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Review article

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Prospects and challenges for nitrogen-atom transfer catalysis

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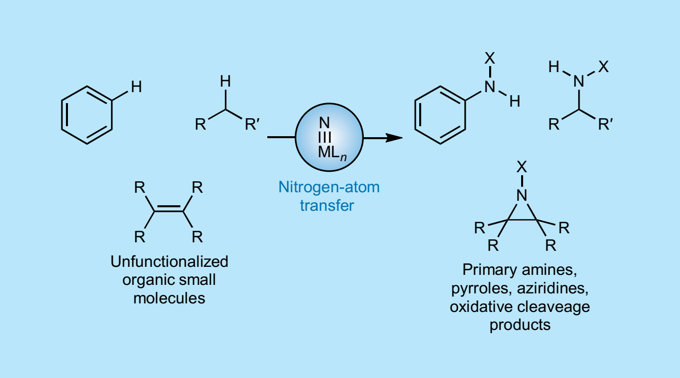
Abstract

Conversion of C–H bonds to C–N bonds via C–H amination promises to streamline the synthesis of nitrogen-containing compounds. Nitrogen-group transfer (NGT) from metal nitrenes ([M]–NR complexes) has been the focus of intense research and development. By contrast, potentially complementary nitrogen-atom transfer (NAT) chemistry, in which a terminal metal nitride (an [M]–N complex) engages with a C–H bond, is underdeveloped. Although the earliest examples of stoichiometric NAT chemistry were reported 25 years ago, catalytic protocols are only now beginning to emerge. Here, we summarize the current state of the art in NAT chemistry and discuss opportunities and challenges for its development. We highlight the synthetic complementarity of NGT and NAT and discuss critical aspects of nitride electronic structure that dictate the philicity of the metal-supported nitrogen atom. We also examine the characteristic reactivity of metal nitrides and present emerging strategies and remaining obstacles to harnessing NAT for selective, catalytic nitrogenation of unfunctionalized organic small molecules.



Sections

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Introduction

Nitrogen-containing small molecules are ubiquitous across the organic chemistry value chain, from commodity chemical feedstocks and synthetic intermediates[1] to agrochemicals, pharmaceuticals and natural products[2,3]. The ubiquity of nitrogen-containing small molecules has stimulated broad interest in developing efficient amination technologies. Classical amination methods such as reductive amination[4], nucleophilic substitution and metal-catalysed Buchwald–Hartwig[5] and Chan–Lam[6] cross-couplings rely on the inherent nucleophilicity of trivalent nitrogen in combination with pre-oxidized substrates to forge new C–N bonds. A complementary set of synthetic methods has emerged around electrophilic and radical sources of nitrogen (that is, subvalent nitrogen species), in which N-centred oxidation enables umpolung reactivity to be accessed. Reagents that provide subvalent nitrogen equivalents, such as iminoiodinanes, hydroxylamine derivatives and *N*-aminopyridinium salts, have been applied in the amination of organometallic nucleophilies (for example, Grignard and organolithium reagents)[7], C–C π-bonds and C–H bonds[8–10].

Reaction of C–H and C–C π-bonds with subvalent nitrogen fragments provides a strategy to streamline access to nitrogen-containing small molecules by obviating the need for substrate pre-oxidation. This can be accomplished by nitrogen-group transfer (NGT) chemistry, which involves addition of a nitrene equivalent (that is, the monovalent nitrogen fragment (NR)) to a substrate of interest (Fig. 1). The inherent instability of free nitrenes (when not stabilized by coordination to a transition metal), towards unimolecular decomposition or rearrangement pathways, often prevents bimolecular substrate functionalization. For this reason, *N*-alkyl, *N*-aryl, *N*-sulfanyl and *N*-acyl nitrenes find limited application in amination chemistry[11,12].

To overcome challenges inherent to intermolecular amination reactions with unstabilized nitrenes, transition metal-catalysed nitrene transfer chemistry represents an attractive conceptual framework[13–17]. In metal-catalysed NGT catalysis, the choice of transition metal, ancillary ligand and N-substituent of the nitrene fragment provide the opportunity to modulate the N-centred reactivity by controlling the (electronic) structure of the transient metal nitrene intermediate. Stabilization of the nitrene fragment can even allow for the transfer of imidogen fragments (that is, NH transfer) in limited cases[18,19]. Critically, because the C–H functionalization step in NGT chemistry proceeds at an M–NR fragment, one of the N-substituents in the ultimate amination product depends on the structure of the nitrene precursor, and the identity of the N-substituent impacts the N-centred reactivity during the C–H cleavage event.

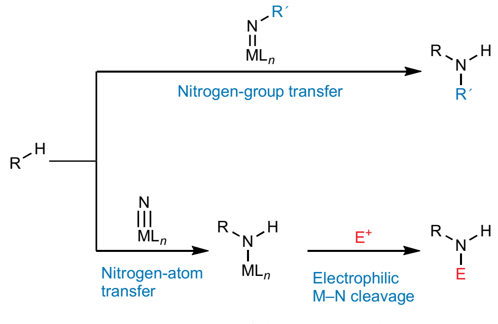


Fig. 1 | NGT versus NAT. A comparison of the synthetic disconnections characteristic of nitrogen-group transfer (NGT) and nitrogen-atom transfer (NAT) chemistry.

Although often referred to as nitrogen-atom transfer (NAT) in the literature, because the N-atom is intrinsically linked to the N-substituent, these reactions should be described as NGT reactions.

In concept, NAT chemistry represents a synthetically complementary amination strategy based on the formal addition of atomic nitrogen to organic small molecules. Free nitrogen atoms can be generated within plasmas and have been used to functionalize polyethylene and polystyrene surfaces; however, these methods are harsh, unselective and result in low nitrogen incorporation[20]. Simple diatomic and triatomic metal nitrides (that is, MN and MXN species) have been generated by ablation of rhenium[21], tantalum[22] and cerium[23] targets in an N_2 atmosphere. These unligated species can engage in NAT chemistry with strong C–H bonds, including those of methane; however, these reactions suffer from low selectivity and harsh conditions (Supplementary Fig. 1). In similarity with the metal nitrenes discussed earlier, ligand-supported metal nitrides are of interest owing to the ability to use the metal ion and ancillary ligand structure to tune the reactivity of the supported nitrogen atom. Accordingly, ligand-supported metal nitrides exhibit a reactivity continuum from nucleophilic to electrophilic and thus enable NAT chemistry with a diverse array of substrate classes.

NAT differs from NGT chemistry in that it decouples the substrate bond activation step from the identity of the N-substituent and thus the same insertion step could potentially be applied to the preparation of a wide variety of N-functionalized products without re-optimization of the amination reaction (Fig. 1). The primary product of NAT from a metal nitride to a C–H bond is a metal amide (that is, M–N(H)R), and subsequent electrophilic cleavage introduces the ultimate N-substituent: protonolysis of the incipient metal amide provides access to the same products as NGT of imidogen fragments; electrophilic cleavage with hydrocarbyl electrophiles, such as alkyl halides, provides entry into the products of unstabilized nitrene transfer that are unavailable by intermolecular nitrene addition owing to the inherent reactivity of these species. NAT catalysis is still rapidly developing, and as such broad synthetic diversification via NAT chemistry has yet to be demonstrated. Finally, whereas M–N complexes can be accessed from a diverse array of N-atom precursors[24–27], including dinitrogen[28], M–NR complexes typically require the use of energetic, bespoke nitrene transfer reagents.

This Review seeks to present opportunities and discuss extant barriers to the catalytic application of NAT processes for functionalizing simple organic molecules. This Review does not cover the rich inorganic NAT chemistry of nitride complexes with CO, CO_2 or hydrogenation reactivity relevant to ammonia synthesis. Previous reviews have discussed aspects of nitride structure and reactivity before 2014 (refs. 24,29–32). In the years since, novel reactivity modes (for example, activation of metal nitrides with light) and catalytic application of metal nitride intermediates have been reported. We begin with a discussion of the relationship between structure and reactivity in terminal M–N complexes. The stoichiometric reaction chemistry of both isolated and transient metal nitride complexes provides the basis to examine the diverse array of substrate functionalization mechanisms available to these complexes. We draw comparison between the synthetic opportunities available to NAT and NGT catalysis and give particular attention to discussing the emerging examples of, and ongoing challenges to, catalytic NAT chemistry.

