Nucleophilic Nitrenoids Through \( \pi \)-Acid Catalysis: Providing a Common Basis for Rapid Access into Diverse Nitrogen Heterocycles

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Abstract: Nitrogen heterocycles are some of the most important and sought-after structural motifs in synthetic chemistry. General methods that can be applied towards a structurally diverse range of different scaffolds are rare. This Focus Review discusses an emerging area with the field of \( \pi \)-acid catalysis based on the activation of carbon-carbon triple bonds in conjunction with nucleophilic nitrenoids. The resulting approach provides ready access into \( \alpha \)-imino metal carbene reactivity patterns that can be employed in a number of quenching processes to realize a variety of powerful new transformations. The resulting methods are characterized by high efficiency, simple and straightforward reaction set-ups, mild conditions, and excellent functional group tolerance. In this Focus Review the different nucleophilic nitrenoid types are explored showing how they can be used across a range of (poly)cyclization and formal cycloaddition processes to provide an alternative and direct disconnection pathway in the generation of \( N \)-heterocyclic motifs.

1. Introduction

Nitrogen-containing heterocycles are recurring scaffolds found in numerous natural products and important biological targets. With a structural diversity as wide as their applicability, the pursuit of efficient synthetic methods toward these targets remains of crucial import. The new construction strategies and/or mild conditions associated with transition metal-based methods offer attractive alternatives to classical \( N \)-heterocycle formations and often provide greater functional flexibility.[1] General methods that can be applied to access a range of structural motifs and that will tolerate a variety of other functional groups in the surrounding molecular architecture are of particular interest as they can enable substantial advances in the development and application of new or important scaffolds. However, substantial challenges remain in this area, not least due to the breath of reactivity profiles encountered across different nitrogen-containing heterocycles, such as sensitive \( \pi \)-rich heteroaromatics or structures rich in basic sites capable of coordinating and deactivating catalysts.

The advent of \( \pi \)-acid catalysis in molecular synthesis has had a substantial impact on \( N \)-heterocycle synthesis.[2] In large part this is due to the exceptional functional group compatibility and chemoselectivity that is encountered under the mild reaction conditions, particularly those associated with gold(I) catalysis.[3] Exciting new tools are being developed for the generation of complex heterocyclic scaffolds from readily accessible functionality based on reactivity of simple \( \pi \)-systems such as alkynes, alkenes, and allenes. The straightforward practical aspects of this area of catalysis are also appealing to users due to the relatively simple reaction set-ups and work-ups, alongside the use of generally robust, bench-stable, and readily prepared precatalysts that show good general coverage across diverse reactivity lines.

In this review we focus on an emerging aspect of this field where \( \alpha \)-imino metal carbene intermediates are invoked as the basis for a wide range of powerful \( N \)-heterocycle-forming processes (Figure 1). The reactivity of this motif is generated from the interaction of an alkyne with a nitrene equivalent and a \( \pi \)-acid catalyst. In contrast to the electrophilic aspect usually associated with nitrenes,[4] nucleophilic nitrene equivalents are required to successfully interact with the electrophilic alkyne-\( \pi \)-acid complexes.

This non-exhaustive review is narratively structured by the type of reactivity employed rather than purely chronologically. The potency and generality of each reactivity mode will be discussed for transformations where the carbon–nitrogen bonds from interaction of a nitrenoid and alkenes are contained within a nitrogen heterocycle formed in the reaction.

Figure 1. General retrosynthetic basis for the reactivity covered in this review.

1.1. Reactivity Basis

The general basis for the reactivity under discussion is that on coordination of an alkyne to a \( \pi \)-acid (A→B, Scheme 1), suitable nitrogen-based reagents C can interact with the electrophilic

Scheme 1. Reactivity outline for use of nucleophilic nitrenoid equivalents in the formation of \( \alpha \)-imino metal carbened.
philic carbon framework by nucleophilic attack to generate a vinyl metal carbene species \( \text{D} \) that can evolve to the \( \alpha \)-imino metal carbene \( \text{E} \) on elimination of a nucleofuge \( (\text{X}) \). Processes that invoke the interaction of a metal–nitrogen bond, as metallonitrenoid or metallonitrene, in the addition across the \( \pi \)-system are not discussed here, but have been shown to give access to related intermediates.\[^6\,\,^6\]

