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Sulfenyl Ynamides in Gold Catalysis: Synthesis of Oxo-functionalised 4-aminoimidazolyl Fused Compounds by Intermolecular Annulation Reactions

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Abstract: Functionalised *N*-heterocyclic pyridinium *N*-aminides have been designed and synthesised to evaluate a nitrenoid-based annulation strategy into imidazole-fused oxo-substituted frameworks of importance to medicinal and agrochemical discovery programmes. Sulfenyl substituted ynamides were identified as privileged reactants affording productive gold-catalysed annulation reactions with these and other nitrenoids. This annulation method provides selective and efficient access into geminally amino-sulfenyl substituted nitrogen heterocycles under mild reaction conditions.

**Keywords:** Ynamides; Gold catalysis; Heterocycles; Annulations; Sulfur

Ynamides have become an invaluable tool for reaction discovery since the advent of broadly effective methods for their preparation.[1,2] They have been particularly efficacious in the discovery of π-acid-catalysed[3] transformations. The nitrogen substituent enhances the alkynes ligating π-donor properties and delivers a keteneiminium species that provides high reactivity and regiocontrol (Figure 1a).[4] Ynamides have underpinned the discovery of efficient intermolecular annulations with nucleophilic nitrenoids, allowing convergent and efficient access into nitrogen heterocycles (Figure 1b).[5] Following initial reports with *N*-pyridinium aminides,[6,7] various nitrenoid types have been developed for annulations, including (benzo-fused)isoxazoles,[8,9] dioxazoles,[10] oxadiazoles,[11] azides,[12] azirenes[13] and sulfilimines[14] amongst others.[15]

Aminoimidazole and *N*-fused imidazole motifs have been targeted for methodology development programmes due to their importance as bioactive molecules.[16] Our group introduced a nucleophilic nitrenoid strategy to prepare heteroaromatic-fused 2-aminoimidazoles in an expedient and modular fashion by the use of *N*-substituted *N*-pyridinium aminides alongside ynamides.[7,17] Having established that diazine, pyridine and fused 1,3-azole substitution patterns can be incorporated, we questioned whether this approach could be used to build imidazole rings around more functionalised and non-aromatic motifs (Figure 2a). Structures featuring imidazole rings fused to oxo-substituted heterocycles have shown potency in medicinal and agrochemical applications (Figure 2b)[18] and hence were deemed appealing targets for the annulation methodology. However, the addition of electron-withdrawing carbonyl groups within the nitrenoids was expected to be a challenge for the annulation strategy. A further competing coordination site for the electrophilic gold catalyst is introduced while the nucleophilic character of the aminide group is diminished (Figure 2c). Here we report on the viability of using the gold-catalysed ynamide-nitrenoid strategy to access imidazo-fused oxo-substituted heterocycles. We identify sulfenyl ynamides, a barely-explored subclass of ynamides, as highly effective for gold-catalysed nitrenoid reactions.

In order to determine whether a nitrenoid-based approach to bioactive oxo-substituted heterocyclic motifs was viable, we investigated whether *N*-hetero-

a) Ynamides as enabling tools for π-acid reaction discovery

π-rich ⟹ aids complex formation ⟹ highly electrophilic complex for regiodefined attack
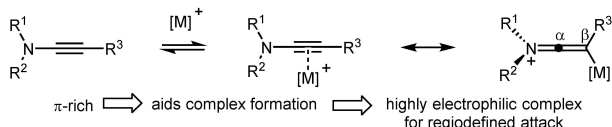
b) Nucleophilic nitrenoids in annulation reactions
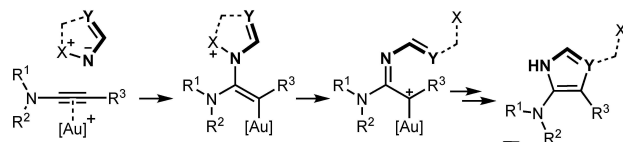
Nucleophilic nitrenoids for formal cycloaddition include:

X = Pyridine or Me₂S

Figure 1. The enabling reactivity profile of ynamides and their use in annulations with nucleophilic nitrenoids.
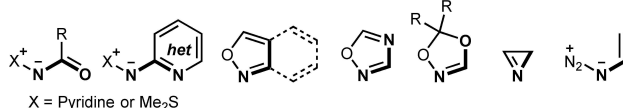
a) N-Heterocyclic aminides as nucleophilic nitrenoids in annulations

