Organic azides: “energetic reagents” for the intermolecular amination of C–H bonds

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This feature article provides an overview of the application of organic azides for the intermolecular amination of sp³ and sp² C–H bonds. The catalytic activity of several metal complexes was reviewed underlining both synthetic and mechanistic aspects of the C–H amination. The majority of the aminated compounds reported in literature have been collected in this paper to provide a compendium of published procedures. In addition, the discussion of involved mechanisms has been included to assist the reader to envisage the future potential of organic azides in the synthesis of aza-derivatives.

1. Introduction

Since the first preparation of organic azides (RN₃) in 1864,¹ this class of molecules has been involved in an increasing number of applications over the last 15 years, as documented by SciFinder (Fig. 1). Among all possible applications, organic azides are largely used as atom-efficient aminating agents due to the formation of eco-friendly molecular nitrogen as the only side product of the “NR” transfer reaction to an organic molecule.²,³

The insertion of a nitrene moiety into an organic framework is efficiently catalysed by transition metal complexes and allows the synthesis of aza-compounds which often display important biological and pharmaceutical characteristics.⁴ As azides are active towards several classes of organic molecules, the amination

Fig. 1 Manuscripts and patents on organic azides reported by SciFinder in the 1998–2013 period.
reaction displays a great chemical versatility and it can be conducted using mild experimental conditions and no oxidant agent is required.

Considering the scientific interest to establish efficient methodologies to synthesise nitrogen containing molecules, several reviews on the use of organic azides as nitrogen sources have been published and great emphasis has been devoted to the amination of C–H bonds due to their ubiquity in almost all organic skeletons. Furthermore, the insertion of an azamoiety into a hydrocarbon C–H bond allows the conversion of low cost reagents into high-added value aminated compounds.

This feature article provides an overview of the intermolecular C–H bond aminations by organic azides reported in Scheme 1, by underlining both synthetic and mechanistic aspects. The intramolecular amination was amply reviewed and it is not covered in this article.

We sincerely apologise if some important contributions to this topic have been unintentionally omitted.

2. Amination of activated sp³ C–H bonds

The insertion of a nitrene functionality into an activated C–H bond was initially studied by taking advantage of the thermal and photochemical instability of organic azides. Reactions were conducted without the assistance of a transition metal complex and consequently drastic experimental conditions were required.

Later, a transition metal was employed to promote the cleavage of the Nα–Nβ bond (Scheme 2) and selectively insert the nitrene functionality into a specific position of the organic backbone.

In 1967 Kwart and Khan reported on the catalytic activity of copper powder in the amination of cyclohexene and since then several transition metal catalysts have been developed to promote the amination of activated sp³ C–H bonds. The most representative classes of catalysts are reported in Fig. 2.

2.1. Amination catalysed by metal porphyrin complexes (A)

2.1.1. Synthetic results. Among all the classes of catalysts reported in Fig. 2, metal porphyrin complexes (A) are widely used to promote the amination of both benzylic and allylic substrates by organic azides (Scheme 1, paths a and b respectively).

Cenini et al. reported in 2000 that cobalt(II) porphyrin complexes are active catalysts that promote the amination of

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both allylic and benzylic C–H bonds by using aryl azides as nitrene sources.\textsuperscript{21–24} Aryl azides were chosen due to their stability–reactivity relationship that allows their use without any particular experimental caution.\textsuperscript{25} The benzylic amines were obtained together with the corresponding imines when the initially formed amine can be further oxidised by another \( \text{ArN}_3 \) molecule. The stoichiometric by-product of this second step is the primary amine of the azide employed (Scheme 3).

The scope of the reaction was investigated and the obtained products are reported in Chart 1.\textsuperscript{22}

The reaction works well with azides bearing EWG on the aryl moiety indicating an electrophilic role of \( \text{ArN}_3 \) in the catalysis.

The cobalt(II) porphyrin-catalysed amination of benzylic substrates was then performed by Zhang\textsuperscript{26} by using 2,2,2-trichloroethoxycarbonyl azide (Troc\( \text{N}_3 \)) as the nitrene source. The benzylic amines reported in Chart 2 were obtained without the contemporary formation of the corresponding imines. Troc\( \text{N}_3 \) was demonstrated to be a better aminating agent than other azides such as sulfonyl, phosphoryl, and carbonyl azides confirming the electrophilic nature of azides in the catalytic process. It must be mentioned that the synthesis of compound 24, even though obtained in a low yield, represents the synthesis of an \( \alpha \)-amino ester by the direct amination of the corresponding carboxylic ester.