Reactivity modes of terminal M–N complexes

Coordination of nitrogen atoms to transition metal complexes provides the opportunity to use synthetic chemistry to control the lifetime and reactivity of the supported N-atom[33,34]. Depending on the identity of

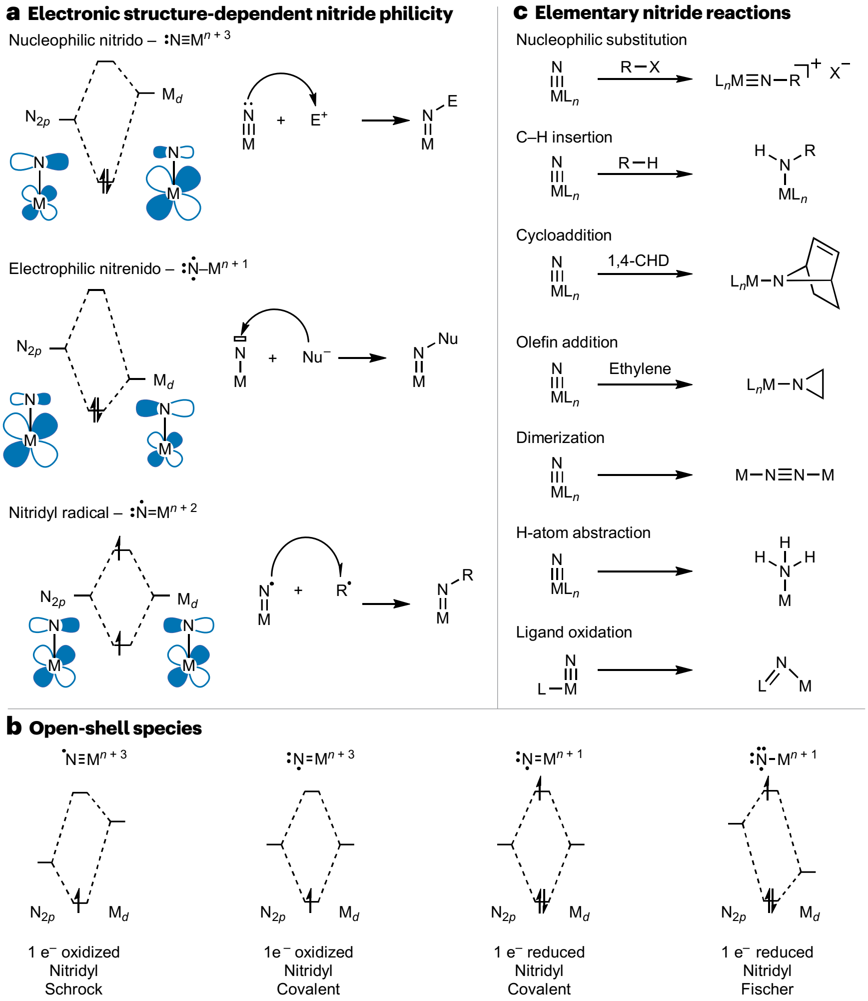


Fig. 2 | Electronic structure and reactivity of metal nitrides. a, Structure-dependent nitrogen philicity. Early metal nitrido complexes tend to react as N-centred nucleophiles, late metal metallonitrenes can exhibit electrophilic character and nitridyl radicals can participate in one-electron reactions. **b**, Open-shell species formed by one-electron oxidation or reduction of M–N complexes provides additional structures and opportunities to modulate reactivity at nitrogen. **c**, Elementary reaction steps that are characteristic of M–N complexes. CHD, 1,4-cyclohexadiene.

the transition metal ion and the structure of the ancillary ligand set, the M–N fragment can display electrophilic, nucleophilic or ambiphilic character, as well as engage in one-electron elementary steps[29,33–36].

Owing to the low electronegativity and attendant high-energy *d*-orbitals of the early transition metals, terminal M–N bonds of these metals are polarized towards the nitrogen. The resulting complexes are characterized as metal nitrido complexes and tend to react as N-centred nucleophiles (Fig. 2a). Typical reactions of early metal nitride complexes include nucleophilic displacement of halides from alkyl, silyl or benzyl halides and acylation chemistry with carboxylic acid derivatives. Late-transition metals, which are more electronegative and thus have lower energy *d*-orbital manifold, can display electrophilic nitride behaviour. In the limit of M–N polarization towards the metal, nitrenido[29,37] (recently termed metallonitrene) character – in which two electron holes are localized on the nitrogen atom – is possible. Some nitrides such as **38** (ref. 38) and **50** (ref. 39) (vide infra) retain metal–nitrogen multiple bond character while still displaying electrophilic reactivity. Electrophilic nitrides engage in chemistry such as C–H insertion and olefin aziridination reactions. Between the nitrido and metallonitrene extrema, metal nitridyl species arise when the orbital energies of the metal and nitrogen fragments are similar. These complexes display N-centred radical character and often participate in radical addition and H-atom transfer chemistry.

One-electron oxidation and reduction of M–N complexes provides an additional opportunity to control the activation of metal-supported N-atoms[29,40,41] (Fig. 2b). Schrock-type nitridyls result from one-electron oxidation of complexes with low-lying nitrogen *p*-orbitals, and Fischer-type nitridyls are one-electron-reduced complexes with high-lying nitrogen *p*-orbitals. One-electron oxidation and reduction of M–N fragments with similar nitrogen *p*-orbital and metal *d*-orbital energies gives rise to covalent-type reduced and oxidized compounds. Although complexes of this type have been reported, they have not yet been used for the synthesis of organic small molecules.

In addition to the reaction pathways described earlier, including nucleophilic substitution, electrophilic activation of olefin and C–H bonds and H-atom transfer chemistry, metal nitrides can also engage in cycloadditions and oxidative olefin cleavage reactions (Fig. 2c). The high degree of reactivity of some M–N fragments means that intermolecular NAT chemistry must compete with potential nitride dimerization to generate N_2, intramolecular ligand functionalization chemistry and sequential H-atom abstraction (HAA) processes that generate metal amido species[39,41–50].

In the following sections, we examine the stoichiometric reaction chemistry of metal nitrides with a focus on functionalization of organic small molecules. This discussion is organized by nitride philicity, with nucleophilic reactions discussed first followed by electrophilic and radical transformations. Finally, reactions that incorporate the metal centre in the NAT step (that is, cycloadditions) and olefin cleavage reactions are discussed.

Nucleophilic reactivity of M–N complexes

Many metal nitride complexes, and in particular those of the early transition metals, display nitrogen-centred nucleophilicity. These complexes are particularly sought after in the context of N_2 splitting and additionally have found application in the synthesis of amides and nitriles (vide infra)[28]. Nucleophilic substitution of alkyl[51,52] or silyl halides and acylation with carboxylic acid derivatives are typical transformations that highlight the N-nucleophilicity of these nitrides (Fig. 3a). The chemistry of anionic terminal Mo nitride [[[*t*BuOCO]MoN(NMe_2)]Na(DMF)]$_2$ (**1**) is a particularly well-characterized example of this reactivity pattern[53] (Fig. 3b): treatment of complex **1** with various acid chlorides affected nitride acylation to afford the corresponding imido complexes (confirmed by single-crystal X-ray diffraction). This imido can be further transformed to the nitrile through deoxygenation of the imido (Fig. 3b); similar reactivity has been demonstrated from related Mo species[54] as well as from Ti (ref. 55), Nb (refs. 56,57) and W (ref. 58) (Supplementary Fig. 2).

Nitrides of the mid-transition metal series can also display N-centred nucleophilicity as exemplified by the reaction of (PNP) Re(N)(Cl) (**2**) with ethyl triflate (Fig. 3c), which results in the

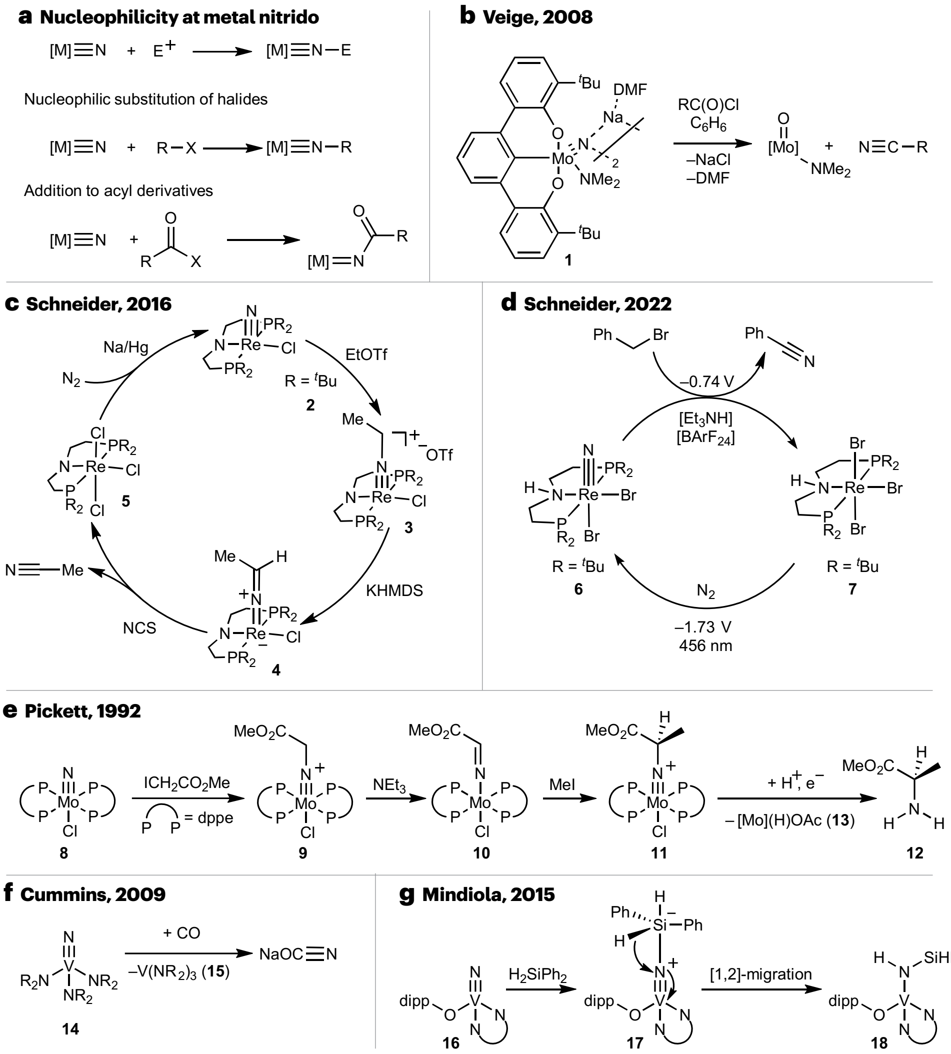


Fig. 3 | Nucleophilic nitrides. a, Characteristic reactivity of nucleophilic nitrides. Nucleophilic nitrides tend to react with electrophiles through either nucleophilic substitution of halides or addition to acyl derivatives. **b**, Reaction of **1** with acyl chlorides terminates in the formation of Mo oxo and nitrile[53]. **c**, A synthetic cycle for nitrogen-atom transfer (NAT) to EtOTf to form acetonitrile[59]. **d**, A synthetic cycle for NAT to benzyl bromide to form benzonitrile under photoelectrochemical conditions[60]. **e**, Electrosynthesis of amino acid ester **13** through NAT from Mo nitride **8** (ref. 61). **f**, Nucleophilic vanadium nitride **14** reacts with CO to form sodium isocyanate[62]. **g**, Nucleophilic vanadium nitride **16** reacts with diphenylsilane to afford the Si–H inserted **18** (ref. 63). DMF, *N*,*N*-dimethylformamide; EtOTf, ethyl triflate; KHMDS, potassium hexamethyldisilazide; NCS, *N*-chlorosuccinimide.

