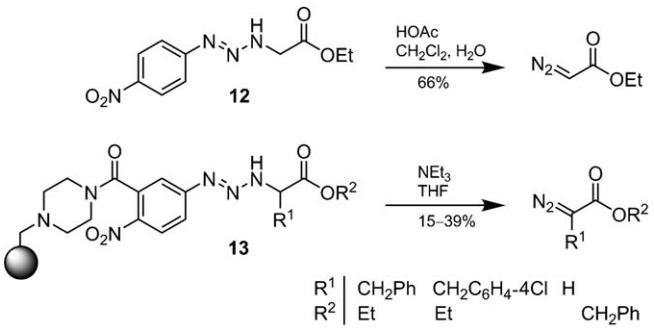
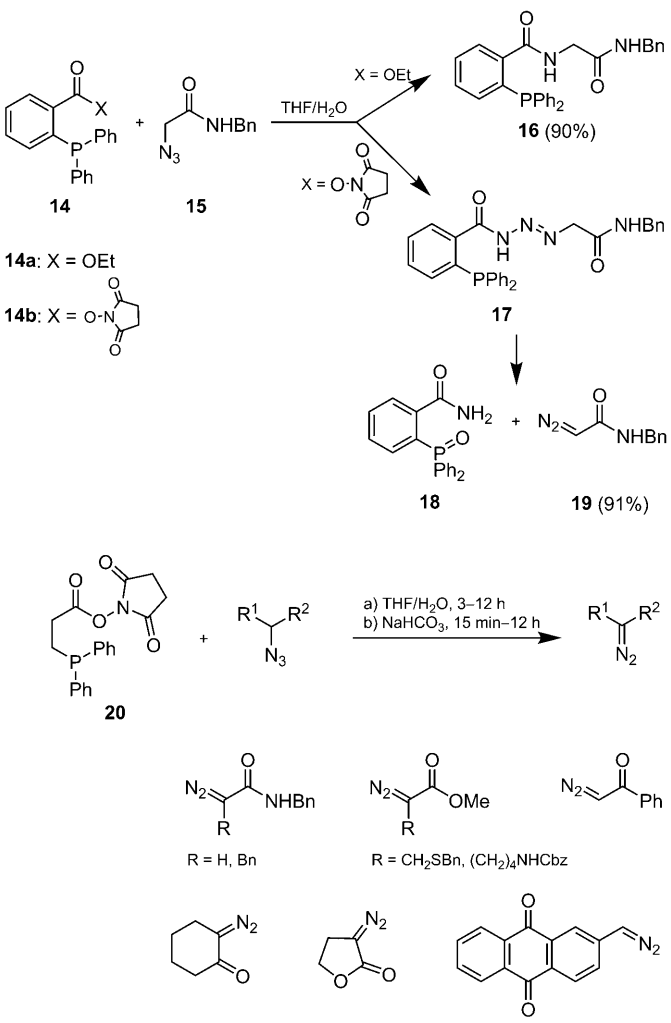
α-diazocarboxylic ester and an aromatic amine when treated with an acid[42] or a base[43] (Scheme 9). Owing to the limited scope and the moderate yields, the synthetic value of this method has remained limited.



Scheme 9. Synthesis of α-diazoacetates by fragmentation of triazenes.

The conceptually novel conversion of organoazides into diazo compounds, with the fragmentation of an acyltriazene as the key step, is expected to be much more successful (Scheme 10).[44] Here, the phosphane reagent and the reaction conditions must meet certain requirements in order to suppress competing reactions such as the conversion of the azide into a primary amine (Staudinger reaction) or the formation of a carboxamide (Staudinger ligation). Thus, ethyl ester **14a** reacts with azide **15** to yield the Staudinger ligation product **16**, while succinimidyl ester **14b** cleanly gives acyltriazene **17**, which then undergoes fragmentation into carboxamide **18** and α-diazoacetamide **19** (slowly in THF/H_2O, rapidly in the presence of NEt_3 or saturated aqueous $NaHCO_3$). (Diphenylphosphanyl)propionate **20** was identified as the phosphane reagent of choice, and allowed the preparation of various functionalized α-diazocarboxylates and α-diazocarboxamides, acyclic and cyclic α-diazocarbonyls, 2-diazomethyl-9,10-anthraquinone, and even 9-diazofluorene from the corresponding azides in mostly good yield. Also, benzyl azide was converted into the expected benzyltriazene. Although the latter does not follow the fragmentation pattern, it reacts with Boc-phenylalanine at elevated temperature—likely via the short-lived benzyldiazonium ion—to form the benzyl ester (Boc-Phe-OBn, 50% yield). In this respect, benzyltriazene can be considered as a substitute for the unstable phenyldiazomethane.