While all the reactions discussed in this review can reasonably be viewed as proceeding through an \( \alpha \)-imino metal carbene \( \text{E} \) synthon in a general retrosynthetic sense, and may be referred to as such, it is important to note that this brief analysis will not capture many important aspects of the reactivity or indeed always represent the actual intermediates involved. Two points in particular should be borne in mind in order to avoid an over-simplified picture of the reactivity. First, both \( \text{D} \) and \( \text{E} \) have electrophilic character, so reaction at the carbon center might occur either alongside or after elimination of the nucleofuge.\[^7\] While reaction at either \( \text{D} \) or \( \text{E} \) can and might lead to the same outcomes, the differences between these discrete intermediates, such as orbital involvement, bond lengths, or charge distribution, can substantially affect the resulting reactivity profile, for instance in chemo- and regioselectivity.

Second, the carbon–metal double bond and metallated carbo-cation representations of a metal carbene \( \text{E}^\text{E'} \) are used interchangeably in the context of seeking to provide an overall picture of accessible reactivity profiles and not to define the precise bonding in specific cases.\[^2\,\,^3\,\,^8\,\,^9\]

### 1.2. Nucleophilic Nitrenoids

In analogy to the description of intermediate \( \text{D} \) as a “metal carbenoid”, as its reaction with a nucleophile can afford the same species as reaction at metal carbene \( \text{E}^\text{E'} \) (hence showing metal carbene-like reactivity), the term “nucleophilic nitrenoid” is employed here as a catch-all to cover a variety of nitrogen-based reagents by virtue of their ability to act as a source of nitrene character over the course of the reaction (Scheme 1). These neutral species must be capable of first donating an electron-pair and then subsequently losing a nucleofuge in order to initiate the generation of carbenoid character adjacent to the forming carbon–nitrogen bonds.

As seen in Schmidt-type reactions of alkyl azides, the use of nucleophilic nitrenoids is long-established in powerful synthetic methods.\[^10\] Formation of a carboation \( \text{F} \) (Scheme 2), for instance by Brønsted or Lewis acid activation of a carbonyl, alkene, or alcohol, triggers nucleophilic attack by the azide \( \text{G} \) followed by 1,2-migration back onto the nitrenoid nitrogen with elimination of \( \text{N}_2 \) (\( \text{H} \rightarrow \text{I} \)). Two new carbon–nitrogen bonds are formed as a result of this nucleophilic nitrenoid reactivity, a factor used to great effect in nitrogen heterocycle synthesis.

Generating the carboationic character from a \( \pi \)-acid and alkyne offers new vistas to this powerful approach for two key reasons. First, the electrophilic character is transposed onto a carbon atom from the alkyne fragment, so that general potential for C–C bond formation is established (\( \text{K}^\text{L} \rightarrow \text{M} \), Scheme 2). Second, the potential for reactivity at this center is extended from being purely cationic to carbenic. As shown...
below, the synthetic prospects available from this efficient multisite reactivity patterns were established and built upon from the earliest discoveries in this field in intramolecular strategies.

2. Intramolecular Reactions

2.1. Azides as Nucleophilic Nitrenoids

In 2005, Toste and co-workers reported the gold-catalyzed formation of pyrroles $2$ from homopropargyl azides $1$ (Scheme 3, top).\[11\] Both primary and secondary alkyl azides could be employed in this process alongside alkyl- and aryl-substituted alkenes bearing both electron-rich and electron-poor aryl groups. Selectivity for the reaction between a 1,5-azido-alkyne over a 1,5-enyne was also observed in the formation of $2c$.

This first invocation of the α-imino gold carbene by action of a nucleophilic nitrenoid highlights the practically attractive aspects of such processes. Given their propensity to degrade under acidic conditions the ready formation of free pyrroles showcases the mild nature of gold-catalysis. Hiroya et al. subsequently reported a platinum-catalyzed variation of this transformation to create polysubstituted pyrroles from homopropargyl azides, predominantly those based around a cis-cyclohexane motif (Scheme 2, bottom).\[12\] Intriguingly, it proved beneficial to stir the PtCl$_4$ precatalyst in ethanol for an hour prior to addition of the substrate. In this case the addition of a bulky pyridine base to remove traces of acid was required to isolate the pyrroles in high yield.

