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C(sp^2) – H functionalization of aldimines and related compounds: advances and prospects

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This is the first systematic review of the most relevant approaches to direct C(sp^2) – H bond functionalization of azomethine derivatives. The scope of the applicability of various transformations is analyzed. The review assesses prospects of the application of this functionalization strategy in the multistep synthesis of valuable compounds for use in medicinal chemistry, materials science and related areas.
The bibliography includes 124 references.

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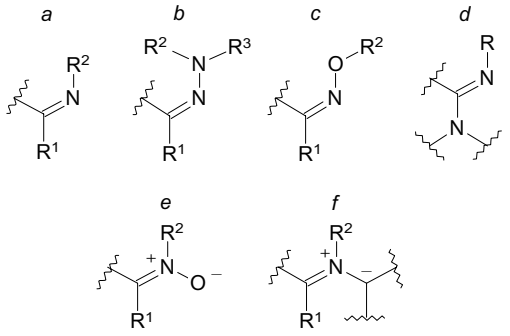


Figure 1. Structural moieties of *N*-derivatives: imines — aldimines (R^1 = H), ketimines (R^1 = Alk, Ar) and Schiff bases (R^2 = Alk, Ar) (*a*); hydrazones — aldohydrazones (R^1 = H) and ketohydrazones (R^1 = Alk, Ar) (*b*); oximes — aldoximes (R^1 = H) and ketoximes (R^1 = Alk, Ar) (*c*); carboxamidines (amidines) (*d*); nitrones — aldonitrones (R^1 = H) and ketonitrones (R^1 = Alk, Ar) (*e*); azomethine ylides (*f*).

1. Introduction

Imines and their derivatives are aza analogues of carbonyl compounds (Fig. 1). Due to the structural similarity to aldehydes and ketones, these compounds are often used as synthetic equivalents of carbonyl compounds; moreover, their use is preferable in certain synthetic schemes.[1] However, the application of these compounds in chemistry is not limited to the above cases. Apart from the use as important building blocks, imine derivatives can directly serve as target molecules. Compounds containing the R – C=N – R′ structural moiety have diverse practical applications, from drugs (*e.g.*, furazolidone, ftivazide, rifampicin, *etc.*) to photoactive materials and dyes (murexide).[2]

In the past years, several reviews have analyzed transformations of imines. The library of original data on this aspect is constantly updated. Particular attention has been given to addition reactions at the C=N bond,[3–6] the 1,3-dipolar cycloaddition to azomethine ylides[7] and azomethine imines[8–10] and the asymmetric hydrogenation of imines.[11] However, transformations with retention of the C=N double bond, in particular functionalization of the azomethine C(sp^2) – H bond, have not been systematically considered until recently, despite the fact that these transformations often precede the above-mentioned methods in retrosynthetic schemes for the preparation of complex compounds. It is worth noting that the C(sp^2) – H functionalization methodology has a number of important advantages. In particular, this methodology meets the fundamental principles of green chemistry, such as atom and step economy, making this strategy highly efficient.[12–14] This review is the first attempt to systematically consider existing data on the C(sp^2) – H bond functionalization of azomethines. First, we describe the available and rather general approaches to the direct replacement of hydrogen at the azomethine bond by a certain functional

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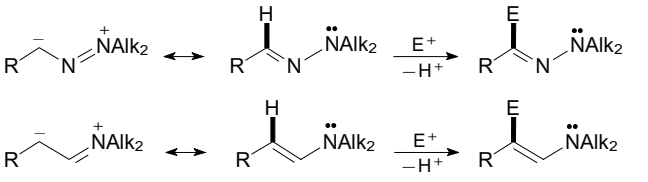
group. Then we demonstrate the advances and prospects of this methodology by considering its successful recent applications in the synthesis of practically important compounds with complex structures. New approaches, which are as yet not universal, are also highlighted.

2. C(sp^2) – H functionalization in azomethine derivatives: main synthetic trends

2.1. Electrophilic substitution of hydrogen in *N*,*N*-dialkyl aldohydrazones. Aza-enamine concept

In 2007, Brehme *et al.*[15] published a review devoted to the chemistry of *N*,*N*-dialkyl aldohydrazones, with the focus on the isoelectronic similarity between the structures of these molecules and enamines (Scheme 1 †).

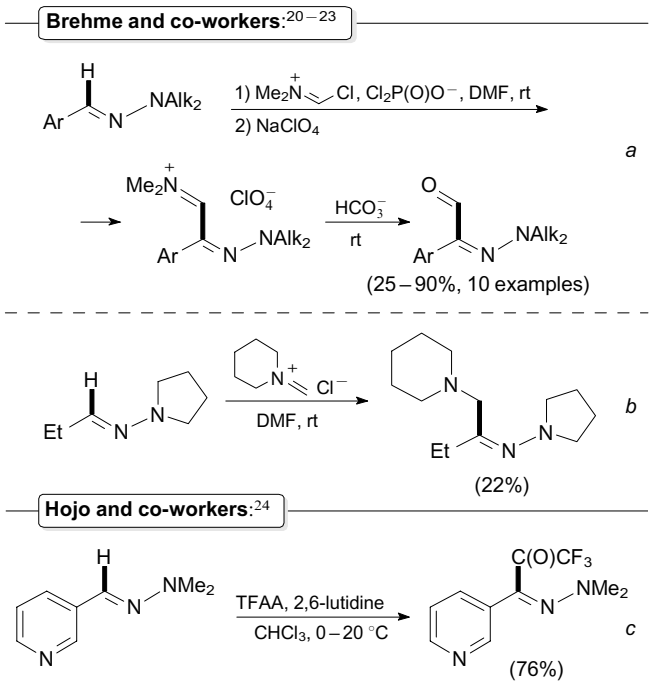
Scheme 1



Evidently, the difference between these compounds is the nature of the atom in the α position with respect to the dialkylamino group (carbon in enamine or nitrogen in hydrazone). Based on the structural similarity, *N*,*N*-dialkyl aldohydrazones can be considered as aza-enamines. The zwitterionic resonance structure of hydrazone presented in Scheme 1 indicates that the reactions of hydrazones can occur with electrophilic reactants. The use of electron-donating substituents, such as pyrrolidine, piperidine or morpholine, as a dialkylamino group leads to a significant increase in the transformation efficiency.[16–19] Examples of such transformations are the Vilsmeier formylation[20–22] (Scheme 2 *a*), Mannich aminomethylation[23] (Scheme 2 *b*), trifluoroacetylation[24] (Scheme 2 *c*), *etc*.

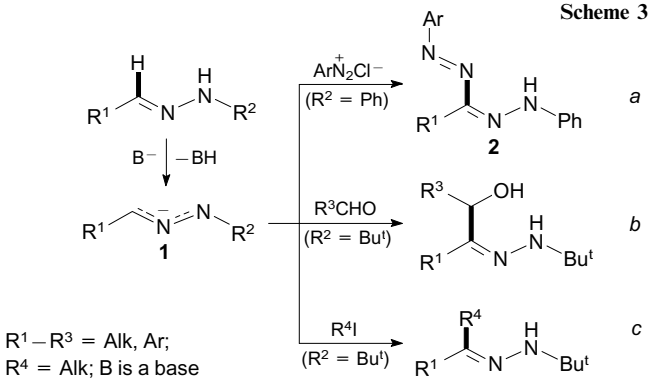
It is worth noting that under particular conditions, mono-*N*-substituted aldohydrazones can be involved in reactions with electrophiles. In this case, hydrazone is initially deprotonated to form ambident anion **1** followed by the coupling with an electrophile to form a carbon–carbon (Scheme 3 *b*,*c*) or carbon–heteroatom bond (see Scheme 3 *a*).‡ The transformations of mono-*N*-phenyl aldohydrazones to formazans **2** using diazonium salts are the best-known examples of these reactions (see Scheme 3).

Scheme 2



TFAA is trifluoroacetic anhydride, rt is room temperature

Scheme 3



† In the review, the bonds to be functionalized and the newly formed bonds are in bold type.

‡ See also examples in Ref. 15 and references therein (*e.g.*, Refs. 8 and 9).

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Translation: T.N.Safonova

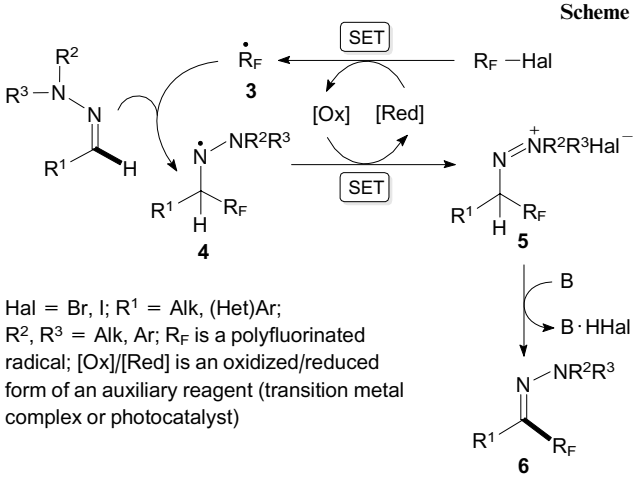
2.2. Radical C(sp^2)–H modification of aldohydrazones

Unlike the aza-enamine concept, which has stood the half-a-century test of time, the radical activation of the C(sp^2)–H bond in aldohydrazones emerged in the 2010s and is, to a large extent, built on the achievements of its predecessor.[25] Most of studies based on the new methodology concerned with the functionalization of hydrazones with fluoroalkyl moieties,[25–33] which is apparently attributed to the use of fluorine-containing compounds in medicinal chemistry and materials science. There are also other examples of this functionalization giving rise, for instance, to new carbon–heteroatom bonds.[34–36]

It is worth noting that advances achieved with this strategy are discussed in detail in a number of recent reviews.[37–39] Here this methodology is demonstrated with selected examples.

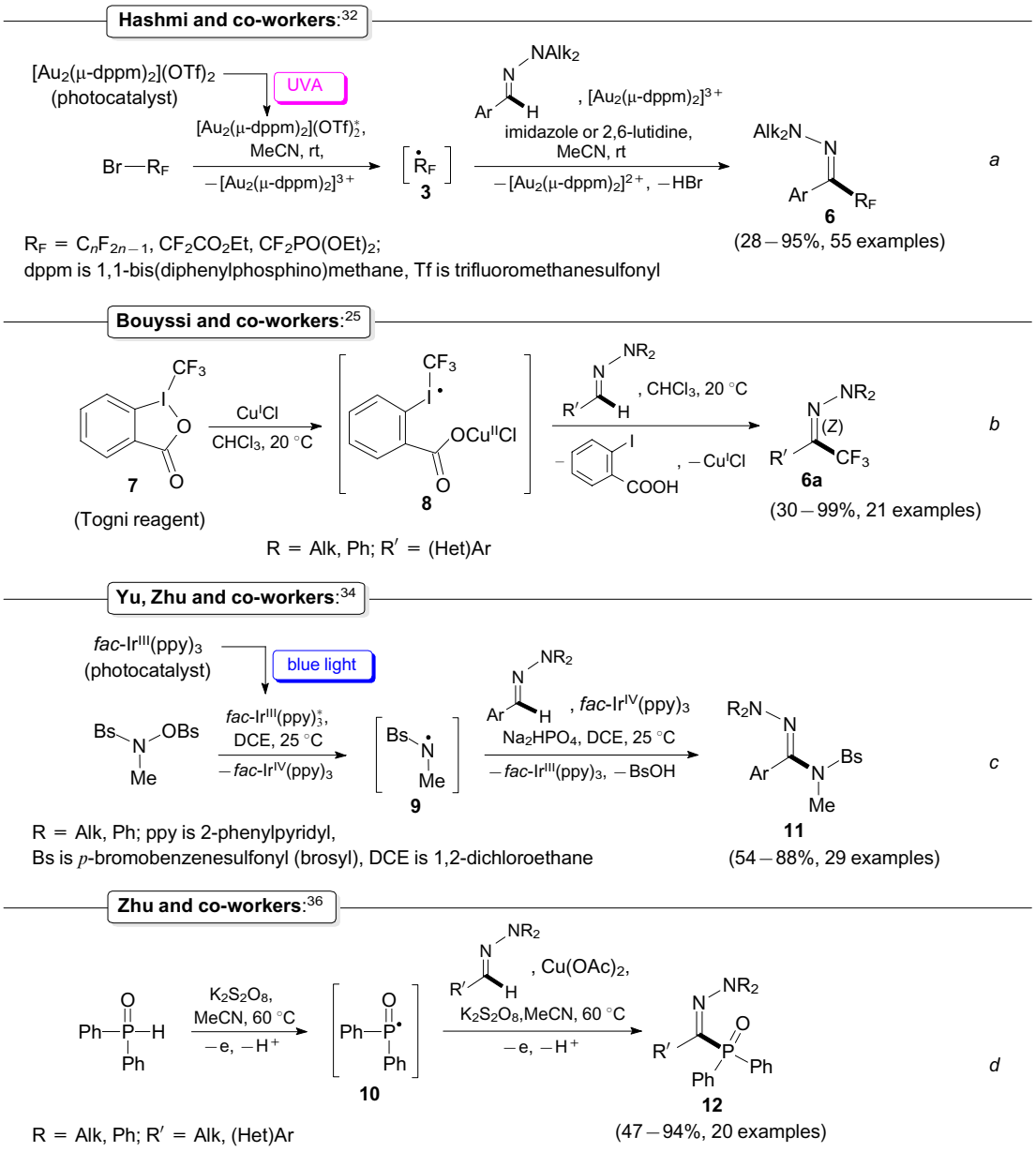
The radical C–H modification of hydrazones most commonly employs the reaction of azomethine derivatives with perfluorinated alkyl halides (Scheme 4; an example of this transformation[32] is also presented in Scheme 5 *a*). The first step involves the generation of perfluorinated radical **3** initiated by a radical initiator *via* a single-electron transfer

Scheme 4



Hal = Br, I; R^1 = Alk, (Het)Ar; R^2, R^3 = Alk, Ar; R_F is a polyfluorinated radical; [Ox]/[Red] is an oxidized/reduced form of an auxiliary reagent (transition metal complex or photocatalyst)

Scheme 5



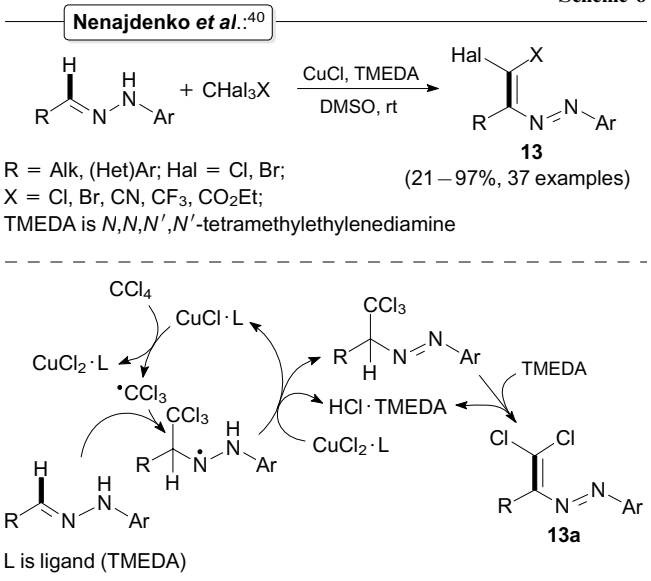
(SET). Transition metal complexes or photoredox catalysts, which have been transferred to the excited state in the UV-Vis region of electromagnetic radiation, can serve as initiators. Then radical **3** is trapped by a hydrazone molecule to form aminyl radical **4**, which, in turn, undergoes single-electron oxidation to hydrazonium cation **5**. This cation can be deprotonated with a base giving reaction product **6**.