Cobalt porphyrin complexes were also effective in aminating allylic C–H bonds (Scheme 1, path b) in moderate yields. It should be noted that the double C\( _\equiv_C \) bond of endocyclic olefins, such as cyclohexene, did not react with the aryl azide to give the corresponding aziridine therefore indicating a good chemoselectivity towards the allylic amine formation.\textsuperscript{24}

Surprisingly, the allylic amination of dihydronaphthalene afforded the benzylic amine of tetrahydronaphthalene, instead of yielding the amine of dihydronaphthalene and neither the aziridination nor the benzylic amination of dihydronaphthalene were observed (Scheme 4) (see below for a mechanistic proposal of this reaction, ref. 39).

All data discussed up to now were collected employing achiral cobalt catalysts. Until very recently, to the best of our knowledge, only the chiral complex 35 (Fig. 3) was reported in
literature for the intermolecular amination of C–H bonds in spite of the potential application of chiral amines as pharmaceuticals. Although the intermolecular aziridination reaction of styrenic double bonds performed in the presence of 35 occurred with some enantioselectivity, the allylic amination of cyclohexene afforded the racemate product, probably due to the presence of an atropoisomer mixture of the catalyst at the working temperature.23

Better synthetic results have been obtained by using ruthenium porphyrin complexes as catalytic species which are active in the amination of both benzylic and allylic C–H bonds.27–29 The commercially available Ru(II)(TPP)CO (TPP = dianion of tetraphenyl porphyrin) was a good catalyst to synthesise compounds 6a, 13a, 14a, 18 (Chart 1), 28, 32 (Scheme 4) and those reported in Chart 3. The best catalytic results were obtained by using aryl azides bearing EWG substituents on the aryl moiety and a high hydrocarbon excess.

While we were writing this review, Che and Lo reported the enhanced catalytic activity of bis(NHC)ruthenium(II) porphyrin complexes in nitrene insertion reactions into saturated C–H bonds (NHC = N-heterocyclic carbene ligands).30 Among the [Ru(porphyrin)(NHC)] complexes tested, [Ru(4-F-TPP)(BIME)2] (BIME = 1,3-di-methyl-2,3-dihydro-1H-benimidazol-2-ylidine) showed the highest activity and allowed the smooth insertion reaction of pentafluorophenyl azide into allylic (cyclohexene) and benzylic (toluene, ethyl benzene, 1-ethyl naphthalene, 1,2,3,4-tetrahydronaphthalene, and 2,3-dihydro-1H-indene) sp3 C–H bonds affording the corresponding amines in 88–96% isolated yields. The nitrene insertion reaction proceeded well also with the unactivated C–H bond of cyclohexane (90%). The authors proposed that the high catalytic activity is due to the strong donor strength of the axial NHC ligand in stabilising the trans M = NR moiety.

The use of chiral [Ru(D4-Por)(BIme)2] (D4 refers to the symmetry of the ligand) as the catalyst led to the formation of the allylic amine 13a (Ar = C6F5) in 91% yield and with 70% ee.30 Ru(porphyrin)CO complexes were also effective in synthesising α- and β-amino esters by amination of benzylic C–H bonds placed in the α or β position to an ester group. This synthesis, already explored by Zhang in the presence of cobalt porphyrins,26 occurred with yields up to 80% in the presence of ruthenium analogous, in spite of the poor reactivity of electron deficient benzylic positions toward electrophilic metallonitrene intermediates. The catalytic procedure is also effective in synthesising the two derivatives of methyl 1,3-phenyllactate 73 and 74 in order to convert them into the corresponding β-lactam (Chart 4).31

Very recently, Che et al.29 demonstrated that the amination of benzylic and allylic substrates by phosphoryl azides is also efficiently catalysed by ruthenium(II) complexes. Among tested catalysts, Ru(F20-TPP)Cl2 performed the best (Chart 5).

A significant contribution to this topic was provided by Che et al. with the investigation of the catalytic activity of Fe(III)-(F20-TPP)Cl.32 What makes this study important is the high sustainability of iron catalysts which are affordable, biocompatible and very reactive. Compounds 13a, 14a (Chart 1), 28 (Scheme 4) and those reported in Chart 6 were isolated in good yields.

The reported methodology displayed a very good chemoselectivity, in fact the allylic amination of α-methyl styrene

![Fig. 3](structure.png)  
**Fig. 3** Structure of Co(II)(TmyrtP) (35) (TmyrtP = dianion of the mesotetraakis([1R]-apopinen-2-yl)porphyrin).
derivatives occurred without the simultaneous formation of corresponding aziridines.

2.1.2. Mechanistic investigation. Over the last decade, the development of synthetic strategies together with the investigation of reaction mechanisms have been constantly researched to fine-tune catalytic efficiencies.

