

# Gold-catalyzed annulations with nucleophilic nitrenoids enabled by heteroatom-substituted alkynes

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# The Chemical Record

## Gold-Catalyzed Annulations with Nucleophilic Nitrenoids Enabled by Heteroatom-Substituted Alkynes --Manuscript Draft--

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<b>Opposed Reviewers:</b>	
<b>Abstract:</b>	<p>The combination of a nucleophilic nitrene equivalent, a triple bond and a <math>\pi</math>-acid catalyst has underpinned numerous efficient transformations for the preparation of azacycles. This personal account details our efforts in developing an annulation strategy. Adding a nucleophilic nitrenoid to an activated alkyne can generate carbenoid character that is then quenched by a cyclisation onto the nitrenoid substituent. The use and development of N -acyl and N -heterocyclic pyridinium- N -aminides as 1,3- N , O and 1,3- N , N -dipole equivalents is discussed in the context of oxazole and heterocycle-fused imidazole formation, respectively. The resulting processes are highly efficient, practically straightforward, and tolerate considerable structural and functional group variation. Our use of heteroatom-substituted alkynes as enabling tools for reaction discovery is discussed. The reactivity accessed from the strong donor-like properties of ynamides is complemented by that obtained from alkynyl thioethers, which are emerging as interesting substrates for <math>\pi</math>-acid catalysis.</p>
<b>Response to Reviewers:</b>	<p>Dear Dinesh, I very much appreciate the thorough comments, correction and suggestions from the referee's. My response is below - with changes to the manuscript highlighted in yellow in the word file. Best wishes Paul</p> <p>Reviewer 1: Dr. Davies summarizes his laboratory's research in gold-catalyzed annulation reactions of several activated alkynes with nucleophilic nitrenoids. While Davies has contributed a review article in this field (Asian JOC 2015, 4, 694), I think this account provides a nice overview for those who are not as familiar with the Davies Group research. There are a few areas that are difficult to understand and a few places where scholarly presentation can be improved. I recommend publication when these are addressed: 1) Scheme 1(b), the X and Y heteroatom notation generalization does not consistent map onto those presented in Scheme 1(c) -- not sure what is the X/Y. This is shown by colour and has been changed so it applies across schemes 1b and 1c and is consistent. Bold bonds have been added for emphasis to help readers track across the reactions.</p>

2) Page 2, line 20: "...we continued explore the synthetic potential" should be "we continued TO explore the synthetic potential..."

Done

3) Define and/or draw the structure of  $\text{PicAuCl}_2$  (text and/or Schemes 3, 5, 8, 10, 11). Ref [15] shows several Au(III) catalysts, none of which uses the 'pic' shorthand. Good point, thanks – drawn in Scheme 3

4) The author is careful in not implicating gold carbene intermediates with  $[\text{Au}]=\text{C}$  double bonds, but rather gold carbenoids with  $[\text{Au}]-\text{C}$  single bonds or 1.5 bonds. I recommend including a brief discussion on the structure of these intermediates somewhere in the introduction.

I have added the following discussion to the introduction. I am not seeking here to discuss the nature of the gold carbene or its representation in detail – it branches the discussion in a way that I don't think is useful for this report, but also that the drawings are given to ensure that they are generally applicable (for instance in some cases the  $\pi$ -acid can be a Bronsted acid, and so a  $\text{C}=[\pi\text{-acid}]$  double bond cannot be.

In the nitrenoid approach, where gold is most commonly but not exclusively used as the  $\pi$ -acid, it is important to note that the intermediacy of an  $\alpha$ -imino-metal carbene D (Scheme 1b) provides a convenient framework to conceptualize reactivity, but may not always describe the actual intermediate involved in some reactions. The vinyl metal carbenoid C is also a potential electrophile and hence formation of the cyclic intermediate E could occur from either C or D, with or after elimination of the leaving group, respectively. Reaction analysis should therefore consider the differences between these intermediates as well as the role of the  $\pi$ -acid, and its ligand sphere if relevant, on the nature of the intermediates

5) Section 2.1 is hard to read, and I would imagine this to really be the case for those who are not familiar with this chemistry.

As listed below, changes have been made to improve the readability of this section.

- When discussing "The oxazole C-2 position derived from the aminide reactant can include aryl, heteroaryl...", it would be helpful to readers if numbers were included with the structure in the scheme. Alternative, all of these words can be replaced with or indicated by "R4".

I prefer to keep the words so that referring to the scheme is not needed, and so have modified that part, including R4.

The substituent at the oxazole C-2 position derives from the R4 group of the aminide reactant and can include aryl, heteroaryl ( $\pi$ -rich and -poor), alkyl, vinyl, alkoxy and amino groups.

- "Choice of ynamide dictates the substituent at C-5 with..." Indicate somewhere that this is "R3"

Done

- "Although an acyclic carbamate undergoes a fragmentary cyclisation, ynamides..." Include the drawing in a scheme.

I have not included a scheme for this, but have given more details in the text – and given a reference to previous reports of such cyclisation. "An acyclic carbamate (NBoc) undergoes a previously reported fragmentary cyclisation to afford an oxazolone.{Hashmi, 2007 #1328}{Istrate, 2008 #1336}"

- The discussion of the substrate scope does not follow the order of the scheme and is quite random. Discusses 3o-p, then 3a-d, then 3k-n. I recommend rearranging either the text or scheme.

Reworked and added compound references so that it runs through in order (though some back and forth is needed subsequently as each example can cover different aspects)

- Page 2, lines 31-32: (1.1 to 1.5 eq.) -- sometimes eq. and other times equiv. "equiv." is generally preferred.

Changed throughout schemes and in text to be consistent

- "This convergent reaction matches a process in which a nascent gold carbene is captured by the acyl substituent to the recently delivered nitrene component". I'm not fully grasping this and I think it will also be hard for the average reader without a scheme.

Changed to "Although the overall reaction is consistent with formation of an  $\alpha$ -imino gold carbene 7 (Scheme 4) followed by cyclisation, a structure-reactivity survey led us to conclude that C-O bond forming cyclisation likely pre-empts formation of a distinct gold carbene"

- Page 2, line 53: "r,beta-unsaturated"?

Alpha – changed

- Scheme 33: 3f is missing the yield.

Added

- "We posited that the O-C5 bond..." Include the atom numbering in the scheme or highlight this bond

Added compound numbering in text: We posited that the C-O bond forms alongside scission of the N,N-bond and elimination of pyridine (6  $\rightarrow$  7).

- "Reconfiguration at the nitrogen centre is required for C=N bond formation, bringing the acyl group into plane." Clarify: Is the author referring to rehybridization of the nitrogen center? Is this the pyridinium nitrogen?

The N-N bond is derived from N(sp<sup>2</sup>) and this becomes a p-orbital as pyridine is eliminated with the nitrogen staying sp<sup>2</sup> but with a change of plane.

Text changed to "As the C=N bond is formed and the pyridine is eliminated the imine nitrogen has rehybridised bringing the acyl group into plane"

- the "...simple pyridine was pleased as significantly more complex pyridine substitution patterns are often required to achieve the desired reactions." Should be more specific: How complex? quinoline and bromopyridine or are there more complex derivatives that are used?

I have reworded this to replace complicated with substituted. "was pleased as more substituted pyridine motifs are often required"

- Page 3, lines 46-47: "12a/b" should be "9a-c"? and "12c" should be "9c"?

Yes, thanks. Both changed.

6) Scheme 4: [Au]<sup>+</sup> over the first arrow should be [Au]<sup>3+</sup>

This generic form is to show that it is an electropositive gold species. [Au]<sup>3+</sup> would indicate a species with three positive charges which is unlikely.

7) Page 4, line 43: (17 $\rightarrow$ 18 $\rightarrow$ 19, Scheme 8) should be (17 $\rightarrow$ 18 $\rightarrow$ 19, Scheme 6)

Changed

8) Scheme 6 could be labeled (a)/(b). Scheme 6(b) 18 $\rightarrow$ 19: loss of MeO<sup>-</sup> (and CO) 6a/b used. And CO added on scheme

9) Scheme 7 and the discussion of the N-aminide synthesis seems randomly placed. Some of these substrates appeared in Scheme 3 and others later. It could make sense to present the substrate synthesis first (prior to the annulation chemistry) or at the very end.

I have moved the paragraph discussing historical context and Huisgen's work to the start of the oxazole section to clean this up. I did look moving the rest as suggested by I was dissatisfied with the impact on the narrative flow. I intend to keep the rest where it is as it follows on with reactivity – namely the competing pathways, and leads into the scale-up examples. But I have restructured this to signpost it more effectively, introducing a new header.

2.3. The preparation of N-acyl pyridinium N-aminides enabling gram-scale processes.

Due to their previous and predominant use as 1,3-C,N-dipoles, little attention had been paid to the preparation of N-acyl pyridinium N-aminides reactants with much variation at the acyl substituent. In order to access the reactants needed to explore the

fuller scope of the oxazole-forming reaction, we adapted the preparative protocols reported by Streith[26] and Kakehi's.[25h, 27] Under these conditions, structurally varied and functionally diverse moieties can be prepared from readily accessible starting materials under mild conditions. Methyl esters are stirred with N-amino pyridinium iodide and potassium carbonate in methanol to provide the desired and bench stable nitrenoids in a single step (Scheme 7, top).

10) Scheme 8 caption: N aminides should be "N-aminides"  
Done

11) Scheme 9: define and/or draw the DTBPAu catalyst. It later appears as DBTP in Scheme 13

Drawn in, and initialism changed to be consistent.(TDBPP)

12) Scheme 10: compound #49 used twice. Compound #54/55 should go above the arrows next to the reactants

Mis-labelled – that is cmpd 51. Moved and added missing yield.

13) Scheme 14: eq. --> equiv.

Changed

14) There are two compound 72f's

Changed numbering

15) Page 7: Cannot find structure C2

This was 73B -changed

16) Scheme 18: This is the only occurrence of cationic [Au(I)]<sup>+</sup> whereas previous examples are with [Au(III)]. Why [Au(I)] here? Are these interchangeable in any of the instances? Reactivity differences? Perhaps a brief discussion to provide some insight.