formation of the corresponding ethylimido complex **3** (ref. 59). Imide **3** serves as an intermediate in a synthetic cycle for the formation of acetonitrile. Deprotonation of **3** with KHMDS results in the formation of the azavinylidene (PNP)Re^{III} fragment **4**. Treatment of ketimido **4** with *N*-chlorosuccinimide results in acetonitrile and (PNP)Re(Cl)$_3$ **5**. Subsequent reduction of **5** with sodium amalgam under an N_2 atmosphere regenerates **2**, which can perform NAT to ethyl triflate to reform **3**. A closely related (PNP)Re(N)(Br)$_2$ (Fig. 3d) was demonstrated to react with benzyl bromide to form benzonitrile under electrochemical conditions[60]. Complex **6** can be regenerated from **7** and N_2 under photoelectrochemical conditions.

Potential applications of nucleophilic nitrides in the synthesis are highlighted by the synthesis of amino acids from nucleophilic Mo nitride **8** (ref. 61). Complex **8** reacts with methyl iodoacetate to form cationic imide **9**, which can be deprotonated (**10**) and alkylated to form **11**. Cathodic activation of the Mo≡N bond of **11** results in the formation of the corresponding amino acid ester **12** and Mo acetate hydride **13** (Fig. 3e).

In the case of a metal nitride with a redox-active centre, some may find the kinetic terms of nucleophile and electrophile less appropriate to describe reactivity and rather describe the nitride as thermodynamically a reductant or oxidant. For example, vanadium (V) nitride **14** reacts with CO to form sodium isocyanate and a reduced vanadium(III) complex **15** (ref. 62) (Fig. 3f). The apparent electrophilic reactivity has been proposed to result from initial nucleophilic attack of the nitride on CO followed by metal-centred reduction to afford the observed V(III) product, with the redox-active vanadium centre serving as an electron reservoir. Similarly, vanadium nitride **16** reacts with diphenylsilane and pinacolborane to give the products of E–H insertion[63] (Fig. 3g). The proposed mechanism for this formally electrophilic insertion involves attack of the nucleophilic nitride on the accessible σ*-orbital of the silane to generate a nitride-silane adduct **17**. The redox-active vanadium centre can then accept electrons from the nitride, and a [1,2]-H migration would lead to product **18**. A similar pathway is proposed for the addition to the B–H bond of pinacolborane through coordination through the boron *p*-orbital. Similar oxidizing behaviour from nucleophilic nitride complexes has been observed for nitrides of mid-row transition metals[64].

Finally, although early metal nitrides typically display N-centred nucleophilicity by virtue of polar M–N linkages, N-centred nucleophilicity can also be observed in later metal nitrides. Even complexes that may be more appropriately described as nitridyl radicals and metallonitrenes frequently display nucleophilic character in addition to reactivity modes made available by nitrogen subvalence (vide infra, ‘Ambiphilic reactivity of M–N complexes’).

Electrophilic reactivity of M–N complexes

Late metal nitride complexes can display electrophilic reactivity at nitrogen. Characteristic reactions of electrophilic nitrides include reactions with classical nucleophiles such as Grignard reagents[65], phosphines[66,67], CO (refs. 62,68) and isonitriles[69–72]. NAT from electrophilic metal nitrides can also affect olefin aziridination via the formation of metal azirido intermediates and C–H amination via metal amido intermediates (Fig. 4a). These reactions may take place through a stepwise cationic or concerted process (Fig. 4b) or radical process (vide infra).

Olefin aziridination. Although Groves and Takahashi[73] reported the aziridination of olefins from an Mn salen nitride via in situ generation of a nitrene, the first bona fide example of NAT from a transition metal nitride to an olefin was reported from transient metal nitrides generated through photolysis of *bis*-phosphine-supported Ni diazido complexes (**19**)[74] (Fig. 4c). Photolysis of **19** in the presence of cyclohexene, followed by an aqueous work-up, afforded 7-azabicyclo[4.1.0]heptane in 23% yield. The reaction was proposed to proceed via singlet nitrene monoazide complex **20** generated by photochemically promoted N_2 extrusion from **19**.

Early work by Lau and co-workers focused on utilization of metal salen nitrido complexes for NAT[75] and, in 1999, they reported that isolable Mn nitrides complex **21** engages in Lewis-acid-promoted olefin aziridination[76] (Fig. 4d). BF_3 and trifluoroacetic acid were found to efficiently promote aziridination, presumably via Mn≡NH and Mn≡N–BF_3 intermediates, respectively. Weak Lewis acids, such as $ZnCl_2$ and Cu(OTf)$_2$, and sterically demanding Lewis acids, such as Al(OTf)$_3$ and Fe(OTf)$_3$, were not efficient activators. Asymmetric NAT was realized from Mn nitrides supported by chiral salen ligands. Similar Lewis acid activation of nitrides has been used in the context of N-group transfer via in situ formation of imides[25] as well as oxo transfer[77–79].

In a similar fashion, cationic Ru(VI) nitrido complex **22**, which is supported by a cyclohexylene-bridged salen ligand, participates in Lewis-base-promoted olefin aziridination[80] (Fig. 4e). At ambient temperature, a CH_2Cl_2 solution of **22** was unreactive towards olefins; however, binding of pyridine to the axial position *trans* to the nitride ligand activates the complex for NAT by weakening the Ru≡N bond. The ligand acceleration effect may be due to geometric changes upon binding of pyridine, which may result in a lowering of re-organization energy needed for NAT[30,80,81]. Similar increases in reactivity upon ligation can be observed in a number of oxo transfer reactions[82,83].

Reactions of **22** with alkenes proceed via Ru(IV) azirido intermediates (**23**), which, in some cases, can be isolated. These azirido intermediates ultimately deliver Ru(III)-bound NH aziridine **24** via HAA. Aryl-substituted alkenes were found to proceed directly to the NH-bound Ru(III) species, suggesting that the Ru(IV) azirido complex may be unstable in these cases. When reacted with alkynes, Ru(N)(salen)(L)$^+$ **22** forms Ru imidazole **26** in CH_2Cl_2 with pyridine or Ru imide **27** in MeOH (Fig. 4f). The formation of these complexes is proposed to proceed via an Ru aziro intermediate **25**, which is then opened by nucleophilic attack to afford imidazole or imine[84].

The electrophilicity of metal nitrides can also be greatly enhanced upon oxidation of the metal complex (Fig. 4g). For instance, although anionic Mn(TTPPC)(N) is stable and unreactive towards styrene, upon one-electron oxidation, the neutral complex **28** is formed, which reacts with styrene to form the Mn azirido product **29** (ref. 85). Upon further oxidation of **28** to cationic **30**, the reactivity towards styrene further increased to be >10^5 times faster than **28**, forming cationic azirido **31**. It should be noted that the oxidation of the metal complexes is corrole-based, with **28** and **30** being best described as Mn(V) complexes bearing a π-cation (**28**) and π-dication corrole (**30**) ligand, respectively.

In addition to electrophilic cleavage of the M–N bonds in azirido intermediates to liberate N-substituted aziridines, nucleophilic openings of the azirido can afford 1,2-difunctionalization products. For example, Ru(F_{20}TPP)(CO) catalyses the amino oxyarylation of alkenes with *O*-(2,4-dinitro-phenyl)hydroxylamine as the nitrogen source under mild conditions[86] (F_{20}TPP is tetrakis(pentafluorophenyl)porphyrin) (Fig. 4h). This reaction was proposed to proceed through the intermediacy of nitride complex Ru(Por)(N)X (**32**), which was detected by MS, although further investigations are needed to establish whether **32** is on path. Nucleophilic opening of the azirido by phenolate affords the observed amino oxyarylation products. Consistent with electrophilic NAT from the intermediate nitride, amino oxyarylation