It is generally assumed that the active intermediate of the metal porphyrin-catalysed nitrene transfer reaction is an imido complex which is formed after the cleavage of the $\text{N}_2\text{N}_b$ azide bond (Scheme 5).

The oxidation state of the metal in the imido complex depends on the oxidation state of the starting catalyst and it is crucial to define the reactivity of the imido intermediate towards the organic substrate.

When the amination reaction is catalysed by ruthenium(n) porphyrins the formation of a bis-imido ruthenium(vi) complex was generally proposed. Some years ago several ruthenium(vi) bis-imido complexes, of the general formula $\text{Ru}(\text{porphyrin})-(\text{NSO}_2\text{R})_2$, were prepared by Che et al. by reacting ruthenium(n) precursors with imino iodinane compounds ($\text{PhI} = \text{NSO}_2\text{R}$). All the complexes were fully characterised and the molecular structure of $\text{Ru}(\text{TMP})(\text{NMs})_2$ (102) ($\text{Ms} = 4-(\text{MeO})\text{C}_6\text{H}_4\text{SO}_2$; $\text{TMP} = \text{dianion of 5,10,15,20 tetramesityl porphyrin}$) was solved by X-ray single crystal diffraction.33–35

$\text{Ru}(\text{vi})(\text{porphyrin})(\text{NSO}_2\text{R})_2$ complexes were active in the stoichiometric nitrene transfer reaction to C–H bonds in the presence of pyrazole ($\text{Hpz}$) as an additional axial ligand. The suggested mechanism is depicted in Scheme 6.

The authors proposed that C–H cleavage is involved in the rate determining step of the reaction on the basis of the large isotopic effect registered for the amination of several substrates. In fact, the formation of a carboradical species by homolytic cleavage of the C–H bond is in accord with the observed $k_\text{H}/k_\text{D}$ values of 6.1–12. Considering that the hydrogen atom of pyrazole is necessary for releasing the amine molecule, $\text{Hpz}$ was always used in stoichiometric excess with respect to the hydrocarbon substrate.

The reaction mechanism illustrated in Scheme 6 was also studied by Density Functional Theory (DFT) calculations.35 Firstly, the molecular structure of 102 was optimised by DFT and achieved data were fitted with those collected by single crystal X-ray diffraction. Then, employed functionals indicated a singlet d2 ground state electronic configuration ($^1\text{A}$) for $\text{Ru}(\text{TMP})(\text{NMs})_2$ (102) that was found at a lower energy than the analogous triplet state. The energy profile of the ethyl benzene amination by 102 indicated that the singlet pathway is the most energetically favoured.

In Scheme 7 the proposed mechanism of the stoichiometric nitrene transfer from 102 to ethyl benzene is provided together with the relative potential energy surface. The last step of the

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**Scheme 5** Metal–imido complex formation.

**Scheme 6** Suggested mechanism for the stoichiometric transfer of a nitrene moiety from a bis-imido ruthenium(vi) porphyrin to a C–H bond.

**Scheme 7** Mechanism of the ethyl benzene amination and relative potential energy surface ($\Delta G$ in kcal mol$^{-1}$) based on DFT calculations.
mechanism illustrated in Scheme 6, which corresponds to the release of the amine and pyrazole coordination, has not been provided.

Another class of bis-imido ruthenium(vi) complexes have been synthesised by Gallo et al. reacting ruthenium(ii) porphyrins with an aryl azide excess. The complex Ru(TPP)(NAr)$_2$ (Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$) (103) was fully characterised and its molecular structure was determined by X-ray single crystal diffraction.$^{26,36}$

Complexes 102 and 103 (Fig. 4) have similar Ru—N distances (1.79(3) Å vs. 1.808(4) Å) in the range of double bonds but the two imido complexes differ in the Ru–N–X (X = S for 102 and X = C for 103) imido angles. The angle of 162.5(3) of 102 indicates almost a linearity of the imido moiety whilst the values of 139.8(3)$^1$ and 143.7(4)$^1$ of 103 indicate the existence of bent imido angles.

Complex 103 displayed a good stability–reactivity relationship; it was stable for days in the solid state and decomposed when left standing in solution for a few hours. The bis-imido ruthenium(vi) complex 103 was active not only in stoichiometric nitrene transfer reaction from 103 to a C–H bond but was also an efficient catalyst of C–H amination. This last feature was essential to propose 103 as a possible key intermediate of the Ru(TPP)CO-catalysed amination reactions.