Previous work

Het. = pyridines, diazines, benz(ox/thi/imid)azoles

Au(I) or Au(III) catalysts

***This work* S-enabled**

b) Examples of biologically active imidazo-fused oxo-heterocycles

Protein kinase inhibitor   Herbicide

Pesticide   cGAS Antagonist   Lymphocyte function-associated antigen-1 (LFA-1) inhibitor

c) Challenges for productive catalysis in the desired series

Preparation and reactivity profile unknown   *Diminished nucleophilicity*   *Competing coordination site*

Figure 2. Representative examples of imidazo-fused hetero-cycles and a nitrenoid-based annulation approach for their preparation.

cyclic *N*-pyridinium aminides could be prepared from thiouracil **1**, rhodanine **5** and hydantoin **6** (Scheme 1 *cf.* Figure 2b). An *S*-methylation[19] and substitution approach[17,20] was successfully developed for the formation of the oxo-dihydropyrimidinyl-bearing nitrenoid **4** and the oxo-dihydrothiazolyl-bearing **8**. The gram-scale preparation of **4** and **8** demonstrated the practicality of these approaches. The use of hydantoin **6** in this sequence was unsuccessful.

Knoevenagel reaction on **8** afforded 5-benzylidene and 5-(2-bromobenzylidene) products **9a/b**. Inverting the order of the synthetic sequence was similarly productive (**5**→**10**[21]→**9a**), and this latter approach was also applicable to hydantoin **6**. *S*-Methylation of the Knoevenagel product **11**[22] was followed by a regioselective *N*-alkylation prior to formation of the aminide **15** (Scheme 1).[23]

The putative nitrenoids were then tested in gold-catalysed annulations against some standard ynamides. As illustrated with aminide **4**, where the oxo group is vinylogously-conjugated to the nitrenoid centre, these systems proved significantly less reactive than previously studied *N*-heteroaryl analogues (Scheme 2 and ESI for a broader study of reaction conditions). No conversion was seen with an oft-employed ynamide **16a**. However, good conversion was seen with the sulfenyl ynamide **18a**.

Highly electrophilic Au(III) and phosphite Au(I) species were shown to catalyse this transformation effectively, while the more electron-rich IPrAu(I) equivalent did not. Ultimately a high yield of the sulfenyl-substituted imidazo[1,2-*a*]pyrimidin-7(8*H*)-one **19a** was obtained from **18a** simply on heating with 1.5 equivalents of **4** in the presence of bench-stable PicAuCl₂ precatalyst in 1,4-dioxane in 2 hours. The role of the sulfonamide group is also integral as no
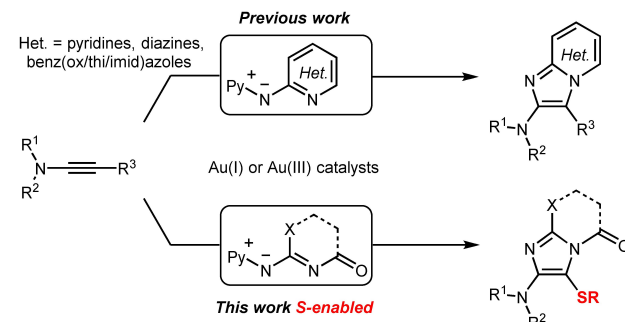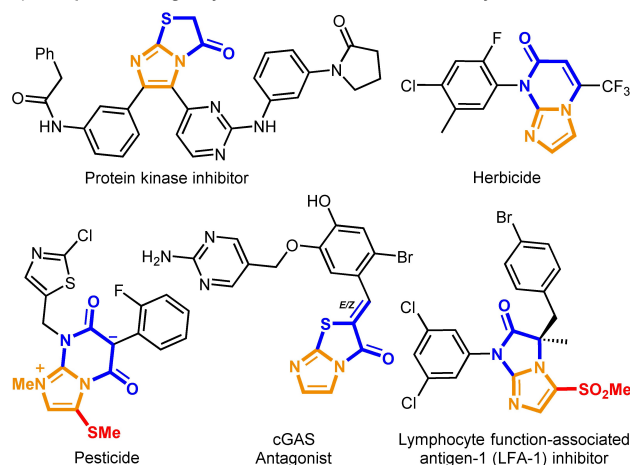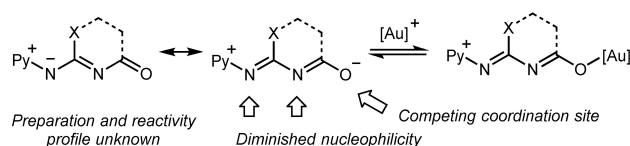
reaction was seen when the methyl(phenylethynyl) sulfane was reacted with **4** under those conditions.