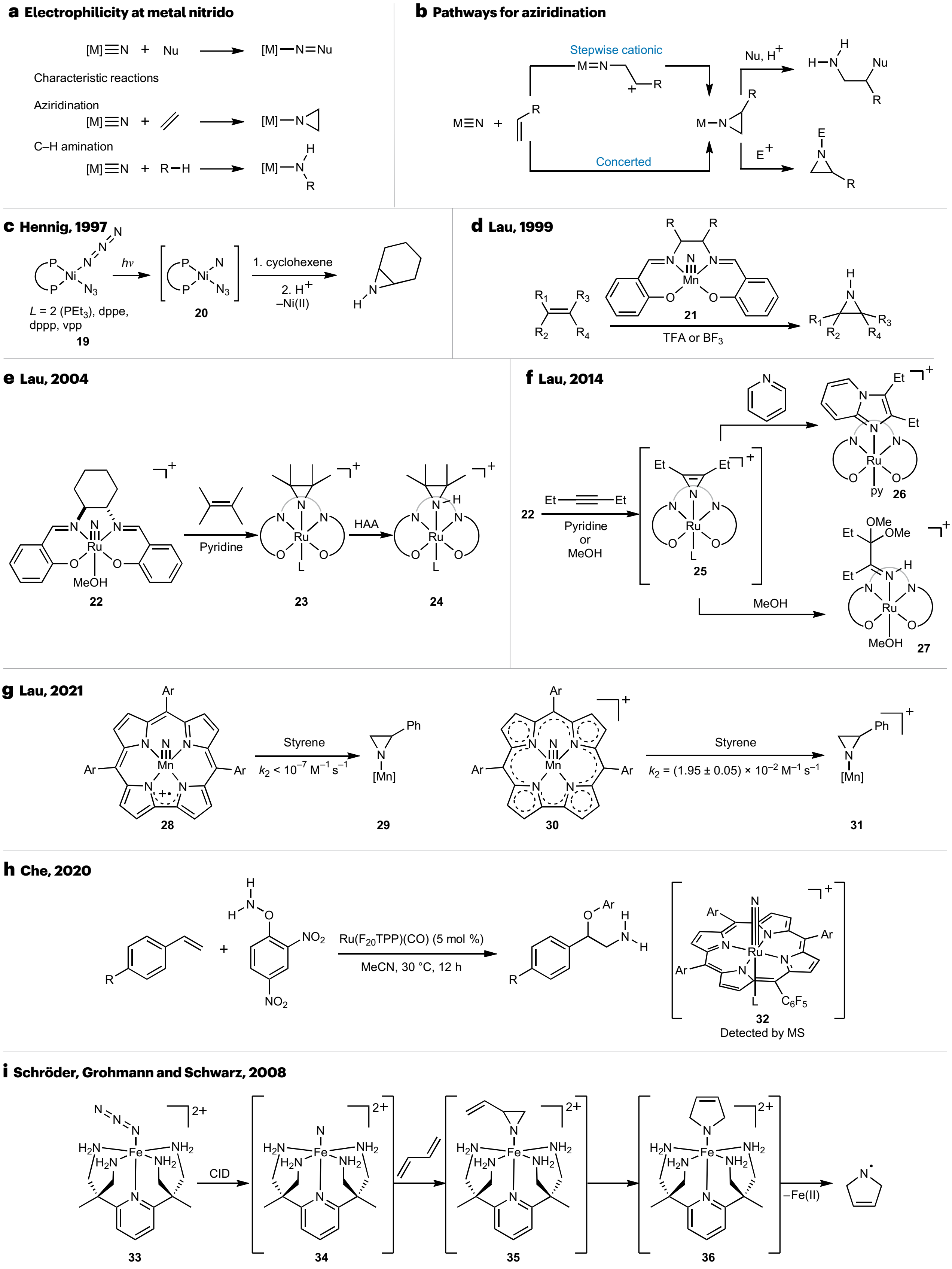

a Electrophilicity at metal nitrido
[M]≡N + Nu → [M]—N=Nu
Characteristic reactions
Aziridination
C–H amination
[M]≡N + R–H → [M]—N(H)R
b Pathways for aziridination
Stepwise cationic
Concerted
M≡N
Nu, H+
E+
c Hennig, 1997
hν
1. cyclohexene
2. H+
–Ni(II)
L = 2 (PEt3), dppe, dppp, vpp
19
20
d Lau, 1999
21
TFA or BF3
e Lau, 2004
Pyridine
HAA
MeOH
22
23
24
f Lau, 2014
Et—≡—Et
Pyridine or MeOH
MeOH
py
25
26
27
g Lau, 2021
Styrene
k2 < 10−7 M−1 s−1
k2 = (1.95 ± 0.05) × 10−2 M−1 s−1
[Mn]
28
29
30
31
h Che, 2020
Ru(F20TPP)(CO) (5 mol %)
MeCN, 30 °C, 12 h
NO2
C6F5
32
Detected by MS
i Schröder, Grohmann and Schwarz, 2008
CID
–Fe(II)
2+
33
34
35
36

Fig. 4 | Aziridination reactions. a, General reactivity of electrophilic nitrides. **b**, Mechanism of stepwise and concerted aziridination from a generic metal nitride and diversification from a generic metal azirido. **c**, Aziridination of cyclohexene from **19** (ref. 74). **d**, Aziridination enabled by Lewis acid activation of stable nitride **21** (ref. 76). **e**, Aziridination of alkenes upon activation of **22** by pyridine[80]. **f**, Aziridination of alkynes with **22** (ref. 84). **g**, Reactivity of Mn nitride corrole is enhanced upon one-electron and two-electron oxidation[85]. **h**, Catalytic aminohydroxylation of olefins via **32** (ref. 86). **i**, Formation of dihydropyrrole radical via aziridination and ring opening[87]. CID, collision-induced dissociation; F_{20}TPP, tetrakis(pentafluorophenyl)porphyrin; HAA, H-atom abstraction; TFA, trifluoroacetic acid.

proceeds in high yields with electron-rich substrates and lower yields with electron-poor substrates.

Azirido intermediates may also engage in electrocyclic rearrangement to afford ring-expanded products such as dihydropyrrole. Azirido intermediacy has also been invoked in the NAT reaction from complex **33** to 1,3-butadiene, which results in the formation of dihydropyrrole radical[87] (Fig. 4i). Upon collisional activation in the gas phase, **33** is converted to **34**, which engages with 1,3-butadiene via the putative intermediacy of azirido intermediate **35**. Electrocyclic rearrangement delivers **36**, which then undergoes homolytic cleavage of the Fe–N bond to liberate dihydropyrrole radical (detected by MS).

C(sp^2)–H amination. C(sp^2)–H amination at electrophilic metal nitrides is typically proposed to proceed via an electrophilic aromatic substitution ($\mathrm{S_EAr}$) mechanism via classical Wheland-type intermediates that subsequently rearrange to the observed metal amido products (Fig. 5a).

Berry and co-workers[88,89] disclosed the first example of electrophilic nitride insertion into an aryl C–H bond in 2011 (Fig. 5b). Either thermal or photochemical activation of formamidinate-bridged $\mathrm{Ru_2}$ azide **37** delivers amido complex **39**, the product of intramolecular C–H amination of a pendant ligand-based arene. Experimental and computational data indicate that C–H functionalization proceeds via an electrophilic aromatic substitution mechanism[38]. Powers and co-workers[90] subsequently established the structure of transient $\mathrm{Ru_2}$ nitride intermediate **38** by in crystallo synthesis.

Intermolecular C(sp^2)–H amination has also been demonstrated via NAT. Treatment of isolable Ru(VI) nitride **22** with phenolic substrates in the presence of pyridine delivers *p*-benzoquinone imine Ru(II) complex **40** (ref. 91) (Fig. 5c). This transformation is proposed to proceed via electrophilic C(sp^2)–H amination at the electron-rich arene substrate to generate transient Ru(IV) anilide **40**, followed by intramolecular redox chemistry and O–H deprotonation to afford imine complex **41**. Phenols with electron-donating substituents display faster reaction rates, which are consistent with electrophilic activation by the Ru nitride.

Although the previous examples rely on NAT from the nitride ground state, photochemically promoted NAT has also been observed. Irradiation of Os nitride complex **42** promotes NAT to aromatic substrates such as anthracene to afford the amido **43** (ref. 27) (Fig. 5d). A major side product in these reactions is the iminato complex, which results from addition of water to the Os amide formed from NAT (Supplementary Fig. 3). Related photochemical activation of isolated U nitrides has also been demonstrated[92] (Supplementary Fig. 4).

C(sp^3)–H amination. In contrast to NAT to C(sp^2)–H bonds, which typically proceeds via π-activation and $\mathrm{S_EAr}$ mechanisms, NAT to C(sp^3)–H bonds typically proceeds via sequential HAA and radical rebound. The resulting metal amide can be functionalized via electrophilic M–N bond cleavage to afford N–H and N-functionalized products (Fig. 5a).

Many metal nitride complexes participate in intramolecular NAT to C(sp^3)–H bonds present in the ancillary ligands[69,93,94] (Supplementary Fig. 5). From a synthetic perspective, intramolecular NAT is of more limited impact than the corresponding intermolecular C–H amination owing to the requirement for multidentate binding of the substrate to the transition metal. In 1997, Henning et al.[74] described the first intermolecular NAT to aliphatic C–H bonds: photolysis of bis-phosphine Ni diazido complexes (**19**) (Fig. 4b) followed by aqueous work-up resulted in cyclohexylamine in <5% yield.