To shed some light on this reaction mechanism, a kinetic and theoretical investigation was undertaken. The kinetic investigation indicated the existence of another important catalytic intermediate which is formed by the reaction of Ru(TPP)CO with a single aryl azide molecule. This ‘‘elusive’’ Ru(iv)(TPP)(NAr)(CO) complex was suggested on the basis of kinetic data, however it was neither isolated nor spectroscopically observed. A DFT theoretical investigation of the allylic amination of cyclohexene confirmed kinetic results and indicated the existence of at least two different mechanisms in which, depending on experimental conditions, ruthenium(vi) (D) or ruthenium(vii) (E) complexes are involved.$^{37}$ The release of the CO axial ligand of D yields a penta-coordinated mono-imido complex which forms E by reacting with another aryl azide molecule. The mechanistic proposal, based on both kinetic and DFT studies (Fig. 5), is reported in Scheme 8.

The computations indicated that both ruthenium(vi) mono-imido (D) and ruthenium(vii) bis-imido intermediates (E) are active in their triplet state which is necessary to accomplish the radical reaction, the associated intersystem crossing is generally feasible. The radical nature of the reaction was experimentally proven by performing reactions in the presence of radical traps such as TEMPO.

It is important to underline that a direct comparison between the two described DFT studies on the activity of complexes 102 and 103 may suggest a false analogy. In fact, the first study describes the stoichiometric transfer of a nitrene functionality from 102 to a C–H bond$^{35}$ while the second analyses the catalytic activity of 103 in the amination of allylic C–H bonds.$^{37}$ From these two different approaches a basic difference emerges, Che, Huang et al. interpreted the reactivity of the imido complex 102 based on the chemical evolution over a singlet ground state, while Manca, Gallo et al. underlined the critical importance of the triplet electronic configuration for the catalytic activity of 103.

A completely different approach was necessary to study the cobalt(vi) porphyrin-catalysed amination of C–H bonds. This is
due to the improbable formation of a diamagnetic cobalt(IV) imido intermediate from the reaction of cobalt(II) porphyrin with organic azide molecules. The first mechanistic proposal was provided in 2003 by Cenini et al. who, on the basis of a kinetic study, proposed that the first step of the benzylic amination by aromatic azides is a reversible coordination of the azide molecule to the cobalt(II) metal centre. This so-obtained cobalt(II) azido-adduct (G) can either react with the benzylic substrate forming the corresponding amine or lose molecular nitrogen in an unimolecular reaction to afford an imido intermediate (G) which could be responsible for the formation of by-products diazene and the primary amine corresponding to the azide employed (Scheme 9).

When deuterated toluene was used instead of toluene as a hydrocarbon substrate, a large isotopic effect (k_H/k_D = 14) was observed indicating that the cleavage of the C–H bond is involved in the rate determining step of the catalytic cycle. A similar mechanism was also suggested for the allylic amination catalysed by cobalt(II) porphyrins.

The mechanism of the cobalt porphyrin-catalysed amination of C–H bonds was further clarified by EPR and DFT studies recently performed by Zhang and de Bruin et al. In this mechanistic investigation it was proposed that the nitrene radical species (G) (Scheme 9) is not only involved in the formation of by-products but it is the key-intermediate of the catalysis. An intermediate of type G was detected by EPR in the reaction of Co(TPP) with TrocN₃ in the absence of a hydrocarbon substrate. The well resolved EPR spectrum was typical for nitrene radical ligand complexes and it fitted well with the simulated EPR spectrum. A DFT study of the reaction between methyl azidoformate, a model of TrocN₃, and ethyl benzene was then performed and it also supported the formation of G as the catalytic active species. The mechanistic proposal and relative energy profiles are shown in Scheme 10 and Fig. 6.

The formation of a cobalt(III) nitrene radical intermediate can also be proposed to understand the unusual formation of the amine of tetrahydronaphthalene from the reaction of dihydronaphthalene with an aryl azide (Scheme 11).

A mechanistic study on the iron(III) porphyrin-catalysed C–H amination has not been reported yet. It was suggested by Che et al. that the starting iron(III) complex can be reduced in situ to an iron(II) nitrene intermediate which evolves into the active iron(IV) imido derivatives. The latter is then responsible for the nitrene transfer reaction to the organic substrate.

2.2. Amination catalysed by metal Schiff base complexes (B)
Schiff base complexes are very active in intramolecular C–H amination and aziridination of olefins by organic azides but, to the best of our knowledge, only two papers by Katsuki et al. were published on the intermolecular amination of allylic and benzylic C–H bonds. The ruthenium(II) chiral catalysts employed (Fig. 7) promoted the enantioselective nitrene transfer from TsN₃ (ref. 40) and SESN₃ (SES = 2-(trimethylsilyl)ethanesulfonyl) to several hydrocarbons.
Among all the complexes reported in Fig. 7, complexes 104 and 109 showed better catalytic efficiency by using TsN$_3$ and SESN$_3$ respectively. All the obtained aminated compounds are shown in Chart 7.