The proposed mechanism for this reaction (Scheme 4) commences with coordination of the electrophilic metal fragment to the alkyne followed by intramolecular nucleophilic attack of the proximal nitrogen of the azide in a 5-endo-dig fashion to form the vinyl gold carbenoid $4$. Subsequent expulsion of N$_2$ forms the gold carbene $5$. A 1,2-shift from the adjacent methylene or methine position and then elimination of gold regenerates the catalyst affording the 2H-pyrrole $6$ that tautomerizes to the pyrrole $2$. An alternative mechanism where the gold catalyst promotes the decomposition of the azide to generate a gold nitrene intermediate was considered less likely on the basis that non-homopropargyl azides are unreactive under these conditions. DFT studies were later reported by Xia and Huang to support this mechanism at the B3LYP/6-31G*- (LANL2DZ) level of theory and provided details of the 2H-pyrrole to 1H-pyrrole isomerization alongside an analysis of how the reaction is affected by the relative ability of the different catalysts to form deactivating chelate structures (Pt ≫ Au).\[13\]

Yamamoto and co-workers demonstrated that analogous reactions of 2-alkynylbenzyl azides $7$ could be used to access substituted isoquinolines $8$ (Scheme 5).\[14\] In this case, the conditions A: AuCl$_3$ (30 mol%), AgSbF$_6$ (90 mol%), THF, 100 °C

Conditions C: a) I$_2$, K$_2$PO$_4$, CH$_3$Cl$_2$, RT or Py$_2$SbF$_6$, HBF$_4$ in Et$_2$O, CH$_3$Cl$_2$, -78 °C

Scheme 3. Gold- or platinum-catalyzed synthesis of substituted pyrroles from homopropargyl azides. dpmm = 1,1-bis(diphenylphosphino)methane.

Scheme 4. Mechanism of homopropargyl azide reaction.

Scheme 5. Synthesis of isoquinoline scaffolds from 2-alkynylbenzyl azides. TBDMS = tert-butyldimethylsilyl; Ts = 4-toluenesulfonyl.
nectivity between the azide and alkyne now allows for direct intramolecular [3+2]-dipolar cycloaddition and formation of the 1,2,3-triazole 9 did indeed compete with the desired pathway. However, isoquinolines and other fused heteroaromatics could be effectively prepared from the primary and secondary benzylic azides at the expense of relatively high catalyst loadings (Scheme 5, conditions A). The same group has shown that an alternative electrophilic activation of this substrate type can be used to access the analogous iodinated isoquinolines 10 (Scheme 5, conditions B). The best choice of iodonium source proved substrate-dependent, with the use of less nucleophilic counterions aiding reactions where the substituents are not bulky or able to stabilize the transition-state well. The method proved applicable even to functionalized substrates such as 10g, which was used as a late-stage precursor to the natural product norchelerythrine (Scheme 5, bottom). In addition to the use of 2-alkynylbenzyl azides to access isoquinolines, isomeric 1-azido-2-(2-propynyl)benzenes react in the same manner with electrophilic reagents or a gold catalyst to form substituted quinolines.

The iodinative cyclisation proceeded by activation of the triple bond followed by attack of the azide. Elimination of the benzylic proton and N₂ affords the 4-iodoisoquinolines. An analogous mechanism can be invoked for the π-acid catalyzed process followed by protodemetalation (Scheme 6).

The potential of the acetylenic Schmidt approach to trigger skeletal rearrangement and hence form new carbon–carbon bonds was identified by Toste and co-workers in their initial report. Azidoalkynes with fully substituted propargylic positions such as 13 react to give 2,3,4-tri- and 2,3,4,5-tetrasubstituted pyrroles such as 14 (Scheme 7). In the absence of a hydride-shift pathway to the forming gold carbene, both 1,2-aryl and ring-expanding 1,2-alkyl migrations (15 → 16) from the adjacent carbon were productive.

The carbocationic character of the putative gold carbene was elegantly exploited by Zhang’s group in a rapid assembly of 2,3-dihydro-1H-pyrrolizines 18 from azido-1,3-enynes 17 (Scheme 8). Conjugating the alkyne to an electron-deficient alkene provided regiocontrol for the required initial 5-exo-dig cyclization of the azido group (19 → 20). The subsequent carbocationic character generated with elimination of N₂ 21/21' triggers a 4π-electrocyclic ring closure to afford the bicyclic scaffold 18 on deprotonation and protodemetalation of 22.