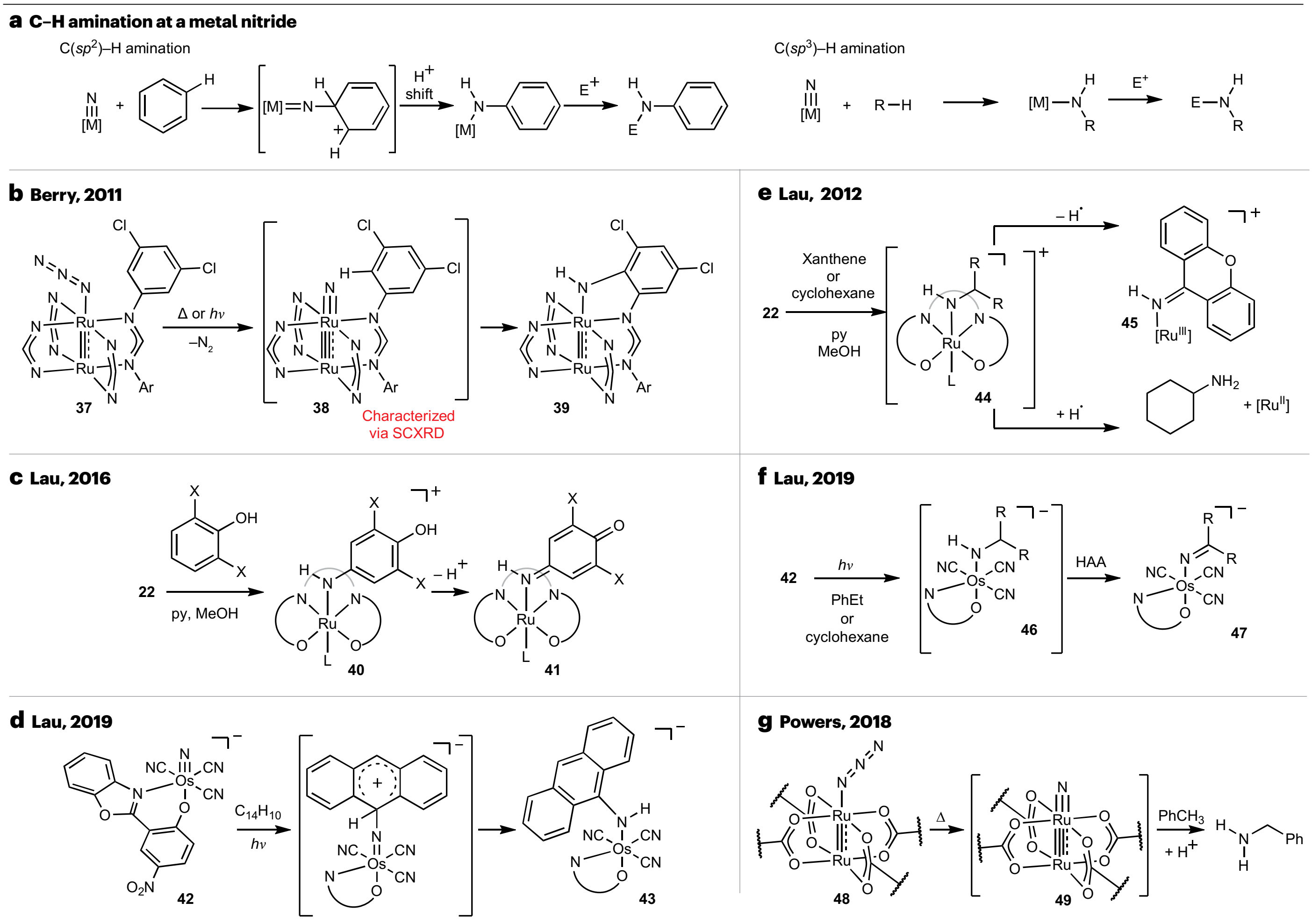
In 2012, Lau and co-workers[81] described NAT to benzylic and aliphatic C–H bonds from $\mathrm{Ru(N)(salen)^+}$ (**22**) (Fig. 5e). At room temperature, MeCN solutions of nitride **22** react with xanthene to afford cationic six-coordinate Ru imine complex **45**. This product presumably forms via NAT to form **44** followed by HAA from the α-carbon (possibly by a second equivalent of **22**). Similar NAT chemistry was observed from **22** to dihydroanthracene. Exogenous pyridine was required to accomplish NAT to substrates with higher C–H bond dissociation energies (BDEs) than dihydroanthracene (DHA) (78.0 kcal mol^{-1}); addition of pyridine accelerates NAT to DHA by more than two orders of magnitude and enables NAT to aliphatic substrates such as cyclohexane (C–H BDE 100.0 kcal mol^{-1})[95] to afford a mixture of cyclohexylamine and cyclohexene. In this case, formation of cyclohexylamine (rather than the amide or imine) was proposed to occur via a second HAA from an additional equivalent of substrate.

Efficient NAT to aliphatic substrates requires efficient radical rebound following HAA. If the rebound step is slow, desaturation and dimerization of the intermediate carbon-centred radical will be competitive with NAT. For example, whereas a mixture of amination and desaturation is observed for the reaction of **22** with cyclohexane, when cyclooctane is used as substrate, only desaturation is observed. By contrast, osmium nitride **42**, which engages in photochemically promoted NAT to benzylic and aliphatic substrates, affords cyclooctylimine **47** (ref. 27) (Fig. 5f). The observation of NAT products suggests that rebound is faster in the Os system than the related Ru system. Similarly, reactions with ethylbenzene, cyclohexane, xanthene and DHA all result in the formation of the corresponding imines, presumably through HAA of the amido **46** by another equivalent of Os nitride.

In an effort to translate the intramolecular C(sp^2)–H amination of formamidinate-bridged $\mathrm{Ru_2}$ complexes to intermolecular NAT chemistry, Powers and co-workers[96] examined the nitride chemistry of carboxylate-bridged $\mathrm{Ru_2}$ sites (that is, **48**) (Fig. 5g). Facile nitride dimerization prevented NAT from molecular species, such as $\mathrm{Ru_2(benzoate)_4N_3}$, but lattice confinement within a microporous metal–organic framework enabled intermolecular NAT to the benzylic C–H bond of toluene via thermally generated nitride **49**. Following acidification, which presumably protonates the incipient benzylamide intermediate, benzylamine is obtained. Kinetic isotope effects measured for the toluene amination were interpreted in the light of an HAA/rebound mechanism for NAT[97].

Ambiphilic reactivity of M–N complexes

Atomic nitrogen ligands supported by late-transition metals often display ambiphilicity, which arises owing to the electrophilicity derived from the polarization of the M–N linkage towards the more electronegative metal centre (Fig. 2a) or low-lying π*-orbitals, which


a **C–H amination at a metal nitride**

b **Berry, 2011**

c **Lau, 2016**

d **Lau, 2019**

e **Lau, 2012**

f **Lau, 2019**

g **Powers, 2018**

Fig. 5 | Electrophilic nitrides. **a**, General reactivity of electrophilic nitrides includes C(sp^2)–H and C(sp^3)–H amination. **b**, Intramolecular C(sp^2)–H amination of **37** upon photolysis or thermolysis[88]. **c**, Intermolecular C(sp^2)–H amination of phenols by **22** results in the formation of benzoquinone imines[91]. **d**, Stable nitride **42** aminates anthracene under photochemical conditions[27]. **e**, Complex **22** engages with C(sp^3)–H bonds of xanthene and cyclohexane to form imines and amines[81]. **f**, Os nitride **42** engages with ethylbenzene and cyclohexane to form imines[27]. **g**, Thermolysis of lattice-confined **48** results in benzylamine formation upon work-up[96]. HAA, H-atom abstraction; SCXRD, single-crystal X-ray diffraction.

can accept electrons and the nucleophilicity derived from the presence of N-centred non-bonding electrons.

Early examples by Meyer demonstrated the ambiphilicity of *trans*-[Os(tpy)(Cl)$_2$(N)]$^+$ (**50**) (Fig. 6a). Complex **50** reacts as an electrophile with triphenylphosphine to afford phosphoraniminato complex **51** and as a nucleophile with trimethylamine *N*-oxide to generate nitrosyl complex **52** (refs. 39,98,99). The ambiphilic reactivity of complex **50** can be understood from analysis of the relevant molecular orbitals. In complex **50**, nucleophilicity arises from a non-bonding, *sp* lone pair localized on the N-atom; the electrophilic reactivity of complex **50** arises from accessible π* LUMOs associated with the metal–nitrogen bond that can accept electrons.

Holthausen, Schneider and co-workers described the synthesis and characterization of Pt–N complex **53** in 2020 (ref. 66) (Fig. 6b). On the basis of a combination of magnetic data, computational results and in crystallo characterization, they described the structure of **53** as a Pt(II) metallonitrene adduct with two nitrogen-centred electron holes. This bonding picture can be understood using a similar bonding manifold to that of **50**, wherein the Pt metallonitrene system **53** has four more electrons than **50** that populate the π*-orbitals, leading to the singly occupied N-centred orbitals. Reaction of **53** with benzaldehyde afforded the corresponding amide complex **54**. The Hammett analysis with *para*-substituted benzaldehydes indicated that this amidation reaction proceeded by nucleophilic addition of the nitrogen ligand to the π-system rather than electrophilic activation of the aldehydic C–H bond. In contrast to the nucleophilic reactivity of **53** with aldehydes, reaction with trimethylphosphine results in **55**, which arises from electrophilic reactivity (owing to two singly occupied *p*-orbitals located on the N-atom) of the Pt–N intermediate with the added phosphine.

Group 10 metallonitrene chemistry was subsequently extended to catalytic C–H amidation with Pd metallonitrene **56** (ref. 37) (Fig. 6c). Photolysis of azide complex in the presence of aldehydes and Me$_3$SiN$_3$ affords the corresponding trimethylsilyl-protected amides. The intermediate Pd metallonitrene **56** was also characterized by in crystallo photochemistry. Density-functional theory (DFT) studies on the transamidation step with trimethylsilyl azide, which allows for catalysis, show that this step is 8 kcal mol^{-1} higher for the Pt analogue, which is consistent with the lack of catalysis with **53**. DFT studies also support the origin of electrophilicity in this complex to arise from singly occupied *p*-orbitals on the N-atom.