A similar pattern was seen in the reactions of all the new nitrenoids (Table 1). Reactions were run with either PicAuCl₂ or a DBTPAu(I)·CH₃CN·SbF₆ catalyst in either 1,4-dioxane or 1,2-DCB (see ESI for a comparison of conditions for particular aminides). Annulation products were formed in good to excellent yields from each of the new aminides with sulfeny-lated-ynamide **18a** (Table 1, entries 1, 5, 13, 16). In contrast, much lower or no reactivity was seen with non-sulfenylated ynamides **16** or **20** (entries 4, 8, 10, 15, 19). The role of the sulfonamide group is also integral as no reaction was seen when the methyl (phenylethynyl)sulfane was reacted with **4** under those conditions. A gram scale preparation of **19a** proceeded in high yield (Entry 1).
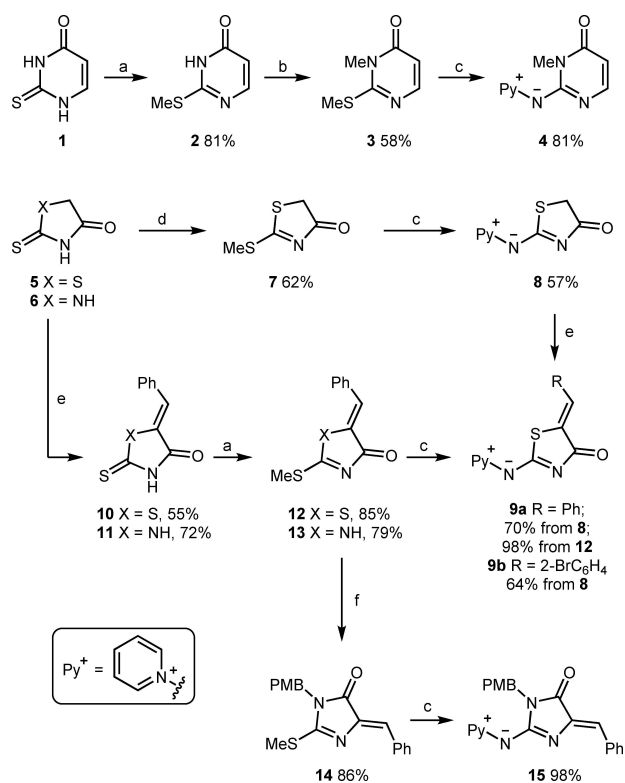
Scheme 1. The development of synthetic sequences for the preparation of pyridinium *N*-aminides bearing oxo-substituted heterocycles. Conditions a) MeI, NaOH, H₂O:EtOH (2:1), 55 °C; b) MeI, LiHMDS, DMF, 0 °C to rt;[24] c) *N*-Amino pyridinium iodide, K₂CO₃, MeOH, rt; d) MeI, DIPEA, DMF, 0 °C to rt; e) Benzaldehyde or 2-bromobenzaldehyde, AcOH, NaOAc, Reflux; f) PMBCl, K₂CO₃, MeCN, reflux. PMB=*p*-Methoxybenzyl.
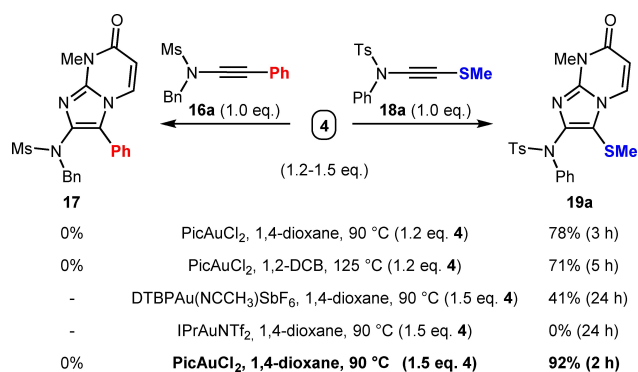
Scheme 2. Surveying the reactivity of *N*-pyridinium *N*-(3-methyl)pyrimidinone aminide **4**.[a]

The thiophenyl-substituted ynamide **18 b** was less reactive than the thiomethyl equivalent **18 a**, requiring longer reaction times across the nitrenoids. (Entries 2, 6 and 17 versus entries 1, 5, and 16). A 1,6-enynamide **18 c**, which introduces a competing coordination site as well as a potential intramolecular cycloisomerisation

pathway, proved less reactive than the other sulfenyl ynamides but still afforded the intermolecular annulation products (Entries 3, 7 and 18).

