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Davies, Paul; Garzon Sanz, Miguel; Martinez Arce, Elsa; Jannapureddy, Raju

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General Entry into *o*-,*o*'-Heteroatom-Linked *N*-(Hetero)aryl Imidazole Motifs by Gold-Catalysed Formal [3+2]-Dipolar Cycloaddition

Miguel Garzón,[a] Elsa M. Arce,[a] Raju Jannapu Reddy[a] and Paul W. Davies[a,*]

[a] School of Chemistry, University of Birmingham, Birmingham, B15 2TT, UK
Fax: +44 (0)1214144403; E-mail: p.w.davies@bham.ac.uk

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Abstract. A general redox-neutral approach into the *o*-,*o*'-heteroatom-linked *N*-(hetero)aryl imidazole family of heteroaromatics has been developed. New types of heteroatom substituted carbimidoyl nitrenoids are efficiently realised from robust, bench-stable *N*-(heteroaryl) pyridinium *N*-aminides by formal gold-catalysed [3+2]-dipolar cycloadditions across ynamides. Broad structural variety and functional group tolerance allows rapid access into diverse functionalised scaffolds, as exemplified by the preparation of 8 different heteroaromatic cores.

Keywords: cycloaddition; dipoles; gold; nitrogen heterocycles; nucleophilic nitrenoids

The *o*-,*o*'-heteroatom-linked *N*-(hetero)aryl imidazole structural motif **A** (Figure 1) covers an array of important tricyclic fused-heteroaromatic systems. The synthetic utility and application of some of these structures have been widely demonstrated. For instance, in the benzo[*d*]imidazo[2,1-*b*]thiazole series, uses include PET-imaging to detect Aβ plaques which are symbols of Alzheimer's disease,[1] inhibitors of tumorigenesis (Triflorcas)[2] or FLT-3,[3] and antiapoptotic,[4] antibacterial[5] and antimicrobial agents (Figure 1).[6] In contrast, the potential of other structures within this class has scarcely been explored. A variety of synthetic routes into certain members of this structurally-related family are known, those involving formation of the shared imidazole ring commonly feature oxidative coupling or the condensation of an aromatic amine with an α-halo-carbonyl equivalent.[7] Here we report a new practically straightforward and non-oxidative strategy that allows ready access into structural and functional group diversity across the general structural motif **A**.

We questioned whether a general route into the tricyclic motif **A** could be realised using a nucleophilic nitrenoid approach to assemble the imidazole ring common to this scaffold.[8] *N*-Heteroaryl pyridinium *N*-aminides **B** were identified as potential 1,3-*N*,*N*-dipole equivalents that could accommodate the requisite structural variety in a formal [3+2]-dipolar cycloaddition (Scheme 1a).

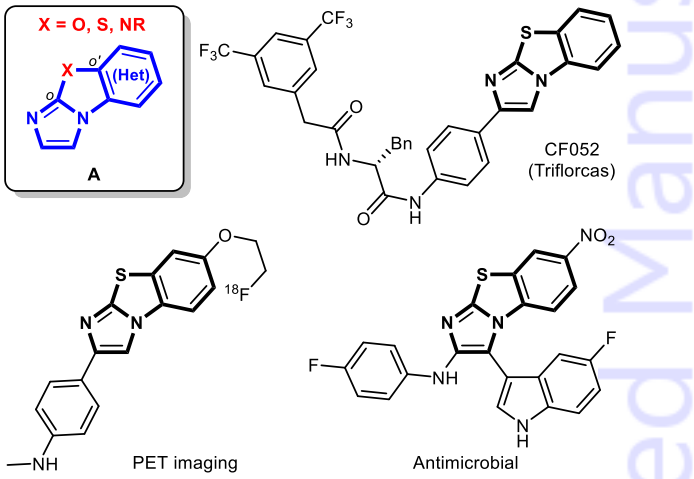

Figure 1. The common *o*,*o*'-heteroatom-linked *N*-(hetero)aryl imidazole motif **A** with examples of benzo[*d*]imidazo[2,1-*b*]thiazole based compounds found in biomedical applications.

We recently reported the synthesis of imidazo-fused azines by gold-catalyzed formal cycloaddition reactions based on the use of nucleophilic nitrenoids (Scheme 1b).[9] The cycloaddition, and the *N*,*N*-dipole character of an imidoyl nitrene, is thought to arise by the attack of *N*-azinyl pyridinium *N*-aminide **C** onto an electrophilic π-complex **D**. The resulting vinyl gold carbenoid intermediate **E** cyclises to the aurated heterocycle **F** on elimination of the pyridine nucleofuge, then followed by the elimination of gold.[10] The explored aminides such as **C** contain an imidoyl nitrenoid embedded within a π-deficient ring. For the desired formation of heterocycles **A**, *N*,*N*-dipole character is required from a π-rich environment of donor-heteroatom substituted carbimidoyl nitrenoids **B**. A strong influence from the donor atom was expected: enhancing the abilities