This situation is also observed with other fluoroalkylating agents, for example, Togni reagent **7** (Scheme 5 *b*).[25] As in the above-considered case, reactive radical species **8** that is initially generated reacts with a hydrazone molecule.

The reactions giving rise to a new carbon – heteroatom bond start with the generation of the corresponding heteroatom-centred radicals, *e.g.*, nitrogen-centred radical **9** (see Scheme 5 *c*)[34] or phosphorus-centred radical **10** (see Scheme 5 *d*).[36] Subsequent steps of the putative transformations are similar to those shown in Scheme 4. As a result, the reactions can afford amidines **11** or phosphorus-containing derivatives **12**, respectively.

Mono-*N*-substituted aldohydrazones can react with radical species in a different way. Thus, Nenajdenko *et al.*[40] demonstrated that the reaction of hydrazones (Scheme 6) with polyhaloalkyl radicals, generated *in situ* from polyhaloalkanes in the presence of a copper(I) complex, can lead to the construction of valuable 1,2-diaza-1,3-diene building blocks **13**. Although transformations accompanied by the migration of the starting azomethine π-bond (see Scheme 6) are not considered in detail in the present review, it should be noted that they are also used in practice. In particular, they can be employed to synthesize various polyfunctional 2*H*-1,2,3-triazole derivatives[41 – 43] and some other valuable organic compounds.[40, 44, 45]

Scheme 6



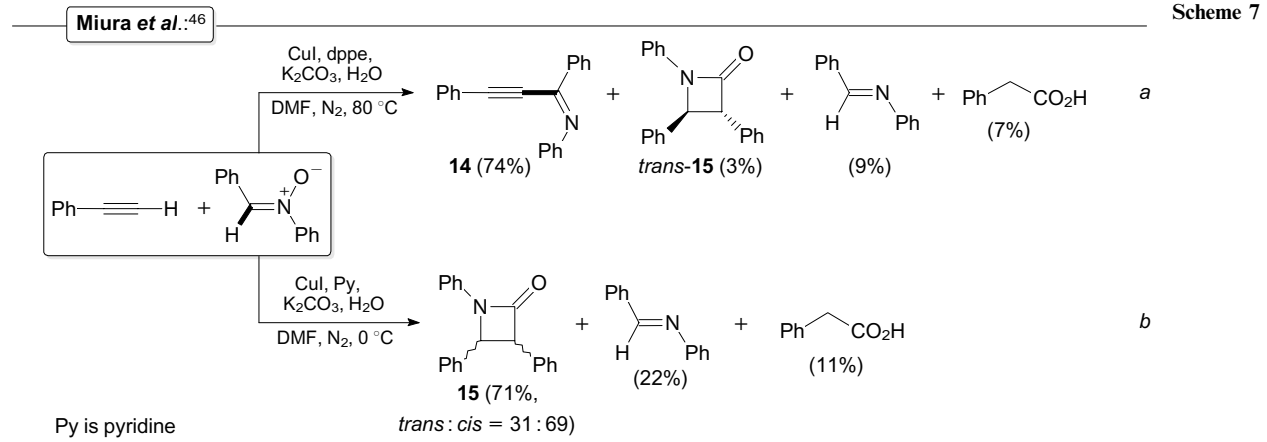
2.3. Transition metal-catalyzed C(sp^2) – H activation of azomethine derivatives

One of the first examples of the use of cross-coupling reactions for the C – H bond functionalization of the azomethine moiety dated back to the mid-1990s, when the research group headed by Miura[46] studied Cu^{I}-catalyzed reactions of arylacetylenes with *C*,*N*-diarylnitrones. The nature of the ligands, such as 1,2-bis(diphenylphosphino)-ethane (dppe) and pyridine, played an important role in these transformations, having a significant effect on the ratio of reaction products. The reaction of phenylacetylene with *C*,*N*-diphenylnitrone using dppe as the ligand resulted in the Sonogashira cross-coupling selectively producing aza-enyne **14** (Scheme 7 *a*), whereas the reaction in the presence of excess pyridine afforded mainly cycloaddition product **15** (see Scheme 7 *b*). The reactions were performed in *N*,*N*-dimethylformamide in the presence of potassium carbonate as a base.

Metal-catalyzed cross-coupling reactions of terminal alkynes with aldonitrones and aldimines were further investigated in the 2010s, when a series of studies of these reactions were carried out.[47 – 49] It was found that copper salts are not necessarily required as catalysts for these reactions. In 2011, Studer's group[49] reported the zinc triflate-catalyzed cross-dehydrogenative coupling (Scheme 8). Commercially available 3,3′,5,5′-tetra(*tert*-butyl)-4,4′-diphenoquinone (DPQ) and molecular oxygen were used as a complex oxidant; tertiary amine [diisopropylethylamine (DIPEA) or triethylamine] served as a base. The reaction mechanism involves the activation of the acetylene substrate *via* the deprotonation and the subsequent metalation with zinc triflate followed by the nucleophilic addition of Zn intermediate **16** to a nitrone molecule. Then adduct **17** is oxidized with the DPQ – O_2 system, resulting in the regeneration of the C=N double bond to form target reaction product **18**. The presence of a labile *tert*-butyl substituent at the nitrogen atom promotes the acceleration of the oxidation and an increase in its regioselectivity.

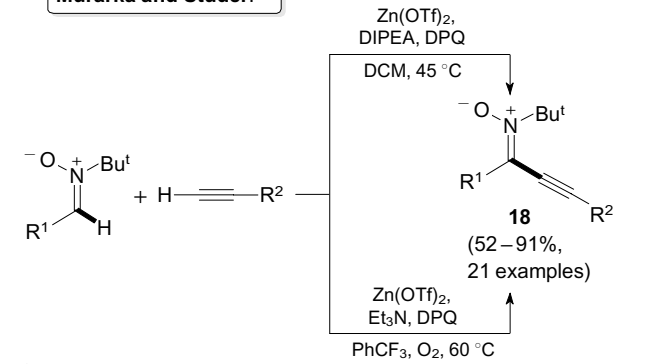
It is worth noting that the substituent at the imine nitrogen atom often plays a key role in cross-coupling

Scheme 7

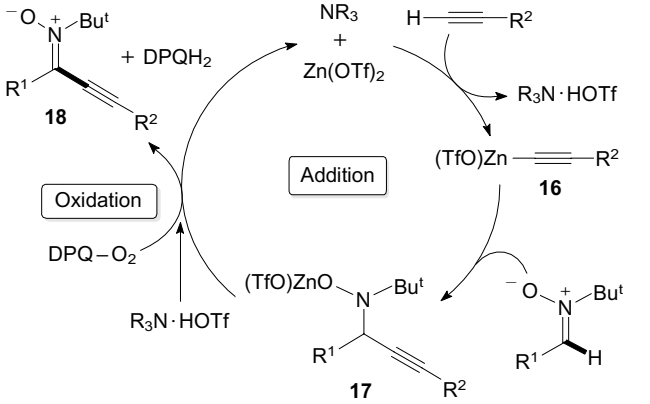


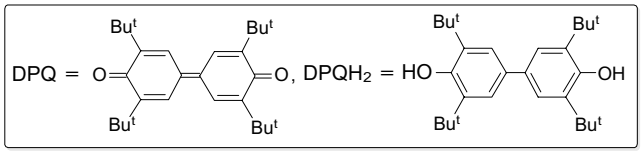
Scheme 8

Murarka and Studer:[49]



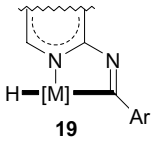
DCM is dichloromethane





reactions. In 2000, Ishiyama and Hartwig [50] showed that the presence of a particular azaheterocyclic moiety at the aldimine nitrogen atom can facilitate the formation of chelated intermediates **19** with some transition metals due to the presence of an additional donor nitrogen atom in the coordination sphere.

Structure 19



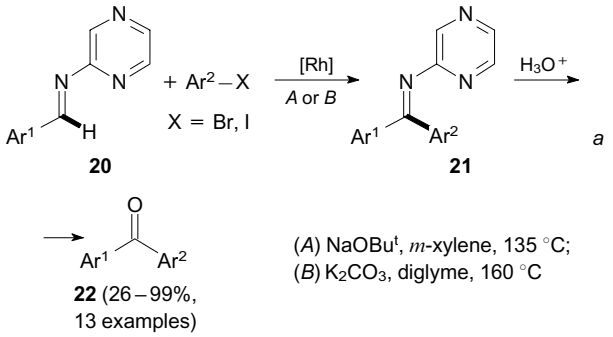
19

It was suggested that the generation of these intermediates is necessary for the activation of the C(sp^2) – H bond in imine and for its subsequent reaction with a substrate. The authors demonstrated the efficiency of this approach by performing rhodium-catalyzed cross-couplings of *N*-(pyrazin-2-yl)-substituted arylaldimines **20** with aryl halides (Scheme 9). These cross-couplings followed by the hydrolysis of intermediates **21** afforded diaryl ketones **22**. Later, it was demonstrated that these transformations can be mediated by a ruthenium catalyst as well.[51]

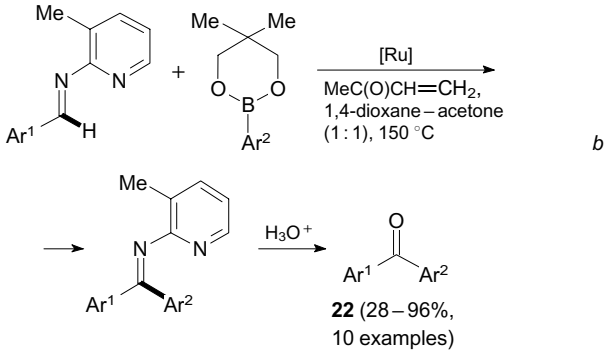
The further progress in the implementation of the metal-catalyzed cross-coupling strategy was achieved in the late 2000s when it was applied to the C(sp^2) – H functionalization of cyclic azomethine derivatives. In particular, both C – H/R – X couplings (X = Hal or pseudohalogen) [52 – 56] and cross-dehydrogenative (C – H/R – H) couplings [57 – 59] involving these substrates were accomplished (Scheme 10 *a*). Moreover, methods that do not require transition metal catalysis have been extensively developed for these com-

Scheme 9

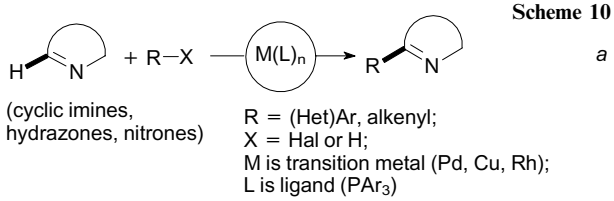
Ishiyama and Hartwig:[50]

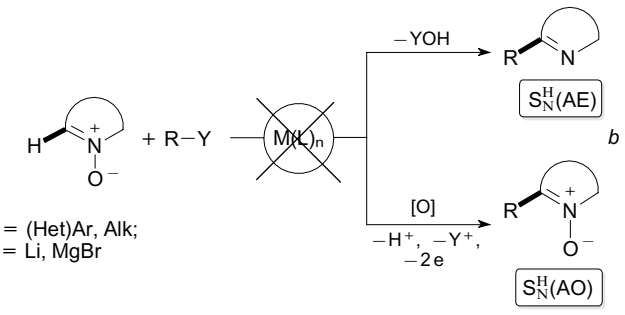


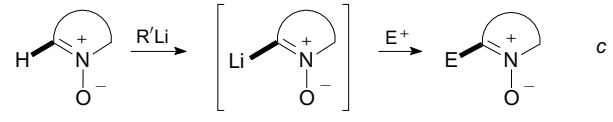
Jun and co-workers:[51]



Scheme 10







R′Li = Bu^{s}Li, LDA (lithium diisopropylamide);
E is electrophile (ketone or π-deficient hetarene)

pounds in recent years. These methods are based on the nucleophilic substitution of hydrogen (S_N^H) in cyclic aldonitrones *via* an addition – elimination (AE) or addition – oxidation (AO) mechanism (see Scheme 10 *b*)[60–64] and the α-lithiation of nitrones followed by coupling with electrophilic reagents (see Scheme 10 *c*).[65–70] The C – H modifications of cyclic aldimines and related compounds are considered in a special publication,[71] in which recent advances in this field are discussed in detail.

