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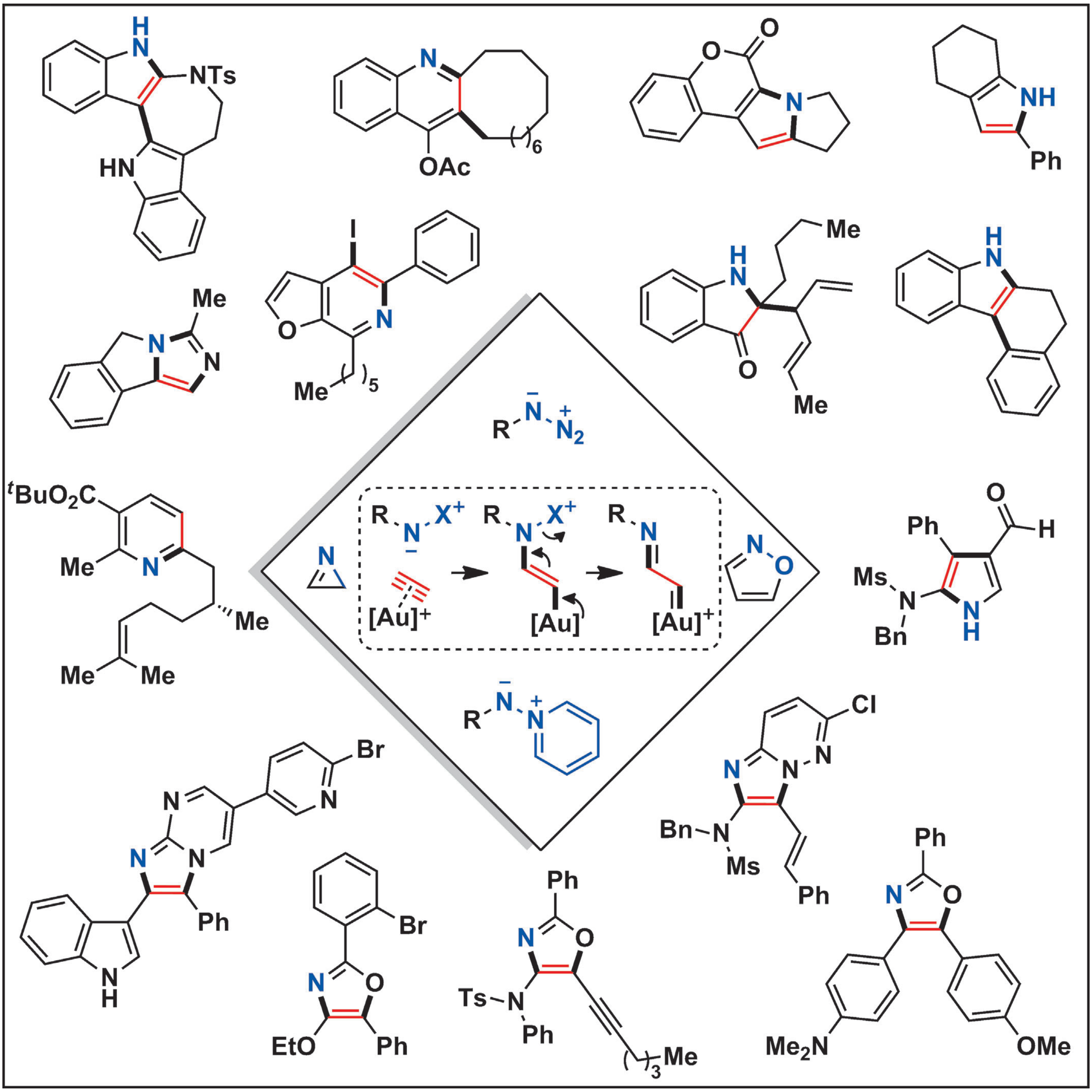
Heterocyclic Chemistry

Nucleophilic Nitrenoids Through π-Acid Catalysis: Providing a Common Basis for Rapid Access into Diverse Nitrogen Heterocycles

Paul W. Davies* and Miguel Garzón[a]



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 π-acid catalysis based on the activation of carbon-carbon triple bonds in conjunction with nucleophilic nitrenoids. The resulting approach provides ready access into α-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 π-rich heteroaromatics or structures rich in basic sites capable of coordinating and deactivating catalysts.

The advent of π-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 π-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 α-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 π-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-π-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 alkynes are contained within a nitrogen heterocycle formed in the reaction.

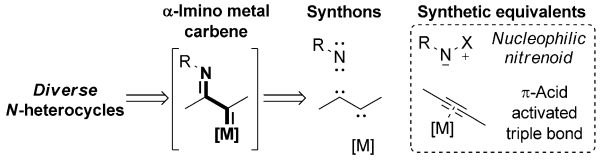
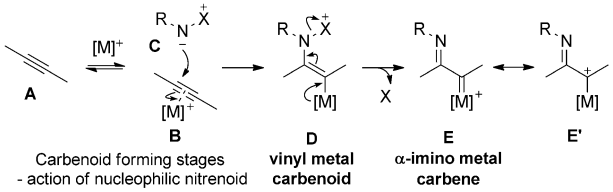


Figure 1. General retrosynthetic basis for the reactivity covered in this review.

1.1. Reactivity Basis

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



Scheme 1. Reactivity outline for use of nucleophilic nitrenoid equivalents in the formation of α-imino metal carbenes.

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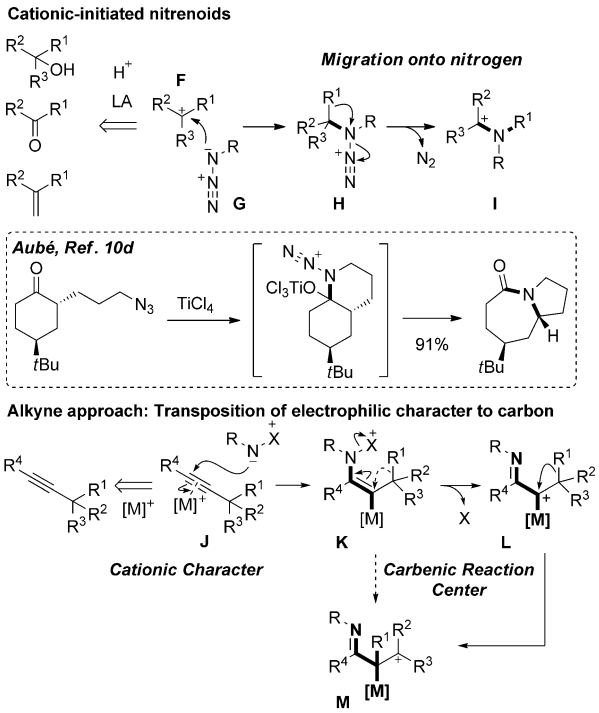
philic carbon framework by nucleophilic attack to generate a vinyl metal carbenoid species **D** that can evolve to the α-imino metal carbene **E** on elimination of a nucleofuge (X). Processes that invoke the interaction of a metal–nitrogen bond, as metallonitrenoid or metallonitrene, in the addition across the π-system are not discussed here, but have been shown to give access to related intermediates.[5,6]

While all the reactions discussed in this review can reasonably be viewed as proceeding through an α-imino metal carbene **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 **D** and **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 **D** or **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 carbocation representations of a metal carbene **E**/**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]



Scheme 2. Potential of the alkyne-based approach in transposing and extending reactivity profiles of nucleophilic nitrenoids (represented in 1,2-migration).