Imidazo[2,1-*b*]thiazolones **21 a–c** were similarly produced from aminide **8** bearing an enolisable carbonyl in direct conjugation (Entries 5–7). The reactivity trend across **18 a–c** was more pronounced than with aminide **4**. The Knoevenagel-adducts **9 a/b** lacking enolisable sites and with an extended conjugation to attenuate the carbonyl groups influence proved more reactive. Both the *S*-methyl and *S*-phenyl ynamides **18 a/b** afforded high yields of heterocycles **22/23** (Entries 9 and 13) and productive outcomes were even seen with non-sulfenylated ynamides (Entries 10–12 and 14–15).

Use of hydantoin-derived nitrenoid **15** granted direct access to (*Z*)-2-ylideneimidazo[2,1-*b*]thiazol-3 (2*H*)-one products **24 a–c** on reaction with sulfenyl ynamides despite the steric crowding around the iminoyl group (Entries 16–18). Again, no reaction was seen with a non-sulfenylated ynamide (Entry 19).

A saccharin-derived nitrenoid **25** was then prepared to test the effect of an alternative electron-withdrawing group at the aminide (Scheme 3). No reaction was seen with ynamide **20**, but again annulation occurred with sulfenyl ynamide **18 a** to deliver the benzo[*d*]imidazo [1,2-*b*]isothiazolyl **26**.

Crystal structures were obtained for the heterocycles derived from rhodanine, thiouracil, hydantoin and saccharin and confirm the regioselectivity of the annulation (Figure 3).[25]

When compared with previously employed nitrenoids, the outcomes fit a model where the carbonyl or sulfonyl substituent diminishes the reactivity of the aminide. Both nitrogen atoms of the putative 1,3-*N*,*N*-dipole unit are deactivated which adversely affects the initial nucleophilic attack and the cyclisation stages of the annulation (Scheme 1c). The reactivity-enhancing effect of a sulfenyl substituent could be explained by sulfur-gold interactions stabilising the polarised gold keteneiminium contribution **B'** to generate a more effective electrophile (Scheme 4). Sulfur-gold interactions could also conceivably help to favour productive gold-ynamide coordination over unproductive interaction with nitrenoid.[26,27] Invoking a stabilising dative[28]
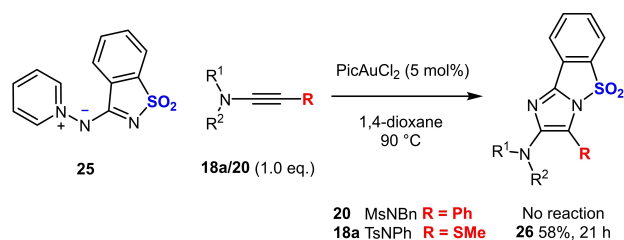
Scheme 3. A saccharin-derived nitrenoid and its use to access the benzo[*d*]imidazo[1,2-*b*]isothiazolyl structure.

Table 1. Comparing the reactivity of aryl- and sulfenyl substituted ynamides in annulations by a gold-catalysed formal [3+2]-dipolar cycloaddition with oxo-functionalised nucleophilic nitrenoids.[a]

4, 8
9a/b, 15

16a/b R[1] = Ms, R[2] = Bn, R[3] = Ph/thiophen-2-yl
18a-c R[1] = Ts, R[2] = Ph
R[3] = SMe/SPh/SCH$_2$CH$_2$CHCH$_2$
20 R[1] = Ts; R[2] = Ph; R[3] = Ph

PicAuCl$_2$ (5 mol%)