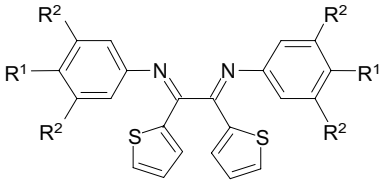
3. Synthetic value and application prospects of direct azomethine C(sp^2) – H functionalization

In modern organic chemistry imines and their derivatives often serve as intermediates in the synthesis of complex molecular structures (chiral amines, azaheterocyclic compounds, *etc.*), which are used mainly for the design of promising pharmacologically active molecules and functional materials. In these cases, the methodology of their C – H functionalization is employed as a convenient synthetic tool for performing desired reactions. Transformations in which azomethine compounds are generated *in situ* (*e.g.*, in the reaction of amines with aldehydes) followed by their C(sp^2) – H modification in a one-pot process are also often employed. Examples of these reactions and prospects of their application are considered below.

3.1. Reactions involving aldimines, amidines and their salts

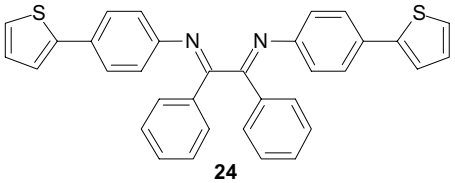
The synthesis of new 1,4-diazabutadiene (α-diimine) ligands was reported in 2009.[72] These ligands are widely used for lanthanide and transition metal complexes. The novelty of synthetic approaches was the modification of these compounds with thienyl moieties either directly bound to azomethine C atoms (compounds **23**) or spaced apart from imine nitrogen atoms by phenyl spacers (**24**).

Structures 23, 24



23

R^1 = H, F, Bu^t, OMe;
R^2 = H, Me

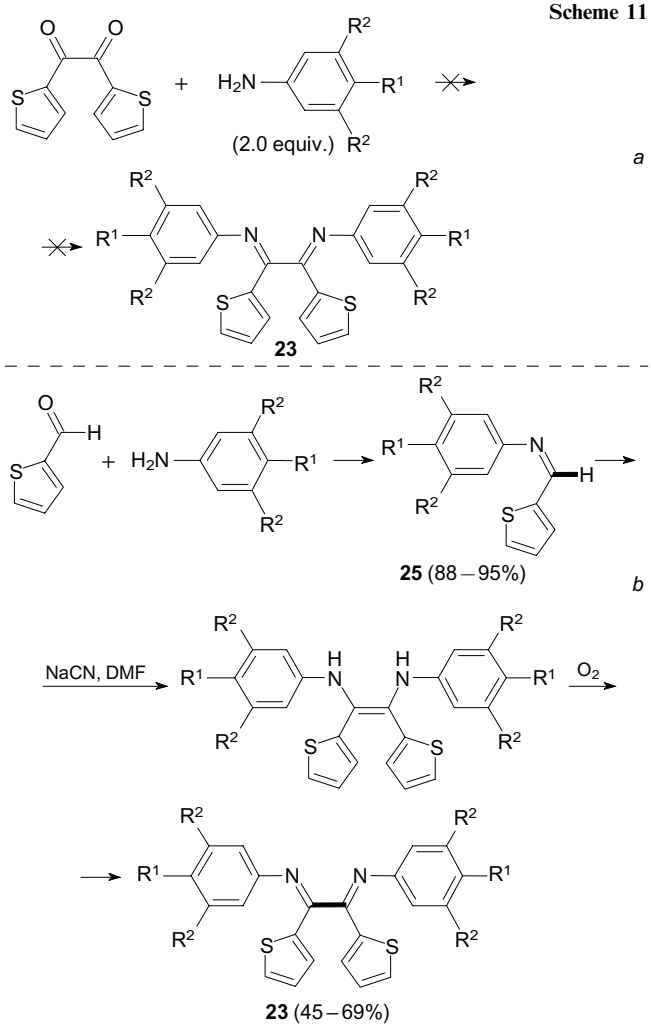


24

Initially, Powell *et al.*[72] made an attempt to prepare these compounds using a traditional approach based on the reaction of the corresponding α-diketones with primary amines (Scheme 11 *a*), but this was not a success. Therefore, they developed a procedure based on the cyanide-catalyzed coupling of two aldimine moieties **25** followed by the oxidation with oxygen and synthesized target molecules (in particular, compounds **23**) in satisfactory yields (see Scheme 11 *b*).

Emsermann *et al.*[73] employed similar methods to synthesize metal complexes with ^{13}C isotope-labelled unsymmetrically substituted *N*-heterocyclic carbenes (NHC).

Scheme 11

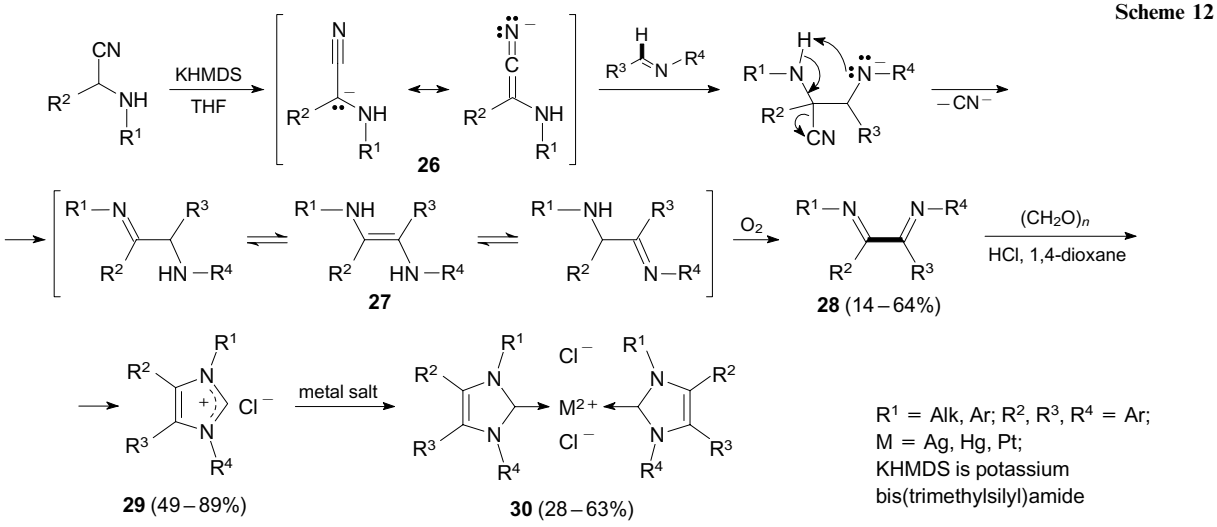


These compounds are of interest in studies of electronic asymmetry of molecules by NMR spectroscopy. In these studies, NMR-active metals (Ag, Hg, Pt) were used to form complexes with substituted 2-[^{13}C]-imidazolium salts serving as ligands. As in the above case, the ligands were synthesized by the coupling of aldimines. The difference is that two structurally different substrates were used in the latter synthesis. Aldimine was added to deprotonated α-aminonitrile **26**, and the resulting enediamine **27** was oxidized (Scheme 12) to form diimines **28**. The latter were cyclized to 1,3,4,5-tetrasubstituted imidazolium chlorides **29** using synthetic equivalents of formaldehyde — chloromethyl methyl ether (MOMCl) or paraformaldehyde — in the presence of hydrochloric acid. The subsequent reaction with metal salts (or oxides) afforded target complexes **30**.

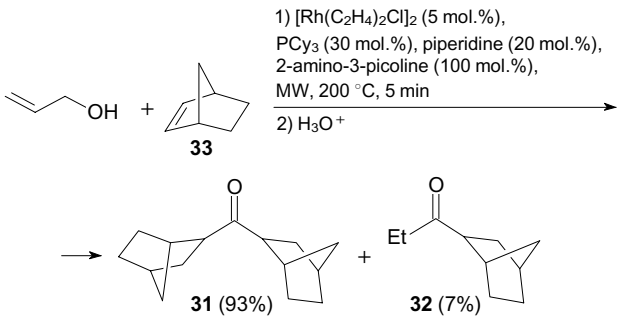
Another example is the Rh^I-catalyzed synthesis of dialkyl ketones **31** and **32** from allyl alcohol and norbornene (**33**) under microwave (MW) irradiation, involving the intermediate activation of the aldimine C(sp^2) – H bond (Scheme 13).[74] In this process, allyl alcohol serves as the hydroacylating agent alternative to aliphatic aldehydes. The use of aldehydes as substrates is undesirable because under these conditions, they are prone to be involved in aldol condensation as side reactions.

Allyl alcohol can be transformed into aldehyde (propanal) *via* olefin isomerization (Scheme 14).[75] The resulting carbonyl compound is easily trapped by 2-amino-3-picoline

Scheme 12



Scheme 13



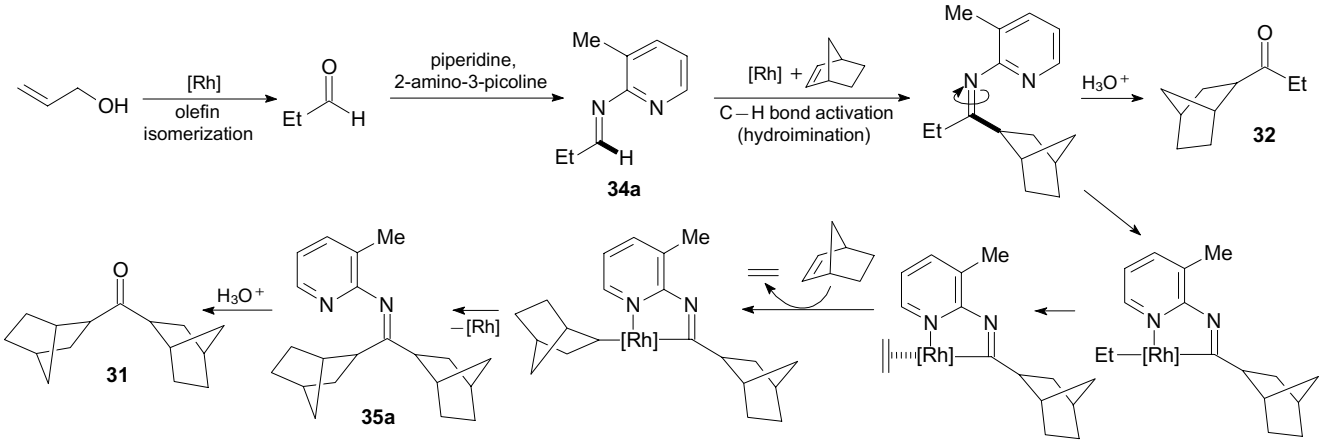
Cy is cyclohexyl

to form aldimine **34a**, which is sequentially transformed into ketimine **35a** and ketone **31** *via* chelation-assisted hydroacylation of alkene followed by hydrolysis. (These processes are mentioned in Section 2.3.) This makes it possible to avoid side reactions.

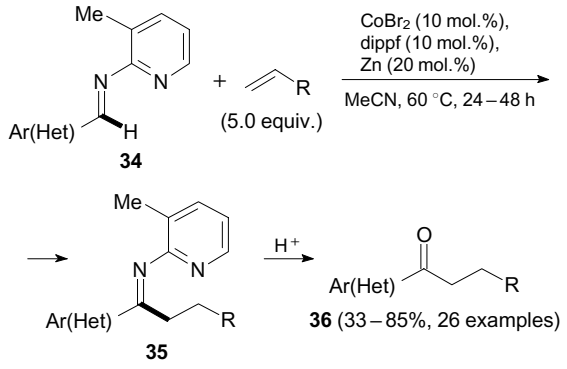
Yang *et al.*[76] considered similar processes in the study of the chelation-assisted hydroacylation of olefins with *N*-(3-picolin-2-yl)-substituted aldimines **34**. They used cobalt as a transition metal to catalyze the reaction of arylimines with alkenes. A significant advantage of this catalysis over rhodium catalysts is that the reactions can be performed at much lower temperatures (60 °C for a Co catalyst *versus* > 130 – 150 °C for Rh-catalyzed processes). Besides, cobalt compounds, being similar to rhodium compounds in chemical activity,[77 – 81] are much more commercially available. A Co complex with the 1,1′-bis(diisopropylphosphino)ferrocene ligand (dippf), which is generated by the reduction of $CoBr_2$ with zinc dust in the presence of bis(diisopropylphosphino)ferrocene, was proposed as a catalytic system of choice.[76] Under these conditions, the reaction with aldimines can involve vinylsilanes, styrenes and aliphatic olefins to form ketimines **35** and then ketones **36** (Scheme 15).

In 2008, the researchers at the Institute of Chemistry of Natural Substances (Gif-sur-Yvette, France) developed a new method for the synthesis of α-iminonitriles **37** (Scheme 16).[82] This one-pot three-component reaction is in essence the oxidative version of the Strecker synthesis. It is worth noting that α-iminonitriles are important intermediates in the synthesis of α-keto acids, amides, *N*-alkyl ketene imines, cyanoenamides, amidines, *etc.*[83, 84] Although different methods are available for the synthesis of these compounds, they are generally multistep and have a limited use. The method proposed by Fontaine *et al.*[82] is based on the nucleophilic addition of trimethylsilyl cyanide to an aldimine molecule, generated *in situ* from primary amine and aldehyde, giving α-aminonitrile **38**, which can be oxidized directly to target product **37**. 2-Iodoxybenzoic acid (IBX, **39**) served as the oxidant. Besides, the presence

Scheme 14

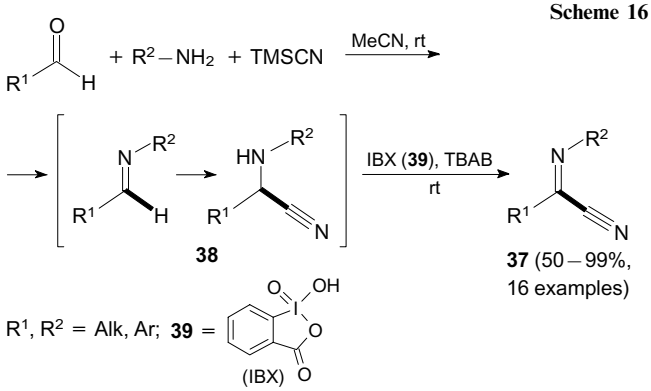


Scheme 15



R = Alk, (Het)Ar, TMS; TMS is trimethylsilyl

Scheme 16

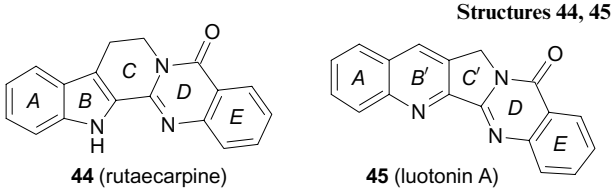


of a catalytic amount of tetra-n-butylammonium bromide (TBAB) as an additional component was found to be of importance. The yields of α-iminonitriles **37** were up to 99%.