Several of the previous examples were also with cationic Au(I) (phosphite stabilised) I have added a sentence earlier

"The reactions again proceed smoothly with close stoichiometry of reactants in the presence of either an electrophilic phosphite Au(I) precatalyst or the PicAuCl<sub>2</sub> complex, which are interchangeable in this chemistry to some extent and to date are the two most effective catalysts for the aminide-type nitrenoids."

The nature of the active catalyst is worthy of further research, and the following statement has been added into the conclusions

Reviewer 2: The manuscript named "Gold Catalyzed Annulations with Nucleophilic Nitrenoids Enabled by Heteroatom-Substituted Alkynes" is a very interesting personal overview of a well known chemical transformation. The insights given by the author in nucleophilic cycloadditions like the annulations mentioned are invaluable and is a in-demand topic since plenty of molecules can be prepared by this route, especially those in fine chemistry. I found it of easy comprehension and very informative, though I believe there is room for improvement. Therefore, I will recommend its publication after a Minor Revision.

General Overview: Overall, the manuscript is well written, and accomplishes its goal. More than 80% of the references are from the last decade and relevant for the theme, making the Personal Account a trending topic in Organic Synthesis. Nonetheless, there are minor issues in some parts of the manuscript that are important for its full acceptance in "The Chemical Record", ranging from some ideas missing to technical mistakes. In this sense, I will try to make suggestions, but only with the intention to enhance the excellent job done:

1. From your vast experience, I would like to know if there is a possible correlation between the type of gold pre-catalyst and the type of nucleophilic nitrenoid necessary for a cycloaddition, or whether the type of pre-catalyst affects the product distribution. If there is any, I think it could be insightful for the readers studying this type of reaction; Broadly speaking the aminide type systems which are the main focus of this report are best with the more electropositive systems e.g. Au(III) and Phosphite Au(I). This point is now covered in the text – see response to Reviewer 1. I've also added "The most effective catalyst was a N-heterocyclic carbene stabilized Au(I) complex. This

observation contrasts with the inefficiency of such pre-catalyst systems with the N-substituted pyridinium N-aminide reactants, and highlights the importance of the type of nitrenoid in elucidating the most effective conditions” to highlight that it is the type of nitrenoid that is critical to the type of complex used. In the conclusions I have highlighted this point as “Effective annulations are obtained using Au(III) or phosphite-stabilised Au(I) based pre-catalysts, with phosphine or N-heterocyclic carbene stabilised Au(I) performing poorly.”

Given the uncertainty over the active catalyst species (rather than pre-catalyst), further speculation may be unhelpful, but I have commented on some of the challenges in the conclusion:

“Looking forward, further investigation into the precise mechanistic details of these  $\pi$ -acid catalyzed nitrenoid reactions will be important to gain a detailed understanding of key off-cycle processes and catalyst speciation in order to aid reaction and catalyst design.

”

2. Why is gold the only precious metal cited as a catalyst in this manuscript? Is there a particular reason for why this kind of reaction is better with this element? I would like to see an honest opinion coming from an expert like the author, since mechanistic details of these reactions like in <https://doi.org/10.1080/01614940.2019.1594016> can sometimes not be clear or the only reason to afford a plausible explanation;

Gold is the precious metal catalyst being used in the studies being reviewed, so in that sense there is not much to be said beyond it working better than the other systems tried in those studies. I don't entirely follow the query with respect to the review that is referred to, but I have added some statements into the outlook section to discuss the role of other metals/catalysts that hopefully address this, but also bring out some key points again. .

Strong Bronsted acids or other, cheaper, metal catalysts like Zn(II) have been used to achieve the desired reactions. That approach is undoubtedly an important direction to pursue with great potential for the development of more sustainable synthetic methods and for reaction discovery in its own right. However, it remains to be seen whether such methods will match or indeed surpass the reaction generality that can be achieved with gold catalysis. As shown in the reactions of alkynyl thioethers and isoxazoles, the use of gold catalysis delivers the annulation pathway that was not accessible under Zn(II) catalysis, so in that case at least the approaches complement each other. In our experience, gold catalysis appears to offer a uniquely broad applicability, certainly as a tool for reaction discovery.

3. I felt that challenges in the research of this topic are missing, besides better comprehension of the enabling role of thioethers in Au catalysis that was clear in the text. Economic factors associated to the reaction conditions, acquisition of proper gold catalysts or even product stability overtime could be possible barriers for a better widespread of this chemical transformation?

I have added to the conclusions to highlight some of the points.

“The methods are readily amenable for use on gram scale as demonstrated across the reactions described above. As the heterocycles formed in these annulation processes are ubiquitous as constituents or precursors to bioactive compounds, there would appear to be significant scope to explore the validity of these convergent nitrenoid-based approaches for the directed synthesis of bioactive or other target molecules. The current use of precious metal catalysis at reasonably high loadings (~1 to 10 mol%) represents a challenge for wider uptake of these annulation approaches. Strong Bronsted acids or other, cheaper, metal catalysts like Zn(II) have been used to achieve the desired reactions. That approach is undoubtedly an important direction to pursue with great potential for the development of more sustainable synthetic methods and for reaction discovery in its own right. However, it remains to be seen whether such methods will match or indeed surpass the reaction generality that can be achieved with gold catalysis. As shown in the reactions of alkynyl thioethers and isoxazoles, the use of gold catalysis delivers the annulation pathway that was not accessible under Zn(II) catalysis, so in that case at least the approaches complement each other. In our experience, gold catalysis appears to offer a uniquely broad applicability, certainly as a



	<p>tool for reaction discovery. The challenge of cost and sustainability could also be addressed through the development of more effective gold catalysts that can be used at much lower loadings. Looking forward, further investigation into the precise mechanistic details of these <math>\pi</math>-acid catalyzed nitrenoid reactions will be important to gain a detailed understanding of key off-cycle processes and catalyst speciation in order to aid reaction and catalyst design."</p> <p>4. Please, check the final sentence in page 3, lines 55-57: "A discrete gold carbene, which was also considered unlikely as a result of the lack of stability from the electropositive Au(III) precatalyst". I think the sentence does not make sense, maybe a proper connector is missing; Yes, I have deleted this sentence as actually it does not add too much.</p> <p>5. Please, check the schemes in the manuscript for errors. For example, in Scheme 3, molecule 3f has it's yield percentage missing; Done</p> <p>6. In page 4, line 49, please check if the correct word isn't "naphtyl" in place of "napthyl".  Thanks, this is changed to Naphthyl</p> <p>Reviewer 3: The author has chosen an excellent topic and he has written in a very nice way. I enjoyed reading this article. He has covered all the recent publications int his area. I have only two things to add or the author should think about: 1. Can he find some applications of the reported reactions? Can he mention whether these reactions have been applied for the synthesis of natural products or pharmaceuticals? In terms of published work and the reactions that I focus on stemming from our work then no, these are not yet applied in such target synthesis to my knowledge. We hope to be able to report on this area soon, but for now I have added a statement in the conclusion to highlight this as a prospective area of interest. As the heterocycles formed in these annulation processes are ubiquitous as constituents or precursors to bioactive compounds, there would appear to be significant scope to explore the validity of these convergent nitrenoid-based approaches for the directed synthesis of bioactive or other target molecules.</p> <p>2. Can he also comment on the scale up of the reported reactions?  This has been highlighted more in the section of oxazole formation "The multigram preparation of functionalised oxazole 30 illustrates the scalability of these processes (Scheme 8). A relatively low catalyst loading (1 mol%) is combined with an efficient 1:1.1 stoichiometry of the reactants 28 and 29. "The gram-scale reactions were then already mentioned later on for subsequent transformations, and the following statement has been added into section 3 to make this point more explicitly. "As in the oxazole synthesis, these transformations are also successfully performed on gram scale." The following is added to the conclusion to reiterate the point. "The methods are readily amenable for use on gram scale as demonstrated across the reactions described above."</p>
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Dedication	



# Gold-Catalyzed Annulations with Nucleophilic Nitrenoids Enabled by Heteroatom-Substituted Alkynes

Paul W. Davies<sup>\*[a]</sup>

**Abstract:** The combination of a nucleophilic nitrene equivalent, a triple bond and a  $\pi$ -acid catalyst has underpinned numerous efficient transformations for the preparation of azacycles. This personal account details our efforts in developing an annulation strategy. Adding a nucleophilic nitrenoid to an activated alkyne can generate carbenoid character that is then quenched by a cyclisation onto the nitrenoid substituent. The use and development of *N*-acyl and *N*-heterocyclic pyridinium-*N*-aminides as 1,3-*N,O* and 1,3-*N,N*-dipole equivalents is discussed in the context of oxazole and heterocycle-fused imidazole formation, respectively. The resulting processes are highly efficient, practically straightforward, and tolerate considerable structural and functional group variation. Our use of heteroatom-substituted alkynes as enabling tools for reaction discovery is discussed. The reactivity accessed from the strong donor-like properties of ynamides is complemented by that obtained from alkynyl thioethers, which are emerging as interesting substrates for  $\pi$ -acid catalysis.

## 1. Introduction

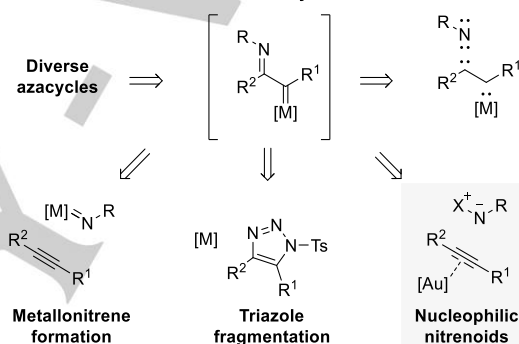
The ubiquity of nitrogen-containing heteroaromatic motifs as key motifs in pharmaceuticals, agrochemicals, bioactive natural products, probes, sensors, catalysts and functional materials, and as precursors to other desirable motifs, underpins considerable efforts in transformation discovery. Advances in those areas are enabled by new preparative methods that facilitate efficient access to azacyclic motifs, and with new substitution patterns. In recent years a diverse range of efficient heterocycle-forming transformations have been developed via the intermediacy of putative  $\alpha$ -iminometal carbene reactivity patterns (Scheme 1a). Different routes have been realized for the formation of these desirable reactive intermediates from alkynes. These include the interaction of an alkyne with a metallonitrene,<sup>[1]</sup> the fragmentation of *N*-sulfonyl triazoles formed from dipolar cycloaddition between alkynes and azides,<sup>[2]</sup> and the reaction of a  $\pi$ -acid activated alkyne with a nucleophilic nitrene equivalent<sup>[3]</sup> (termed here as

“nucleophilic nitrenoids” as a catch-all phrase concerning the similar function of disparate structures<sup>[4]</sup>). These new approaches generally feature mild conditions, for significant bond-forming processes, and good functional group tolerance.