Alongside substitution on the azidoenzyme skeleton, cyclic and acyclic esters and ketones as well as benzenesulfonyl groups could be employed to access the desired reactivity. Thermally-induced [3+2]-dipolar cycloaddition to form triazoles competed with the desired reaction. Problems associated with triazole formation included deactivation of the catalysts and were minimized by using the azidoenzyme starting materials immediately after purification by chromatography and, when necessary, increasing the catalyst loading up to 10–15 mol%. As a result, when the tether length between azide and alkyne was increased, the tetrahydroindolizine core 24 could be formed in high yield over the 1,2,3-triazole 25 (Scheme 9).
The utility of the 2,3-dihydro-1H-pyrrolizine synthesis was demonstrated by its application in the formal synthesis of 7-methoxymitosene, which is accessible in eight steps from the product of catalysis \( \text{Scheme 10} \) \([17, 18]\).

The reactivity of 2-alkynylaryl azide derivatives \( \text{Scheme 11} \) under gold catalysis was independently reported in close conjunction by the groups of Gagosz and Zhang. \([19]\) Both groups demonstrated how this approach provides rapid access to highly useful indole derivatives. The electrophilic character generated at the C3 position of the indole \( \text{Scheme 11} \) provides an umpolung contrast to the usual nucleophilic character at that position and can be trapped by both external and internal nucleophiles.

A variety of different nucleophiles were employed alongside 2-alkynylaryl azides, with both studies using an N-heterocyclic carbene stabilized cationic gold catalyst \( \text{Scheme 12} \). With some crossover of application between the studies, Wetzel and Gagosz’s report mainly focused on intermolecular trapping of the \( \alpha \)-imino gold carbene \( \text{Scheme 11} \). The reaction of an allylic alcohol is followed by Claisen rearrangement of the initial adduct to give 2,2-disubstituted indolin-3-ones \( \text{Scheme 12} \), a motif found in a number of natural products and biologically active compounds \( \text{Scheme 12} \). Zhang and co-workers predominantly explored the use of carbon nucleophiles, such as (hetero)aromatics, enol ethers, and alcohols to form the indoles \( \text{Scheme 14} \).

Both studies reported that when phenols and aniline were used as trapping agents the nucleophilic attack comes from the \( \text{para} \) position of the arene ring affording outcomes consistent with an electrophilic aromatic substitution mechanism. An interesting observation noted by Zhang and co-workers was that regioselectivity diminished as the reaction temperature was lowered \( \text{Scheme 13} \). This was rationalized on the basis that higher temperature aids in the extrusion of \( \text{N}_2 \) favoring formation of the gold carbene intermediate \( \text{Scheme 12} \), whereas at lower temperatures, the nucleophile may react through an \( \text{S}_\text{N}2' \) process with the gold carbenoid \( \text{Scheme 12} \). As the \( \text{C}/\text{C}_0 \text{Au} \) bond is shorter in \( \text{Scheme 12} \) than \( \text{Scheme 11} \), the bulk of the gold-ligand sphere can be expected to be more sterically imposing at the
reacting center affording higher selectivity in the reaction with the nucleophile.

Gong and co-workers recently expanded the reactivity of α-imino gold carbene 32 by intermolecular trapping of this intermediate with propargyl alcohols to enter a Saucy–Marbet rearrangement/allene hydroamination cascade (Scheme 14).[20] The resulting heterocycle tolerates the presence of various electronically different aromatic groups, alkyl chain bearing labile or bulky substituents, and even indole derivatives. Of particular note is the transfer of the chirality from the propargyl alcohol into the final product 38d, giving excellent values of enantioselectivity. The propargyl Claisen rearrangement is proposed to follow either a thermally induced (40→41) or a gold-catalyzed pathway (42→44), with the latter favored by the authors in analogy to similar transformations.[21]