Scheme 10. Phosphane-mediated conversion of organoazides into diazo compounds. Bn = benzyl.

2.5. An N-Isocyanophosphoranimine as a CN_2 Building Block

The acylation of diazomethane or (trimethylsilyl)diazomethane with a carboxylic acid chloride constitutes a standard method for the synthesis of α-(diazomethyl)ketones (Scheme 3, path G). Given the above-mentioned reservations about both these diazo compounds, this method is hardly used when diazo compounds are to be synthesized on a larger scale. A solution to this problem is eventually offered by the use of *N*-isocyanotriphenylphosphoranimine (**21**) as a CN_2 building block (Scheme 11).[45] Hydrolysis of the addition product formed from **21** and an acid chloride yields a hydrazidoyl chloride **22**, which is easily converted into an α-diazoketone. Process chemists have recently optimized the preparation of **21** from formic acid hydrazide and PPh_3/CCl_4, and diazoketone **23** was produced on a 30 mmol scale in 86% overall yield.[46]

2.6. Electrophilic Substitution at the Diazo Function

In the category of electrophilic substitution reactions at the diazo carbon atom[19] (Scheme 3, path G), the aldol-type C–C coupling of diazoacetates with aldehydes or imines has attracted much attention in recent years. The long-known nucleophilic addition of diazocarbonyl compounds to the carbonyl group of aldehydes and ketones has usually been carried out in the presence of a strong base (*n*-butyl lithium, LDA, KHMDS, KOH, NaH).[19c,47] In recent studies, the synthesis of β-hydroxy-α-diazocarboxylates **24** has been

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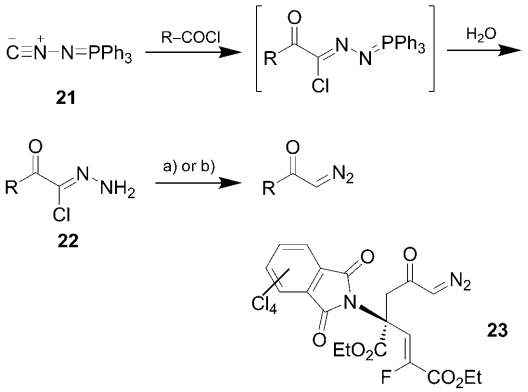


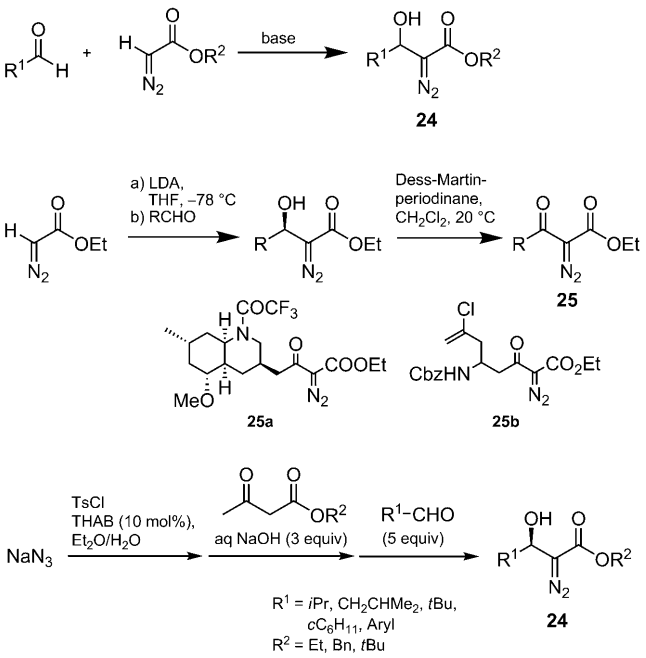
Scheme 11. Synthesis of α-diazoketones by acylation of *N*-isocyanotriphenylphosphoranimine. Reaction conditions: a) *p*TsCl (0.28 equiv), NEt_3 (1.5 equiv), CH_2Cl_2, 12 h;[45] b) anhydrous $ZnBr_2$ (20 mol%), $HNiPr_2$ (1.3 equiv), CH_2Cl_2, 35 min.[46]