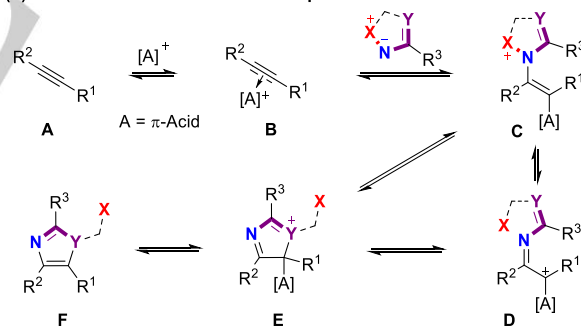
There are complementary aspects to each strategy; for the  $\pi$ -acid-enabled nucleophilic nitrenoid approach, the ability to incorporate nitrene fragments bearing diverse substituents is particularly noteworthy. The introduction of different *N*-substituents coupled with the ability to quench the forming carbene character on those substituents leads to a new approach to intermolecular annulations, initially realized in formal (3+2) dipolar cycloadditions (Scheme 1b). The use of this conceptual framework has since led to a huge array of powerful new azacycle forming transformations alongside the introduction of a diverse range of nucleophilic nitrenoid types (Scheme 1c).<sup>[5]</sup>

In the nitrenoid approach, where gold is most commonly but not exclusively used as the  $\pi$ -acid, it is important to note that the intermediacy of an  $\alpha$ -imino-metal carbene **D** (Scheme 1b)

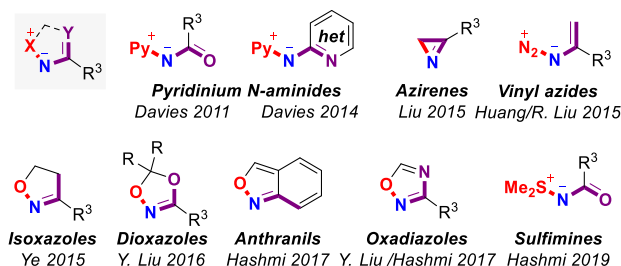
(a)  $\alpha$ -Imino-metal carbene like reactivity



(b) General  $\pi$ -acid based annulation processes



(c) Representative nucleophilic nitrenoids for (3+2) annulations



**Scheme 1.** General overview of the nucleophilic nitrenoid based approach to annulation reactions.

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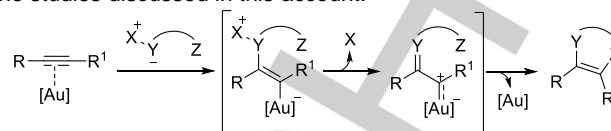
provides a convenient framework to conceptualize reactivity, but may not always describe the actual intermediate involved in some reactions. The vinyl metal carbenoid **C** is also a potential electrophile and hence formation of the cyclic intermediate **E** could occur from either **C** or **D**, with or after elimination of the leaving group, respectively. Reaction analysis should therefore consider the differences between these intermediates as well as the role of the  $\pi$ -acid, and its ligand sphere if relevant, on the nature of the intermediates.

A number of reviews have captured the rapid advances made in this subfield of field of  $\pi$ -acid catalysis,<sup>[6]</sup> these include Garzón and Davies exploring the combination of nucleophilic nitrenoids and  $\pi$ -acid catalysis for diverse *N*-heterocycle synthesis in 2015,<sup>[4]</sup> Aguilar and Santamaría showcasing the value of  $\alpha$ -imino gold carbenes as intermediates for heterocycle synthesis in 2019,<sup>[7]</sup> and Ye and Liu and coworkers broad exploration of nitrene and carbene transfer in gold catalysis in 2021.<sup>[8]</sup> In this personal account I summarize my team's contributions to the development of annulation reactions using nucleophilic nitrenoids.

## 2. *N*-Acyl pyridinium *N*-aminides as 1,3-*N,O* dipole equivalents

Our interest in nucleophilic nitrenoids arose from investigating the synthetic utility of carbene character generated from triple bonds under  $\pi$ -acid catalysis.<sup>[9]</sup> The use of an oxygen-transfer approach to generate metal carbene character from triple bonds<sup>[10]</sup> had led to us developing a regioselective route into  $\alpha,\alpha'$ -disubstituted imidocarbene equivalents from the intermolecular reaction of a pyridine *N*-oxide and an ynamide under gold catalysis.<sup>[11]</sup> While we continued to explore the synthetic potential of using ynamides<sup>[12],[13]</sup> as  $\alpha$ -amido diazo surrogates by oxygen-transfer,<sup>[14]</sup> we envisaged that a group-transfer approach could be used to underpin new reactivity. Specifically we sought to investigate whether a group transfer process could be used to

the means to quench the developing carbene character, schematically illustrated as in our initial report (**A**  $\rightarrow$  **D**, Scheme 2).<sup>[5a]</sup> This nitrenoid-based annulation concept forms the basis of the studies discussed in this account.



Scheme 2. Initial visualisation of the annulation concept.

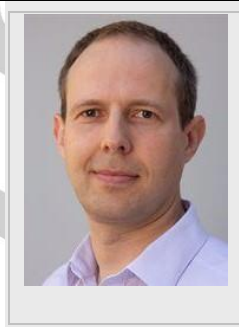
### 2.1. Reactions between ynamides and pyridinium *N*-acyl aminides

We initiated a study into intermolecular access to  $\alpha$ -imino gold reactivity patterns by using *N*-acyl pyridinium *N*-aminides as prospective acyl nitrene transfer agents. In 2011 we reported that the reaction of ynamides **1** and aminides **2** in the presence of a  $\text{PicAuCl}_2$  precatalyst<sup>[15]</sup> led to the formation of 4-*N*-oxazoles **3** with complete regioselectivity (Scheme 3).<sup>[5a, 16]</sup> This formal (3+2) cycloaddition has the aminide reactant **2** functioning as 1,3-*N,O*-dipole equivalent with the elimination of pyridine.

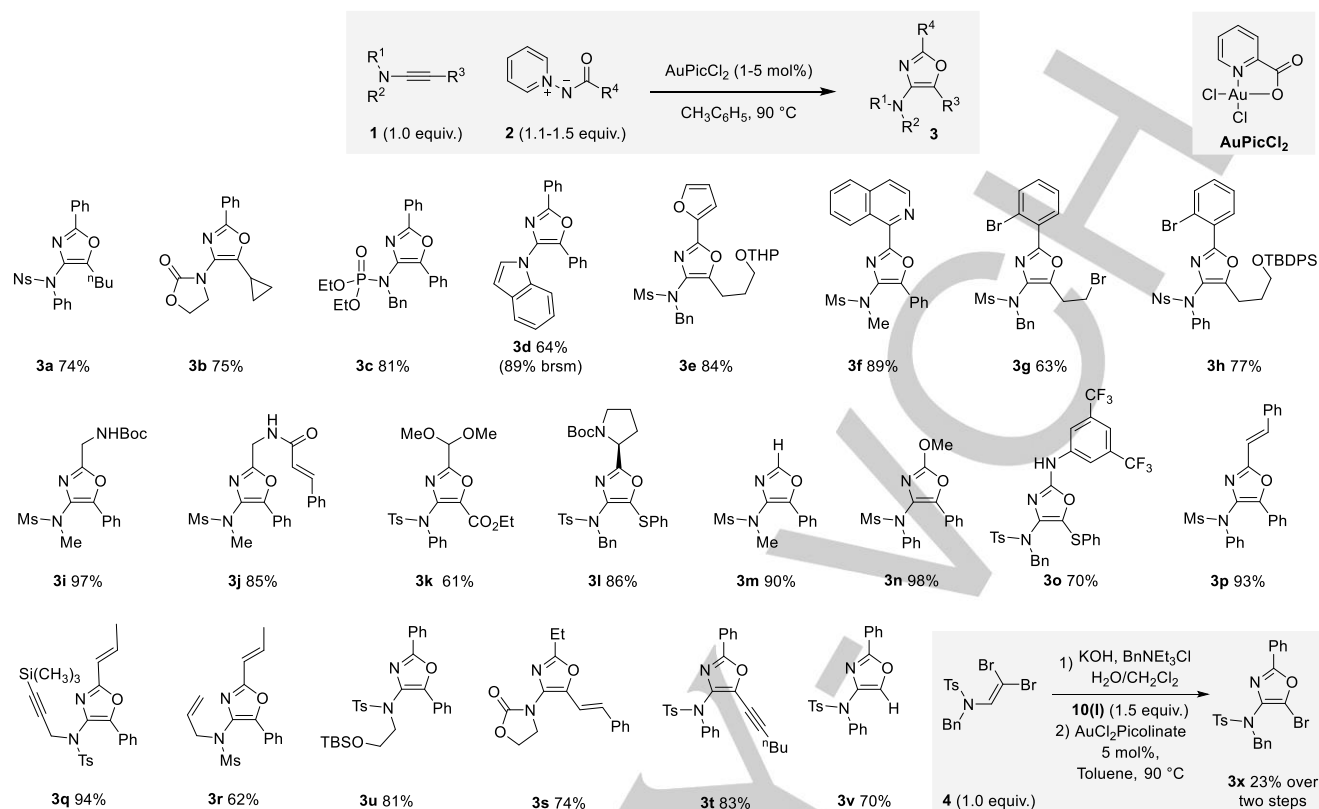
Huisgen's<sup>[17]</sup> seminal studies demonstrated that an acyl nitrene, a 1,3-*N,O* dipole, will react with an alkyne to afford an oxazole. However this approach has not seen significant uptake, in stark contrast to the ubiquitous use of dipolar cycloadditions to prepare other azoles such as triazoles.<sup>[18]</sup> The relative reactivity profile of the required dipoles is striking. While triazole formation requires a readily isolated and handled azide, oxazole formation requires an *in situ* generated dipole. These acyl nitrenes are highly electrophilic, prone to rearrangement by C $\rightarrow$ N migration and display relatively indiscriminate reaction with other components of the reaction system such as solvent.<sup>[19]</sup> The nucleophilic nitrenoid approach with *N*-acyl pyridinium *N*-aminides voids these issues, unveiling the acyl nitrene character in conjunction with  $\pi$ -acid catalysis to render the alkyne electrophilic.