Nitride ambiphilicity has also been invoked in the reactions of Mn(VI) nitride **57** with variously substituted styrene derivatives[100] (Fig. 6d). Mn(VI) nitride **57** engages in aziridination chemistry with styrene; the resulting Mn(IV) azirido **58** is rapidly oxidized in solution to afford free N–H aziridine (protonated by H_2O in the solvent) and an Mn(V) oxo complex. The Hammett analysis with various *p*-substituted styrenes results in a V-shaped plot, with the nitride displaying electrophilic character in the presence of electron-rich styrenes and nucleophilic character in the presence of electron-deficient styrenes.

Radical reactivity of M–N complexes

Although more rarely encountered, metal nitrides can also engage in one-electron elementary steps to accomplish substrate functionalization via radical pathways (Fig. 6e). In 2015, Smith and co-workers described NAT from Fe(IV) nitride **60**-*R* (*R* = ^{t}Bu, Mes), supported by a tri(carbene)borate ligand (Fig. 6f), to styrene to afford the corresponding aziridine[26]. The authors interpreted solvent-independent NAT reaction rates and Hammett analysis as consistent with a radical addition reaction via a nucleophilic nitridyl radical. These results are supported by calculations that indicate a small energy gap between the singlet ground state and a low-lying triplet excited state, in which there is α-spin density that is localized on the nitride. The resulting metal azirido complex **59** can be opened through electrophilic cleavage of the M–N bond with trimethylsilyl chloride or methyl iodide. Treatment of **59** with trimethylsilyl chloride results in the release of the trimethylsilyl-protected aziridine and generation of the corresponding Fe(II) chloride.

The aziridination reaction from **60**-^{t}Bu was found to be reversible as thermolysis of a 1:1 mixture of the nitride and styrene leads to an equilibrium mixture of corresponding azido complex **59** and nitride **60** (ref. 101). Aziridine cross-metathesis is also observed as upon heating complex **59** in the presence of electron-poor styrenes, formation of **61** is observed (Fig. 6f). Thermolysis of **60**-^{t}Bu with mono-β-deuterostyrenes results in styrene isomerization as well as aziridinated product; as such, NAT is proposed to proceed through a stepwise rather than concerted pathway.

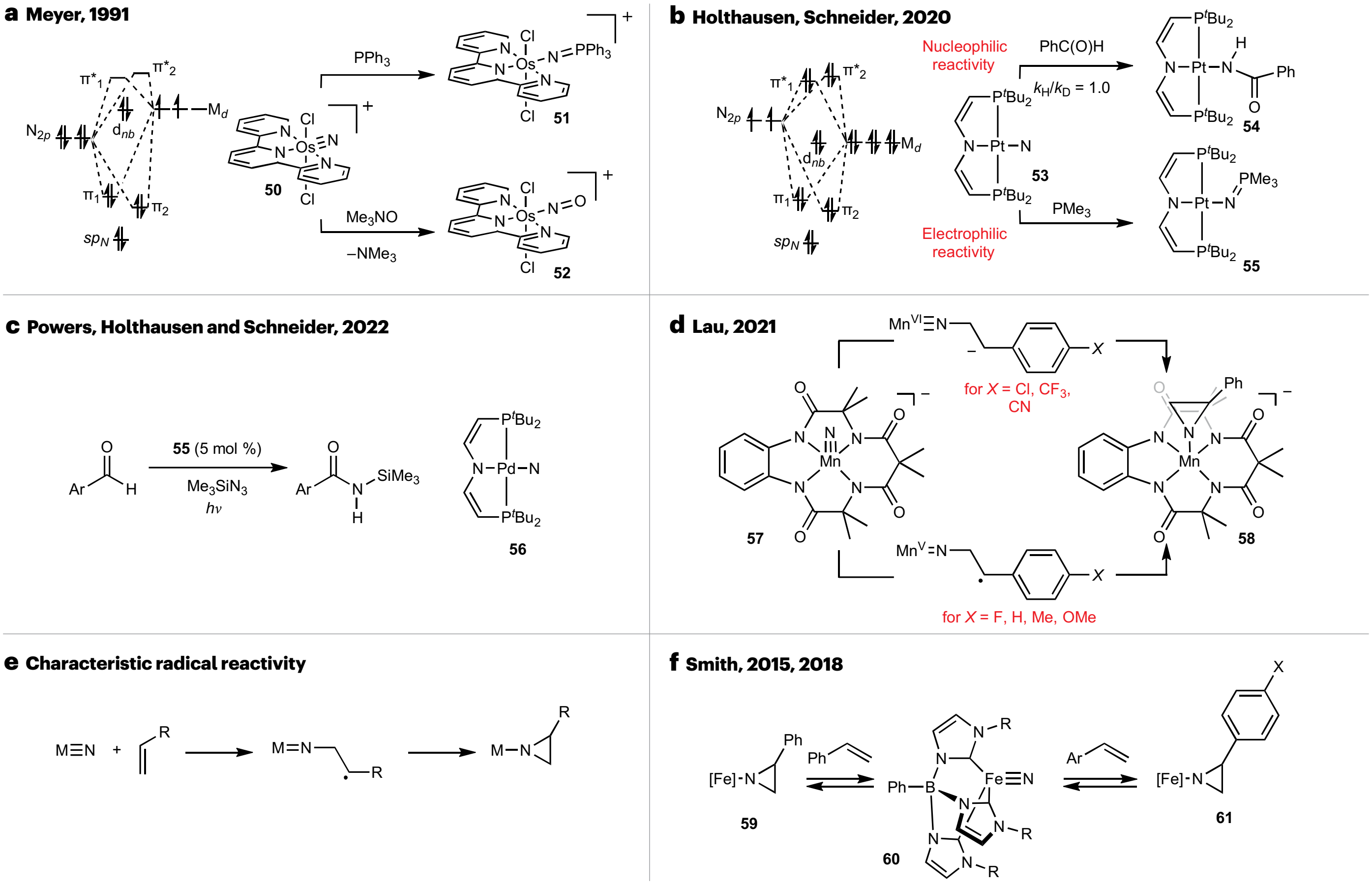


Fig. 6 | Ambiphilic and radical nitrides. a, Ambiphilic nitride **50** reacts with both triphenylphospine and trimethylamine *N*-oxide. **b**, NAT from **41** for catalytic amidation of aldehydes[39,98,99]. Ambiphilic nitride **53** reacts with both electrophiles and nucleophiles[66]. **c**, NAT from **56** for catalytic amidation of aldehydes[37]. **d**, Mn-based **57** participates through both electrophilic and nucleophilic pathways to form azirido complex **58** (ref. 100). **e**, Characteristic reactivity of radical nitrides. **f**, Aziridination of styrenes by **60** (refs. 26,101).

Cycloaddition reactivity of M–N complexes

Cycloaddition reactions provide additional mechanisms for NAT from metal nitrides to unsaturated organic small molecules, and both [2 + 2] and [4 + 1] cycloaddition reactions are well documented (Fig. 7a,b).

[4+1] Cycloadditions. [4 + 1] Cycloaddition reactions between M–N fragments and 1,3-dienes result in the construction of two C–N bonds and a five-membered azacycle. Os(VI) nitride **62** reacts with 1,3-cyclohexadienes to afford a bicyclic amido complex **63** as a result of a [4 + 1] addition of the nitride to the diene[102] (Fig. 7c). Reaction with electron-rich 1-methoxy-1,3-cyclohexadiene is more rapid than 1,3-cyclohexadiene, which is consistent with a mechanism in which the LUMO of the M–N fragment and the HOMO of the diene are the frontier orbital combination that dictates reactivity. Replacing the anionic tris(1-pyrazolyl)borate ligand with either tris(1-pyrazolyl)methane or terpyridine (affording *cis*-dichloro and *trans*-dichloro complexes) affords cationic osmium nitrides that undergo cycloaddition with cyclohexadienes at enhanced reaction rate, which is ascribed to the greater electrophilicity of the nitride in these complexes. The cycloaddition reaction with **62** is reversible: dissolution of the pure Os(IV) cyclic amide **63** in acetonitrile results in an equilibrium mixture of complex **62**, diene and cyclic amide. No osmium cycloadducts are observed in reactions with other cyclic or acyclic dienes.

Four-coordinate Fe nitride **60**-Mes participates in analogous [4 + 1] cycloaddition chemistry with cyclohexadienes to afford azabicyclic intermediate **64** (Fig. 7d). In contrast to the Os chemistry described earlier, subsequent retro-[4 + 2] chemistry ensues to ultimately deliver pyrrolide complex **65** and ethylene[103]. The disparate fates of the Os-azabicyclic and Fe-azabicyclic intermediates (compounds **63** and **64**, respectively) are ascribed to the electronic and coordinative saturation of Os complex **63**, which may prevent further retro-Diels–Alder to afford the pyrrolide.