mediated by other bases: DBU,[48a] DBU in water,[48b] tetramethylguanidine on silica gel,[48c] quaternary ammonium hydroxide as a phase-transfer catalyst,[49,50] MgO nanoparticles,[51] magnesium/lanthanum mixed oxide in water[51]). Asymmetric catalytic versions of this reaction are also known. For example, the coupling of ethyl diazoacetate with aromatic or aliphatic aldehydes, when catalyzed by the chiral complex obtained from $Zr(OtBu)_4$ and (*S*)-6,6′-Br_2binol (binol = 2,2′-dihydroxy-1,1′-binaphthyl), gave *ee* values of up to 87%.[52a] Even higher enantioselectivities (87–98% *ee*) were achieved in a magnesium-catalyzed asymmetric version (Bu_2Mg (10 mol%), (*S*,*S*)-ProPhenol (5 mol%), *cis*-cyclopentane-1,2-diol (5 mol%), THF, −20 °C).[52b]

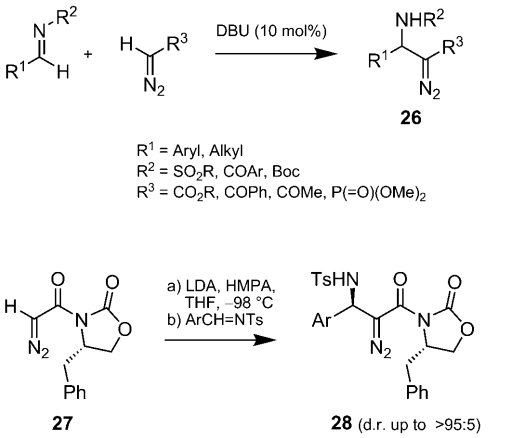
The aldol-type synthesis of β-hydroxy-α-diazocarboxylic acid esters followed by a mild and selective oxidation with Dess–Martin periodinane[53a] or *o*-iodoxybenzoic acid (IBX)[53b] constitutes a synthesis of 2-diazo-3-oxocarboxylic esters **25**. This synthesis can also be applied to obtain more highly functionalized diazo compounds, for example, **25a**,**b**.[53a] Even the one-step preparation of **25** is possible (aldehyde, ethyl diazoacetate, DBU, IBX, DMSO).[53b]

Nishida and co-workers have described an unconventional approach to diazoesters **24**.[50] They have combined three reaction steps into a one-pot procedure (preparation of tosyl azide, diazo-group transfer onto an acetoacetate and cleavage of an alkaline to obtain a diazoacetate, and an aldol-type reaction of the latter with an aldehyde), all of which were promoted by the same phase-transfer catalyst (Scheme 12). With a chiral quaternary cinchonidinium chloride as the phase-transfer catalyst for the aldol reaction, target compound **24** ($R^1 = R^2 = tBu$) was obtained with *ee* values of up to 81%.

The recently described coupling of nucleophilic diazo compounds with imines (aldimines or ketimines), although analogous to the reaction leading to **24**, was successfully performed only with the sufficiently electron-deficient *N*-acyl and *N*-sulfonyl imines. In this manner, α-aminodiazoalkanes, β-amino-α-diazocarboxylates, -ketones, and -phosphonates **26** could be obtained (Scheme 13).[47,48a,54] Starting with the chiral diazocarboxamide **27**, an auxiliary-controlled, highly



Scheme 12. Synthesis and transformation of β-hydroxy-α-diazocarboxylic esters. LDA = lithium diisopropylamide, THAB = tetrahexylammonium bromide.