The scope of the reaction between ynamides and *N*-acyl pyridinium *N*-aminides proved to be remarkably broad, substantial functional group and structural variety is accommodated on both reactants (Scheme 3).<sup>[5a, 16]</sup> Ynamides derived from various sulfonamides, a phosphoramidate and a cyclic carbamate all function well, as does an *N*-alkynyl indole (**3a-3d**). An acyclic carbamate (NBoc) undergoes a previously reported fragmentary cyclisation to afford an oxazolone.<sup>[20]</sup> The substituent at the oxazole C-2 position derives from the  $\text{R}^4$  group of the aminide reactant and can include heteroaryl ( $\pi$ -rich and -poor, **3e,f**), aryl (**3a,g,h**), functionalized alkyl (**3i-l**), proton (**3m**), alkoxy (**3n**), amino (**3o**), and vinyl (**3p-r**) groups. The reaction also proved tolerant to other functionality, including protected ethers, amines, carbamates, halides and enolisable esters.<sup>[5a, 16]</sup> Aliphatic, aromatic, benzylic, allylic and propargylic groups can also be included on the nitrogen atom (e.g. **3m-s**). The C-5-substituent is derived from the ynamide ( $\text{R}^3$ ). Aryl (**3c**), alkyl (**3a,g,h**), carboxylic ester (**3k**), sulfenyl (**3o**) substituents are all readily incorporated, as are extended  $\pi$ -systems. 1,3-Enynamides and 1,3-dynamides are used to access

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introduce a functionality onto an alkyne that would also provide



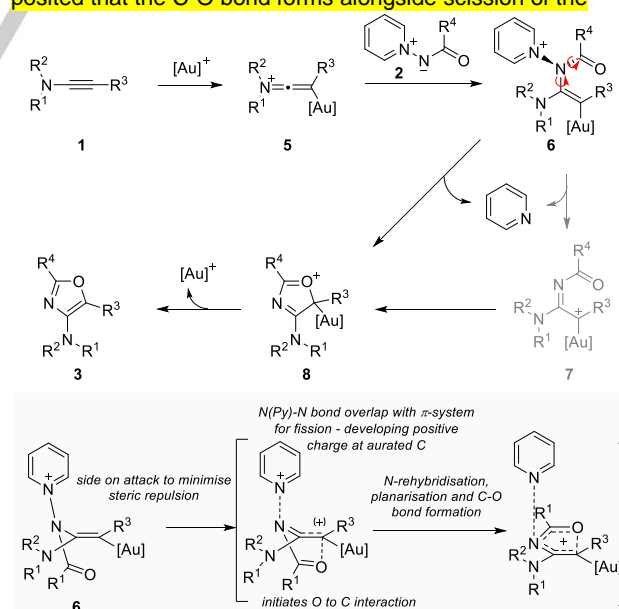
**Scheme 3.** Representative scope for the reaction of ynamides with N-acyl pyridinium N-aminides to give 4-N oxazoles.

oxazoles **3s** and **3t**, respectively. The 5-bromo oxazole **3x** is also accessible, prepared in two steps from **4**.

These reactions are straightforward to set-up and work-up. Only a slight excess of aminide **2** (1.1 to 1.5 equiv.) is required to ensure consumption of the ynamide. The polar nature of the residual aminide reactant facilitates purification with a simple filtration through a plug of silica gel often sufficient to remove residual polar reactant, allowing isolation of the pure oxazole with little processing.

Although the overall reaction is consistent with formation of an  $\alpha$ -imino gold carbene **7** (Scheme 4) followed by cyclisation, a structure-reactivity survey led us to conclude that C-O bond forming cyclisation likely pre-empts formation of a distinct gold carbene. Potential competing reactions, such as cyclopropanation with N-allyl ynamides (cf. **3m**, Scheme 3) or 4- $\pi$  electrocycloisomerisation with enynamides (cf. **3o**), were not observed despite their precedent from related  $\alpha$ -oxo gold carbenes.<sup>[21]</sup> Both pathways have also subsequently been validated in reactions of ynamides with different types of nucleophilic nitrenoids.<sup>[51, 22]</sup> Alkyl substituted ynamides could be used to access oxazoles in high yields despite the well-established precedent for 1,2-insertion pathways when gold carbene character is generated adjacent to methylene groups.<sup>[11]</sup> Concomitant with our initial study, Li and Zhang showed that N-sulfonyl pyridinium N-aminides could be used as nitrene-transfer agents to access the  $\alpha,\beta$ -unsaturated amidines by exactly that pathway.<sup>[23]</sup> These indications that the

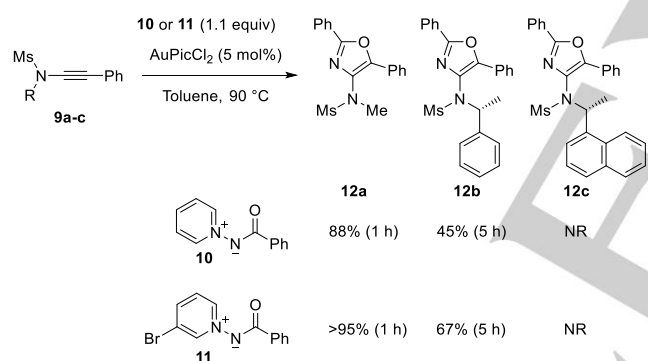
cyclisation step must be relatively fast led us to propose that cyclisation occurs at the vinyl gold carbene **6** formed on attack of the aminide onto gold activated ynamide (Scheme 4).<sup>[5a, 16]</sup> We posited that the C-O bond forms alongside scission of the



**Scheme 4.** Mechanistic outline for the oxazole-forming annulation reaction.

**N,N-bond and elimination of pyridine (6 → 7).** The N,N-bond must align to the vinyl gold  $\pi$ -system for cleavage, polarizing the aurated carbon. As the C=N bond is formed and the pyridine is eliminated the imine nitrogen has rehybridised bringing the acyl group into plane (Scheme 4, box).

The broad reactivity seen with acyl nitrene equivalents derived from simple pyridine was pleasing as more substituted pyridine motifs are often required to achieve desired reactions in related oxidation chemistry.<sup>[24]</sup> The choice of nucleofuge might affect multiple aspects of the reaction including the reagent's nucleophilicity, N,N-bond cleavage, and competing interactions with the substrate and catalyst as its concentration increases over the course of the reaction. A study with more substituted systems did however identify that optimization of that group can be beneficial. For instance the use of a 3-bromopyridine derivative **11** led to higher yields with ynamides **9a-c** compared to the parent aminide **10** in the same reaction time (Scheme 5). However this modification was not sufficient to induce reactivity in a very hindered naphthyl derived ynamide **9c**. The ability to modify the nucleofuge component more widely and retain function under these reaction conditions was demonstrated by Hashmi's group in 2019 using *N*-acyl sulfinimines to achieve the same oxazole formations where dimethylsulfide replaces pyridine as the leaving group.<sup>[25]</sup> A cyclic alternative to such nitrenoids for oxazole formation was introduced by Liu and co-workers in 2016 with dioxazoles, in which case the leaving group is acetone.<sup>[5g]</sup>



**Scheme 5.** The effect of modifying the nucleofuge in the nucleophilic nitrenoids.

## 2.2. 1,3-C,N and 1,3-N,O character of *N*-acyl pyridinium *N*-aminides.

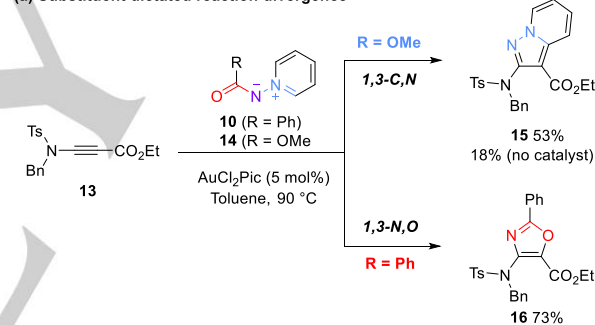
The 1,3-*N,O* dipole function of the aminides observed with ynamides under gold catalysis contrasts with their 1,3-*C,N* dipole character that has been exploited in a variety of transformations that elaborate the pyridine, including dipolar cycloaddition onto other  $\pi$ -systems.<sup>[26]</sup> Such reactivity was only seen in a specific combination of aminide and ynamide under gold catalysis: Ester-substituted ynamide **13** was reacted with aminide **14** leading to formation of the pyrazolo[1,5-*a*]pyridine **15** (Scheme 6a). Only ester-substituted oxazole **16** was formed when aminide **10** was used instead. The combination of an electrophilic alkyne and an aminide with a leaving group allow for productive C,N-alkyne cycloaddition (**17**→**18**→**19**, Scheme 6b), but this pathway is

unproductive in the absence of a good leaving group at the acyl position leading to reaction through tautomeric species **20**.

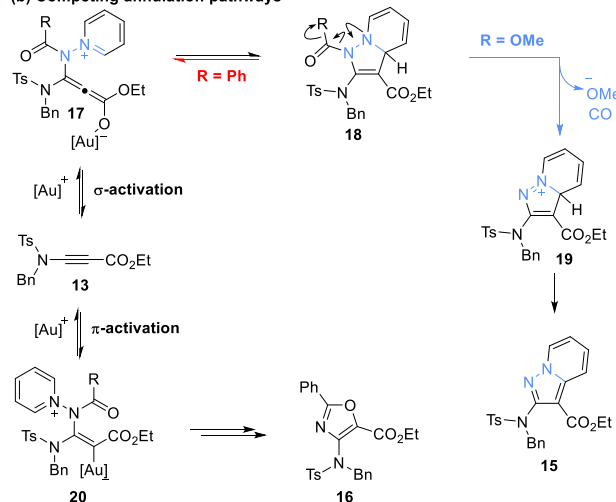
## 2.3. The preparation of *N*-acyl pyridinium *N*-aminides enabling gram-scale processes.