1,4-dioxane, 90 °C
or 1,2-DCB, 125 °C

19, 21-24
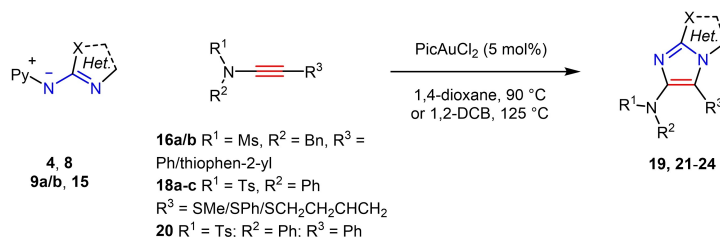
Entry		R[1]	R[2]	R[3]	T (h)	Yield
1	**4**	Ts	Ph	SMe	3	**19a** 90%[b]
2	**4**	Ts	Ph	SPh	24	**19b** 85%
3	**4**	Ts	Ph	S⌒⌒	5.5	**19c** 76%
4	**4**	Ts	Ph	Ph	22	NR
5	**8**	Ts	Ph	SMe	24	**21a** 78%[c]
6	**8**	Ts	Ph	SPh	24	**21b** 50%[c]
7	**8**	Ts	Ph	S⌒⌒	24	**21c** 34%[c]
8	**8**	Ts	Ph	Ph	22	NR
9	**9a**	Ts	Ph	SPh	1.5	**22a** 98%[d]
10	**9a**	Ts	Ph	Ph	22	**22b** 67%[d]
11	**9a**	Ms	Bn	Ph	5	**22c** 74%[d]
12	**9a**	Ms	Bn	Thiophen-2-yl	22	**22d** 75%[d]
13	**9b**	Ts	Ph	SMe	3.5	**23a** 98%[d]
14	**9b**	Ms	Bn	Ph	22	**23b** 38%[d]
15	**9b**	Ms	Me	PMP	22	NR
16	**15**	Ts	Ph	SMe	18	**24a** 88%
17	**15**	Ts	Ph	SPh	22	**24b** 45%
18	**15**	Ts	Ph	S⌒⌒	24	**24c** 44%
19	**15**	Ts	Ph	Ph	22	NR

[a] Isolated yield after purification by column chromatography. Reactions performed in 1,4-dioxane at 90 °C at 0.2 to 3.5 mmol unless otherwise stated.
[b] **19a** 3.5 mmol (1.39 g).
[c] Using DTBPAu(NCMe)SbF$_6$ (5 mol%).
[d] Reactions performed in 1,2-DCB at 125 °C. PMP = *p*-Methoxyphenyl.

or hyperconjugative[29] interaction between the gold and sulfur can explain the lower reactivity observed with *S*-phenyl ynamide **18b** over *S*-methyl ynamide **18a**. Both interactions would limit conformational flexibility and position the sulfur substituent toward the incoming nitrenoid whereby increasing steric bulk would hinder the initial nucleophilic attack and the subsequent cyclisation steps (Scheme 4 inset).[30]

There are only a few isolated examples of sulfenyl ynamides being used in catalysis.[31,32] Their success alongside the new nitrenoids led us to explore the wider potential of sulfenyl ynamides in nitrenoid-based annulations in order to access heterocycles with vicinal amino-sulfenyl substitution patterns. C2-Amino-C3-sulfenyl imidazo-[1,2-*a*]-pyridines have been identified as inhibitors of human rhinovirus[33] and as anthelmintics,[34] while sulfenylated-heterocycles and their *S*-oxide derivatives are of general interest due to

their biological activity[35] and synthetic utility.[36] Thus, it seemed appealing to see whether annulations of sulfenyl ynamides allowed access to these substitution patterns on diverse heterocyclic motifs in a regioselective and convergent fashion.

Broad tolerance and applicability was seen when we examined the combination of sulfenyl ynamides with various aminide-based nitrenoids (Scheme 5).[7,17] Imidazole-fused heterocycles **27–38** were obtained in generally high to quantitative yields through reactions that were more effective and/or faster than with non-sulfenyl ynamides. Of particular note were the formation of the caffeine-derived heterocycle **36** and the pyridine-fused system **38** as the required nitrenoids had both reacted sluggishly in previous studies with ynamides.[17]

The ability of this annulation approach to access highly heterosubstituted heterocycles is demonstrated