Several years later, this approach was successfully applied to synthesize such pentacyclic alkaloids as phenanthroindolizidines and phenanthroquinolizidines **40** (Scheme 17) exhibiting anticancer and antiamoebic activity.[85] In this case, a cyano group was introduced into aldimine **41** prior to the intramolecular aza-Diels – Alder cyclization followed by the reductive decyanation of cycloadduct **42** and aryl – aryl coupling of the resulting *cis*-stilbene **43**.

The synthesis of the pentacyclic alkaloids rutaecarpine (**44**) and luotonin A (**45**) was reported[86] in 2016, both compounds being synthesized for the first time from the common precursor. Evidently, the structures of these compounds have a common quinazolinone moiety, which served as the key building block in the synthesis of both molecules. It should be noted that the challenge was to find the conditions optimal for the appropriate closure of the fused rings *B*, *C* and *B′*, *C′* in these alkaloids.

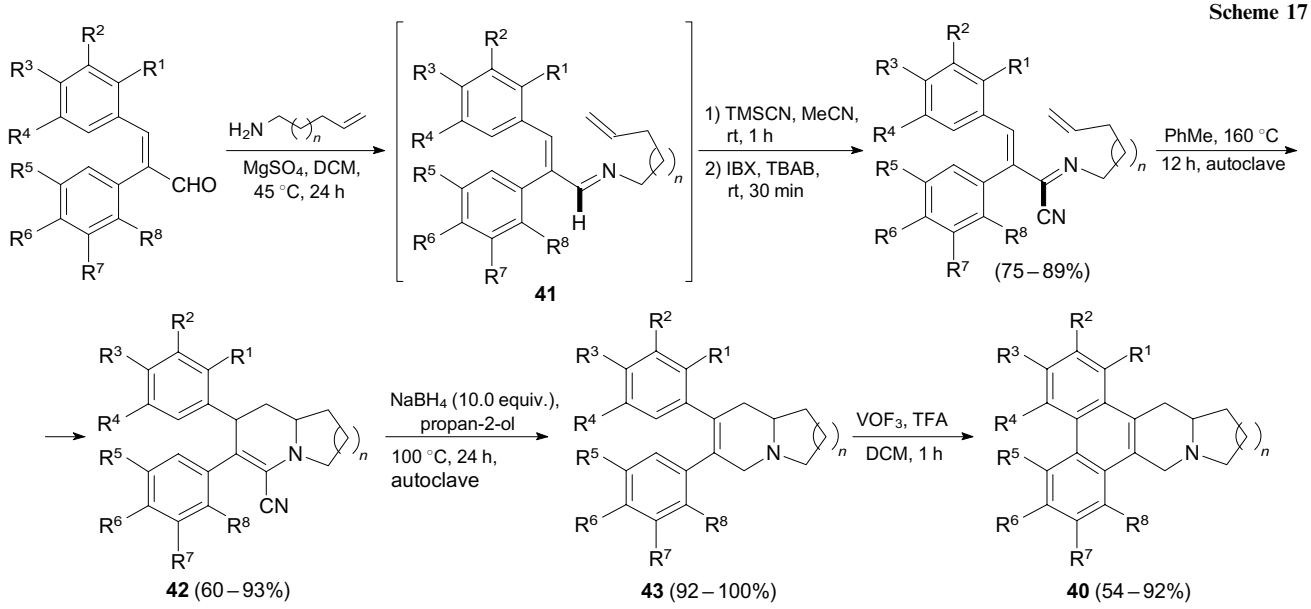
Structures 44, 45



Based on the retrosynthetic analysis, Kwon *et al.*[86] developed a strategy for the synthesis of target molecules. The first step involves the construction of common aldimine synthon **46** (Scheme 18) *via* the condensation of ethyl 2-aminocinnamate with quinazolin-4-one-2-carbaldehyde. The indole ring closure of rutaecarpine was accomplished *via* the cyanide-catalyzed aza-Stetter reaction, which was successfully used by this research group[87,88] for similar transformations. The piperidine ring *C* was built up in two steps, involving the reduction of the ethoxycarbonyl moiety to a hydroxy group and the subsequent intramolecular Mitsunobu reaction. Therefore, target rutaecarpine **44** was synthesized in four steps in an overall yield of 38%.

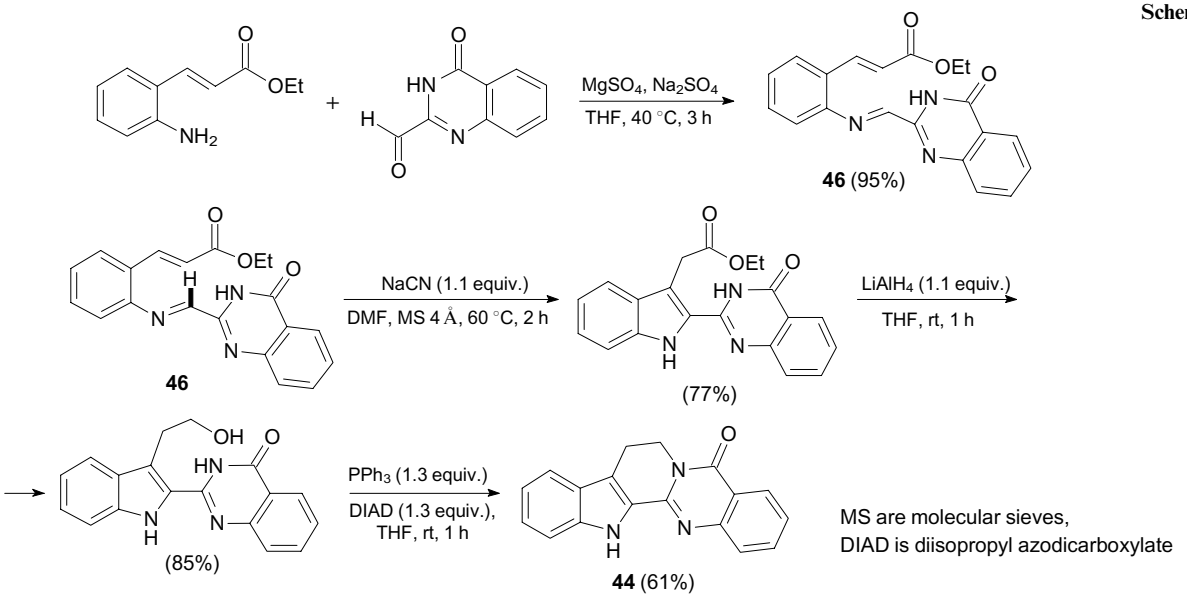
The researchers suggested the thermal 6π-electrocyclization as the most appropriate method for the closure of the quinoline ring of luotonin A (using aldimine precursor **46**) giving target intermediate **47** in the highest yield (Scheme 19). Then, as in the case of rutaecarpine, attempts

Scheme 17

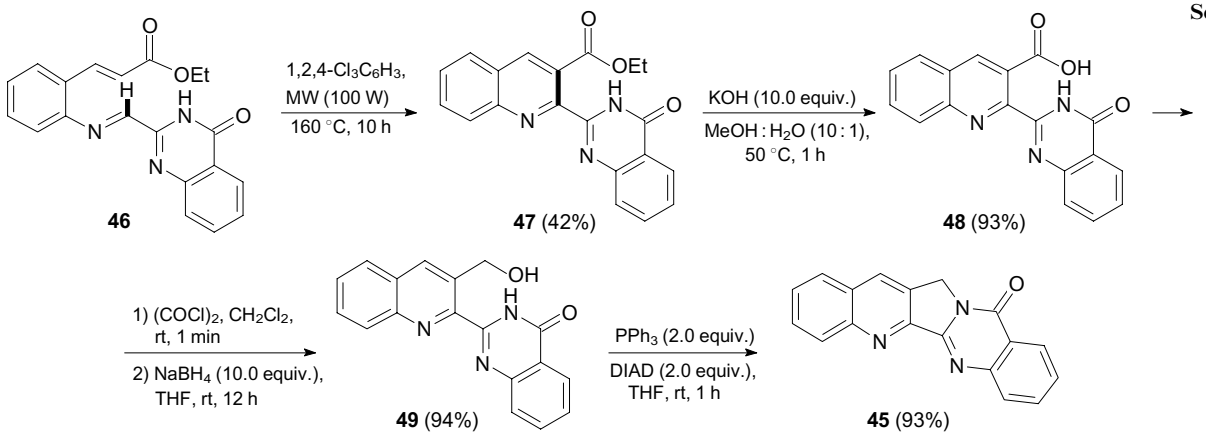


n = 1, 2; R1 – R8 = H, OMe; TFA is trifluoroacetic acid

Scheme 18



Scheme 19

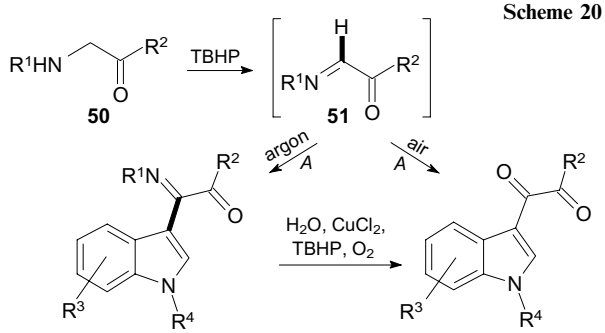


were made to reduce the ester group to an alcohol moiety, but they were unsuccessful. Therefore, the authors used an alternative route. First, ester **47** was hydrolyzed to acid **48**, which was transformed into acyl chloride followed by the reduction to alcohol **49**. The subsequent intramolecular Mitsunobu reaction gave target luotonin A (**45**) in an overall yield of 34%.

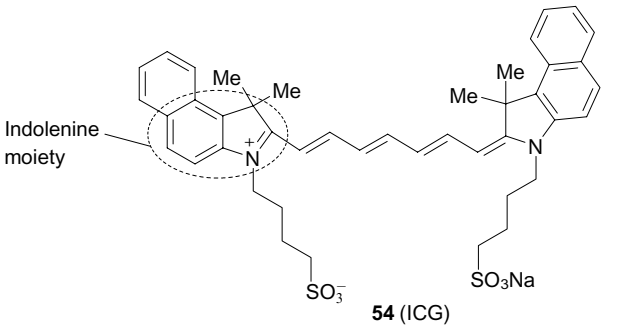
In 2012, Wu *et al.*[89] described a new method for the synthesis of 2-(1*H*-indol-3-yl)-2-iminocarbonyl compounds based on the C–H-modification of aldimines. The proposed procedure involves the Cu-catalyzed reaction of α-aminocarbonyl compounds **50** with 1*H*-indoles in the presence of *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 20). In the first step, the oxidative dehydrogenation of α-aminocarbonyl compound **50** with TBHP affords aldimine intermediate **51**, which alkylates the indole molecule at the position 3. Under inert conditions, the reaction produces 2-(1*H*-indol-3-yl)-2-iminocarbonyl compound **52**; in the presence of atmospheric air, α-diketone **53**. Compound **52** can be hydrolyzed to α-diketone **53** by the treatment with TBHP and copper dichloride in the presence of oxygen.

In the same year, Doi *et al.*[90] developed a rather facile method for the synthesis of new symmetrical and unsymmetrical functionalized indocyanine green (ICG, **54**) derivatives. Compound **54** is a near-infrared (NIR) fluorescent dye with a high molar absorption coefficient, which is used for noninvasive optical imaging in clinical diagnostics.[91] In order to develop new NIR fluorescent probes for *in vivo*

Scheme 20



Structure 54



54 (ICG)

imaging, efforts are continuing to search for structural components that facilitate the enhancement of fluorescence efficiency and an increase in photostability, a fluorescence quantum yield and solubility of compounds and to find molecular targets for these derivatives.

The goal of the research by Doi *et al.*[90] was to synthesize ICG derivatives having lower hydrophobicity compared to their analogues (which would increase their nonspecific interactions with serum proteins). Derivatives of the cyclic imine indolenine, which is a non-aromatic structural isomer of indole, served as key intermediates. The azomethine C—H bond was functionalized in the synthesis of unsymmetrical ICG derivatives (Scheme 21). 3*H*-Indolium salt **55** [synthesized from 1,1,2-trimethyl-(1*H*)-benz[*e*]indole and 1,4-butane sultone according to a standard procedure[92]] and glutaconic aldehyde dianilide **56** (as hydrochloride), taken in a two-fold excess, served as substrates. This coupling at room temperature afforded unstable product **57**, which reacted with another indolium salt (**58a** or **58b**) on heating in ethanol to form products **59a**,**b** in good yields.