The best catalytic results have been achieved by using SESN$_3$ as the nitrene source and 109 as the catalyst. Yields and enantioselectivities up to 99% and 99% ee respectively were obtained. It is worth noting that also the regioselectivity of the amination reaction was extremely high and that this data represents the best results in terms of enantioselective C–H amination by organic azides.

Iridium(III) Schiff base complexes were also tested as catalysts in the amination of indane using SESN$_3$ as the aminating agent; unfortunately the reaction occurred in low yields and modest enantioselectivities.

2.3. Amination catalysed by dipyrromethene complexes (C)

2.3.1. Synthetic results. Iron(II) dipyrromethene complexes reported in Fig. 8 were recently synthesised and tested as C–H amination catalysts by Betley et al.$^{42,43}$ All the complexes 134–138 were fully characterised and, in some cases, the X-ray molecular structure determination was also provided. The oxidation state of iron atoms was assigned by magnetic measurements being consistent with high spin ($S = 2$) Fe(II) metal centres.

Initially, toluene was reacted with adamantyl azide (AdN$_3$) in the presence of complex 135 as the catalyst to yield the corresponding benzylic amine.$^{42}$ Then, in order to enlarge the reaction scope, other substrates were aminated in the presence of iron catalysts (Fig. 8).$^{43}$ Complexes 137 and 138 showed the best catalytic efficiency to synthesize benzylic (139–143) and allylic (144–148) amines respectively (Chart 8).

2.3.2. Mechanistic investigation. In order to study the catalytic mechanism, the amination of toluene by adamantyl azide, as a model reaction, was investigated in the presence of 135.

When the reaction was run in an equimolar toluene/toluene-d$_8$ mixture, an isotope effect $k_H/k_D$ of 12.8 was observed indicating that the C–H bond cleavage was involved in the rate determining step of the cycle (Scheme 12).

The authors suggested the formation of imido complex H which is responsible for hydrogen atom abstraction from the toluene substrate after which a radical rebound process finally yields the desired benzylic amine.

The formation of type H complex was supported by the isolation of terminal imido complex 149 from the stoichiometric reaction of p-$^t$BuC$_6$H$_4$N$_3$ with 136 (Fig. 9).
The X-ray analysis of 149 disclosed the formation of a terminal iron-imido bond with a limited multiple-bond character. This structural feature together with theoretical and magnetic data indicated the formation of a high-spin Fe(III) (d^5, S = 5/2) centre antiferromagnetically coupled with an imido-based radical (S = 1/2). The resulting complex can be indicated as a high-spin (S = 2) iron(II) imido radical species.

It is noteworthy that complex 149 was able to deliver the nitrene moiety to C–H bonds to support its probable involvement in the catalytic cycle.

2.4. Amination catalysed by β-diketiminato complexes (D)

2.4.1. Synthetic results. β-Diketiminato copper(I) complexes 150 and 151 were employed by T. H. Warren et al., T. R. Cundari, T. H. Warren et al. as precursors of imido derivatives 152–154 shown in Scheme 13.44,45 All these complexes were obtained by the reaction of 150 or 151 with an organic azide and also were completely characterised by X-ray diffraction analysis.

When the synthesis of 153 was conducted at room temperature for a long time, the intramolecular insertion of an adamantly nitrene functionality into a C–H bond of one β-diketiminato ortho-methyl group of 153 was observed yielding complex 155 (Scheme 13). This reaction demonstrated the capacity of this class of complexes to insert a nitrene functionality into a C–H bond.

In order to avoid the intramolecular side reaction and to promote intermolecular aminations, complex 151, which presents two chlorine atoms on the aryl ortho positions, was used as the starting material for the synthesis of imido complex 154. The intramolecular amination of the copper complex was not observed and 151 was a competent catalyst for the intermolecular amination of benzylic substrates. Compound 139 (Chart 8) together with compounds 156–158, reported in Chart 9, were obtained in good yields.

2.4.2. Mechanistic investigation. Imido complexes (β-diketiminato)Cu(NR) were studied from a computational perspective by using several methods66 providing a potentially controversial scenario. In fact, a DFT study revealed a triplet (S = 1) ground state, but CASSCF (Complete Active Space Self-Consistent-Field) calculations indicated that the singlet state (S = 0) is also energetically accessible and potentially active. The two species differ because the singlet copper nitrene has bent geometry, whereas triplet copper nitrene is linear.