1.2. Nucleophilic Nitrenoids

In analogy to the description of intermediate **D** as a "metal carbenoid", as its reaction with a nucleophile can afford the same species as reaction at metal carbene **E/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 carbocation **F** (Scheme 2), for instance by Brønsted or Lewis acid activation of a carbonyl, alkene, or alcohol, triggers nucleophilic attack by the azide **G** followed by 1,2-migration back onto the nitrenoid nitrogen with elimination of N_2 (**H**→**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 carbocationic character from a π-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 (**K**/L→**M**, Scheme 2). Second, the potential for reactivity at this center is extended from being purely cationic *to carbenic*. As shown

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Miguel Garzón was born in Madrid (Spain) and studied chemistry at the Universidad Complutense de Madrid, where he undertook his final year project under the supervision of Prof. Maria Josefa Ortiz Garcia on the design and synthesis of fluorescent dyes. Miguel is currently a Ph.D. fellow in the Davies Group, where he is investigating the use of nucleophilic nitrenoids in gold-catalyzed cycloadditions.

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.

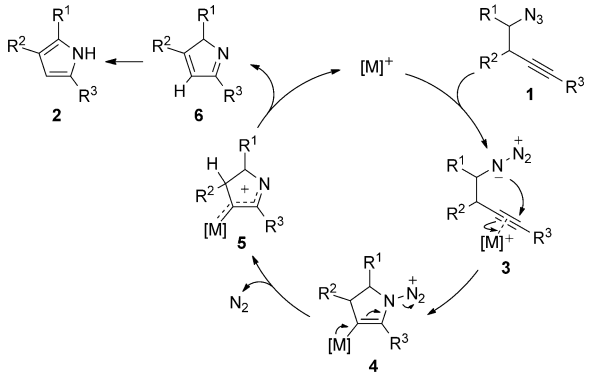
2. Intramolecular Reactions

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 alkynes 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**.

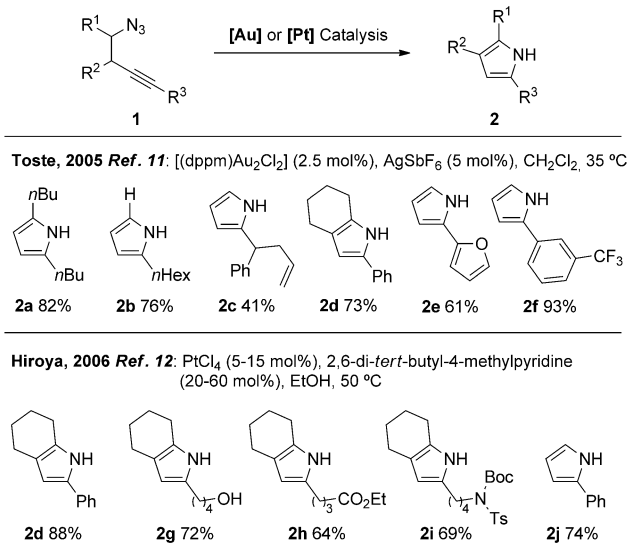
This first invocation of the α-imino gold carbene by action of a nucleophilic nitrenoid highlights the practically attractive aspects of such processes. Given their propensity to degrade under acidic conditions the ready formation of free pyrroles showcases the mild nature of gold-catalysis. Hiroya et 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 2*H*-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 2*H*-pyrrole to 1*H*-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]

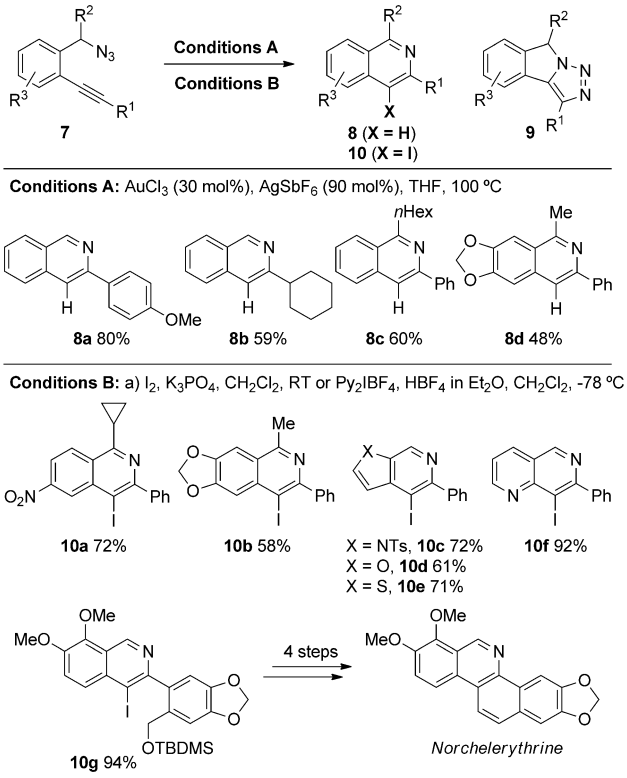


Scheme 4. Mechanism of homopropargyl azide reaction.

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 con-



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



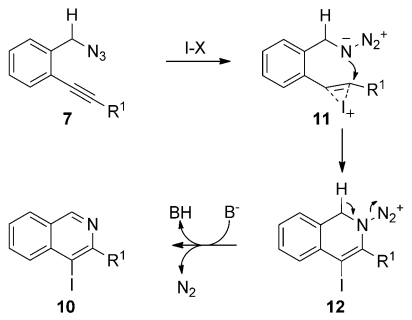
Scheme 5. Synthesis of isoquinoline scaffolds from 2-alkynylbenzyl azides. TBDMS = *tert*-butyldimethylsilyl; Ts = 4-toluenesulfonyl.

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).[15] 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.[16]

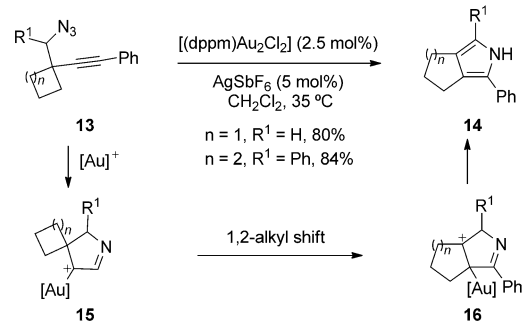
The iodinative cyclisation proceeded by activation of the triple bond followed by attack of the azide. Elimination of the benzylic proton and N_2 affords the 4-iodoisoquinolines. An analogous mechanism can be invoked for the π-acid catalyzed process followed by protodemetallation (Scheme 6).

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.[11] 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.