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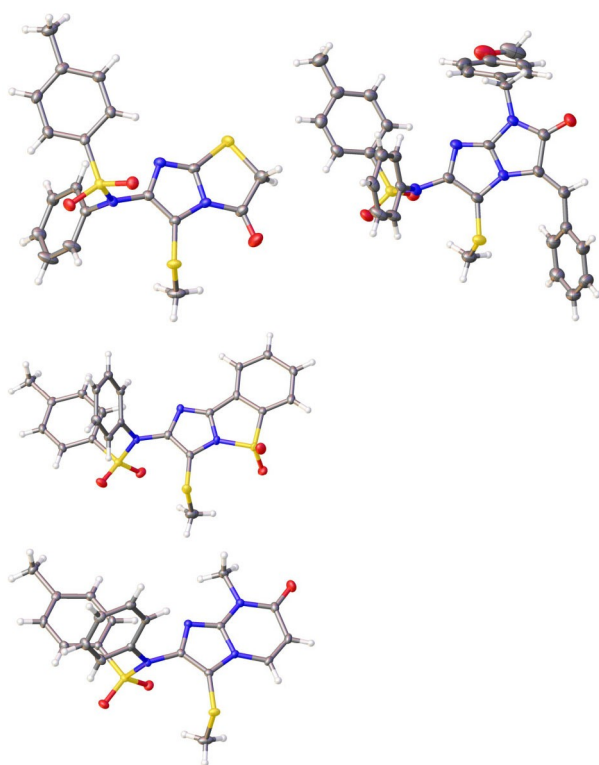
Figure 3. Crystal structures of, from top-left clockwise, **21 a**, **24 a**, **19 a** and **26** with ellipsoids drawn at the 50% probability level. The structure of **21 a** contains two crystallographically-independent molecules of which only one is shown.
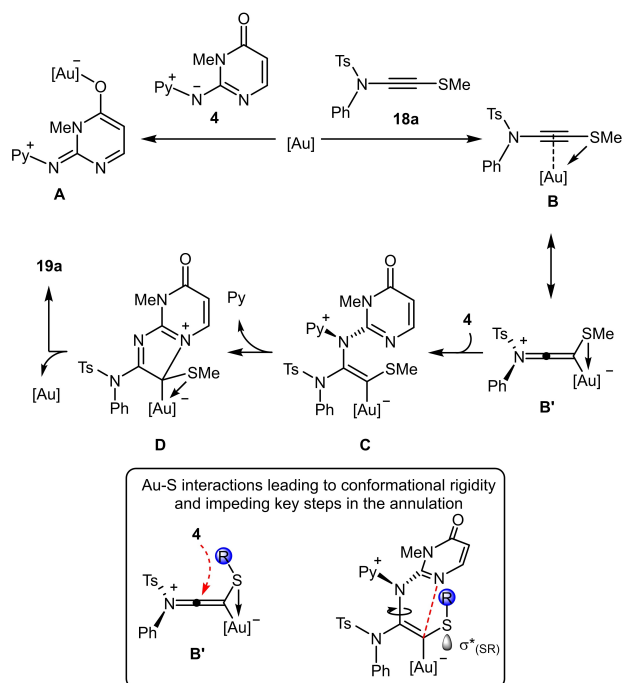
Scheme 4. Proposed mechanistic rationale for the gold-sulfur interaction responsible of the enhancement in reactivity.

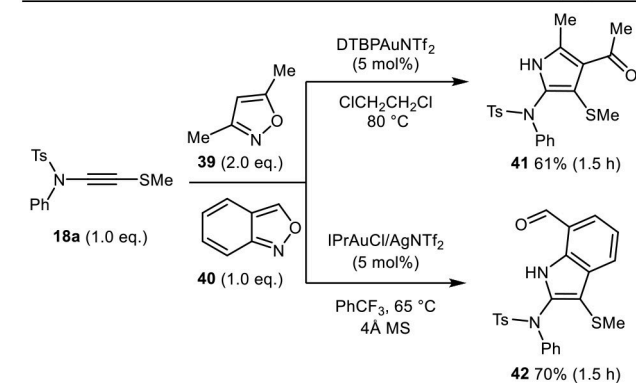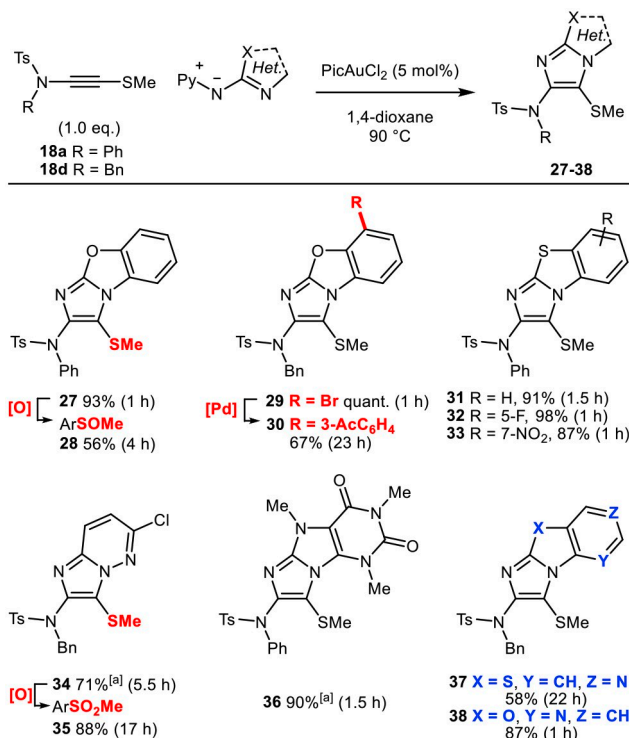**Scheme 5.** The use of sulfenyl ynamides with other nucleophilic nitrenoids. [O] = mCPBA (2.2 eq.), DCM, 0 °C to rt; [Pd] = Pd (PPh₃)₄ (5 mol%), K₂CO₃, 1,4-dioxane:H₂O, 85 °C; [a] Using 1,4-dioxane at 90 °C.