[2+2] Cycloadditions. [2 + 2] Cycloadditions involve construction of both C–N and M–C bonds in the key NAT step and thus do not have analogues in the chemistry of free nitrogen radicals; [2 + 2] and retro-[2 + 2] sequences can affect the conversion of alkynes to nitriles via stoichiometric nitrile–alkyne cross-metathesis (NACM). As an example, oxidation of Mo(IV)-alkyne adduct **67** leads to the formation of nitriles at room temperature[104] (Fig. 7e). To confirm the origin of the N-atom, ^{15}N-labelled

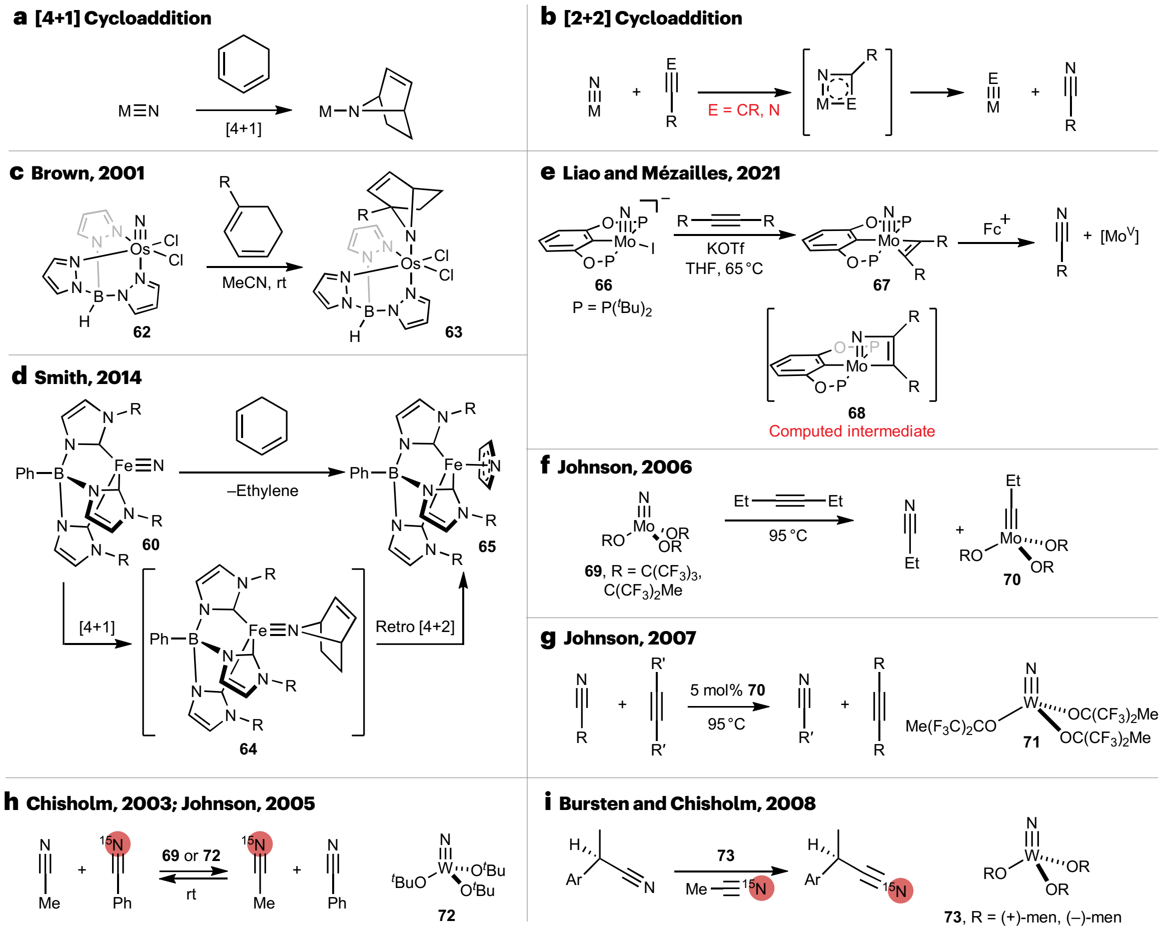


Fig. 7 | Cycloaddition reactions from metal nitrides. a, General [4 + 1] cycloaddition reaction from metal nitrides. **b**, General [2 + 2] cycloaddition reaction from metal nitrides. **c**, Os-based **62** engages with cyclic dienes to form bicyclic **63** (ref. 102). **d**, Pyrrolide **65** formed from cycloaddition, and retro-cycloaddition with **60** (ref. 103). **e**, Stoichiometric nitrile–alkyne cross-metathesis (NACM) from **67** (ref. 104). **f**, Stoichiometric NACM from **69** (ref. 105). **g**, Catalytic NACM from W-based **71** (refs. 105,106). **h**, Catalytic nitrile–nitrile cross-metathesis for ^{15}N-labelling of nitriles[109,110]. **i**, ^{15}N-enrichment of enantiomerically pure small molecules by enantiospecific N-atom exchange[106].

67 was prepared and treated under the same reaction conditions to afford the ^{15}N-labelled nitrile. The DFT analysis of the potential energy surface supports a pathway consisting of a [2 + 2] addition to form **68** followed by a retro-[2 + 2] to liberate the observed nitrile. A reaction pathway including **67** — in which the C–C bond is nearly coplanar with the M–N bond — was calculated to be the lowest energy pathway for nitrile formation; a similar pathway from the Mo(IV) centre **66** was calculated to be endergonic, consistent with the lack of observed reactivity.

Stoichiometric NACM has also been demonstrated from complexes **69**-R of form $Mo(N)(OR)_3$ (R = $C(CF_3)_2Me$, $C(CF_3)_3$) when reacted with alkynes to irreversibly form alkylidyne complex **70** (ref. 105) (Fig. 7f). This contrasts with W analogue **71**, which showed a preference for the nitride form over the alkylidine form, presumably owing to the lower electronegativity of the W centre[106,107]. Though active for alkyne cross-metathesis, treatment of the Mo complexes with excess alkyne and excess nitrile does not result in incorporation of the N-atom from the nitrile into the alkyne.

Catalytic NACM was first reported from tungsten nitrides bearing fluorinated alkoxide ligands (**71**)[106,107] (Fig. 7g). Combination of $W(N)(O = C(CF_3)_2Me)_3$ (**71**) with 3-hexyne in toluene led to the formation of the tungsten–alkylidyne complex along with propionitrile. Application of a catalytic amount of $W(N)(O = C(CF_3)_2Me)_3$ (5 mol %) in the presence of anisonitrile and 3-hexyne leads to the formation of propionitrile via NACM. Calculated transition states for the reaction show, similar to **65**, approach of the alkyne so that the C–C bond is coplanar to the W–N bond followed by a [2 + 2] reaction to form the metallocycloazabutane and retro-[2 + 2] to liberate the nitrile product. Similar NACM was reported from $N{\equiv}Mo(OSiPh_3)_3$, although the reaction requires high temperatures and achieves only slightly more than two turnovers[108].

The ability for metal nitrides to perform [2 + 2] cycloadditions has also been leveraged as a method to ^{15}N enrich samples through nitrile–nitrile cross-metathesis (NNCM) with commercially available ^{15}*N*-acetonitrile. The first example of NNCM was reported in 2003 from complex **72**, which was found to catalyse degenerate N-atom exchange between ^{15}N-enriched acetonitrile and benzonitrile[109] (Fig. 7h); ^{13}C enrichment of the C-atom on the cyano group on acetonitrile was used to exclude the possibility of cyano group cross-metathesis. This reaction was proposed to proceed through the same metallocyclobutane intermediate as NACM (Fig. 7b; E = N). NNCM has since been reported from azide-derived **69**-R (R = $C(CF_3)_2Me$, $C(CF_3)_3$)[110] and chiral **73** (ref. 111), which has provided access to ^{15}N-enriched enantiomerically pure small molecules by enantiospecific N-atom exchange (Fig. 7i).

Oxidative cleavage reactivity of M–N complexes

Oxidative cleavage of C–C double bonds has been explored for biomass valorization[112]. More challenging than cleavage of C–C multiple bonds is C–C σ-bond cleavage owing to strength of the C–C σ-bond and the lack of polarity of the linkage, which makes other C–X bonds more likely to be activated. Metal nitride complexes have found application in both oxidative C–C π-bond and σ-bond cleavage reactions (Fig. 8).

Oxidative cleavage of C–C π-bonds. Intermolecular C–C double bond cleavage via NAT was first reported in 1999 from *cis*-$Os(N)(terpy)(Cl)_2^+$ (**74**). Reaction with aryl-substituted alkenes results in the formation of η^2-azaallenium complexes **75** (ref. 113). Consistent with typical trends for electrophilic olefin activation, the reaction proceeds more quickly with *cis*-olefins than *trans*-configurations. Furthermore, electron-rich olefins display enhanced reaction rates, whereas electron-poor olefins do not react[114]. The resulting azaallenium complex **75** retains significant reactivity and can be further treated with trimethylamine *N*-oxide to afford the nitrile complex **76** or reduced with $NaBH_4$ to form the neutral imine complex **77** as the major product as well as the doubly reduced amine complex **78** as the minor product. Analogous reactivity is also available from *trans*-$Os(N)(terpy)(Cl)_2^+$ (**50**) and $(Tpm)Os(N)(Cl)_2^+$ (Tmp = tris(1-pyrazolyl) methane), although the scope is restricted to dienes.

Glossary

Metallonitrene	A recently introduced term, also called a metal nitrenido. A possible electronic formulation of the [M]–N fragment in which two electron holes are localized on the nitrogen atom.
Metal nitrene	An [M]–NR fragment.
Metal nitrides	An [M]–N fragment.
Nitrogen-atom transfer	(NAT). A reaction in which the substrate is engaged by a metal nitride.
Nitrogen-group transfer	(NGT). A reaction in which the substrate is engaged by a metal nitrenoid.

Complex **74** has also been used in the synthesis of isoquinolines via direct NAT to indenes[115] (Fig. 8c). Computational analysis of the N-atom insertion step indicates that the reaction proceeds via a stepwise cationic aziridination (Fig. 4b). Electrocyclic ring opening of the aziridine through C–C bond cleavage of the three-membered ring results in the formation of the azaallenium **79**, which can then be deprotonated to form free isoquinoline and reduced Os(II) complex **80**.