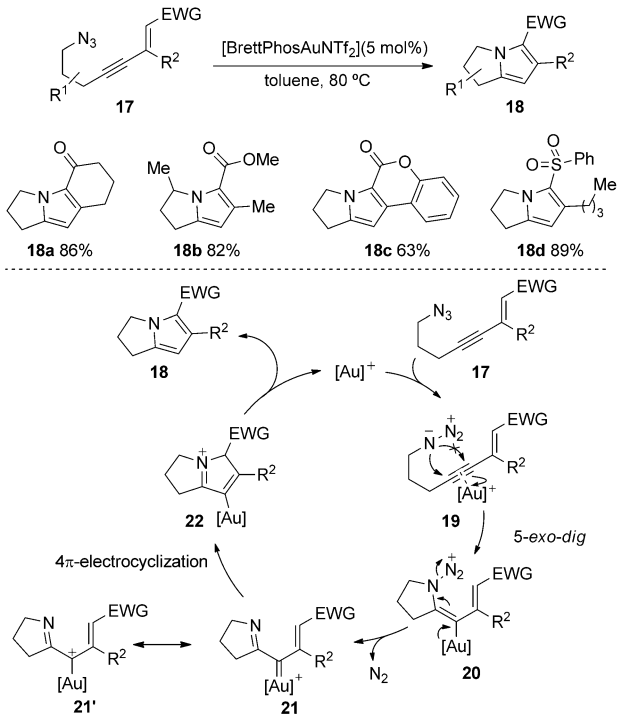
The carbocationic character of the putative gold carbene was elegantly exploited by Zhang's group in a rapid assembly of 2,3-dihydro-1*H*-pyrrolizines **18** from azido-1,3-enynes **17** (Scheme 8).[17] Conjugating the alkyne to an electron-deficient alkene provided regiocontrol for the required initial 5-*exo-dig* cyclization of the azido group (**19**–**20**). The subsequent carbocationic character generated with elimination of N_2 **21**/**21'** triggers a 4π-electrocyclic ring closure to afford the bicyclic scaffold **18** on deprotonation and protodemetallation of **22**.



Scheme 6. Iodonium activation of the triple bond in isoquinoline synthesis.



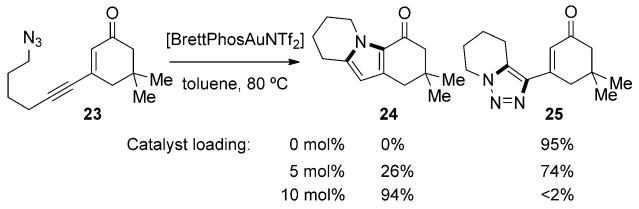
Scheme 7. Tandem cyclisation-ring expansion adaptation of the homopropargylic azide reaction.



Scheme 8. Synthesis of 2,3-dihydro-1*H*-pyrrolizines starting with 5-*exo-dig* cyclisation of alkynyl azides. BrettPhos = 2-(dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl. EWG = electron-withdrawing group; Tf = trifluoromethanesulfonyl.

Alongside substitution on the azidoenyne 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 azidoenyne 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).

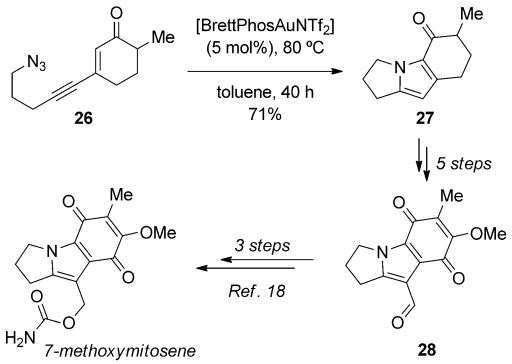


Scheme 9. Effects of the catalyst loading in the formation of tetrahydroindazolines.

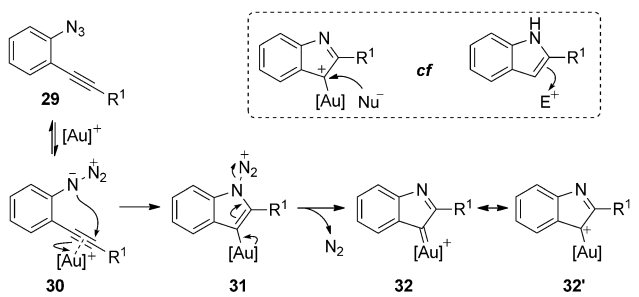
The utility of the 2,3-dihydro-1*H*-pyrrolizine synthesis was demonstrated by its application in the formal synthesis of 7-methoxymitosene, which is accessible in eight steps from the product of catalysis **27** (Scheme 10).[17,18]

The reactivity of 2-alkynylaryl azide derivatives **29** 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 **32**/**32′** provides an umpolung contrast to the usual nucleophilic character at that position and can be trapped by both external and internal nucleophiles (Scheme 11).

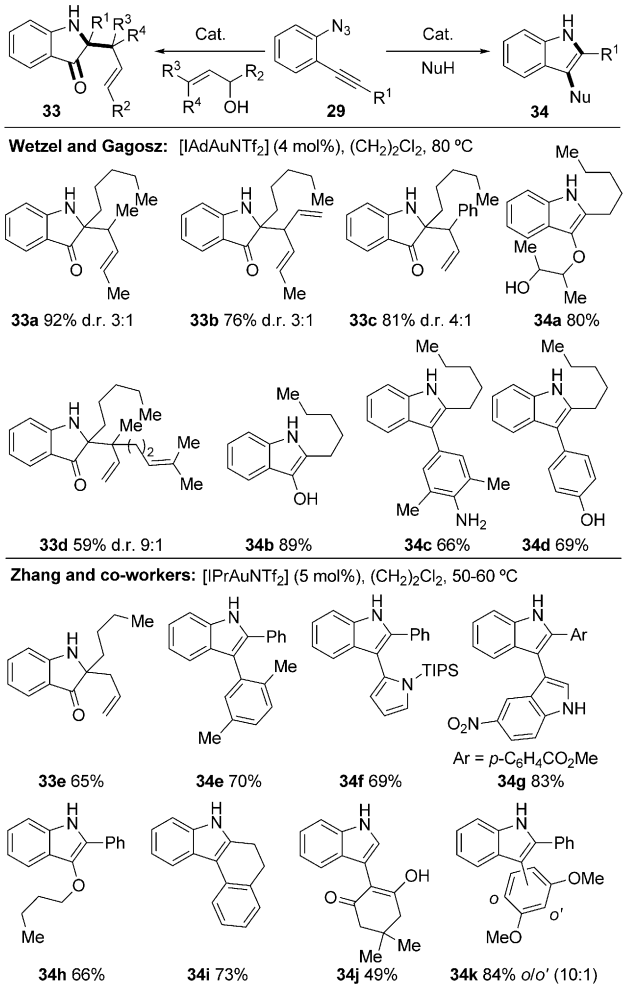
A variety of different nucleophiles were employed alongside 2-alkynylaryl azides, with both studies using an *N*-heterocyclic carbene stabilized cationic gold catalyst (Scheme 12). With some crossover of application between the studies, Wetzel and Gagosz's report mainly focused on intermolecular trapping of



Scheme 10. Formal synthesis of 7-methoxymitosene.