Due to their previous and predominant use as 1,3-*C,N*-dipoles, little attention had been paid to the preparation of *N*-acyl pyridinium *N*-aminides reactants with much variation at the acyl substituent. In order to access the reactants needed to explore the fuller scope of the oxazole-forming reaction, we adapted the preparative protocols reported by Streith<sup>[27]</sup> and Kakehi's.<sup>[26h, 28]</sup> Under these conditions, structurally varied and functionally diverse moieties can be prepared from readily accessible starting materials under mild conditions. Methyl esters are stirred with *N*-amino pyridinium iodide and potassium carbonate in methanol to provide the desired and bench stable nitrenoids in a single step (Scheme 7, top). Switching solvent to acetonitrile facilitates the use of other reactive electrophiles such as the isocyanate **23**. Carboxylic acids, such as proline derivative **25**, can be employed using a one-pot protocol incorporating activation with alkyl chloroformates.<sup>[16]</sup>

(a) Substituent dictated reaction divergence

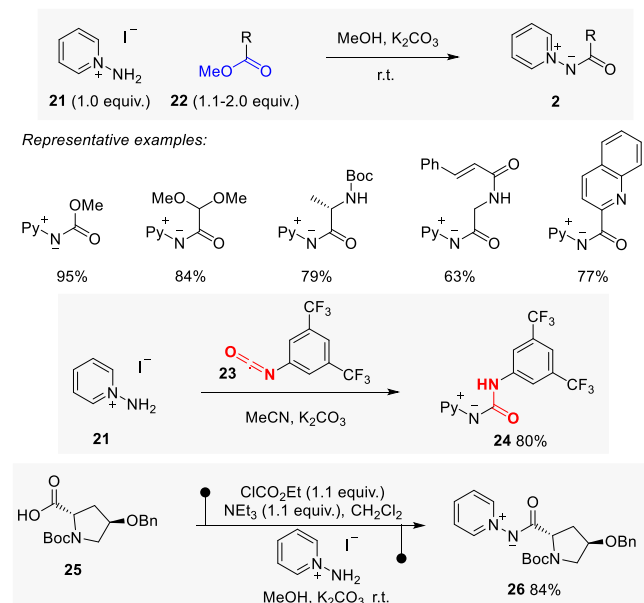


(b) Competing annulation pathways



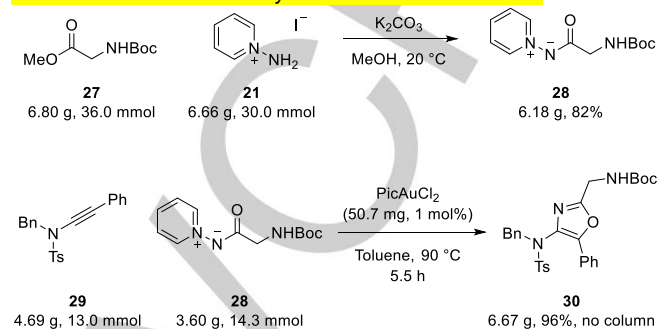
**Scheme 6.** The role of acyl substituent in affecting 1,3-*C,N* or 1,3-*N,O*-dipole character in the reaction with ester substituted ynamides.



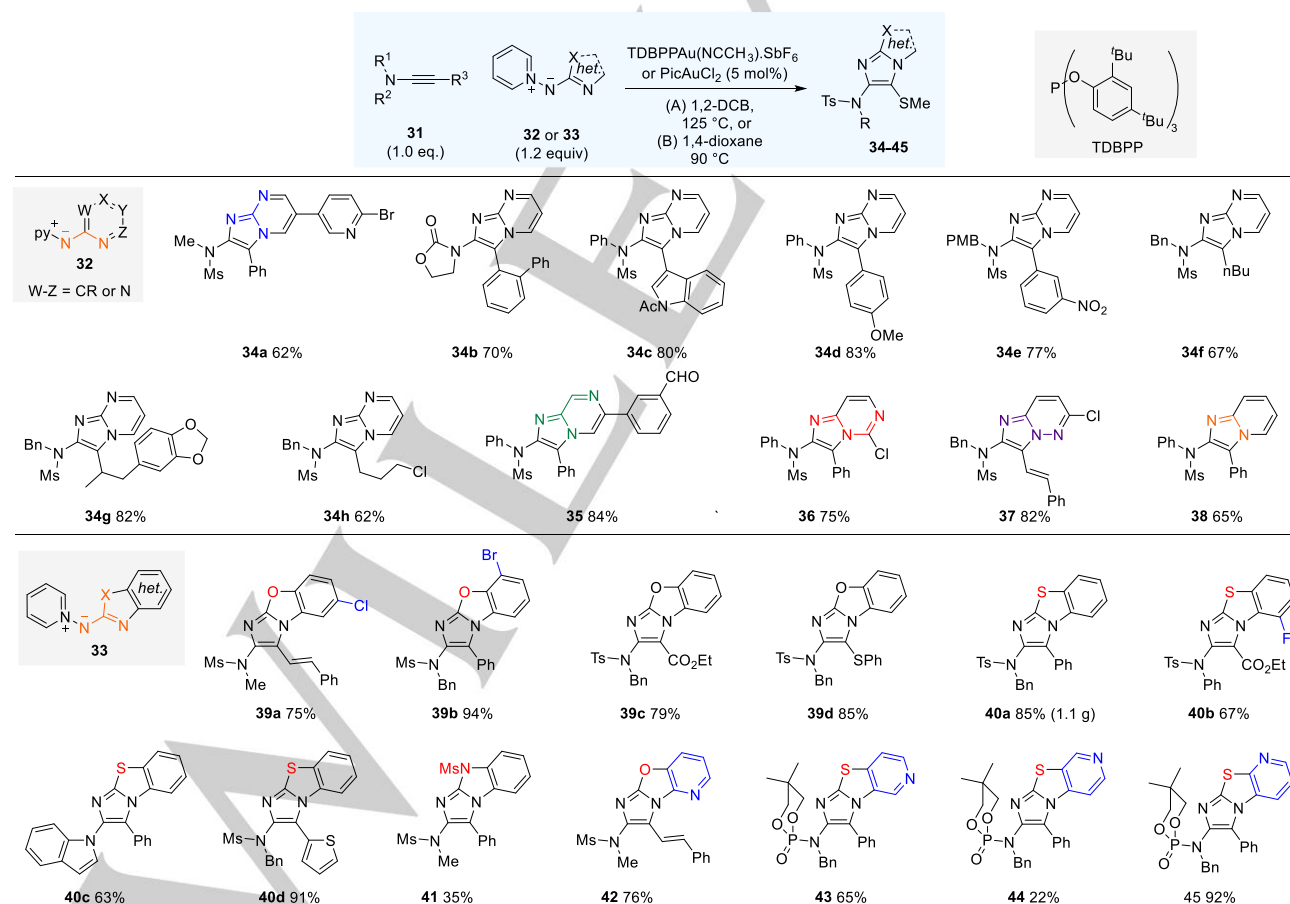


**Scheme 7.** The straightforward preparation of *N*-acyl pyridinium *N*-aminides under mild and functional group tolerant conditions from carboxylic esters (top), isocyanates (middle) and carboxylic acids (bottom).

The substrate preparation steps and the oxazole formation are all practically straightforward and **have proven** amenable to gram scale preparations, often avoiding the need for column chromatography. The multigram preparation of functionalised oxazole **30** illustrates the scalability of these processes (Scheme 8). A relatively low catalyst loading (1 mol%) is combined with an efficient 1:1.1 stoichiometry of the reactants **28** and **29**.<sup>[29]</sup>



**Scheme 8.** Multigram preparation of *N*-acyl pyridinium *N*-aminides and 4-*N* oxazoles.



**Scheme 9.** Using pyridinium-*N*-(heterocyclic)aminides as 1,3-*N,N* dipole equivalents with representative examples. TDBPP = Tri(2,4-di-*t*-butylphenyl)phosphite.

### 3. *N*-Azacyclic pyridinium *N*-aminides as 1,3-*N,N*-dipole equivalents

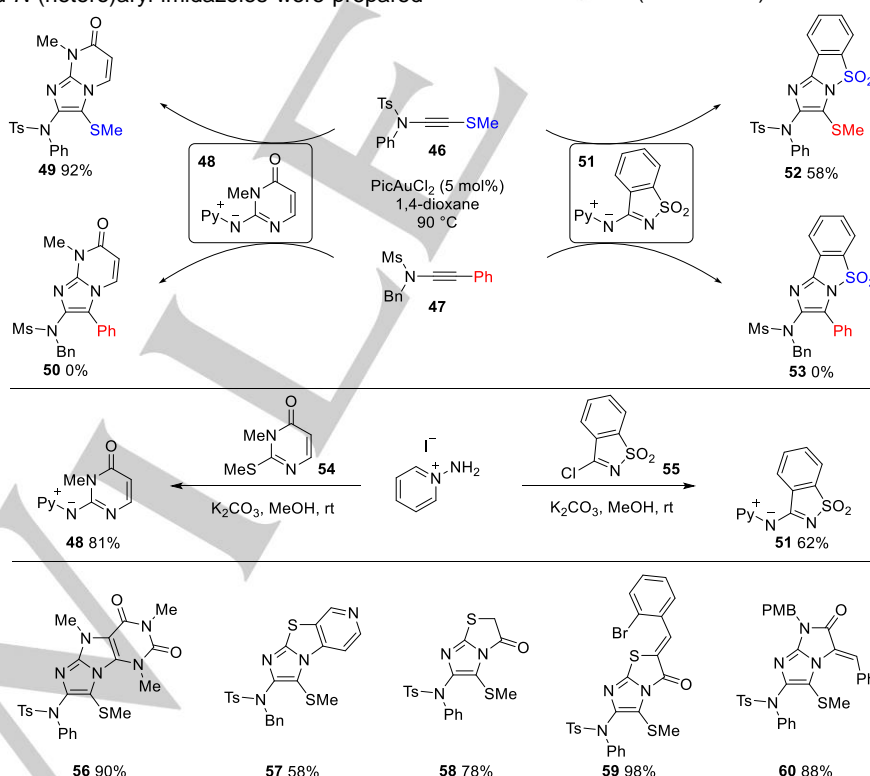
In 2014 we validated the annulation concept as a more general strategy on reporting that pyridinium-*N*-(pyridinyl/diazinyl heteroaryl)-aminides **32** could be used as *N*-nucleophilic 1,3-*N,N*-dipole equivalents to prepare amino-imidazo[1,2-*a*]diazine and amino-imidazo[1,2-*a*]pyridine structures **34–38** (Scheme 9).<sup>[5b]</sup> Notably, the reaction could be applied to all diazine classes providing a standardized method to access members of these important structures whose derivatives find widespread use in the medicinal and materials fields.