One year later, Martin *et al.*[93] investigated the reactivity of *N*-heterocyclic carbenes (NHCs), examined the possibility of preparing oxyallyl derivatives from NHCs and evaluated their ability to undergo redox transformations. Oxyallyl derivatives (Fig. 2) are biradical molecules. They are considered as intermediates in a number of rearrangements and cycloaddition reactions, in particular, in the

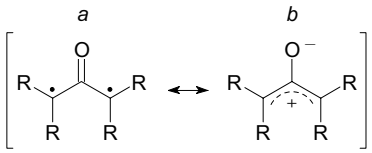
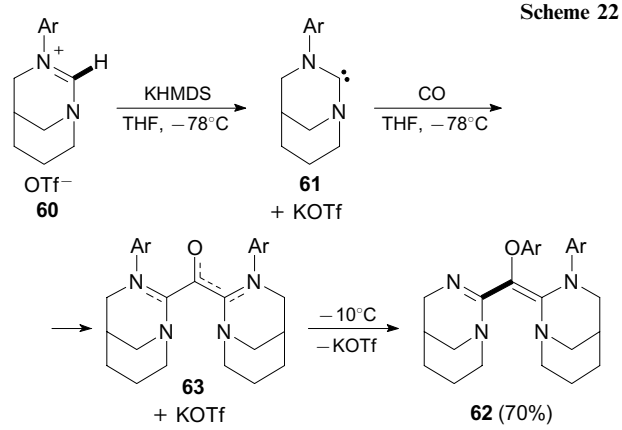


Figure 2. Oxyallyl species in the singlet biradical (*a*) and zwitterionic mesomeric (*b*) forms.

prostaglandin biosynthesis *in vivo*.§ These compounds can, in principle, be synthesized by the reaction of appropriate carbenes with carbon monoxide; however, this method lacks generality. For example, classical NHCs do not have sufficient electrophilicity for this transformation. The authors proposed an unusual method. They used amidinium salt **60** as the starting substrate (Scheme 22), the deprotonation of which at low temperature gave anti-Bredt NHC **61**.[94, 95] In this intermediate, one of the two nitrogen atoms is in a bridgehead position of the bicyclic carbene. Bredt's rule[96] states that bicyclic bridged structures cannot contain a double bond at the bridgehead carbon atom and, as a

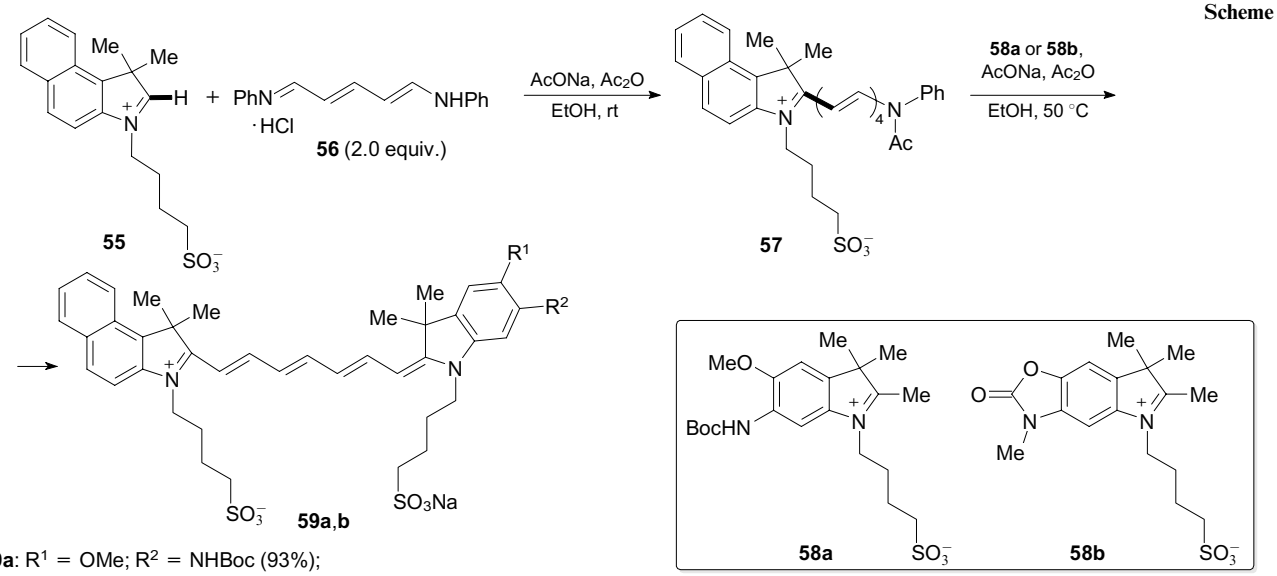
Scheme 22



Ar = 2,6-$Pr^i_2C_6H_3$

§ The characteristic features of oxyallyl derivatives are considered in Ref. 93; see also references therein (*e.g.*, Refs. 9 – 11).

Scheme 21



59a: R^1 = OMe; R^2 = NHBoc (93%);
59b: R^1 = R^2 = OC(O)NMe (75%); Boc is *tert*-butoxycarbonyl

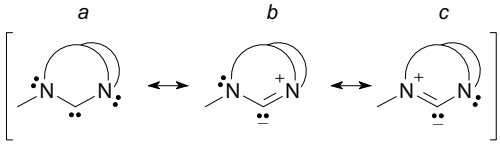


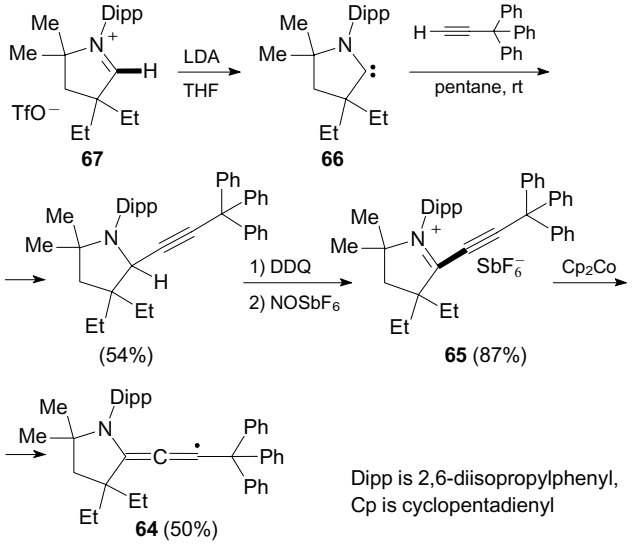
Figure 3. Anti-Bredt *N*-heterocyclic carbene (*a*) and its resonance structures, unfavourable (*b*) and favourable (*c*).

consequence, one of the resonance structures of this anti-Bredt NHC is virtually absent (Fig. 3). Therefore, only one nitrogen atom still exhibits π-donor properties, whereas the bridgehead nitrogen acts only as a σ-acceptor. This was expected to increase the electrophilicity of the carbon atom.

It was found that the bubbling of carbon monoxide through a solution of anti-Bredt carbene **61** (at −78 °C) resulted in the intense formation of a new dark-blue compound, the structure of which was determined by ^{13}C NMR spectroscopy at −40 °C. Upon a further increase in the temperature to −10 °C, the solution of this compound again changed the colour, and the spectrum of this solution showed a new set of signals. The resulting compound **62** was isolated and characterized (in particular, by X-ray diffraction). Hence, the authors suggested that the dark-blue intermediate is target oxyallyl derivative **63**. Therefore, the authors succeeded in performing the C−H functionalization of the starting azomethine derivative (amidinium triflate **60**) *via* an unusual reaction pathway.

Noteworthy is the study [97] published in 2017 by the same research group. The authors characterized propargyl and allenyl radicals, representatives of which were isolated in the crystalline state. Although this research was not focused on the C−H functionalization of azomethine derivatives, it deserves consideration. Thus, it was reported that the synthesis of radicals **64** (Scheme 23) can be accomplished by the reduction of alkynyliminium salts **65**, which are generated from cyclic alkyl amino carbenes (CAACs) **66**. The latter are relatively stable compounds (some of these compounds are stable even in the solid state at room temperature). The traditional method for the synthesis of these compounds is based on the deprotonation of aldiminium salts **67**.[98] Recently, it was found [99, 100] that CAACs can add to sp-hybridized C−H bonds at room temperature, which

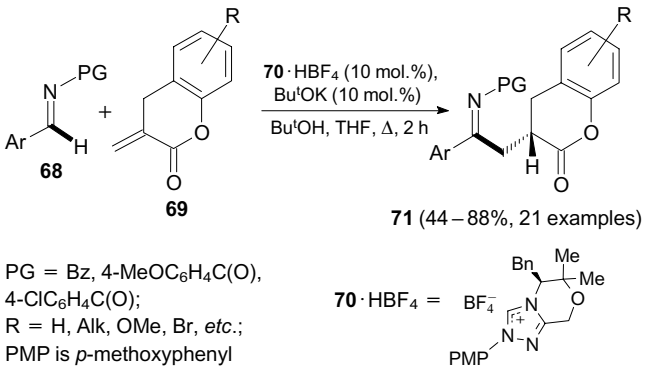
Scheme 23



makes it possible to introduce alkyl moieties into these molecules. The subsequent hydride elimination from adducts **66** under the treatment with a stoichiometric amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by the treatment with nitrosyl hexafluoroantimonate affords alkynyliminium salts **65** in good yields. The radicals are generated by the chemical reduction of these salts with cobaltocene (1 equiv.) or tetrakis(dimethylamino)ethylene (0.5 equiv.). It is worth noting that the stability of these radicals in solution, their tendency to undergo dimerization and their existence in solid state depends on the substituents in the carbene and alkynyl components. For example, radical **64** containing the trityl-substituted acetylene moiety and ethyl groups in the CAAC component was fully characterized both in solution and the single-crystal state, whereas related radicals with other substituents were more prone to form dimers, due to which attempts to isolate these compounds in solid state failed.

The study reported in 2019 [101] dealt simultaneously with C(sp^2)−H functionalization of azomethine derivatives and nitrogen-containing carbenes. The authors performed the enantioselective intermolecular aza-Stetter reaction involving aldimines **68** with protecting groups (PGs) and 3-methylenechroman-2-ones **69**. In this case, NHC derivative **70** served as the catalyst of choice for the transformation, and products **71** were isolated in moderate to high yields (Scheme 24).

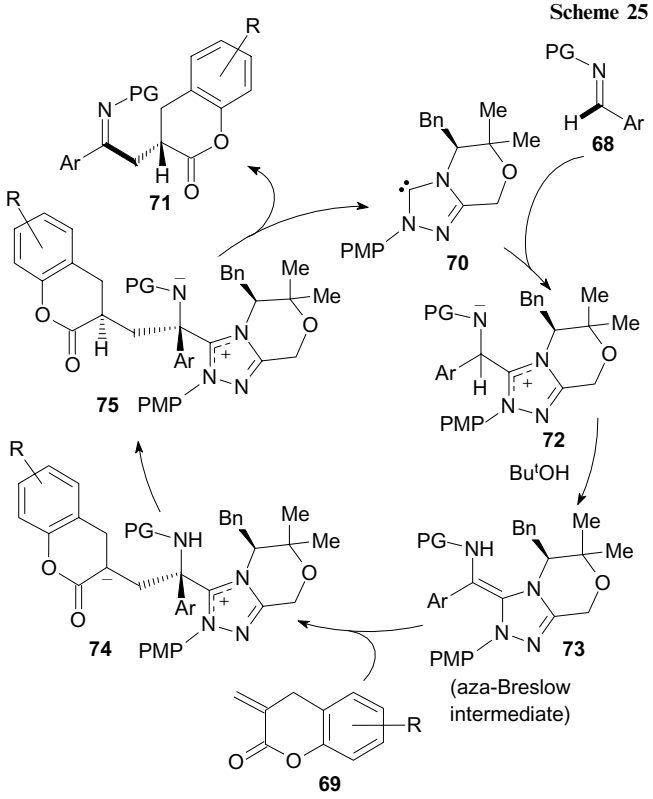
Scheme 24



A series of control experiments were performed to study the reaction mechanism, and the putative catalytic cycle of the reaction was proposed (Scheme 25). Fernando *et al.*[101] suggested that NHC **70** can add to aldimine **68** to form intermediate **72**, and the subsequent the ButOH-mediated tautomerization gives aza-Breslow intermediate **73**. The latter, in turn, undergoes 1,4-addition to chromanone **69** to form enolate **74**. The subsequent stereoselective protonation promotes the formation of intermediate **75**, and the elimination of the catalyst molecule from **75** directly affords target enantiomerically enriched γ-imino lactone **71** and completes the catalytic cycle.

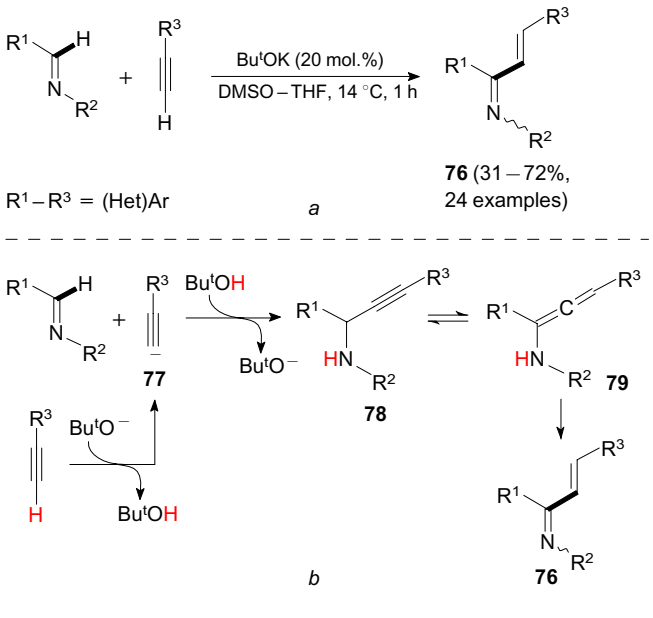
To finalize the analysis of transformations of aldimines, let us mention the recent study performed by Trofimov *et al.*[102] They performed the atom-economic synthesis of practically valuable 1-azadienes **76** (Scheme 26*a*) by the base-catalyzed C−H-vinylation of aldimines. Terminal acetylenes are used as vinylating agents; potassium *tert*-butoxide, as a base. The authors proposed a putative mechanism of this reaction (see Scheme 26*b*), which

Scheme 25



involves the deprotonation of alkyne with a base and the subsequent addition of anion **77** to the C=N bond of aldimine giving propargylamine **78**. The latter can undergo prototropic isomerization to 1-azadiene **76** through the generation of allene intermediate **79**. The authors also suggested an alternative mechanism based on the nucleophilic addition of the C–H moiety of aldimine to an acetylenic triple bond. This mechanism is similar to the benzoin condensation accompanied by the addition of an aldehyde C–H bond to the C=O group. Bidusenko *et al.*[103] applied a similar synthetic strategy for *N*-benzyl-substituted ketimines, from which a series of (*E*,*Z*)-2-aza-

Scheme 26



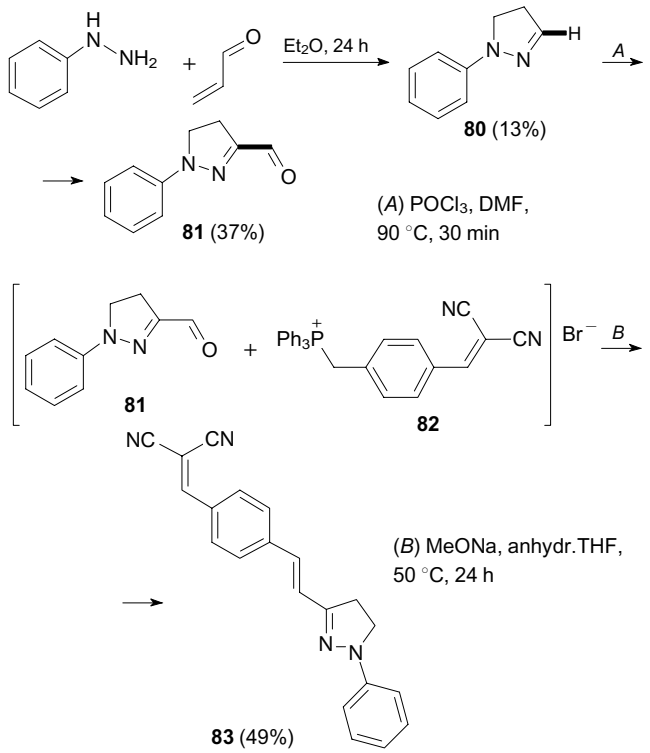
diene derivatives were synthesized with good stereoselectivity.