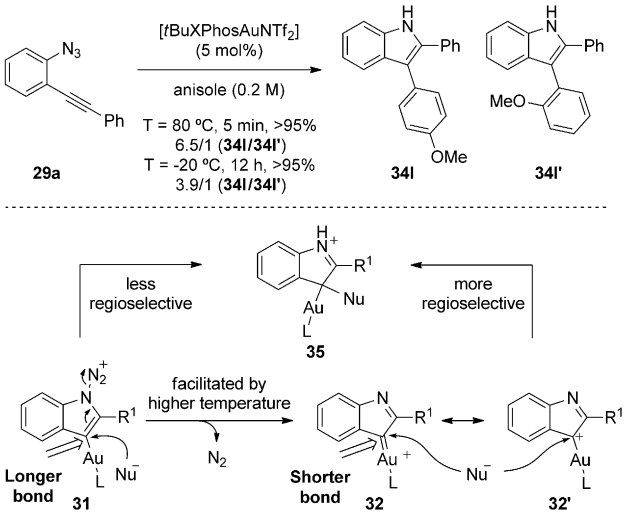
Scheme 11. Umpolung reactivity at the C3 position of indole.



Scheme 12. Rapid synthesis of substituted indoles and indolin-3-ones. IAd = 1,3-di-1-adamantylimidazol-2-ylidene; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

the α-imino gold carbene **32** (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 **33**, a motif found in a number of natural products and biologically active compounds (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 **34**.

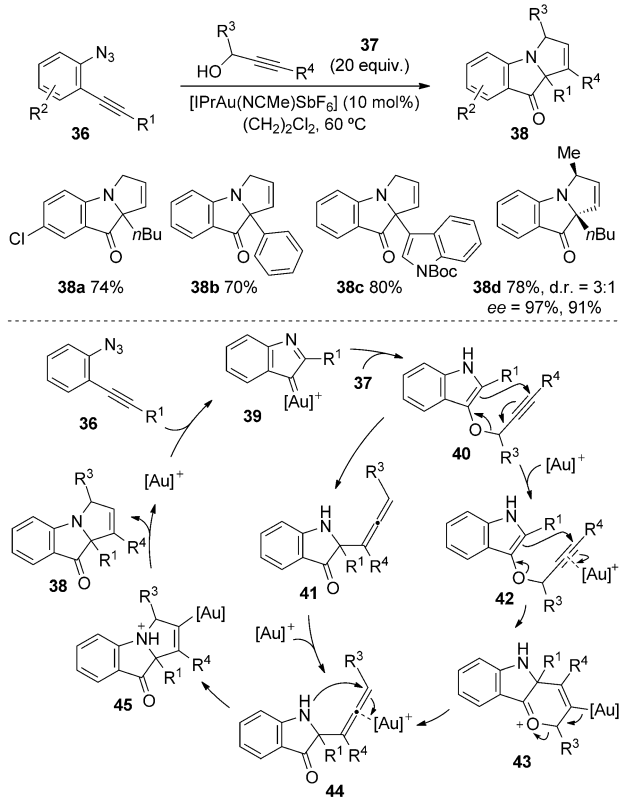
Both studies reported that when phenols and aniline were used as trapping agents the nucleophilic attack comes from the *para* position of the arene ring affording outcomes consistent with an electrophilic aromatic substitution mechanism. An interesting observation noted by Zhang and co-workers was that regioselectivity diminished as the reaction temperature was lowered (Scheme 13). This was rationalized on the basis that higher temperature aids in the extrusion of N_2 favoring formation of the gold carbene intermediate **32**, whereas at lower temperatures, the nucleophile may react through an S_N2' process with the gold carbenoid **31**. As the C–Au bond is shorter in intermediate **32** than **31** the bulk of the gold-ligand sphere can be expected to be more sterically imposing at the



Scheme 13. Rationale for the effect of temperature in the regioselectivity. *t*BuXPhos = 2-di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl.

reacting center affording higher selectivity in the reaction with the nucleophile.

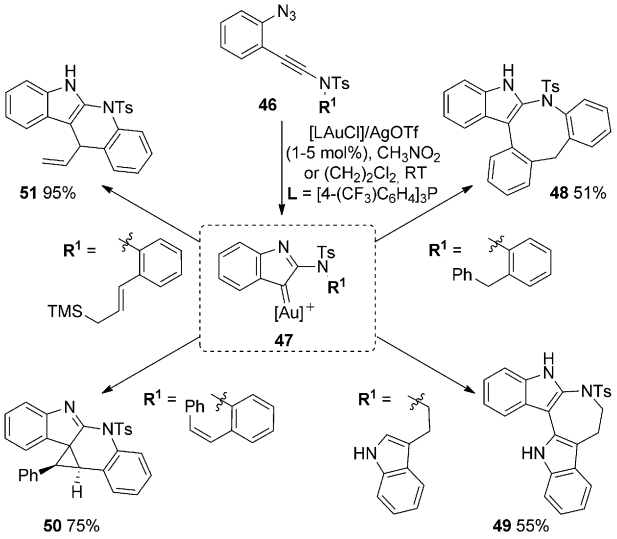
Gong and co-workers recently expanded the reactivity of α-imino gold carbene **32** by intermolecular trapping of this intermediate with propargyl alcohols to enter a Saucy–Marbet rearrangement/allene hydroamination cascade (Scheme 14).[20] The



Scheme 14. Cascade reaction of 2-alkynylaryl azides with propargyl alcohols. Boc = *tert*-butyloxycarbonyl.

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 **38 d**, giving excellent values of enantiomeric excess despite the low diastereoselectivity. 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 azidoynamides **46** (Scheme 15). A relat-

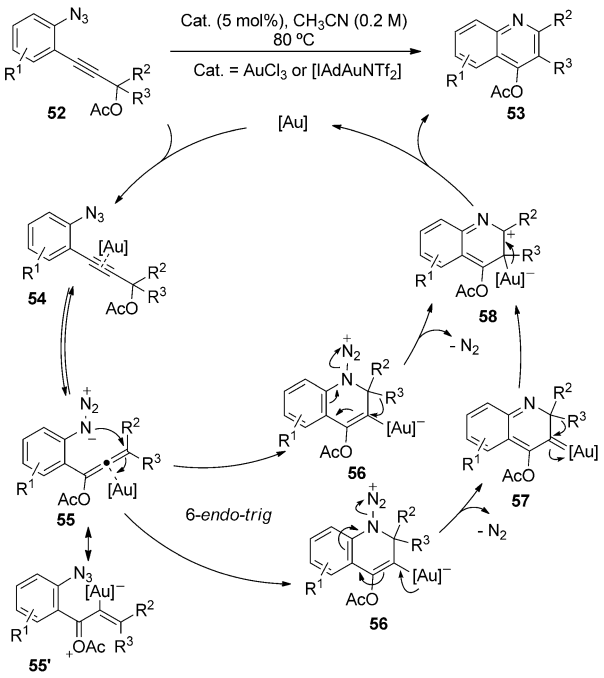


Scheme 15. Gold-catalyzed synthesis of indole-fused polycyclic scaffolds.