The kinetic isotope effect $k_{H}/k_{D} = 5.3$, registered in the amination of ethyl benzene catalysed by 151, suggested that nitrene C–H insertion may be the rate limiting step of the catalysis. The mechanism reported in Scheme 14 was proposed.

2.5. Amination catalysed by dirhodium complexes (E)

As supported by all data discussed up to now, best synthetic results were obtained by employing azides bearing EWG irrespective of the catalyst used. The positive effect of electrophilic azides has been recently underlined by the efficiency of nonafluorobutanesulfonyl azide ($N_{3}SO_{2}(CF_{2})_{3}CF_{3}$, $NN_{3}$) which aminated benzylic substrates in the presence of Rh$_2$(OAc)$_4$.47 No amination reaction occurred in the absence of the transition metal complex.

The scope of the reaction was explored and the obtained aza-derivatives are reported in Chart 10.

The practical importance of this reaction is also due to the chemical versatility of polyfluoroalkanesulfonamides. The reported methodology can be used for the synthesis of a variety of secondary amines by a stepwise procedure. The N-alkylation reaction affords N,N-disubstituted nonafluorobutanesulfonamides which can then be transformed into the corresponding N-alkylated amines.

3. Amination of unactivated sp$^3$ C–H bonds

Some of the catalysts mentioned up to now were also active in promoting the amination of compounds containing unactivated sp$^3$ C–H bonds such as alkanes (Scheme 1, path c).
These reactions confirm the high reactivity of some metallo-imido complexes or metallo-azido adducts (Scheme 5) in transferring the nitrene functionality into C–H bonds with high dissociation energy. Moreover, the amination of alkanes by organic azides constitutes a cost-effective strategy to obtain, in one pot, nitrogen containing molecules.

The syntheses of aza-derivatives shown in Chart 11 were performed in the presence of Rh$_2$(OAc)$_4$, Cu(i) complex 151, Fe(III)(F$_20$-TPP)Cl, or Ru(IV)(F$_20$-TPP)Cl$_2$ (ref. 29) as the catalyst. It is difficult to compare the catalytic productivity of the different methodologies exploited for synthesising products of Chart 11 due to the diversity of employed experimental conditions. Generally speaking, to insert a nitrene functionality into a strong C–H bond of alkanes it is necessary to employ an azide which displays a strong electrophilic character. However, in the presence of the copper catalyst 151 (Scheme 13), also an alkyl azide such as adamantyl azide was reactive enough to aminate a cyclic alkane (Chart 11, product 175).

Very recently, Chang et al. reported on the catalytic activity of [IrCp*Cl$_2$]$_2$ (ref. 48) in the amination of ketoxime derivatives. The catalysis occurred in the presence of silver salt AgX which is necessary to form a cationic iridium complex as the catalytically active species (see paragraph 4.1.2. for the proposed mechanism). The reaction productivity was enhanced by adding acetate as an additive. The catalytic system [IrCp*Cl$_2$]/AgNTf$_2$/AgOAc (Tf = triflate) was active in promoting the formation of a large class of compounds reported in Chart 12.

The procedure reported above was also effective for late-stage C–H functionalisation of natural molecules with potential biological activities.

4. Amination of sp$^2$ C–H bonds

4.1. Amination of aromatic sp$^2$ C–H bonds

The amination of aromatic sp$^2$ C–H bonds has been amply studied for more than ten years but only recently organic azides have been considered as direct aminating agents. The latter procedure allows the amination to proceed without the formation of waste products except for N$_2$ (Scheme 1, path d). The presence of a directing group (DG) is always required (Scheme 15).

The catalysts employed to drive the reaction have a standard formula [M(L)Cl$_2$]$_2$ where M = Rh(III), Ru(II), and Ir(III). These catalysts were always employed in the presence of silver salt AgX which is able to generate the catalytic active cationic species [M(L)]X$_2$ from the neutral precursors (see below for mechanistic studies).

4.1.1. Synthetic results. The direct aromatic amination by organic azides was disclosed by Chang et al. in 2012 and since then many efforts have been made by the same research group to investigate in depth the reaction scope. Initial studies were performed in the presence of rhodium(iii) complexes and [RhCp*Cl$_2$]$_2$ was active in a very large pool of reactions in the presence of an excess of AgSbF$_6$ as the silver salt. Several aryl azides such as adamantyl azide were reactive enough to aminate a cyclic alkane (Chart 11, product 175).

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The procedure reported above was also effective for late-stage C–H functionalisation of natural molecules with potential biological activities.
skeletons, azides and directing groups were tested and a massive number of aza-derivatives were obtained.