Fujii, Ohno and co-workers showed how the cyclization of 2-alkynylarylazides could be combined with ynamides to take advantage of the flexibility that the ynamide N-substituent offers to readily append alternative π-systems with which to quench the α-imino gold carbene 47.[22, 23] This approach provides rapid access to a range of indole-fused polycyclic scaffolds, such as 48 to 51 from azidynamides 46 (Scheme 15). A relat-
afforded the fused tricycles 60, whilst substrates with two
different propargylic substituents 61 afforded product ratios
(62/63) consistent with the migratory aptitude of each group
(Me<alkyl<viny1<H). In those cases, the use of AuCl3 gave
higher selectivity (62a–c, Scheme 17). However, due to their in-
stability some products could only be obtained using[(IAd)AuNTf2] rather than the more Lewis acidic AuCl3 (62d).
The presence of an aryl substituent at the propargylic position
(64) under gold(I) conditions saw formation of the isoquinoline
65 alongside an oxindole derivative 66, which was potentially
derived from thermally induced cyclisation between the azide
and the allene.
Xiao and Zhang showed that the α-imino gold carbene in-
termediates generated from azidoalkynes 67 could also be
trapped intermolecularly with nitriles 68 to afford bicyclic imi-
dazoles 69 (Scheme 18).[27] Competition with triazole formation
(70) was observed, and notably this side reaction appeared to
be catalyzed by gold. Methanesulfonic acid was added to the
reactions in order to avoid catalyst deactivation from the basic
nitrogen atoms in both the desired and undesired heterocyclic
products. A variety of nitriles could be employed successfully
including those with aryl groups, conjugated or skipped
double bonds, and alkyl chains with labile groups. However,
the nitrile was required to be used as the solvent in order to
achieve good reaction efficiency.
Formation of the imidazole core represents a [2+2+1] as-
sembly where, following 5-exo-dig cyclization, the desired α-
imino gold carbene 71 is captured by a nitrile affording dipole
72, which on subsequent cyclization delivers the bicyclic scaf-
dfold 69 (Scheme 19). The inability to achieve effective reaction
with reduced nitrile equivalence contrasts with related oxidativo-[2+2+1] transformations of alkynes to prepare disubstitut-
ed oxazoles.[28]
2.2. Azirines as Nucleophilic Nitrenoids

An alternative route into α-imino gold carbene intermediates from alkynes was recently introduced by Gagosz and co-workers using azirines (Scheme 20). These strained, three-membered, C–N double-bond-containing rings function as alkenyl nitrene equivalents. While their use to access metal-nitrene complexes are known, this new nucleophilic aspect provides an attractive route to access the carbenoid reactivity without formation of any byproduct. The positive charge in the initial adduct 74 can be stabilized with ring-opening to access the N-vinyl α-imino gold carbene 75.

Heating 2-propargyl 2H-azirines 77, derived in two steps from the carbonyl 76 through the oxime, with a gold catalyst resulted in the formation of polysubstituted pyridines 78 (Scheme 21). Substitution was tolerated at the azirine scaffold, propargylic position, and alkyne terminus, including terminal alkynes, which required longer reaction times. Diastereoisomers arising from functionalization at the propargylic position were found to react at distinct rates, to the point that in an extreme case only one reacted. Comparing the separable diastereomers of azirine 79 under the reaction conditions showed that while the anti isomer was more reactive than the syn isomer, it also gave rise to a mixture of two isomeric products 80 and 81, with the latter arising from a migration of the aromatic ring, while 79Ant afforded 80 only.

In the proposed reaction mechanism (Scheme 22) a 5-endodig cyclization to form intermediate 83, in which cationic charge can perhaps be stabilized by overlap with the vinyl gold π-system (represented in 84), is followed by ring-opening to 85, then 1,2-shift of a migrating group (generally H except in 79 where the aromatic ring can also migrate). Intermediate 86 eliminates gold to give pyridine 87. The authors postulated that a more concerted mechanism with simultaneous ring-opening and 1,2-shift (83–88) might better account for the different kinetics between diastereomers. The relative stereochemistry of syn and anti isomers in 83 could have a major impact on transition states from the relationship between the propargylic group and the ester of the azirine. A DFT-based investigation of the reaction mechanism by Wu, Zhao and co-worker favored the sequential pathway, and justified the difference of selectivity between diastereomers on the basis of the stability of the carbocation and steric interaction with the bulky ligand on the catalyst, though the concerted reaction mechanism could not be optimized.

As a contrast, a recent metal-free pyridine synthesis was reported from alkene-tethered azirines 89 (Scheme 23).

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Scheme 20. Azirines as nitrenoids in the synthesis of heterocycles.