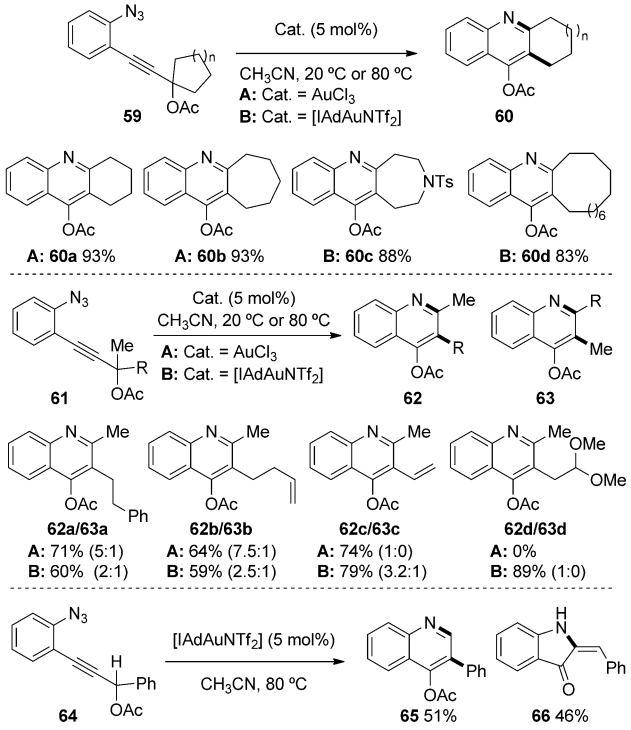
ed transformation trapping the intermediate from reaction of the azidoynamide intramolecularly with alcohols and sulfonamides was very recently reported by Ye and co-workers.[24]

Gagosz and co-workers proved that modifying the 2-alkynylaryl azides could be used to divert the initial reactivity away from α-imino gold carbene formation in a synthesis of functionalized quinolines **53** from alkynylaryl azides **52** (Scheme 16).[25] The introduction of a propargylic carboxylate sees the reaction commence with gold-catalyzed rearrangement into the gold-allenoxy complex **55**,[26] which is then trapped by a 6-*endo*-*trig* attack from the azide. Evolution of the resulting intermediate **56** can occur by a 1,2-shift of one of the substituents at the propargylic position, either with (**56**→**58**) or after (**56**→**57**→**58**) elimination of N_2, affording quinoline **53** on release of gold.

Often indistinguishable outcomes were obtained using either gold(I) or gold(III) catalysts for a range of polysubstituted quinolines (Scheme 17). Ring expansion of cyclic systems



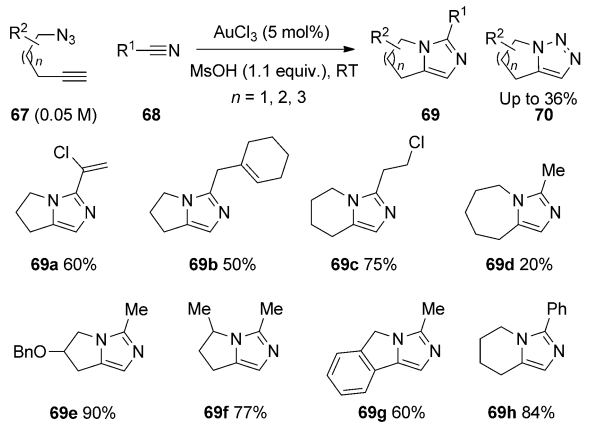
Scheme 16. Diverting gold-catalyzed reactions of 2-alkynyl arylazides to form quinolines.



Scheme 17. General conditions for the gold-catalyzed synthesis of polysubstituted quinolines.

59 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 < vinyl < H). In those cases, the use of $AuCl_3$ gave higher selectivity (**62a**–**c**, Scheme 17). However, due to their instability some products could only be obtained using [(IAd)$AuNTf_2$] rather than the more Lewis acidic $AuCl_3$ (**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.

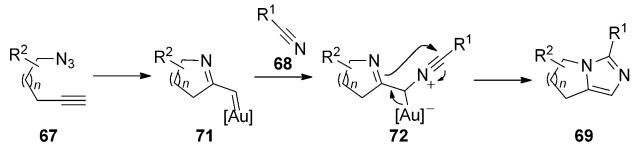
Xiao and Zhang showed that the α-imino gold carbene intermediates generated from azidoalkynes **67** could also be trapped intermolecularly with nitriles **68** to afford bicyclic imidazoles **69** (Scheme 18).[27] Competition with triazole formation



Scheme 18. Gold-catalyzed synthesis of bicyclic imidazoles. Bn = benzyl; Ms = methanesulfonyl.

(**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.

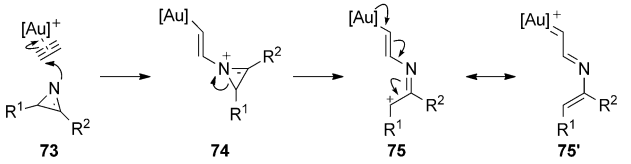
Formation of the imidazole core represents a [2+2+1] assembly where, following 5-*exo*-*dig* cyclization, the desired α-imino gold carbene **71** is captured by a nitrile affording dipole **72**, which on subsequent cyclization delivers the bicyclic scaffold **69** (Scheme 19). The inability to achieve effective reaction with reduced nitrile equivalence contrasts with related oxidative [2+2+1] transformations of alkynes to prepare disubstituted oxazoles.[28]



Scheme 19. Mechanism for the gold-promoted synthesis of fused imidazoles.

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).[29] These strained, three-membered, C–N double-bond-containing rings function as alkenyl nitrene equivalents. While their use to access metal-nitrene



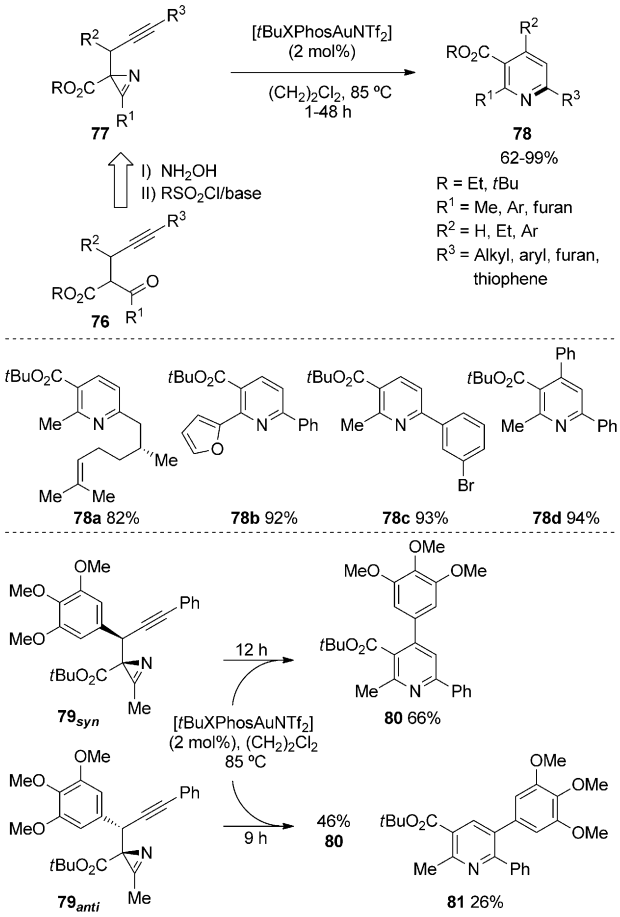
Scheme 20. Azirines as nitrenoids in the synthesis of heterocycles.

complexes are known,[30] 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**.