The reactions again proceed smoothly with close stoichiometry of reactants in the presence of either an electrophilic phosphite Au(I) precatalyst or the PicAuCl<sub>2</sub> complex, which are interchangeable in this chemistry to some extent and to date are the two most effective catalysts for the aminide-type nitrenoids. Excellent regioselectivity and functional group tolerance was observed. Organohalides, electrophilic and basic sites, heterocycles, strongly activating and reactivity functional group such as nitro and aldehydes were all readily incorporated (Scheme 9). The ynamide could also be functionalized with alkyl, aryl and vinyl substituents. Notably, a bulky ortho-phenyl group did not prevent reactivity (**34b**). Subsequently, the annulation strategy was used to access more varied *N*-heterocycles featuring 1,2-fused imidazole motifs. A range of tricyclic structures **39–45** based on *o*,*o'*-heteroatom-linked *N*-(hetero)aryl imidazoles were prepared

by this method (Scheme 9).<sup>[30]</sup> More forcing conditions were required with aminides **33** compared to the reactions with diazine-derivatives **32**. While excellent functional group and structural tolerance was again seen, alkyl-substituted ynamides generally afforded complex mixtures.

The use of aminides such as **48** and **51** incorporating oxo-substituted and non-aromatic heterocycles that were appealing for medicinal and agrochemical applications was examined (Scheme 10).<sup>[31]</sup> These reactants proved to be less reactive than previously studied analogues **32/33**. For instance, aminides **48/51** proved unreactive in the presence of a commonly used ynamide **47**, but reacted with the sulfenylated ynamide **46** to give the desired annulation products **49** and **52** in good yield. The presence of additional Lewis basic sites to sequester the gold catalyst and the conjugation of the *N,N*-dipole into carbonyl groups affecting both the initial attack and the cyclisation steps of the reaction. A wider study illustrated that sulfenylated ynamides are privileged substrates for nucleophilic nitrenoid-based annulation reactions affording excellent yields of variously functionalised heterocycles such as **56–60**, but also including different types of nitrogen-based reactants.

The pyridinium-*N*-(heteroaryl)-aminide reactants for these annulations are readily prepared by substitution reactions building upon the pioneering methods of Alvarez-Builla and co-workers.<sup>[32]</sup> In addition to halogenated heterocyclic precursors such as **55**, we found that substrates with embedded or elaborated thioamide or thiourea motifs were useful starting points.<sup>[31, 33]</sup> S-Methylation could be followed by nucleophilic substitution as demonstrated with thiouracil **54** (Scheme 10).



**Scheme 10.** The sulfenyl effect of *N,S*-substituted alkynes with more elaborated pyridinium-*N*-(heterocyclic)aminides as 1,3-*N,N* dipole equivalents.

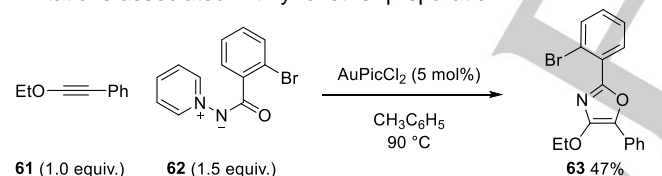
The generality of this method as a route into heterocycle fused imidazoles is demonstrated by its use in preparing 19 different types of heterocyclic cores, and the variety of substitution patterns accessible around these structures from simple and readily assembled building blocks (Schemes 9 and 10). As in the oxazole synthesis, these transformations are also successfully performed on gram scale.

The mechanism of these regiospecific reactions were considered to be analogous to that proposed for oxazole formation and were borne out in a computational study by Zhang and Geng on the reactions to form imidazo-pyrimidines and imidazo-pyrazines.<sup>[34]</sup>

#### 4. Beyond ynamides, extending the potential of nitrenoid based annulations

Since 2015 a range of different nucleophilic nitrenoids classes have been developed for annulation processes via putative  $\alpha$ -imino gold carbene reactivity patterns.<sup>[5-8]</sup> The preparative utility of ynamides for the discovery of efficient intermolecular reactions is clearly illustrated by their use in all these initial studies. Indeed, our initial foray into ynamide chemistry inspired a wider investigation of their synthetic utility in our group.<sup>[35]</sup> However, in order to enable much greater applicability of the annulation strategy, we have been looking to see whether these transformations can be achieved alongside more varied alkyne substitution patterns.

In our initial study we reported that an ynol ether **61** could be used as a direct alternative to ynamides in reactions with an *N*-acyl pyridinium *N*-aminide leading to the alkoxyoxazole **63** (Scheme 13).<sup>[5a]</sup> Despite the potential of this approach for the formation of desirable oxy-functionalised heterocycles<sup>[36]</sup> we have not explored this beyond proof-of concept, in part due to the limitations associated with ynol ether preparation.

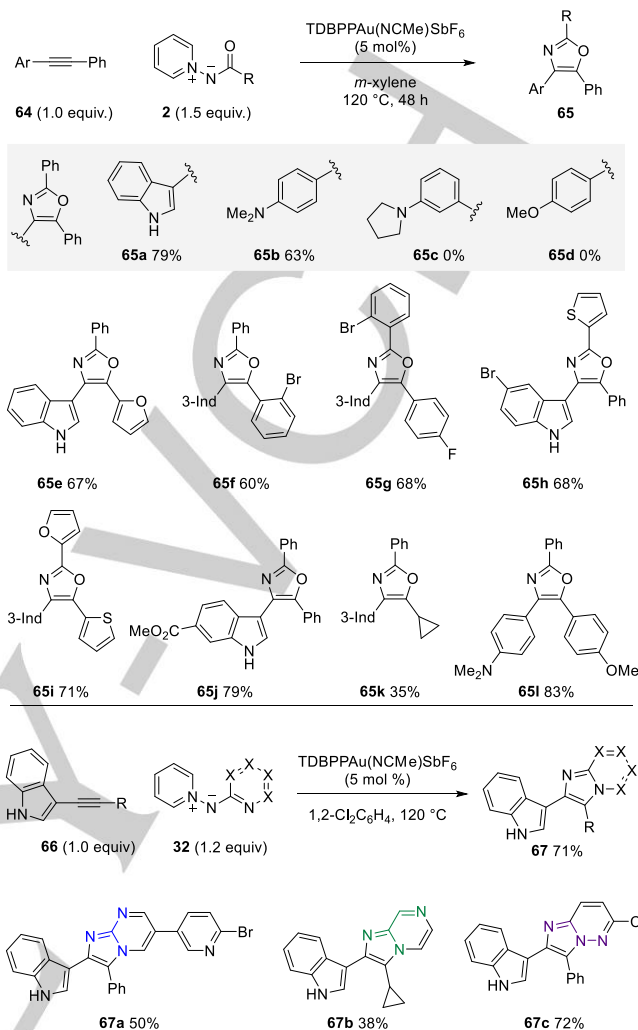


**Scheme 12.** The annulation of an ynol ether for the formation of a 4-alkoxyoxazole.

Oxazoles with 2,4,5-all carbon substitution patterns can also be accessed by reaction with *N*-acyl pyridinium *N*-aminides so long as the starting alkyne features a remotely conjugated nitrogen atom.<sup>[37]</sup> For instance, 3-alkynyl indoles and 4-alkynyl anilines are reactive but the 3-alkynyl anilines or 4-alkynyl anisoles do not react (**65a-d** Scheme 13). The reactions were again completely regioselective, showing good functional group tolerance. They provide a modular entry into (hetero)aryl-heteroaryl axes also being applicable to the fused imidazole motifs such as **67**.<sup>[5b]</sup>

##### 4.1. Alkynyl thioethers

Building upon our work with other heteroatom-substituted alkynes, and our wider interest in the gold catalyzed reactions of sulfur-



**Scheme 13.** Nucleophilic nitrenoid based annulations using alkynes with remotely conjugated activating groups.

containing moieties<sup>[10a, 14a, 14b, 38]</sup> we examined the use of readily accessed and robust alkynyl thioethers.<sup>[39]</sup> While sulfur-containing compounds are of innate value,<sup>[40]</sup> and a sulfonyl group can be used to access valuable higher oxidation level analogues, there has also been significant progress in cross-coupling reactions using C-S bonds to access C-C and C-heteroatom bonds rendering the putative products appealing.<sup>[41]</sup> These little explored substrates<sup>[42]</sup> were found to be effective in gold catalyzed reactions with *N*-acyl pyridinium *N*-aminides affording sulfonylated oxazoles **69a-c** (Scheme 14).<sup>[43]</sup> On investigating this reactivity, several general points became apparent:

- The sulfonyl group enables reactivity.

No reaction was seen when desulfonylated analogues **68d-e** were employed (Scheme 14). However, the all-carbon substituted oxazole **69e** can be accessed by Ni(0)-catalyzed cross-coupling from **69b**,<sup>[43]</sup> illustrating a prospective synthetic benefit of the alkynyl thioether approach.

- The reactions of alkynyl thioethers are regioselective,



In contrast to ynamide reactions which only give one regioisomer, as explained through regioselective addition to a keteniminium intermediate, both 4- and 5-sulfenyl oxazoles are accessible.