In order to give the reader an overview of the synthetic potentiality of [RhCp*Cl2]2-based catalysis, several classes of aminated compounds are summarised in Chart 13. The chemical nature of all the substituents is not provided due to space constraints.

Classes A, B and C have been obtained by reacting benzamide derivatives with aryl, benzyl and alkyl azides. Even if the reactivity of alkyl azides is generally modest in sp3 C–H aminations, all of these three classes of azides afforded high yields of desired compounds. The catalytic system also works well in the amination of aromatic ketones with satisfactory yields (class D).

In view of positive synthetic results, Chang et al. turned their attention to the amination of aryl ketoximes and data indicated that the NO2Me group is also very active as well to correctly drive the C–H amination (classes E, F and G).

A large number of aza-derivatives were synthesised by using N-heterocyclic compounds as directing groups (DG) (classes H–N) and the best results were achieved by using azides bearing electron withdrawing groups (EWG). Interestingly, when purine was present on the aryl moiety as the DG, it was possible to isolate the mono and bis-aminated compounds depending on the experimental conditions employed (classes O and P).

Compounds belonging to classes A, D, H, M and F (Chart 13) were also obtained by using the [RuCl2(p-cymene)]2-based catalytic system. In 2013 two manuscripts by Chang et al.64 and Jiao et al.65 contemporarily appeared on this topic reporting almost identical results. The only difference between the two papers is the silver salt employed; AgNTf2 (Tf = triflate) was used by Chang et al. while Jiao et al. used AgSbF6. In both reported syntheses, sulfonyl azides were employed as aminating agents.

[RuCl2(p-cymene)]2/AgNTf2 combination in the presence of the acid additive 2-(NO2)C6H4COOH was also active in the amination of 2-phenyl piridines by using acyl azide as a nitrene source. Isolated compounds are reported in Chart 14.

The synthetic strategy illustrated above for the amination of aromatic C–H bonds was further improved by employing milder experimental conditions in terms of temperatures and times of reactions and catalyst loading. This goal was reached by running aminations in the presence of [IrCp*Cl2]/AgNTf2 catalytic systems. The amination of aryl benzamides by acyl azides was effective in obtaining twenty-five aza-derivatives and their general synthesis is reported in Scheme 16.

The authors also tested the applicability of the catalytic procedure to aminate aromatic compounds containing other directing groups, finding that this methodology displayed a general applicability and that it can also be exploited to synthesise natural molecules such as peptides.

To enlarge the reaction scope, the [IrCp*Cl2]/AgNTf2 catalytic system was tested in amination reactions with sulfonyl or aryl azides as aminating agents. Several compounds belonging to almost all the classes reported in Chart 13 were obtained under mild experimental conditions, together with a new class of aza-derivatives achieved by aminating aryl carbamates with tosyl azide (Chart 15).

4.1.2. Mechanistic investigation.

The mechanism of the aromatic amination promoted by [M(L)Cl2] was investigated in detail. In all cases the first step of the catalysis was the reaction of [M(L)Cl2] with silver salt AgX during which the chlorine atom of the pre-catalyst was replaced by a non-coordinating anion X/C0. The driving force of the reaction was the AgCl formation (Scheme 17).
For all catalytic systems presented in paragraph 4.1 it is possible to envisage a sequence of analogous mechanistic steps. First, the formed [M(L)]X2 complex can generate, by reaction with the aromatic substrate, a cationic metallacycle active species (I), which can coordinate the azide to promote the insertion of the nitrene unit into the aromatic C–H bond. Scheme 18 provides a general mechanism which will be discussed in more depth for each catalytic system below.

As shown in Scheme 18, the directing group (DG) plays a key role in the mechanism responsible for the formation of the metallacycle I. The unsaturated metallacycle I can coordinate the organic azide yielding IV either by formation of the metal-imido complex III (path a) or by directly releasing molecular nitrogen (path b). The reaction of IV with a proton source reforms the catalytic active species I with the contemporary formation of the aromatic amine.

The mechanism of the [RhCp*Cl₂]/AgSbF₆ catalytic system was investigated by kinetic and theoretical studies and by isolating several intermediates.⁶¹ Complexes of type I and IV (Scheme 18) were isolated from the reaction of 2-phenyl pyridine with p-toluenesulfonazide (TsN₃) and fully characterised also by X-ray diffraction analysis (Scheme 19).

The involvement of complexes 214 and 215 in the catalytic cycle was supported by the catalytic activity of 214 in the amination of 2-phenyl pyridine by TsN₃ and by the release of the aromatic amine from 215 when it was left reacting with a 2-phenyl pyridine excess as the proton source. This protodemetalation reaction was the last step of the cycle, being responsible for the regeneration of the catalyst I.