3.2. Reactions involving aldohydrazones

It should be emphasized that researchers dealing with retrosynthetic schemes for the synthesis of various compounds from aldimines employ also conventional methods, such as the electrophilic substitution of hydrogen in aldohydrazones.

Thus, in 2014 Mysliwiec *et al.*[104] synthesized pyrazoline derivatives containing a system of conjugated π-bonds. These compounds have high dipole moments and hyperpolarizability, which are important characteristics of materials for nonlinear optics and luminescent chromophores. One of intermediate steps in the synthesis of these structures involves the Vilsmeier formylation of 1-substituted pyrazoline **80** (Scheme 27), formal cyclic hydrazone, to form pyrazoline-3-carbaldehyde **81**. The Wittig olefination with ylide **82** affords target push-pull pyrazoline derivative **83**.

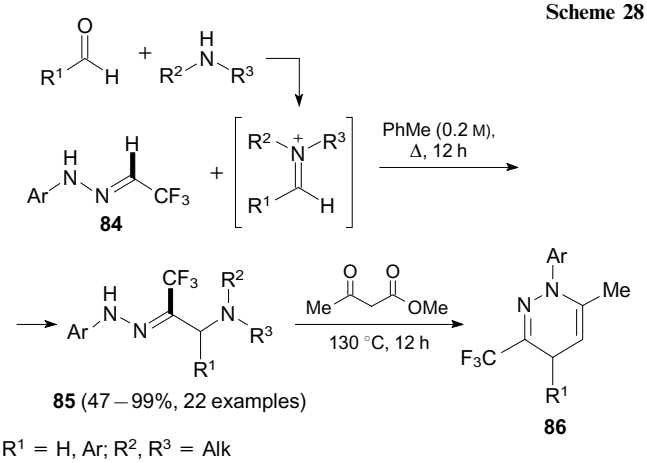
Scheme 27



Within the framework of the aza-enamine concept, another approach was developed in 2018 by researchers at the Ecole Polytechnique (Palaiseau, France).[105] They performed Mannich reactions with poorly known trifluoroacetaldehyde NH-hydrazones **84** (Scheme 28). Formaldehyde and aromatic aldehydes were used as carbonyl substrates. The reactions afford hydrazones **85**, which can serve as useful building blocks for the direct construction of trifluoromethyl-substituted heterocycles **86**. The latter can easily be prepared by heating compounds **85** with β-keto esters, *e.g.*, with acetoacetic ester.

The ability of aldohydrazones to reverse the polarity forms a basis of another research performed in the same year by Zabaleta *et al.*[106] In particular, the authors accomplished the enantioselective addition of hydrazones (Scheme 29 *a*) to electrophilic *N*-acyl- or *N*-thiocarbamoyl

Scheme 28



iminium ions **87**. The latter can be generated *in situ* from appropriate nucelophilic dihydropyrroles **88** under chiral Brønsted acid-catalyzed conditions (binaphthol-based phosphoric acid **89a** proved to be efficient). These reactions afforded a series of enantiomerically pure α-substituted proline derivatives **90**. Later, compound **90a** was used for the synthesis of compounds **91** (see Scheme 29 *b*) structurally similar to anti-amnesic pyrrolidines acting as prolyl endopeptidase (PEP) inhibitors.

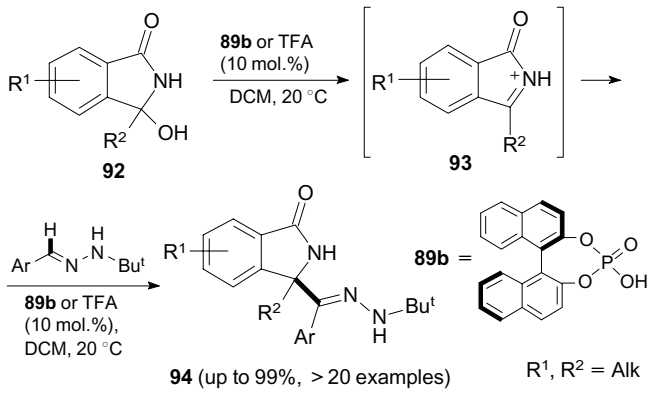
The reaction between *N*-mono-*tert*-butyl-substituted aldohydrazones and 3-hydroxyisoindolin-1-ones **92** (Scheme 30) occurs in an unusual way.[107] In this case, chiral phosphoric acid **89b** or trifluoroacetic acid can serve as the Brønsted acid catalyst. The difference from the above example is that iminium cation **93** is generated from hydroxy derivative **92** rather from enamide. Compounds **94** were synthesized mainly in high yields. It should be noted that such molecules containing an isoindolinone moiety are of interest for medicinal chemistry.

The synthesis of formazans by the reaction of aldohydrazones with diazonium salts is the most popular procedure based on the aza-enamine concept. Thus, the synthesis of new formazan derivatives was considered in several publications in the last one-and-a-half year.[108 – 111] Formazans are of interest due to their photophysical properties and the practical application as dyes. Meanwhile, it has recently been demonstrated[108] that these molecules can be used as antibacterial agents. For example, chromium bisformazan complex **95** (Scheme 31) exhibited high bactericidal activity against the bacteria *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Bacillus subtilis*.

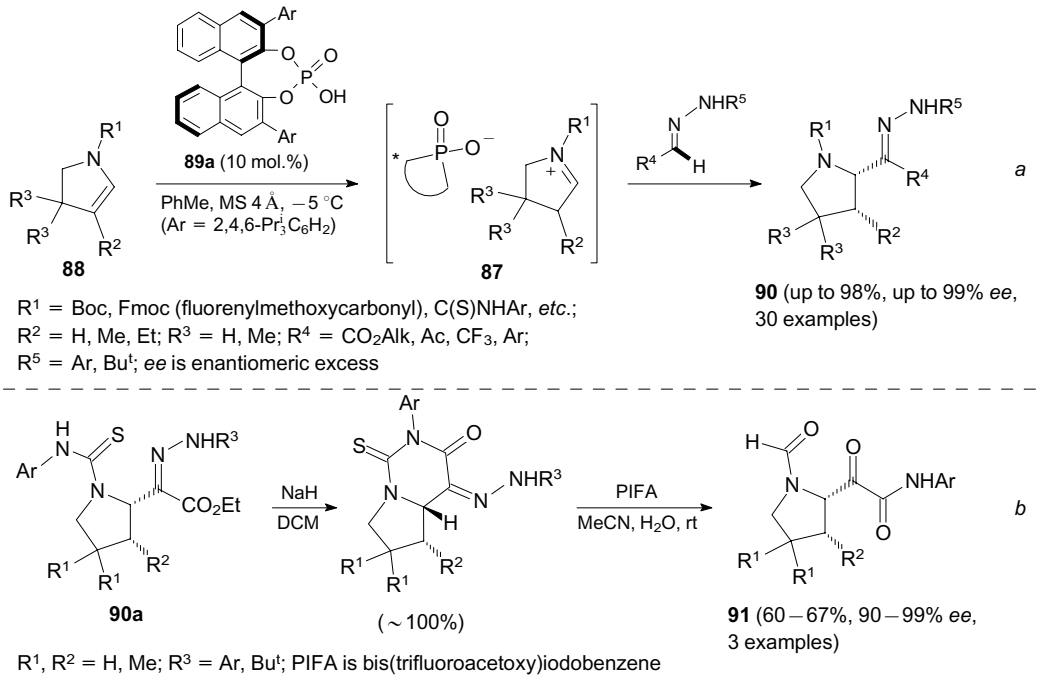
Besides, formazans serve as precursors for the synthesis of stable verdazyl radicals **96** (Scheme 32).[111] Due to the unique physicochemical properties, these radicals are attractive for biomedicine, materials science, *etc*.

A recent publication by Wen *et al*.[112] has started a new line of research on the C(sp^2) – H functionalization of aldohydrazones. In addition to investigations of photocatalytic transformations of hydrazones (see Section 2.2), this study demonstrated that the (N=)C – H bond can be activated by electrochemical methods as well. The authors focused on transformations of olefins and showed that the

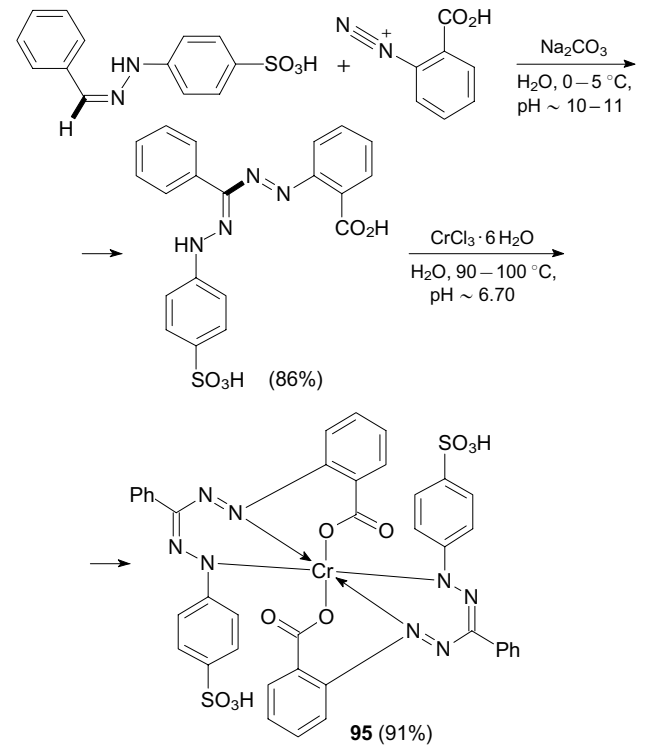
Scheme 30



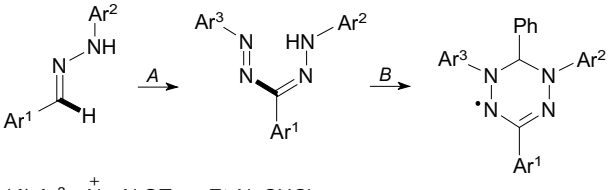
Scheme 29



Scheme 31



Scheme 32

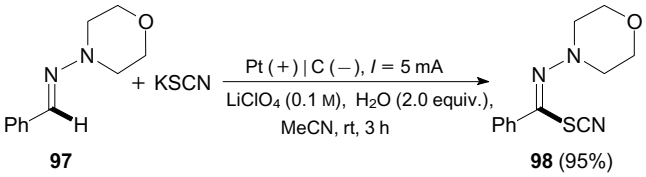


(*A*) $Ar^3-\overset{+}{N}\equiv N\ OTs^-$, Et_3N, $CHCl_3$, 20 °C, 0.5 h; (*B*) BnBr, $Ba(OH)_2\cdot 8H_2O$, DMF, 65 °C, 1 h

96 (88–92%, 7 examples)

procedure, which they developed for the H_2O-controlled thiocyanation of unsaturated substrates, is suitable not only for alkenes but also for their nitrogen analogues. This was demonstrated by performing the corresponding reactions of aldohydrazone **97** with potassium thiocyanate, resulting in the formation of product **98** (Scheme 33). The reaction was carried out in an undivided cell equipped with a platinum anode and a graphite cathode at a constant current density of 5 mA cm^{-2}. A lithium perchlorate solution was used as the electrolyte, and acetonitrile served as the solvent. According to the authors, water plays a key role in the anodic oxidation of KSCN to thiocyanogen $(SCN)_2$. Under these conditions, the thiocyanogen molecule can dissociate

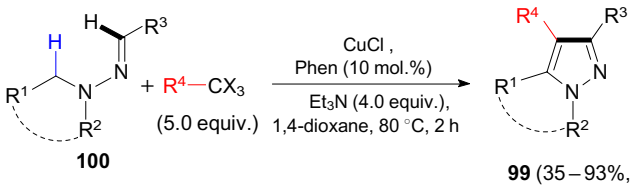
Scheme 33



through a homolytic mechanism to form two thiocyanyl radicals, and the latter can subsequently react with an organic substrate.¶

To complete this section, let us consider three publications related to the tandem functionalization of aldohydrazone derivatives giving new polysubstituted azaheterocyclic compounds. In 2016, a French research group [113] reported the one-pot assembly of functionalized pyrazoles **99** from *N*,*N*-dialkyl aldohydrazones **100** and polyhalomethanes. The reaction proceeds *via* the Cu-catalyzed cascade $C(sp^2)-H$ haloalkylation, $C(sp^3)-H$ cyclization and aromatization (Scheme 34).