Scheme 13. Synthesis of β-amino-α-diazocarbonyl compounds. Boc = *tert*-butoxycarbonyl, HMPA = hexamethyl phosphoramide.

diasteroselective synthesis of α-tosylaminodiazocarboxamides **28** was achieved.[55] The enantioselective coupling of *tert*-butyl diazoacetate with *N*-acyl aldimines mediated by chiral acids has also been reported (hydrogen phosphate derived from 3,3′-di-(9-anthryl)-1,1′-bi(2-naphthol)[56a] and 3,3′-disubstituted 1,1′-binaphthyl-2,2′-dicarboxylic acid,[56b] with *ee* values ranging from 85 to 97%).

2.7. Palladium-Catalyzed C–C Coupling at the Diazo Function

Transition-metal-catalyzed C–C coupling chemistry has recently made inroads in the synthesis of diazo compounds. The palladium-catalyzed cross-coupling of the diazo function

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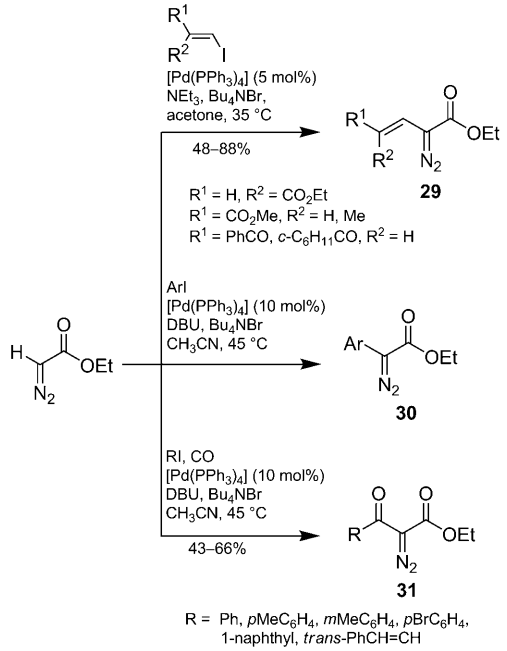
of commercially available ethyl diazoacetate with aryl and vinyl iodides produced the corresponding substituted diazoacetates **29** and **30**, and 2-diazo-3-oxocarboxylates **31** were obtained in the presence of carbon monoxide (Scheme 14).[57]



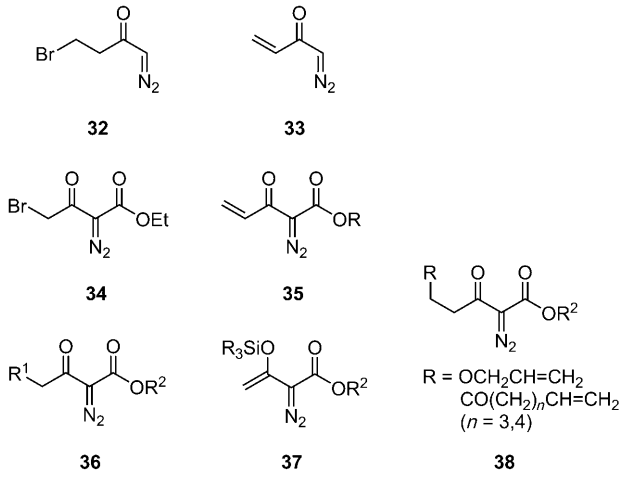
Scheme 14. Substituent variation on diazo compounds using palladium-catalyzed cross-coupling reactions.