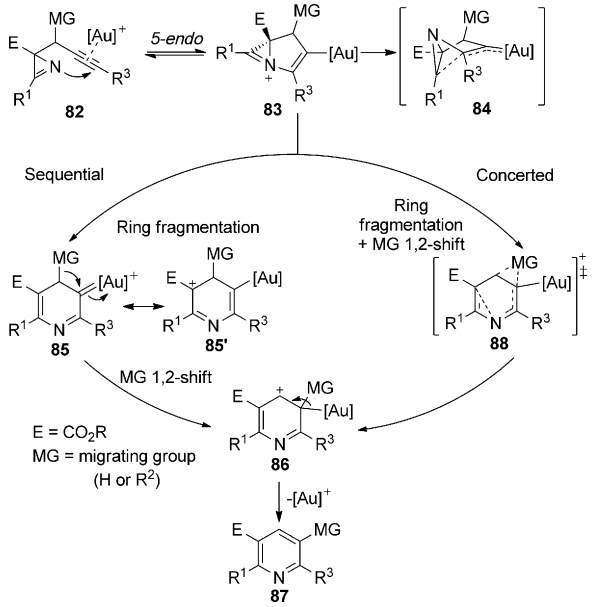
Heating 2-propargyl 2*H*-azirines **77**, derived in two steps from the carbonyl **76** through the oxime, with a gold catalyst resulted in the formation of polysubstituted pyridines **78** (Scheme 21). Substitution was tolerated at the azirine scaffold, propargylic position, and alkyne terminus, including 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 **79**$_{syn}$ afforded **80** only.

In the proposed reaction mechanism (Scheme 22) a 5-*endo*-*dig* 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 coworker 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.[31]

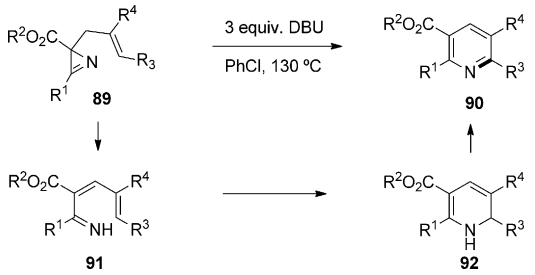
As a contrast, a recent metal-free pyridine synthesis was reported from alkene-tethered azirines **89** (Scheme 23).[32] Base-



Scheme 21. Synthesis of polysubstituted pyridines from 2-propargyl-2*H*-azirines.



Scheme 22. Plausible mechanisms for the gold-promoted synthesis of polysubstituted pyridines.



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

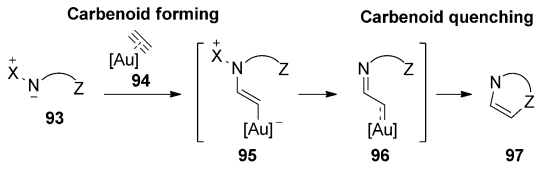
promoted ring-opening of the azirine delivers a 1-azatriene **91** that undergoes 6π-electrocyclization and subsequent oxidation of **92**. A mechanism involving activation of the azirine by gold complexes could be ruled out in Gagosz's work as no reaction occur with a substrate lacking the alkyne moiety.[29]

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 π-acid catalysis to access highly convergent and general routes into nitrogen heterocycles.[34]

3.1. Aminides as Dipole Equivalents

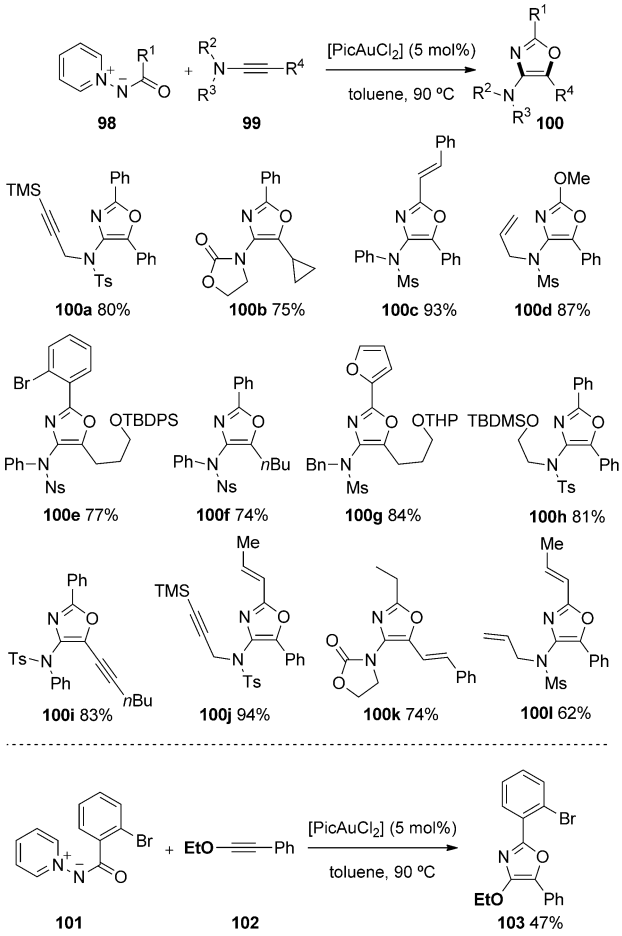
Davies et al. proposed that the intermolecular interaction of a nucleophilic nitrenoid and a π-acid-activated triple bond could form the basis of a formal cycloaddition strategy. The valency of nitrogen allows it to act as a nucleophilic nitrenoid equivalent to generate an α-imino gold carbenoid **95**/**96**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



Scheme 24. Schematic of formal cycloaddition strategy.

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.

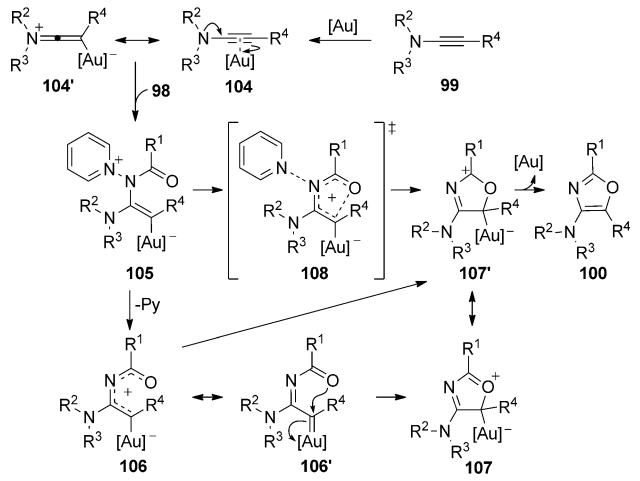
Superb regioselectivity was observed in all cases providing rapid and efficient access into fully substituted 4-*N*-oxazoles with substantial functional group tolerance and variation possible at the C2, C5 and *N* positions. In addition to the ynamides,[36] an ynol ether **102** was also shown to be a competent substrate providing access to the alkoxyoxazole **103**.



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 aminide **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 α-aminogold carbene **106** followed by interaction of the oxygen lone pairs with the electrophilic carbon center (**106**/**106′**→**107**) or a bis-heteroatom 4π-electrocyclization (**106**→**107′**). In light of the propensity of α-imino and α-oxo gold carbenes to undergo 1,2-insertion from adjacent alkyl groups,[34a,39] the authors pro-



Scheme 26. Mechanism for the synthesis of trisubstituted oxazoles.