Scheme 34



99 (35–93%, 27 examples)

R^1 = Alk, Ar; R^2 = Alk; R^3 = Ar; R^4 = Cl, Br, CN, CO_2Et, Bz; X = Cl, Br; Phen is 1,10-phenanthroline

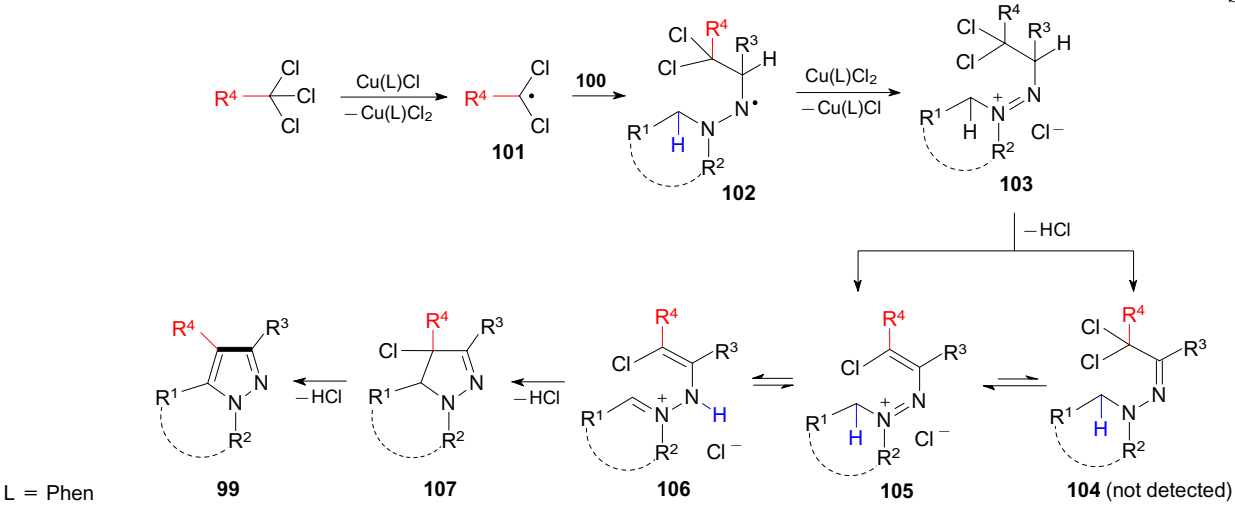
The proposed mechanism includes the formation of electrophilic haloalkyl radical **101** (Scheme 35) in the presence of a copper(I) complex promoting the elimination of a halogen atom from the polyhalomethane derivative to form a copper(II) complex. Radical **101** is trapped by hydrazone **100** giving haloalkylated aminyl radical **102**. The oxidation of the latter with copper(II) leads to the regeneration of the copper(I) complex and the formation of diazenium intermediate **103**, which can be deprotonated to haloalkylated hydrazone **104**. The lone pair of the terminal nitrogen atom in compound **103** can also induce the elimination of a halide anion giving rise to diazenium derivative **105**. An alternative route to derivative **105** involves the elimination of an HHal molecule directly from intermediate **103**. Upon elimination of HCl, iminium cation **106** (tautomer of diazenium cation **105**) can undergo intramolecular cyclization giving pyrazoline **107**. Finally, the aromatization of this compound through the elimination of another HCl molecule produces target pyrazole **99**.

The research group [114] at the Yale University (USA) demonstrated the possibility of the dual C–H activation in the reaction of aldohydrazones **108** with alkynes (Scheme 36 *a*). This reaction can afford annulated azaheterocycles — azolopyridazines **109**. The authors found that this reaction can occur both in intermolecular and intramolecular fashion (see Scheme 36 *b*).

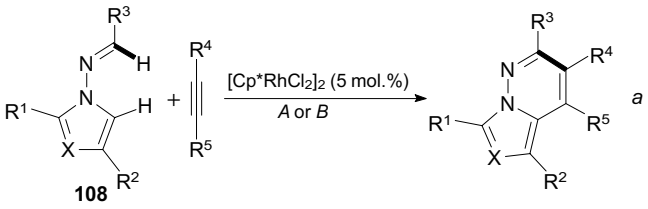
It is worth noting that the intramolecular cyclization of alkynyl-containing aldohydrazones **108a**,**b** yields tricyclic reaction products **109a**,**b** rather than bicyclic ones. The proposed catalytic cycle is represented in relation to the intermolecular reaction of hydrazone **108c** with diphenylacetylene (Scheme 37). First, two sequential concerted metalation–deprotonation (CMD) steps generate five-membered rhodacycle **110**. The coordination of this intermediate by alkyne affords complex **111**, which is followed by the selective migratory insertion of alkyne into the rhodacycle to give vinyl rhodium derivative **112**. The sub-

¶ The mechanism of electrochemical thiocyanation has been considered in detail for the reaction of potassium thiocyanate with olefin.[112]

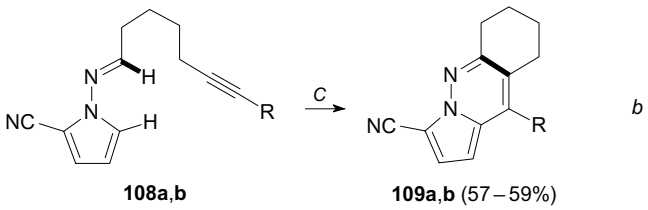
Scheme 35



Scheme 36

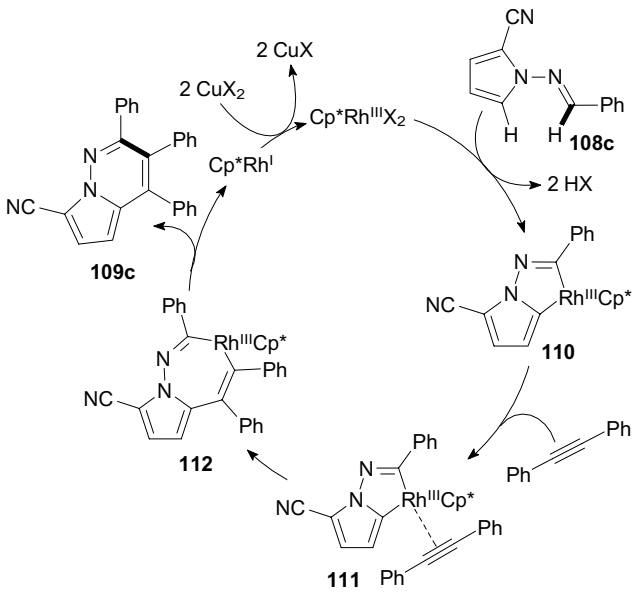


X = CH, N; R^1 = H, Alk, Ac, CN, CO_2Et;
R^2 = H, CO_2Me; R^3 = Alk, (Het)Ar, OMe, NMe_2;
R^4, R^5 = Alk, Ar, CO_2Me;
(*A*) $Cu(OAc)_2$ (2.0 equiv.), 1,4-dioxane (0.2 M), 140 °C, MW, 1 h;
(*B*) AgOAc (2.0 equiv.), PivOH (4.0 M), THF (0.2 M), 120 °C, 16 h

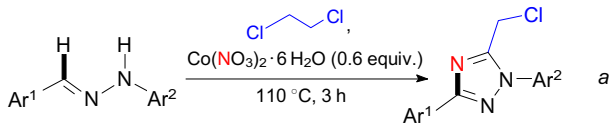


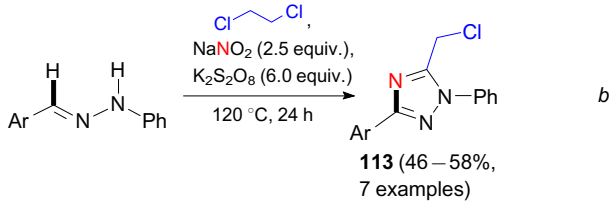
(*C*) $[Cp^*RhCl_2]_2$ (5 mol.%), AgOAc (2.0 equiv.), PivOH (4.0 equiv.), THF (0.1 M), 120 °C, 16 h; R = Ph (**a**), Pr^n (**b**);
Cp* is pentamethylcyclopentadienyl,
Piv is pivaloyl (trimethylacetyl)

Scheme 37



Scheme 38



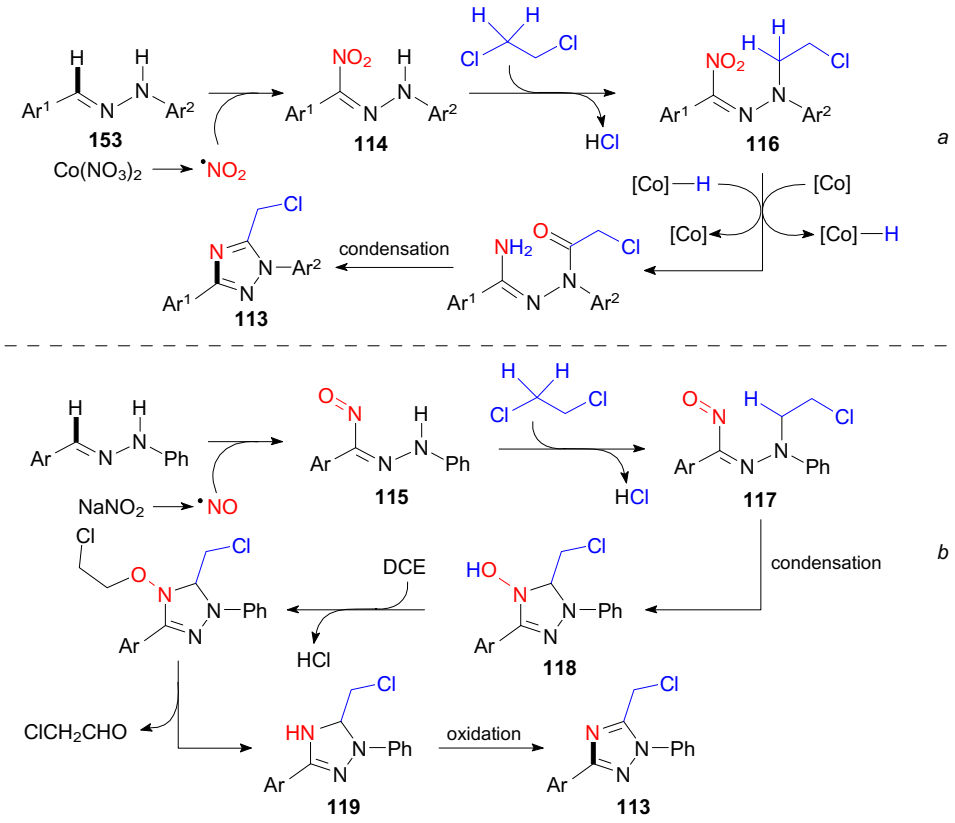


sequent reductive elimination leads to the release of reaction product **109c** and the rhodium(I) complex, which is regenerated to the rhodium(III) complex in the presence of a stoichiometric amount of the oxidant.

Hao *et al.*[115] developed a method for the synthesis of substituted 1,2,4-triazoles **113** from arylhydrazones (Scheme 38 *a*) *via* a tandem nitrification, reduction and cyclization protocol.

In this approach, cobalt nitrate served as a nitrogen source to construct the triazole ring and also mediated the redox processes during the synthesis. Besides, 1,2-dichloroethane was used as both the solvent and a reactant. The authors also proposed an alternative approach to the synthesis of triazoles **113** from the same precursors, which did not require the presence of cobalt salts (see Scheme 38 *b*). In this case, sodium nitrite served as the nitrogen source. A large excess of potassium persulfate as the external oxidant was required for this process. The authors proposed plau-

Scheme 39

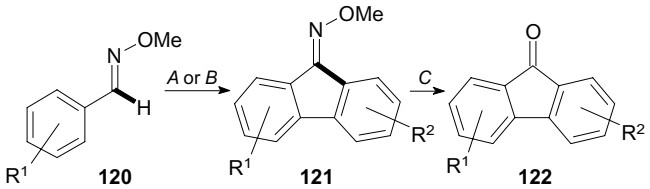


sible mechanisms for both reactions (Scheme 39 *a*,*b*). In both cases, the C(sp^2) – H bond functionalization of aldohydrazone had a radical nature, although the trapped radicals were different. Thus, it was suggested that the cobalt nitrate-mediated pathway involves the generation of the $NO_2^{\bullet}$ radical under thermal conditions, which reacts with azomethine to form intermediate **114** (see Scheme 39 *a*). By contrast, the reaction of sodium nitrite with potassium persulfate (or under thermal conditions) leads to the generation of the NO$^{\bullet}$ radical, which can react with the starting molecule to form intermediate **115** (see Scheme 39 *b*). Correspondingly, the subsequent steps in the two mechanisms are different. According to the former mechanism, intermediate **114** is alkylated at the NH moiety with dichloroethane to give intermediate **116**. This step is followed by two competitive redox reactions involving cobalt compounds: the reduction of the nitro group to the amino group and the oxidation of the sp^3-hybridized carbon atom to the carbonyl group. This gives intermediate **114**, which undergoes intramolecular condensation to final product **113**. According to another mechanism, intermediate **115** is alkylated with dichloroethane to form compound **117**, which undergoes intramolecular condensation to derivative **118**. The latter, in turn, can be reduced in two steps to triazoline **119**, and the subsequent oxidation of **119** gives final product **113**.