Scheme 22. Plausible mechanisms for the gold-promoted synthesis of polysubstituted pyridines.
promoted ring-opening of the azirine delivers a 1-azatriene 91 that undergoes $\pi$-electrocyclization and subsequent oxidation of 92. A mechanism involving activation of the azirine by gold complexes could be ruled out in Gagosz’s work as no reaction occur with a substrate lacking the alkyl moiety.[29]

3. Intermolecular Reactions

In addition to the immediate nitrogen-heterocycle-forming potential of intramolecular reactions,[33] intermolecular reactions of alkynes with nucleophilic nitrenoids have been introduced, which take advantage of the functional group compatibility of $\pi$-acid catalysis to access highly convergent and general routes into nitrogen heterocycles.[34]

3.1. Aminides as Dipole Equivalents

Davies et al. proposed that the intermolecular interaction of a nucleophilic nitrenoid and a $\pi$-acid-activated triple bond could form the basis of a formal cycloaddition strategy. The valency of nitrogen allows it to act as a nucleophilic nitrenoid equivalent to generate an $\alpha$-imino gold carbenoid 95/96 whilst also delivering the means with which to quench it (96 $\rightarrow$ 97, Scheme 24).[35]

![Scheme 23](image)

Scheme 23. An alternative use of azirines to access pyridines. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

This concept was first realized in the intermolecular reaction of pyridinium N-acyl aminides 98 with ynamides 99 affording trisubstituted 1,3-oxazoles 100 by a formal [3+2]-dipolar cycloaddition across the triple bond (Scheme 25).[35] In this reaction the bench-stable pyridinium aminides 98 act as N-nucleophilic equivalents to 1,3-N,O-dipoles/acyl nitrenes.

Superb regioselectivity was observed in all cases providing rapid and efficient access into fully substituted 4-N-oxazoles with substantial functional group tolerance and variation possible at the C2, CS and N positions. In addition to the ynamides, an ynl ether 102 was also shown to be a competent substrate providing access to the alkoxyoxazole 103.

![Scheme 24](image)

Scheme 24. Schematic of formal cycloaddition strategy.

![Scheme 25](image)

Scheme 25. Intermolecular synthesis of trisubstituted oxazoles by gold-catalyzed formal [3+2] cycloaddition. Ns = 2-nitrophenylsulfonyl; Pic = Pyridine-2-carboxylate; TBDPS = tert-butylphenylsilyl; THP = tetrahydropyran; TMS = trimethylsilyl.

Various substituents, including heteroatom, alkyl, vinyl, and aryl groups could be appended at the C2 position in the resulting oxazoles through choice of starting aminide. Substantial variation was also possible on the nitrogen and carbon positions of the ynamide despite the possibility of competing pathways such as aza-Claisen rearrangement.[37] In addition to smooth reactions of ynamides with diverse carbon substituents including aryl, heteroaryl, vinyl, and alkynyl groups, alkyl substituents were also well tolerated.

The proposed mechanism involves nucleophilic attack of amide 98 onto the gold-ynamide complex 104, with regioselectivity determined by contribution of the gold-keteniminium (104’),[6b, 22, 38] to form vinyl gold carbenoid 105 (Scheme 26). Several cyclisation pathways are possible: stepwise elimination of the pyridine nucleofuge to form the N-acyl $\alpha$-aminogold carbene 106 followed by interaction of the oxygen lone pairs with the electrophilic carbon center (106/106’ $\rightarrow$ 107) or a bis-heteroatom $\pi$-electrocyclization (106 $\rightarrow$ 107). In light of the propensity of $\alpha$-imino and $\alpha$-oxo gold carbenes to undergo 1,2-insertion from adjacent alkyl groups,[34a, 39] the authors pro-
posed that C–O bond formation might occur alongside N–N bond scission and development of the cationic π-system (105 → 108 → 107). Deaerative aromatization then affords the desired product 100.

Chatzopoulou and Davies subsequently reported conditions that allowed the formation of all-carbon trisubstituted oxazoles by this formal [3+2]-dipolar cycloaddition approach (Scheme 27). \[40\] In contrast to the use of ynamides, more forcing conditions were required alongside the use of electrophilic cationic gold(I) catalyst bearing bulky phosphite ligand 110 for effective intermolecular reaction with these challenging unsymmetrical internal alkynes. The influence of a remote nitrogen able to delocalize its lone pair onto the alkyne was crucial for both reactivity and regiocontrol. Free 3-indolyl-oxazoles 111a–d were formed cleanly as was the single regioisomer of 111h from an alkyne bearing two nominal directing groups, whereas no reaction occurred with meta-aniline or para-anisole derivatives 111f–g.