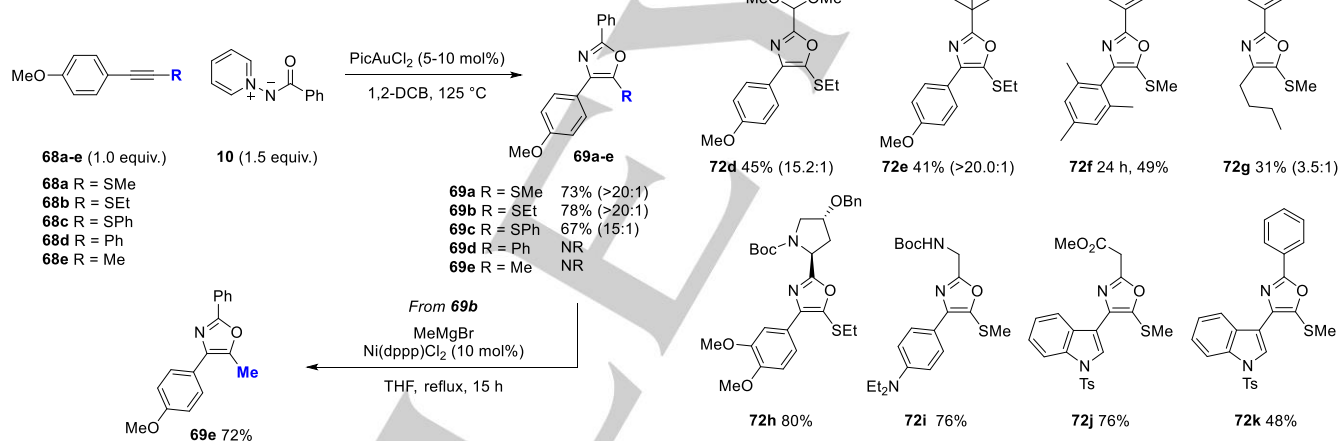
- The regioselectivity obtained with alkynyl thioethers is inverted when compared to ynamides and ynol ethers.

The 4-sulfenylated oxazoles would be favored if a ketenethionium pathway were dominant in analogy to the control from ynamide and ynol ethers. Instead, 5-sulfenylated oxazoles are consistently formed as the major isomers. Such activation has been invoked in a number of gold catalysed processes.<sup>[44]</sup>

- The level of selectivity was sensitive to all substituents on both reactants.

Selectivity for the 5-sulfenyl oxazole is reinforced using electron-donating groups on the alkyne, but is not dependent on it with reactions of neutral, aryl and alkyl, substituents still favouring the 5-sulfenyl oxazole (Scheme 15). Larger, or less flexible S-substituents afforded slower reactions and lower regioselectivities e.g. **69c** vs **69a**). Similarly, large acyl substituents also see lower regioselectivities.

More forcing conditions were required for effective reaction compared to ynamides but once again good structural and functional group tolerance was observed in these annulations. For instance, the route provides access into sterically-congested bis-(hetero)aryl linkages (**72f**) and peptidic oxazoles such as **72h/i** (Scheme 15).

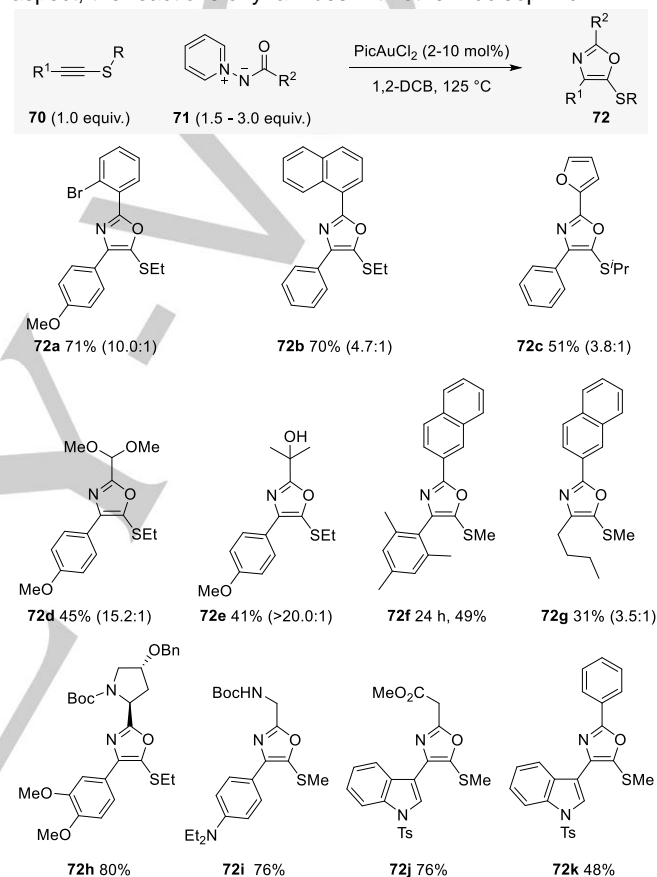


**Scheme 14.** The enabling effect of sulfenyl substitution in the annulation reaction. Ratios of regioisomers between 5-sulfenyloxazoles and 4-sulfenyl oxazoles are given in parentheses.

The enabling function of the sulfur substituent in favoring  $\beta$ -selective addition of the nucleophilic nitrenoid requires further study. In terms of regioselectivity, along with polarizing influence, dative interactions in three-membered metal-C-S systems,<sup>[45]</sup> and stabilizing  $\sigma_{\text{C-Au}}$  to  $\sigma^*_{\text{C-S}}$  hyperconjugation<sup>[46]</sup> were proposed as possibly aiding the slippage of gold towards sulfur from an alkynyl thioether-gold  $\pi$ -complex on the approach of the nucleophile (which at its most extreme extent might be visualized as **73<sup>B</sup>**). With

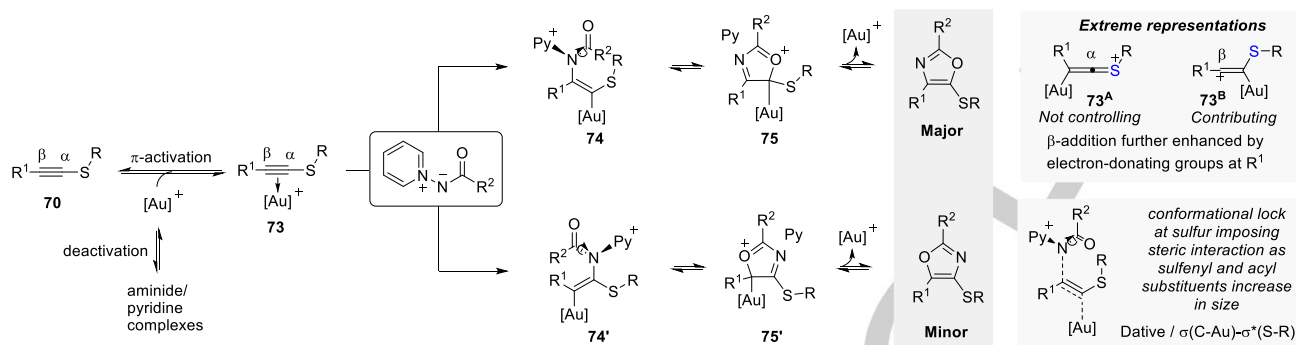
electron donating groups making the alkyne better ligand to gold, competing against coordination to the nucleophilic nitrenoid and the released nucleofuge, they will also further distort the ground state toward extreme form **73<sup>B</sup>**).

With donor-activated systems such as ynamides,  $\alpha$ -attack of the nucleophile sees gold carbene character develop  $\beta$  to the heteroatom and adjacent to the alkyne substituent. Variation of that group, as needed to explore substrate scope, thus influences the reactivity profile of the gold carbene. While our oxazole and imidazole forming methods are relatively unaffected by that aspect, the reactions of ynamides with other nucleophilic

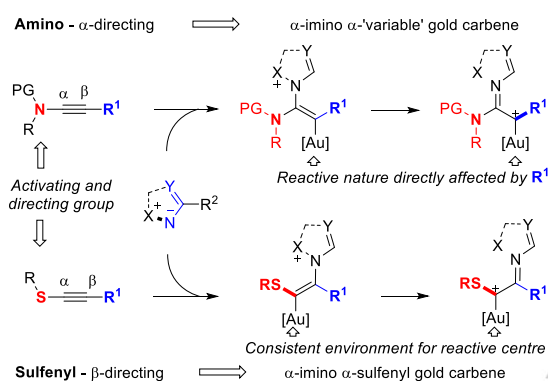


**Scheme 15.** Representative examples showing the convergent assembly of sulfenylated oxazoles. Ratios of regioisomers between 5-sulfenyloxazoles and 4-sulfenyl oxazoles are given in parentheses.

nitrenoids are more significantly affected, and competing pathways dominate over the (3+2) annulation as different substituents are introduced.<sup>[47]</sup> The unexpected  $\beta$ -selectivity observed with alkynyl thioethers sees the metal carbene always flanked by the sulfenyl group. This provides an environment that is potentially less influenced by variations at the alkyne substituent and therefore it might provide a potentially more consistent reactivity profile across a wider reaction scope (Scheme 17).