Considering that all the efforts to isolate or spectroscopically detect complexes of type II and III failed, Chang et al.⁶¹ performed a DFT study to shed some light on the catalytic mechanism. The theoretical study indicated rhodium(IV) imido complex formation as an energetically favourable process (path a, Scheme 18) and ruled out the direct conversion of I into IV by a concerted mechanism (path b, Scheme 18).

A kinetic isotope effect kH/kD (with values in the range 2–4) was observed in the amination of different substrates when they were tested in mixture with their deuterated form. These experiments indicated that the C–H bond cleavage was involved in the rate determining step of the cycle. An analogous mechanism was proposed by the same authors for the [IrIIICp*Cl₂]₂-catalysed reactions.⁶⁶ Mechanistic studies conducted on [RhIIICp*Cl₂]₂-catalysed reactions laid the foundations to express an analogous mechanism for the aromatic amination catalysed by [RuIIICl₂(p-cymene)]₂. The metallacycle 216 of type I (Scheme 18) was isolated and structurally characterised by Chang et al.⁶⁴ from the reaction of 2-(p-tolyl)pyridine with [RuIIICl₂(p-cymene)]₂. The treatment of 216 with sulfonyl azide gave the corresponding amido complex 217 which was detected by mass spectroscopy (Scheme 20).

A kinetic isotope effect kH/kD was registered indicating that the C–H cleavage is the rate limiting step of the process. The mechanistic analogies between ruthenium(n) and rhodium(n) catalysed processes allow the authors to assume equivalent catalytic cycles for both aminations of aromatic C–H bonds (Scheme 18).

4.2. Amination of sp² C–H bonds of indoles and aldehydes

The reaction of indoles with organic azides afforded different compounds depending on the nature of the catalyst employed. When the [RhCp*Cl₂]₂/AgSbF₆ catalytic system was used, the
The insertion of the nitrene moiety from an aryl azide was observed at the C2 position of the indole skeleton. The same position was also aminated by sulfonyl azides in the presence of [Cp*Rh(MeCN)3](SbF6)2 as the catalyst. In Chart 16 the obtained C2 aminated indoles are displayed.

It should be noted that the reaction of indoles with aromatic azides did not afford the corresponding aminated compounds when the catalyst [RhCp*Cl 2]/AgSbF6 was replaced by [Cp*Rh(MeCN)3](SbF6)2. In both cases, the DG pyrimidyl group can easily be removed yielding a wide class of 2-amino substituted indoles.

A different reactivity of aromatic azides towards indoles was observed by Che et al. by performing reactions in the presence of Ru(TPP)CO as the catalyst; the diimination of indoles was achieved instead of the formation of C2 aminated compounds.70 The study of the reaction scope allowed the synthesis of twenty differently substituted indoles (Chart 17).

2,3-Diimination products were the only obtained aminated compounds and the monoiminated or aminated indole was neither obtained nor detected when the reaction was also performed by using an excess of indole.

A preliminary mechanistic study indicated that, when 3,5-(CF3)2C6H3N3 was used as the aromatic azide, the bis-imido ruthenium(VI) porphyrin can be suggested as the catalytic active intermediate.

Organic azides are also competent aminating agents of sp2 C–H bonds of aldehydes. In 2008 Cundari and Warren et al. reported on the catalytic activity of complex in the amida- tion of benzaldehyde with AdN3 (Scheme 21).

The deuterium kinetic isotope effect for the reaction of benzaldehyde, benzaldehyde-d6 and N3P(O)(OCH2CCl3)2 gave a kH/kD value of 4.1 indicating that the C–H bond cleavage is the rate determining step of the catalysis.

5. Conclusions

The aim of this feature article is to present the state of the art on the use of organic azides as efficient reagents for intermolecular amination of C–H bonds. The incredible number of reported aza-compounds points out the great versatility of this class of aminating agents, which are currently receiving great interest from the scientific community.

Several catalysts have been tested and in some cases complementary results have been reached in the presence of different catalytic systems. Therefore, it is possible to afford structurally dissimilar aza-derivatives starting from similar starting materials. Many efforts have been made to optimise...
catalytic protocols and to understand mechanisms with the belief that it is always necessary to have knowledge of catalytic pathways for planning more efficient synthetic procedures.

Considering the social request for eco-friendly chemical processes to synthesise fine chemicals, we strongly believe that organic azides are going to occupy a prominent role as aminating reagents in the near future. The production of benign N₂ as the only by-product, coupled with the high atom efficiency and selectivity of nitrene transfer reactions, is an ideal starting point to design new and more sustainable synthetic procedures.

Notes and references