As illustrated in the thermally or photochemically induced reactions of acyl azides with alkynes, the electrophilicity of the 1,3-N,O-dipoles/acyl nitrenes classically required for [3+2]-dipolar cycloaddition across an alkyne renders them prone to favor other rearrangement and insertion pathways and unsuitable for practical 1,3-azole formation. \[41\] This formal [3+2]-dipolar cycloaddition strategy overcomes this fundamental challenge by providing access to N-nucleophilic 1,3-N,O-dipole character. The reactivity of N-substituted pyridinium N-aminides through their interaction with a π-acid-activated alkyne also contrasts with the usual reactivity arising from their innate 1,3-C,N-dipolar character employed in a variety of transformations. \[42\] A related formal [3+2]-cycloaddition approach using acyl sulfonylum ylides alongside alkynes under gold-catalysis was independently reported by the groups of Skrydstrup and Maulide. \[43\]

Garzón and Davies established that the formal [3+2]-dipolar cycloaddition concept can be applied more widely to the formation of other azoles. \[44\] The use of pyridinium N-(heteroaryl)aminides 112 as 1,3-N,N-dipolar equivalents proved possible allowing rapid access into a diverse array of fused imidazole structures 114 (Scheme 28). Electrophilic catalysts were again most effective in these processes, using either gold(III) precatalyst or phosphite gold(I) complex 110.

Productive and scalable catalysis was achieved alongside excellent structural and functional group compatibility despite...
the presence of a large number of basic nitrogen atoms in starting materials, intermediates, and products that could coordinate and deactivate the gold species. As a result, direct access into the important building block and pharmacophore motifs of imidazo[1,2-a]pyrimidines 115, imidazo[1,2-a]pyrazines 116, imidazo[1,2-c]pyrimidines 117, imidazo[1,2-b]pyridazines 118, and imidazo[1,2-α]pyridines 119[44] is achievable in short order in a practical and gram-scalable fashion (Scheme 28). Sensitive functionality, such as aldehydes, aryl halides, and alkenes, were well tolerated. High yields with alkyl substituents could be achieved (115b) though more byproducts consistent with a competing C–H insertion pathway at the gold carbene intermediate were observed than in the analogous reactions with N-acyl aminides (cf. Scheme 25). This result could be linked to a slower cyclization due to the disruption of the diazine/pyridine aromatic ring at that step in the formation of the fused imidazoles.

3.2. Isoxazoles and Azirines as Dipole Equivalents

Two attractive strategies for the efficient synthesis of polysubstituted 2-aminopyrroles by such formal [3+2]-dipolar cycloadditions were independently reported by the groups of Lu and Ye,[46] and Huang.[47] The gold-catalyzed reaction of an ynamide 120 with either an isoxazole 121 or a 2H-azirine 122 provided rapid entry into highly substituted core structures under mild and functional group tolerant conditions (Scheme 29). Both processes involved reaction of the heterocycle with the gold-activated ynamide followed by a ring-opening process to unveil the overall nucleophilic 1,3-N activated ynamide followed by a ring-opening process to give a vinyl gold carbenoid. As a result, direct transformation of the gold-enamide moiety to the azirine 2H-position or by stepwise, gold-assisted ring-opening to give α-imino gold carbene intermediate 128 and 4π-electrocyclization.[47] On elimination of gold, hydride shift in 129 afforded the desired pyrrole 124.

In the isoxazole system, ring-opening of 130 by N–O bond cleavage formed the α-imino gold carbene 131, with carbon–carbon bond formation and cyclization giving the aclypyrrole 132. The different product outcomes resulting from isoxazole substitution can be explained through intermediate 133 generated on deauration. In the absence of a hydride shift pathway (133 → 129) a water-aided deacylation is proposed to provide aromatization (133 → 124, Scheme 31).[46]

The use of ynamides with straight-chain aliphatic groups on the C-terminus rather than Csp2 centers was less effective in both methods. The isoxazoles-based approach afforded the α,β-unsaturated amides 136 by 1,2-insertion into an adjacent C–H bond, whereas reaction with an azirine gave the desired pyrrole 139 but in modest yield (Scheme 32). This difference...
might be rationalized by considering the relative ease with which each series can adopt the geometry required for cyclisation in competition with that required for elimination or hydride shift from an adjacent methylene group. However, other substantial influences on the chemoselectivity and resulting pathways are present, not least the different catalyst systems and hence different stereoelectronic environment around the reacting centers.