3.3. Reactions involving aldoximes

Currently, the C – H functionalization of aldoximes is successfully used in organic synthesis, although it is not as popular as similar transformations of their structural analogues — aldimines, aldohydrazones and aldonitrones. For example, the cross-coupling reactions of aldoxime ethers were applied in the synthesis of such industrially important compounds as fluorenones.[116, 117] The latter are present in many natural products and serve as the basis of some anticancer agents and materials for organic electronics.† Besides, fluorenone derivatives exhibit different pharmacological activity. For example, they can selectively bind or stabilize DNA G-quadruplexes and act as antiviral agents and enzyme inhibitors. According to the procedure proposed by the authors,[116, 117] arylaldoxime methyl ethers **120** are subjected to Pd-catalyzed oxidative cross-coupling with aryl iodides or arenes giving oximes **121**, and their subsequent hydrolysis affords fluorenones **122** (Scheme 40). The plausible reaction mechanism includes two catalytic cycles (Scheme 41).‡ The first cycle involves the formation of palladacycle **123** and its oxidation to a Pd^{IV} intermediate

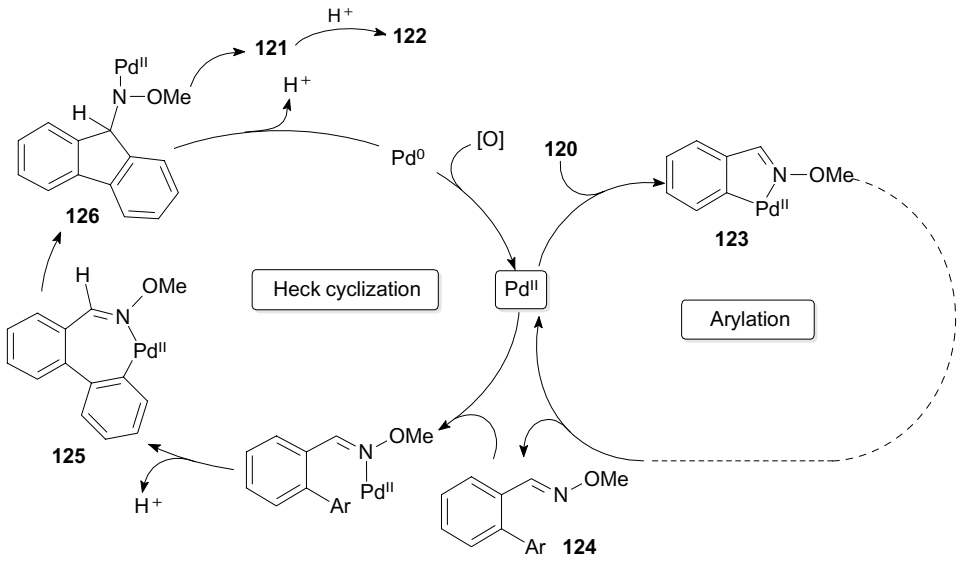
Scheme 40



(*A*) $R^2C_6H_4I$, $Pd(OAc)_2$ (10 mol.%), Ag_2O, TFA, 120 °C, 36 h (63 – 90%, 18 examples);
(*B*) R^2Ph, $Pd(OAc)_2$ (20 mol.%), $K_2S_2O_8$, TFA, 120 °C, 15 h (39 – 91%, 22 examples);
(*C*) HCl, hydrolysis;
R^1 = Alk, Ar, Hal, CF_3, NO_2; R^2 = H, Me, OMe, F, NO_2, CO_2Et

† Practical applications of fluorenone derivatives are considered in Ref. 117 see also references therein (*e.g.*, Refs. 1 – 4).
‡ Intermediates of the arylation cycle are omitted for clarity (indicated by a dashed line) as the least significant compounds within the framework of this review.

Scheme 41

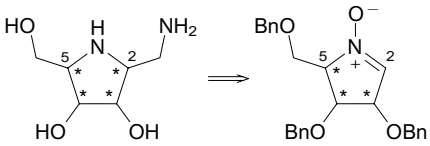


via either the oxidative addition of aryl iodide (see Scheme 40, conditions *A*) or the reaction with potassium persulfate followed by arylation (see Scheme 40, conditions *B*). The subsequent reductive elimination affords intermediate *ortho*-arylated oxime **124**, which is accompanied by the release of divalent palladium. The second catalytic cycle involves the coordination of intermediate **124** to Pd^{II} followed by the formation of seven-membered palladacycle **125**. The subsequent intramolecular insertion of the C=N group into the palladium – aryl bond promotes the formation of intermediate **126** followed by the elimination of β-hydride to form ketoxime **121**. Final acid hydrolysis produces target fluorenone **122** and Pd^0, which undergoes recyclization *via* the oxidation with silver(I) oxide or potassium persulfate.

3.4. Reactions involving aldonitrones

Approaches that are currently used to synthesize practically valuable compounds and involve nitrone derivatives as intermediates [118, 119] are of great importance. For example, a procedure was developed for the design of new inhibitors of human Golgi α-mannosidase II (hGMII),[120] a key enzyme involved in the *N*-glycan biosynthesis in the human body. The inhibition of this enzyme is one of known strategies for cancer treatment.[121, 122] Cheng's

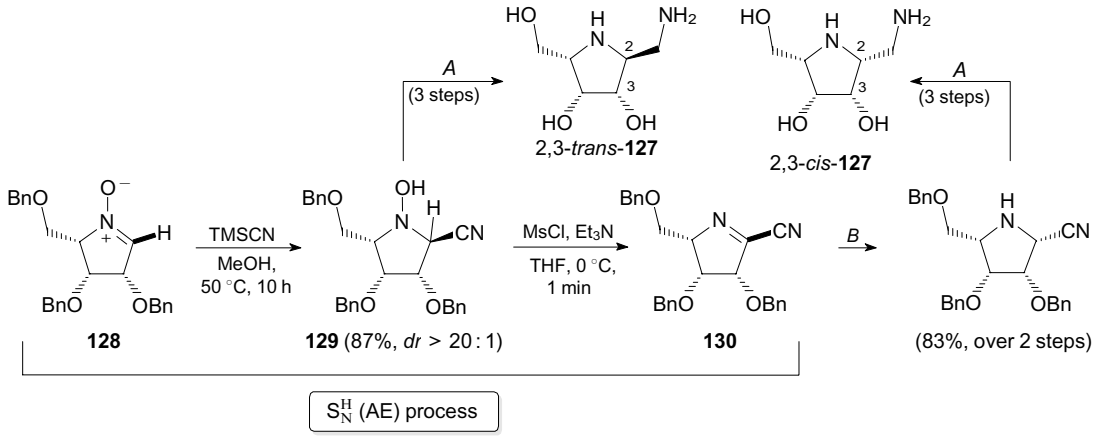
Scheme 42



research group [120] reported a procedure for the synthesis of all 16 optical isomers of 1-aminodeoxy-2,5-dideoxy-2,5-imino-D-mannitol (ADMDP, **127**), which can serve as the basis for the design of a new efficient and selective hGMII inhibitor. Compound **127** is a polyhydroxylated pyrrolidine derivative with four stereogenic centres; its isomers were prepared using eight cyclic nitrones **128** with three chiral centres as precursors (Scheme 42).

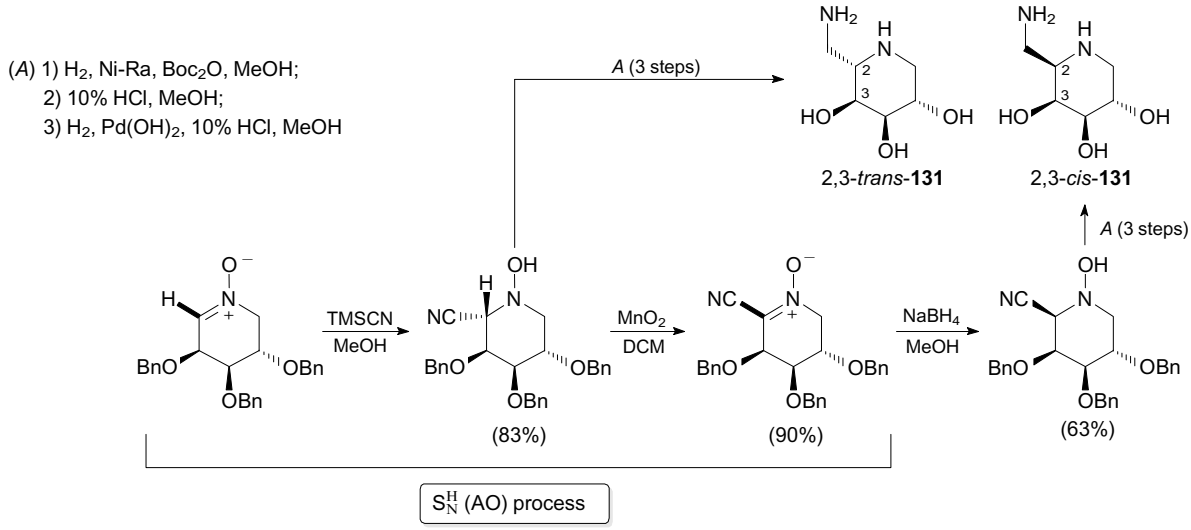
It was shown that both 2,3-*cis* and 2,3-*trans* isomers can be prepared from one nitrone with different stereoconfigurations, the stereochemistry of the product being dependent on the synthesis conditions. In both cases, the first step yields adduct **129** *via* the reaction of nitrone **128** with TMSCN (Scheme 43). The subsequent direct hydrogenation on the Raney nickel (Ni-Ra) catalyst affords the 2,3-*trans* isomer of ADMDP, whereas the elimination of a water

Scheme 43



(*A*) 1) H_2, Ni-Ra, Boc_2O, MeOH; 2) H_2, $Pd(OH)_2$, MeOH; 3) TFA, DCM; (*B*) $NaBH_4$, THF : MeOH (4 : 1), 0 °C, 18 h; Ms is methanesulfonyl

Scheme 44



molecule followed by the two-step hydrogenation of intermediate α-iminonitrile **130** gives product **127** in the *cis* configuration.

This approach was applied by Cheng and co-workers [123] (see Scheme 39) to prepare (3*S*,4*S*,5*S*)-trihydroxypiperidine derivatives **131**, which can act as stabilizing agents for human recombinant α-galactosidase. According to the authors, the stabilization of this enzyme can play a key role in the treatment of the Fabry disease, an inherited lysosomal storage disorder.

Therefore, the above examples of C(sp^2)–H bond functionalization of azomethine derivatives demonstrate the relevance of this methodology in organic synthesis. Broad prospects of this approach may stimulate the development of new procedures and the improvement of available methods. It would be expected that this methodology will find more use for the preparation of functionally significant compounds.

4. Conclusion

To sum up, it should be noted that the C(sp^2)–H functionalization strategy of azomethine derivatives plays a great role in retrosynthetic schemes for the preparation of different practically important classes of organic compounds. The syntheses of pharmacologically active substances, dyes, ligands, natural products and their analogues are only some examples of the application of this methodology in the past decade. Of course, not all approaches used in the above-considered synthetic schemes are based on fundamentally new reactions. Thus, conventional methods (*e.g.*, the azaenamine concept) proved to be efficient for a long time and were extensively employed. Nevertheless, the recently developed tools, which are successfully applied to accomplish the C–H modification of imines and related compounds, deserve special mention.

For instance, the radical functionalization of aldohydrazones, in particular using photocatalytic methods, has attracted great attention in the 2010s. Photocatalytic methods are beneficial from the viewpoint of green chemistry. Thus, they allow the modification of complex systems in the late steps of the synthesis without pre-activation of C–H bonds involved in these reactions. Besides, these processes generally occur under mild conditions without use of alternative energy resources (*i.e.*, visible light or UVA). A start has been made with the development of electrochemical methods for C–H functionalization of azomethines.[112] The main advantage of these methods is that they do not require stoichiometric amounts of chemical oxidants, which are often necessary for the regeneration of the azomethine π-bond in addition–oxidation processes. Another important trend observed when analyzing these methods is the wide use of various tandem reactions and other one-pot processes. These approaches make it possible to decrease the number of operational steps associated with the isolation and purification of intermediates in multistep chemical transformations. Therefore, these transformations are consistent with the principles of the pot, atom, and step economy (PASE),[124] which have gained increasing importance in recent years in the context of sustainable development.

It would be expected that this methodology will be further extended, improved and upgraded mainly within the framework of approaches to radical C–H functionalization of aldimines and related compounds. This particularly applies to cyclic azomethines, because such approaches are poorly explored for these compounds.[71] Meanwhile, the nucleophilic substitution of hydrogen (S_N^H) is a promising tool for the synthesis of acyclic imines, which was successfully applied for cyclic derivatives in the past decade.[71] Studies aimed at increasing the efficiency of the available methods for C–H bond modification of azomethine moieties are expected to continue in the future. Therefore, the strategy for C(sp^2)–H functionalization of aldimines and related compounds will obviously attract the keen attention of synthetic chemists.

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5. List of acronyms and designations

The following acronyms and designations are used in the review:

ADMDP — 1-aminodeoxy-2,5-dideoxy-2,5-imino-D-mannitol,

AE — addition–elimination,

AO — addition–oxidation,

Boc — *tert*-butoxycarbonyl,
Bs — *p*-bromobenzenesulfonyl (brosyl),
CAAC — cyclic alkyl amino carbene,
Cp — cyclopentadienyl,
Cp* — pentamethylcyclopentadienyl,
Cy — cyclohexyl,
DCE — 1,2-dichloroethane,
DCM — dichloromethane,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DIAD — diisopropyl azodicarboxylate,
DIPEA — diisopropylethylamine,
Dipp — 2,6-diisopropylphenyl,
dippf — 1,1′-bis(diisopropylphosphino)ferrocene,
dppe — 1,2-bis(diphenylphosphino)ethane,
dppm — 1,1-bis(diphenylphosphino)methane,
DPQ — 3,3′,5,5′-tetra(*tert*-butyl)-4,4′-diphenoquinone,
Fmoc — 9-fluorenylmethoxycarbonyl,
hGMII — human Golgi α-mannosidase II,
IBX — 2-iodoxybenzoic acid,
ICG — indocyanine green,
KHMDS — potassium bis(trimethylsilyl)amide,
LDA — lithium diisopropylamide,
MOMCl — chloromethyl methyl ether,
MS — molecular sieves,
Ms — methanesulfonyl (mesyl),
MW — microwave irradiation,
NHC — *N*-heterocyclic carbene,
NIR — near-infrared region of the spectrum,
PG — protecting group,
PIFA — bis(trifluoroacetoxy)iodobenzene,
PMP — *p*-methoxyphenyl,
ppy — 2-phenylpyridyl,
Py — pyridine,
R_F — perfluorinated substituent,
rt — room temperature,
SET — single-electron transfer,
S_N^H — nucleophilic substitution of hydrogen,
TBAB — tetra-n-butylammonium bromide,
TBHP — *tert*-butyl hydroperoxide,
TFA — trifluoroacetic acid,
TFAA — trifluoroacetic anhydride,
TMEDA — *N*,*N*,*N*′,*N*′-tetramethylethylenediamine,
TMSCN — trimethylsilyl cyanide,
Ts — *p*-toluenesulfonyl (tosyl),
UVA — near-ultraviolet region (ultraviolet A).

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