with the formation of **29** and its subsequent elaboration by cross-coupling reaction to deliver **30**. Oxidation of these sulfenyl heterocycles proceeded smoothly affording the desirable heteroarylsulfoxide (**27→28**) and heteroarylsulfone (**34→35**).

The sulfenyl ynamide **18 a** also proved productive in reactions with other types of nitrenoids. Smooth and relatively rapid reactions were observed with the *N,O*-heterocycles **39** and **40** introduced by the groups of Ye[8] and Hashmi,[9] delivering 2-amino-3-thiopyrrole and 2-amino-3-thio-indole frameworks **41** and **42** respectively in the presence of Au(I) catalysts.

In summary, new types of pyridinium *N*-aminides have been prepared that bear non-aromatic and oxo-

substituted heterocycles as putative nitrenoids for gold catalysed annulation reactions with ynamides. These species proved generally less reactive than the previously explored *N*-heteroaryl pyridinium *N*-aminides, likely because of reduced nucleophilicity. While several of the new aminides did not react with commonly employed ynamides, each aminide did react smoothly when combined with a sulfenyl ynamide. Imidazo-fused heterocycles were prepared from each nitrenoid under gold catalysis, providing a convergent new route into systems of interest in medicinal chemistry such as imidazo[2,1-*b*]thiazol-3(2*H*)-one, imidazo[1,2-*a*]imidazolone and imidazo[1,2-*a*]pyrimidinone. The reactions are practically straightforward and applicable on a gram scale. Sulfenyl ynamides are effective substrates across a range of different nitrenoids providing access to various nitrogen-heterocycles with geminal amino-sulfenyl substitution patterns in a mild and regioselective fashion.

This study highlights the reactivity-enhancing influence of sulfur substitution in gold catalysis with *N,S*-substituted alkynes behaving as privileged substrates in these annulation reactions. We conclude that the ability to 'switch-on' otherwise unproductive processes offers significant potential for reaction discovery based on π-acid activation and that the wider use of sulfenyl ynamides in such programmes may prove beneficial.

Experimental Section

A heat-gun dried Schlenk tube under argon was charged with ynamide **18 a** (1.11 g, 3.50 mmol), aminide **4** (1.06 g, 5.25 mmol 1.5 eq.) and dichloro(2-pyridinecarboxylate)gold (68.2 mg, 5 mol%) in dry 1,4-dioxane (35 mL) and the mixture was stirred at 90 °C for 3 h. The reaction mixture was allowed to cool down to room temperature and the solvent was removed under reduced pressure. The residue obtained was purified by flash column chromatography [Hexane:EtOAc (3:2)] affording imidazole **19 a** as a beige solid (1.39 g, 90%).

Acknowledgements

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Sulfenyl Ynamides in Gold Catalysis: Synthesis of Oxo-functionalised 4-aminoimidazolyl Fused Compounds by Intermolecular Annulation Reactions

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Oxo-functionalised nitrenoids for convergent heterocycle synthesis

X = S,O,NR

(1.2–1.5 eq.) (1.0 eq.)

low-moderate reactivity

[Au] catalyst

Sulfenyl-ynamides: enabling tools for transformation discovery

26 examples
34–98% yield
sulfenylated heterocycles