**Scheme 16.** Proposed mechanistic outline with alkynyl thioethers.

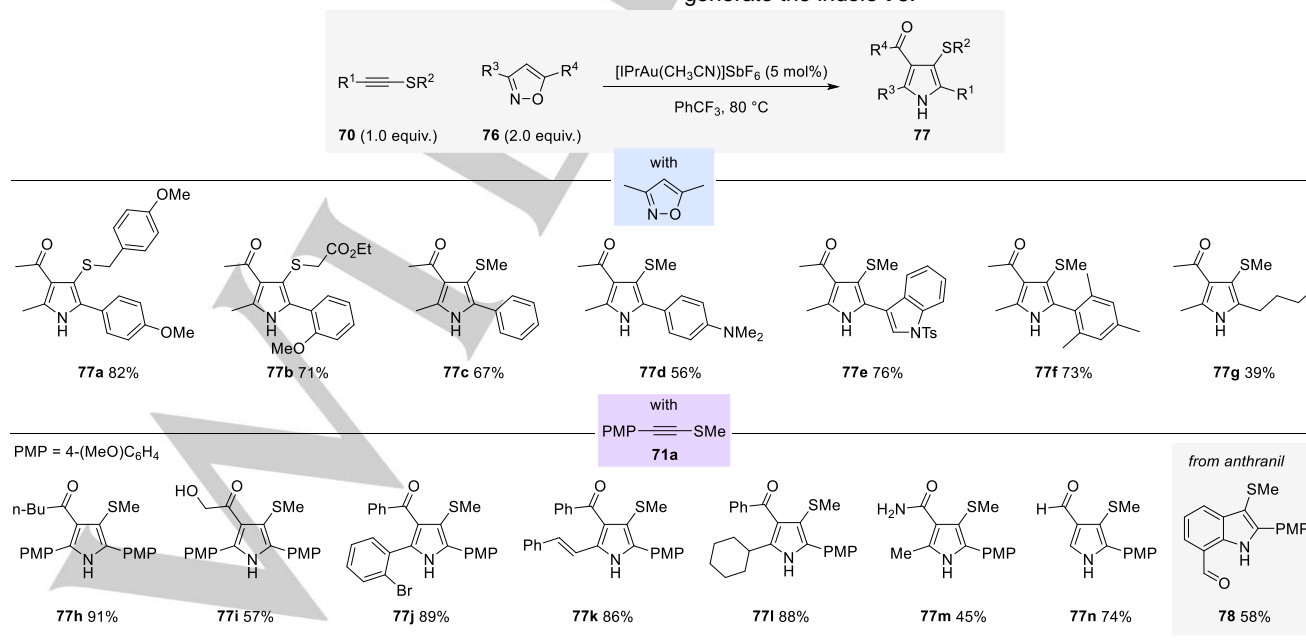


**Scheme 17.** Comparing activation by N- and S-substituted alkynes in  $\pi$ -acid mediated reactions with nucleophilic nitrenoids.

We sought to further test the potential of alkynyl thioethers by reactions with isoxazoles which were introduced by Ye's group as C,N-dipole equivalents for pyrrole synthesis.<sup>[51][48]</sup> Subsequently

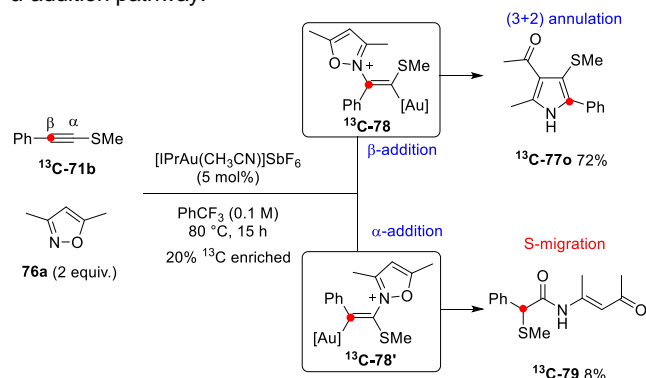
they have been used alongside an array of different alkynes to with different reactivity modes generating more diverse heterocycles.<sup>[49]</sup>

Sulfinylated pyrroles **77** were prepared as single regioisomers under Au(I) catalysis (Scheme 18).<sup>[50]</sup> The most effective catalyst was a N-heterocyclic carbene stabilized Au(I) complex. This observation contrasts with the inefficiency of such pre-catalyst systems with the N-substituted pyridinium N-aminide reactants, and highlights the importance of the type of nitrenoid in elucidating the most effective conditions. The reaction showed similar trends to that seen in the oxazole series, with the  $\beta$ -directing effect maintained. Larger groups on sulfur gave lower reactivity while more electron-donating substituents afforded better yields, although again simple aromatic and aliphatic groups are accommodated **77a-g**. The reaction also proved very tolerant to diversity across the nucleophilic nitrenoid, allowing formation of pyrroles with alkyl, vinyl, aryl and no substituents at C-5 and esters, amides, ketones, aldehydes at C-4 (**77h-n**). Once again the transformation is practical having been applied effectively on over 1 g scale. Similar outcomes were seen with anthranil to generate the indole **78**.

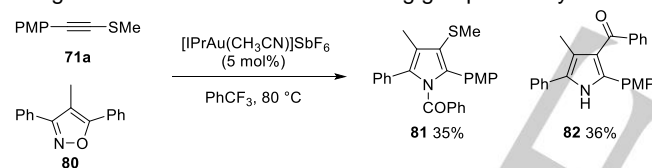


**Scheme 18.** Gold catalysed annulations of alkynyl thioethers with (benzo)isoxazoles.

$^{13}\text{C}$  Labeling studies identified that the C-S connectivity in the starting material is not changed over the reaction, matching the  $\beta$ -selective addition. A small amount of a side-product  $^{13}\text{C}$ -**79** was also observed, which corresponds to those reported by Ye's group on combining isoxazoles with alkynyl thioethers under zinc catalysis to access ketenethionium species,<sup>[51]</sup> showing the minor  $\alpha$ -addition pathway.

**Scheme 19.** Divergent pathways from  $\alpha$ - and  $\beta$ -addition of the nucleophilic nitrenoid.

The reaction of alkynyl thioether **71a** with a trisubstituted isoxazoles **80** led to an annulation with a rearrangement and desulfonylation to give **82**, alongside **81**, raising the prospect of using a thioether as a traceless directing group in catalysis.<sup>[50]</sup>

**Scheme 20.** A desulfonylative annulation reaction with an alkynyl thioether.

## 5. Summary and Outlook

Combining nucleophilic nitrenoids with donor-activated alkynes under gold catalysis has led to a wide array of novel transformations including a new approach to annulations. These annulations provide convergent access into functionalised heterocyclic motifs with desirable, and also new, substitution patterns. Undoubtedly there is great opportunity for the development of new nucleophilic nitrenoid reactants to exploit the preparative potential of the convergent strategy for the efficient synthesis of more varied heterocycles.

*N*-Acyl and *N*-heteroaryl pyridinium *N*-aminides function under this regime as 1,3-*N,O* and 1,3-*N,N* dipole equivalents in formal dipolar cycloaddition reactions with suitable alkynes. These reactants provide routes into oxazoles and heteroaryl-fused imidazoles, respectively. The bench stable nucleophilic nitrenoids are accessible from simple and widely accessible precursors under mild conditions that accommodate significant structural and functional group variation. The resulting annulations are efficient,

using close stoichiometry of the reactants. Effective annulations are obtained using Au(III) or phosphite-stabilised Au(I) based pre-catalysts, with phosphine or *N*-heterocyclic carbene stabilised Au(I) performing poorly.

The use of donor-activated alkynes has proven integral to the successful development of our nucleophilic nitrenoid based reactions, and indeed to the wider field of research. Ynamides are particularly ubiquitous highlighting their value for reaction discovery. Sulfonylated ynamides have been identified as turbocharged substrates and might perhaps be considered more widely as enabling tools in reaction discovery programmes. There is considerable scope to explore other donor-activated alkynes more widely. Ynol ethers can be effective, to potentially deliver ready access into desirable oxygenated heterocyclic motifs, and further uptake might be expected to accompany enhanced preparative routes into these motifs.

Alkynyl thioethers have been identified as promising substrates to expand the reach of the nucleophilic nitrenoid-based annulations. The sulfur-enabling and directing effect has been observed across two different classes of nucleophilic nitrenoids, *N*-acyl pyridinium *N*-aminides and isoxazoles which react to give sulfonylated oxazoles and pyrroles, respectively, and with different types of Au(III) and Au(I) precatalysts. The enabling role of the thioether substituent in gold catalysis requires further study, yet it is already clear that alkynyl thioethers offer significant potential in  $\pi$ -acid mediated chemistry.

The methods are readily amenable for use on gram scale as demonstrated across the reactions described above. As the heterocycles formed in these annulation processes are ubiquitous as constituents or precursors to bioactive compounds, there would appear to be significant scope to explore the validity of these convergent nitrenoid-based approaches for the directed synthesis of bioactive or other target molecules.

The current use of precious metal catalysis at reasonably high loadings (~1 to 10 mol%) represents a challenge for wider uptake of these annulation approaches. Strong Brønsted acids or other, cheaper, metal catalysts like Zn(II) have been used to achieve the desired reactions.<sup>[36, 51-52]</sup> That approach is undoubtedly an important direction to pursue with great potential for the development of more sustainable synthetic methods and for reaction discovery in its own right. However, it remains to be seen whether such methods will match or indeed surpass the reaction generality that can be achieved with gold catalysis. As shown in the reactions of alkynyl thioethers and isoxazoles, the use of gold catalysis delivers the annulation pathway that was not accessible under Zn(II) catalysis, so in that case at least the approaches complement each other.<sup>[50-51]</sup> In our experience, gold catalysis appears to offer a uniquely broad applicability, certainly as a tool for reaction discovery. The challenge of cost and sustainability could also be addressed through the development of more effective gold catalysts that can be used at much lower loadings. Looking forward, further investigation into the precise mechanistic details of these  $\pi$ -acid catalyzed nitrenoid reactions will be important to gain a detailed understanding of key off-cycle

processes and catalyst speciation in order to aid reaction and catalyst design.

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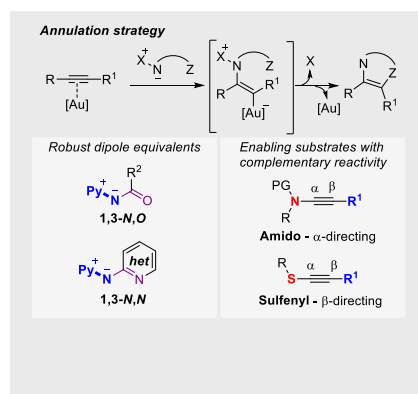
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## PERSONAL ACCOUNT

## Entry for the Table of Contents

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In this account the development of a gold-catalysed alkyne annulation strategy based on the use of nucleophilic nitrenoids to access azacycles is discussed.



Paul W. Davies\*

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**Gold Catalyzed Annulations with Nucleophilic Nitrenoids Enabled by Heteroatom-Substituted Alkynes**