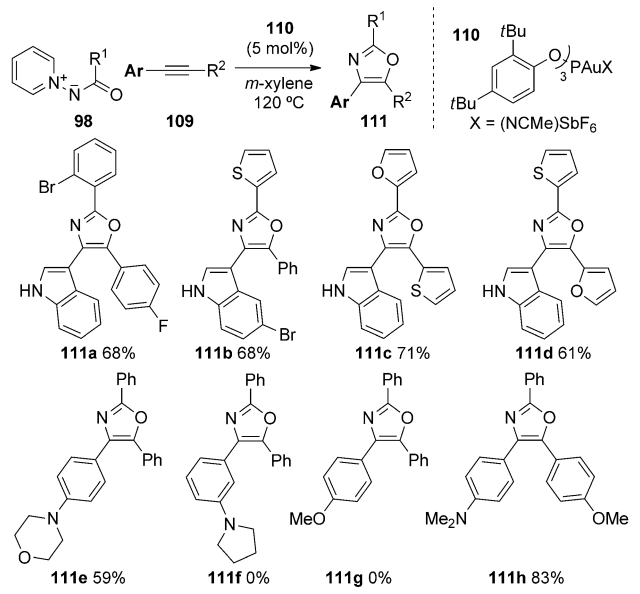
posed that C–O bond formation might occur alongside N–N bond scission and development of the cationic π-system (**105**→**108**→**107′**). Deaurative aromatization then affords the desired product **100**.

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 **111 a**–**d** were formed cleanly as was the single regioisomer of **111 h** from an alkyne bearing two nominal directing groups, whereas no reaction occurred with *meta*-aniline or *para*-anisole derivatives **111 f**–**g**.

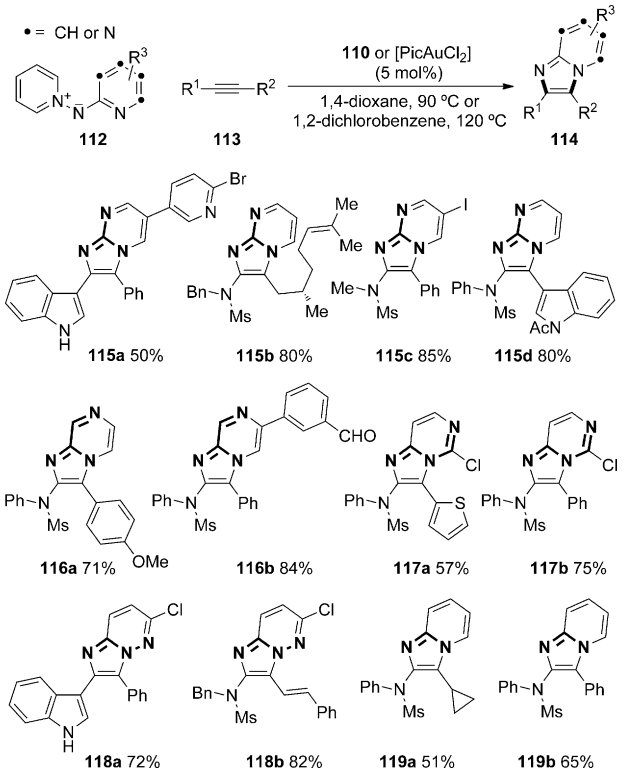
As illustrated in the thermally or photochemically induced reactions of acyl azides with alkynes, the electrophilicity of the 1,3-*N*,*O*-dipoles/acyl nitrenes classically required for [3+2]-dipolar cycloaddition across an alkyne renders them prone to favor other rearrangement and insertion pathways 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 sulfonium 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



Scheme 27. Regioselective formation of all-carbon-substituted oxazoles enabled by the electronic influence of a remote nitrogen atom.



Scheme 28. Synthesis of diverse fused imidazodiazines and imidazopyridines using a formal [3+2]-dipolar cycloaddition strategy.

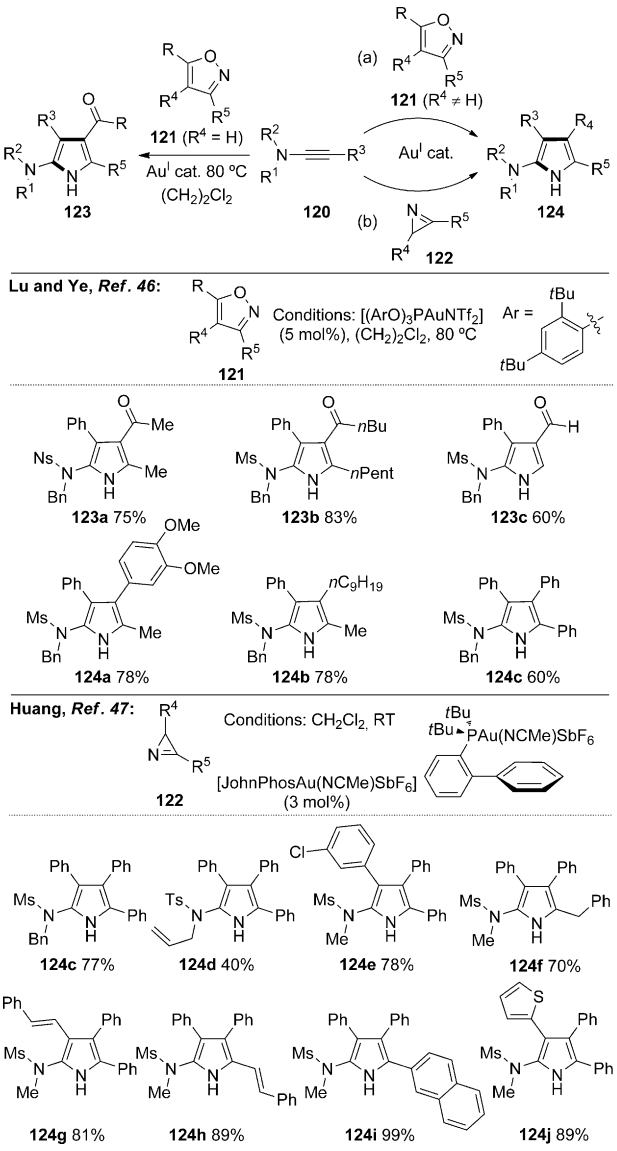
the presence of a large number of basic nitrogen atoms in starting materials, intermediates, and products that could coordinate and deactivate the gold species. As a result, direct access into the important building block and pharmacophore motifs of imidazo[1,2-*a*]pyrimidines **115**, imidazo[1,2-*a*]pyrazines **116**, imidazo[1,2-*c*]pyrimidines **117**, imidazo[1,2-*b*]pyridazines **118**, and imidazo[1,2-*a*]pyridines **119**[45] 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 (**115 b**) though more byproducts consistent with a competing C–H insertion pathway at the gold carbenoid 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 2*H*-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*,*C* dipole/vinyl nitrene character. Interestingly, the isoxazole-based system sees diverging outcomes depending on initial substitution patterns. While the 3,5-disubstituted species **121** ($R^4 = H$) afforded the 4-acylated 2-aminopyrroles **123**, the 3,4,5-trisubstituted isoxazoles **121** provided the deacylated products **124**. Azirines reacted with the transfer of all substituents into the final products (**122** → **124**). Both transformations tolerated structural variation and functionality on the ynamide and the nitrenoid equivalent. Depending on the substitution patterns around the azirine ring, those reactions could be performed at room temperature, or required heating in toluene if electron-donating substituents at the 2*H*-carbon or Csp^3 substituents at the imine carbon were present (**124 f**). The reactions of isoxazoles were generally heated in 1,2-dichlorethane, though a successful example was shown where the reaction was run effectively in water at 100 °C to obtain the desired product in a near-comparable yield.