One can expect that this C–C coupling strategy, which is still novel in diazo chemistry, will find numerous applications and a wider scope in the near future. On the other hand, cross-coupling with arylboronic acids and arylboroxines does not proceed with preservation of the diazo group.[58]

2.8. Additional Functionalization of Diazo Compounds

As a result of its high reactivity, the diazo function is usually only introduced toward the end of a targeted synthesis. However, it is indeed possible to add further functionality to an existing diazo compound without affecting the diazo group. Some recent examples of chemical manipulation at the nucleophilic diazo carbon atom can be found in Sections 2.6 and 2.7. Meanwhile, additional functionalization is also possible at remote reaction centers. The resulting diazo compounds are attractive scaffolds for subsequent intra- and intermolecular carbene and carbenoid chemistry. In particular, diazocarbonyl compounds have been employed for further functionalization, the most relevant examples being compounds **32**–**38** (Scheme 15).

Diazoketones **32** and **33** were treated with *sec*-amines and yielded the corresponding amino diazoketones, which furnished nitrogen heterocycles through intermediate ammonium ylides by transition-metal-catalyzed dediazoniation.[59,60] Analogous reaction sequences have been performed with unsaturated 3-oxo-2-diazocarboxylates **35**.[61] The bromomethylcarbonyl moiety of **34** has been employed for nucleophilic substitution reactions and for formation of the 1,3-thiazole ring system.[62]



Scheme 15. Diazocarbonyl compounds suited for further functionalization.

Acetoacetic ester (**36**, $R^1 = H$) and 4-substituted derivatives thereof can be converted into 5-hydroxo-2-diazo-3-oxoesters through an aldol reaction with aldehydes and ketones: this is achieved either with the help of an amine base (DBU[62a] or DABCO (1,4-diazabicyclo[2.2.2]octane)[62b]) or with boron[63] or titanium enolates[64,65] of **36**. A comparable reaction of an α-diazoketone and an α,β-unsaturated aldehyde is also known (a) ethyl 8-diazo-9-oxodec-5-enoate, KHMDS, −78 °C; b) 2,4-decadienal, LiBr, −78 °C; c) tBuPh$_2$SiCl, DMAP. HMDS = 1,1,1,3,3,3-hexamethyldisilazane).[66] The silylenol ether function of **37** ($SiR_3 = SiMe_2tBu$) can be engaged in Mukaiyama aldol reactions with aromatic and aliphatic aldehydes, in Mukaiyama–Michael reactions with α,β-enones, and in Mannich reactions with aromatic aldimines.[67] These transformations are catalyzed effectively and efficiently by metal triflates ($Sc(OTf)_3$ and $La(OTf)_3$,[67a] and even better is $Zn(OTf)_2$[67b]). The synthesis of diketo diazoester **39** (Scheme 16) serves as a representative example. Originally, the Mukaiyama aldol reaction of **37** with aldehydes or ketones was mediated by a stoichiometric amount of titanium(IV) chloride as a Lewis acid.[68] At this point, it should be recalled that the first Lewis acid mediated reactions of diazoesters **37** with electrophiles were directed toward the synthesis of β-lactams carrying a diazo-containing side chain:[69] from these compounds, the bicyclic carbapenam ring system could be generated by rhodium-catalyzed intramolecular carbenoid N–H insertion.[69a] By starting from commercially available 4-acetoxyazetidin-2-one **40**, a practical synthesis for carbapenam **41**, which is a precursor of the antibiotic thienamycin, became available[69a] (Scheme 16).

Combination of ethyl 2-diazoacetoacetate with basic pyridine carbaldehydes could also be achieved along the silylenol ether route, this time mediated by boron trifluoride (a) **36** ($R^1 = H$, $R^2 = Et$), TMSOTf, NEt_3, −78 °C; b) pyrCHO, $BF_3{\cdot}OEt_2$. pyr = 2-, 3-, 4-pyridyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl).[64] In an analogous reaction,