The synthetic potential and functional group tolerance of the pyrrole synthesis was demonstrated in the synthesis of a lipoxigenase inhibitor precursor through the use of a bromoethyl substituent on the ynamide nitrogen (140). After reaction with isoxazole (141) an intramolecular pyrrole N-alkylation was performed to afford the bicyclic scaffold (Scheme 33).[^46]

Huang and co-workers also demonstrated that nucleophilic vinyl-nitrene/1,3-N,C-dipole reactivity could be accessed from a vinyl azide (144) with a gold-activated ynamide to yield the polysubstituted pyrrole (145) analogous to that from azirines (Scheme 34).[^46, 48]

4. Conclusions
The combination of π-acid-catalyzed alkyne activation and reagents capable of acting as nucleophilic nitrenoids has led to the development of a range of powerful and efficient processes for the rapid assembly of nitrogen-heterocycles over the last decade. Such reactions can be viewed in common as proceeding through versatile a-imino metal carbene reactivity patterns triggered by initial attack of the nitrenoid, so far shown to include alkyl and aryl azides, pyridinium-N-aminides, azirines, and isoxazoles. Subsequent evolution of the reactive electrophilic organometallic species, through pathways such as 1,2-migration, cyclopropanation, aromatic substitution, and 4π-electrocyclization, is in keeping with the cationic reactivity patterns of the gold (or platinum) carbenes. The efficacy and superb chemoselectivity of gold catalysis is well demonstrated in this subfield through the structural and functional group tolerance of individual transformations. It is also displayed in at-
taining effective catalysis despite the presence of competing reaction pathways, such as triazole formation, or the formation of reactive and/or coordinating products and byproducts.

The reactivity patterns have been shown to be possible in both intra- and intermolecular modes. The use of azide-based substrates currently dominates the intramolecular series of transformations, though more recently the use of strained azirines has also proved successful, with these strategies being applicable to make heteroaromatics, including oxazoles, fused imidazoles, and pyrroles, and pyridines has also proved successful, with these strategies being applicable to make heteroaromatics, such as pyrroles, pyridines, quinolines, and indoles as well as fused polycyclic frameworks. A relatively little-explored but potent approach is demonstrated in the synthesis of fused imidazoles, where an initial intramolecular reaction is followed by intermolecular quenching. The intermolecular combination of nucleophilic nitrenoid and triple bond has been established as a potent means to access new formal [3+2] dipolar cycloaddition strategies. In combination with electronically-biased alkynes to provide regiocontrol, access to highly substituted and functionalized five-membered heteroaromatics, including oxazoles, fused imidazoles, and pyrroles, has been achieved using a range of nucleophilic nitrenoids.

From the outline of reactivity that has already been established in this field it is clear that there is substantial opportunity to apply this general reactivity basis more widely, for instance by varying the nature of the alkyne and/or nucleophilic nitrenoid, changing their connectivity and/or mode of cyclization or intermolecular attack, and accessing more diverse pathways to quench the forming carbene. When combined with the importance of nitrenogen-heterocycles across a broad range of applications it is apparent that future studies into the reactivity of nucleophilic nitrenoids through π-activation of alkenes are primed to bring powerful new tools to address current synthetic challenges.

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Keywords: cyclizations · gold carbenes · heterocycles · nitrenoids · π-acid catalysis


For an alternative non-nitrenoid gold-catalyzed synthesis of imida-


Contrasting with the non-nitrenoid intermolecular reactions of 2H-azir-
Nucleophilic Nitrenoids Through π-Acid Catalysis: Providing a Common Basis for Rapid Access into Diverse Nitrogen Heterocycles

Life of \( \pi \): The combination of a \( \pi \)-acid catalyst, a carbon-carbon triple bond, and a nucleophilic nitrenoid provides access to versatile α-imino metal carbene reactivity patterns underpinning the discovery and development of a range of powerful new transformations for the rapid and divergent formation of valuable nitrogen-heterocycles.