Both transformations can be viewed as following a broadly similar mechanism to those seen before (Scheme 20 and Scheme 26), via regiocontrolled attack of the nucleophilic nitrenoid to generate a vinyl gold carbenoid (**126** Scheme 30 vs. **130** Scheme 31) with 4π-electrocyclization following α-imino-gold carbene formation.

In the azirine system (Scheme 30), intermediate **126** was proposed to evolve into **127** either by direct nucleophilic addition of the gold-enamide moiety to the azirine 2*H*-position or by stepwise, gold-assisted ring-opening to give α-imino gold

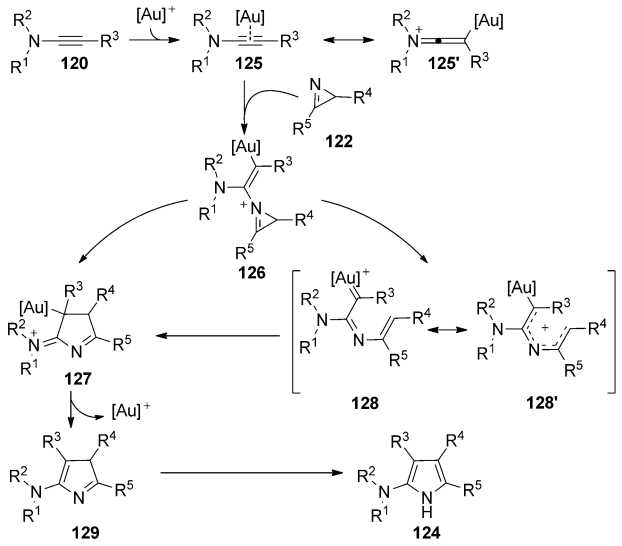


Scheme 29. Nucleophilic nitrenoid equivalents in the synthesis of polysubstituted 2-aminopyrroles.

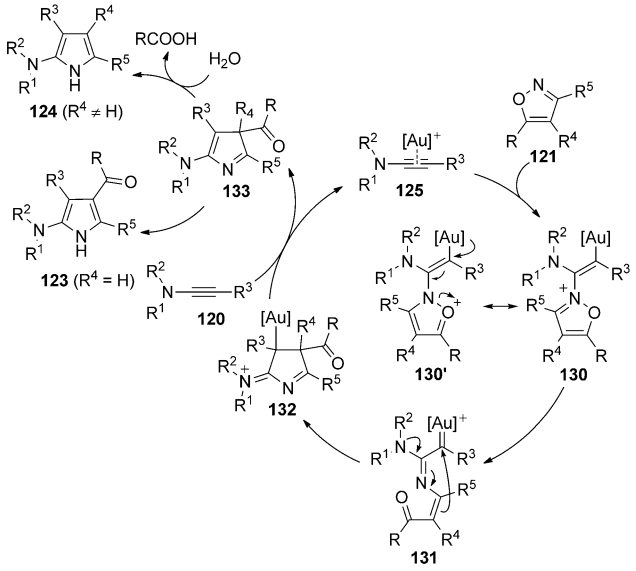
carbene intermediate **128** and 4π-electrocyclization.[47] On elimination of gold, hydride shift in **129** afforded the desired pyrrole **124**.

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 acylpyrrole **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** → **123**) a water-aided deacylation is proposed to provide aromatization (**133** → **124**, Scheme 31).[46]

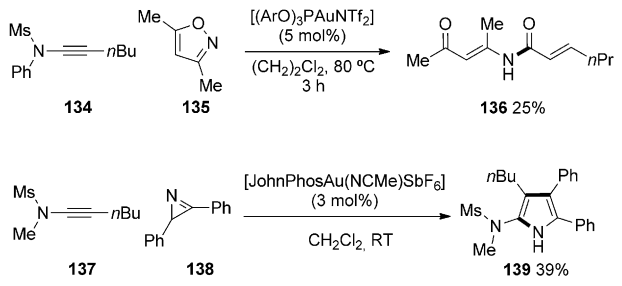
The use of ynamides with straight-chain aliphatic groups on the C-terminus rather than Csp^2 centers was less effective in both methods. The isoxazoles-based approach afforded the α,β-unsaturated amides **136** by 1,2-insertion into an adjacent C–H bond, whereas reaction with an azirine gave the desired pyrrole **139** but in modest yield (Scheme 32). This difference



Scheme 30. Proposed mechanism for the regioselective synthesis of polysubstituted 2-aminopyrroles from 2*H*-azirines.



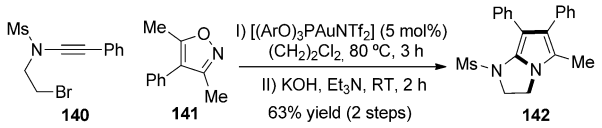
Scheme 31. Proposed mechanism for the formation of polysubstituted 2-aminopyrroles.



Scheme 32. The use of alkyl-substituted ynamides with isoxazoles and azirenes.

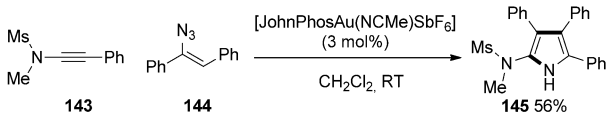
might be rationalized by considering the relative ease with which each series can adopt the geometry required for cyclisation in competition with that required for elimination or hydride shift from an adjacent methylene group. However, other substantial influences on the chemoselectivity and resulting 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 lipoxygenase 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 **142** (Scheme 33).[46]



Scheme 33. Applicability of the pyrrole-forming method.

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]



Scheme 34. Using a vinyl azide in an intermolecular nitrene-transfer reaction.

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 α-imino metal carbene reactivity patterns triggered by initial attack of the nitrenoid, so far shown to include alkyl and aryl azides, pyridinium-*N*-aminides, azirenes, 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 azirenes 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 carbenoid. When combined with the importance of nitrogen-heterocycles across a broad range of applications it is apparent that future studies into the reactivity of nucleophilic nitrenoids through π-activation of alkynes are primed to bring powerful new tools to address current synthetic challenges.

Acknowledgements

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

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FOCUS REVIEW

Heterocyclic Chemistry

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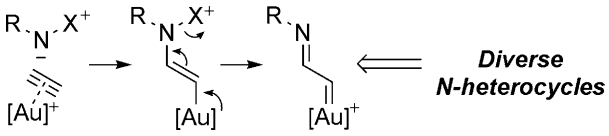
Nucleophilic Nitrenoids Through π-Acid Catalysis: Providing a Common Basis for Rapid Access into Diverse Nitrogen Heterocycles



Life of pi: The combination of a π-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.