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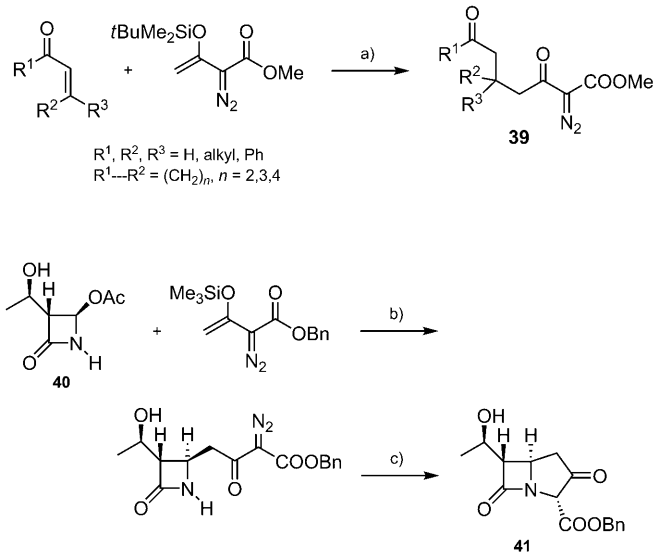

Scheme 16. Lewis acid mediated reactions of silyloxy-substituted diazoesters with electrophiles. Reaction conditions: a) 1. $Zn(OTf)_2$ (0.5–3 mol%), CH_2Cl_2, 0→20°C; 2. aq HCl; b) 1 ZnI_2 (0.5. equiv relative to **40**); 2. hydrolysis; c) $[Rh_2(OAc)_4]$ (cat.).

benzaldehyde diallylacetal was the electrophilic reaction partner.[70] The stereoselectivity of these particular aldol reactions has also been addressed. Only moderate enantioselectivity was achieved when Mukaiyama aldol reactions of 2-diazoacetoacetes were catalyzed with AgF/(*R*)-binap (binap=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl).[67c] In contrast, the addition of the lithium enolate of **36** ($R^1 = H$, $R^2 =$ allyl) to chiral *N*-sulfinylimines was found to be highly diastereoselective.[71]

The diazo function of **37** also tolerates the reaction with thioaroylketene-*S*,*N*-acetals in the presence of mercury(II) acetate, thus resulting in the formation of 3-(3-amino-5-arylthiophen-2-yl)-2-diazoacetic esters.[72]

Unsaturated 3-oxo-2-diazocarboxylic esters such as **38** undergo ruthenium-catalyzed olefin metathesis in moderate to good yield.[70,73] This result deserves particular attention because the same catalyst (the ruthenium–carbene complex, which is better known as the second-generation Grubbs catalyst) reacts with diazoacetic esters by dediazoniation with conversion into the corresponding maleic acid diesters (i.e. the formal carbene dimers).

3. Conclusion and Outlook

More than 100 years after the first synthesis of diazomethane and ethyl diazoacetate, the chemistry of diazo compounds continues to be a vibrant and exciting field of research. As part of these activities, the repertoire of methods and procedures for the synthesis of these synthetically valuable and versatile compounds is continuously being extended. Some of the recent developments were driven by the intention to make the preparation of diazo compounds safer (e.g. the use of more stable azides in diazo-group-transfer reactions, or replacement of diazomethane in the diazomethylation of alcohols), or to render existing methods more environmentally friendly (e.g. replacement of heavy-metal oxidants in the dehydrogenation of hydrazones). With respect to the array of transformations of diazo compounds, in particular their carbenoid chemistry, effective synthetic methods have been developed to enhance the structural and functional complexity of (mainly) diazocarbonyl compounds. Two problems remain, which are probably hard to eliminate: the unsatisfying atom economy and/or the low cost-effectiveness of several methods. Notably, the two oldest methods—alkaline cleavage of *N*-alkyl-*N*-nitrosoureas to obtain diazoalkanes and amine diazotization for the preparation of diazoacetic esters—perform particularly well in both aspects. The development of procedures, by which labile diazo compounds are generated in situ and are submitted immediately to further transformations,[74,75] has not been discussed in detail in this Minireview (but see Section 2.2). Procedures of this kind, which avoid the isolation of labile diazo compounds and often allow them to be present only in low concentration in the reaction medium, are suited to reducing the potential safety hazards and to rendering a synthesis more efficient. They as well as some of the new developments presented here may help to improve the acceptance of diazo compounds in industry.

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