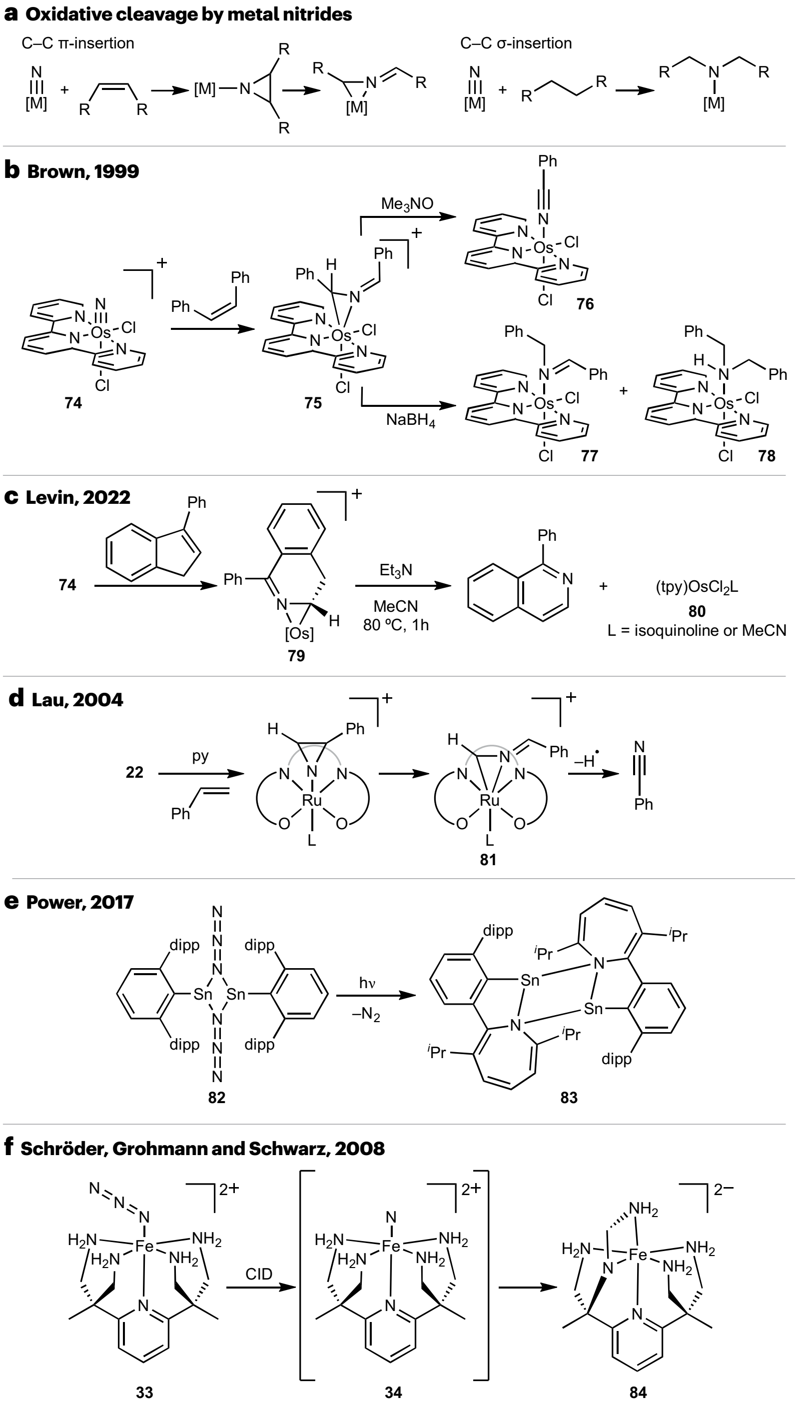
Relatedly, oxidative cleavage of C–C π bonds has been demonstrated from Ru nitride **22** (Fig. 8d). Reaction of $Ru(N)(salen)^+$ (**22**) with excess styrene or *trans*-β-methylstyrene results in the formation of benzonitrile (25%) in addition to the Ru(III) aziridine (Fig. 8d). The presence of nitrile was interpreted as potential evidence of the formation of an η^2-azaallenium intermediate **81** similar to those observed for Os terpy complexes (that is, **75**)[80].

Although insertion into C–C π bonds is relatively common, there is far less precedent for insertion into the π systems of aromatic molecules. The singular example of intramolecular NAT into an aromatic π-system was demonstrated from a tin nitride (Fig. 8e). Thermolysis of Sn complex **82** results in ring expansion of the pendant dipp on the terphenyl to form a seven-membered ring **83** through insertion of the Sn nitride into the C–C bond[116]. Treatment of complex **82** with tris(pentafluorophenyl)borane (BCF) results in binding of the borane to the α-nitrogen of the Sn complex; thermolysis of the resultant complex leads to B–C insertion. Electron paramagnetic resonance (EPR) studies of the thermolysis reaction suggest an Sn nitride as the reactive species.

Oxidative cleavage of C–C σ-bonds. Insertions into C–C σ bonds have also been demonstrated from metal nitrides. Iron nitride **34** can be generated through collisional activation in the gas phase from the azide precursor **33** (ref. 87) (Fig. 8f). This nitride can then undergo further fragmentation to eliminate species consistent with insertion of the nitride into the C–C σ bond of the ligand scaffold **84**.

Conclusions and outlook

The foregoing discussion highlighted the diversity of electronic structures and associated reactivity patterns available to metal nitride complexes and NAT chemistry. Atomic nitrogen ligands of transition metals can display nucleophilic, electrophilic and ambiphilic reactivity as well



a Oxidative cleavage by metal nitrides

b Brown, 1999

c Levin, 2022

d Lau, 2004

e Power, 2017

f Schröder, Grohmann and Schwarz, 2008

Fig. 8 | Oxidative cleavage by metal nitrides. a, General oxidative cleavage reactions from metal nitrides. **b**, Stoichiometric of C–C π-insertion from **74** (ref. 113). **c**, Synthesis of isoquinolines through C–C π-insertion from **74** (ref. 115). **d**, Synthesis of benzonitrile through oxidative cleavage of styrene[80]. **e**, Intramolecular ring-expansion reaction of **82** (ref. 116). **f**, Intramolecular C–C σ-bond insertion[87]. CID, collision-induced dissociation.

as participate in one-electron elementary steps. In addition, cycloaddition and multi-electron oxidative cleavage reactions of C–C π-bonds are available to formally nitride complexes of transition metals. The availability of a diverse array of substrate functionalization mechanisms provides a rich opportunity to develop NAT chemistry as a complementary platform to NGT chemistry for the elaboration of simple organic molecules. Although the wealth of reactivity modes for the activation of organic small molecules has been developed, a number of key challenges remain for the deployment of NAT chemistry in routine synthetic strategy. Areas that are poised for significant growth include catalytic NAT, stimuli-responsive nitride philicity and C–C bond activation.

Catalytic NAT

In contrast to the rich stoichiometric chemistry of metal nitride complexes, the catalytic application of NAT in organic chemistry is almost entirely undeveloped, with the sole examples being the amino-oxyarylation of alkenes from Ru porphyrin **32** (Fig. 4h) (for which definitive evidence of an on-cycle nitride is sparce), oxidative amidation of aldehydes mediated by Pd metallonitrene **56** (Fig. 6c) and NACM from tungsten complex **71** (Fig. 7g). The need for stoichiometric metal reagents or multiple step reactions to 'turn over' synthetic cycles is a key obstacle for the implementation of NAT for organic synthesis. One of the challenges is the need for nucleophilic azide and electrophilic cleaving source to exist in the pot at the same time. Silyl azide reagents such as trimethylsilyl azide can deliver both parts of the reaction; however, if *N*-alkyl products are desired (typically through treatment of M–NR$_2$ with alkyl halide), conditions may lead to simple substitution reactions to generate the alkyl azide. Additionally, the reaction of nucleophilic azides with electrophilic nitrides[117] offers further challenges to catalytic NAT with nucleophilic nitrogen sources.

Stimulus-responsive nitride philicity

The majority of metal nitride complexes (and all those derived from N$_2$) display nucleophilic reactivity at nitrogen. Substrate functionalization via these mechanisms requires substrate pre-oxidation. Opportunities to utilize redox or photochemical stimuli to elicit electrophilic or radical reactivity at the metal-supported nitrogen atom would significantly expand the family of nitride complexes that participate in NAT with unfunctionalized organic small molecules. Although photolysis has been used to generate reactive nitrides from azide precursors, the use of photolysis to access excited state nitrides is more limited. It has been shown that stable nitrides such as Os nitride **42** and a U nitride (Supplementary Fig. 4) can become reactive when photolysed, although this type of reaction is underexplored in the field of NAT. This offers an exciting opportunity to explore previously reported metal nitride complexes, which may be inert under non-photochemical conditions. Progress in stimuli-responsive nitride reactivity has been made in the context of nitride hydrogenation to release ammonia[118,119], but application of similar strategies to organic functionalization reactions is less developed.

Activation of C–C bonds

Like C–H bonds, C–C σ-bonds are ubiquitous in organic small molecules, although they tend to be thermodynamically strong and kinetically inert, making their activation challenging[120]. Activation of the C–C σ-bond by formation of strained rings[121] has been demonstrated as a method to promote this unfavourable reaction. Although only one reported example of gas-phase C–C σ-bond cleavage from a metal nitride exists (Fig. 8f), this reactivity does present an opportunity to develop C–C insertion reactions from metal nitrides. For example, substituted piperidines, one of the most popular N-heterocycles in pharmaceuticals, could formed through nitride insertion into the C–C bond of substituted cyclopentanes and would open new avenues in retrosynthetic schemes.

NAT chemistry has undergone significant development in recent years, but significant additional progress is needed if NAT chemistry is to achieve the broad synthetic utility that characterizes NGT chemistry and catalysis.

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