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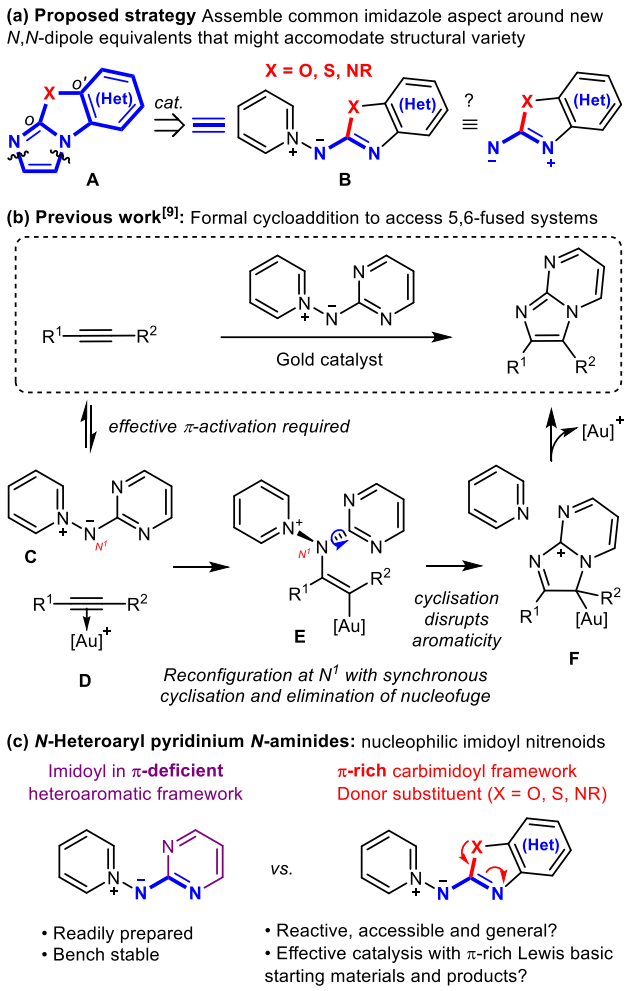


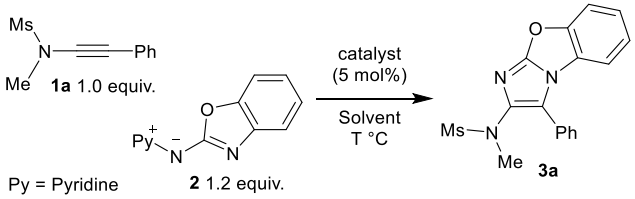
Scheme 1. Unveiling the carbimidoyl nitrene character of *N*-heteroaryl pyridinium *N*-aminides for cycloaddition.

of the product and starting aminide to sequester the electrophilic catalyst would retard reactivity while aromaticity-disrupting cyclisation is a critical step (Scheme 1b). Despite these concerns, and the absence of any previous studies into the reactivity of aminides **B**, the excellent structural and functional group compatibility that has been observed in our[9,11] and others[12] studies into mechanistically-distinct formal cycloadditions with nucleophilic nitrenoids, prompted us to probe this route as a means to access the valuable heterocyclic motif **A**.

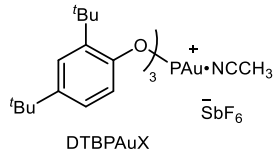
We commenced our study using ynamide, **1a** and the pyridinium *N*-(2-benzoxazolyl)aminide **2**.[13] On reaction with the phosphite gold(I) catalyst DTBPAu·NCCH$_3$.SbF$_6$[11b,14] the desired imidazo-[2,1-*b*]benzoxazole **3a** did form, albeit with modest conversion even at elevated temperature in either *m*-xylene or 1,2-DCB (Table 1, Entries 1-3). Using bench-stable picolinateAuCl$_2$ as a precatalyst at 90 ˚C (Entries 4-6) saw greatly improved conversion and a high yield of **3a** as a single regioisomer (Figure 2).[15]

A similar yield of **3a** was achieved in a substantially-reduced reaction time on running the reaction at 125 ˚C in 1,2-dichlorobenzene (DCB) (Entry 7). Notably, only a slight excess of aminide **2**

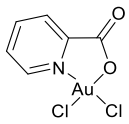
Table 1. Surveying a nucleophilic nitrenoid approach to access *o,o'*-heteroatom-linked *N*-aryl imidazole by gold-catalysed formal [3+2]-dipolar cycloaddition.



Entry	Catalyst	Solvent	T (˚C)	time (h)	Yield (%)[a]
1	DTBPAuX	1,4-dioxane	90	24	(26)
2	DTBPAuX	1,2,-DCB	125	24	44
3	DTBPAuX	*m*-xylene	120	24	44
4	**PicAuCl$_2$**	**1,4-dioxane**	**90**	**24**	**81**
5	PicAuCl$_2$	1,2,-DCB	90	24	76
6	PicAuCl$_2$	$CH_3C_6H_5$	90	24	59
7	**PicAuCl$_2$**	**1,2,-DCB**	**125**	**24**	**84**
8	PicAuCl$_2$	1,2,-DCB	125	24	84[b]
9	None	1,2,-DCB	125	6	-
10	Zn(OTf)$_2$	C_6H_5Cl	100	24	-



DTBPAuX



PicAuCl$_2$

[a] Isolated yield after purification by column chromatography. Yield in parenthesis calculated by ^{1}H-NMR spectroscopy against a known quantity of 1,2,4,5-tetramethylbenzene. [b] Reaction run in an open flask with undried solvent.

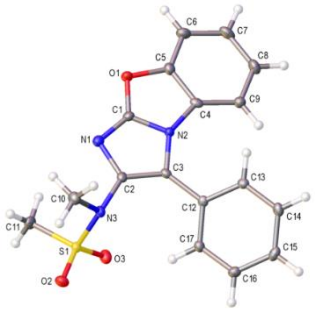


Figure 2. Crystal structure of **3a** with ellipsoids drawn at the 50% probability level.

was needed to achieve full conversion. In addition, the transformation proved to be robust with no loss of yield observed when the reaction was run without any precautions taken to exclude air or moisture (Entry 8). No cycloaddition product was observed either in the absence of catalyst or when Zn(OTf)$_2$ was employed as the catalyst (Entries 9-10).[16-18]

Reacting aminide **2** across a range of ynamides **1a-j** gave single regioisomers of isolated products (Scheme 2).[19] The higher temperature conditions (1,2-DCB at 125 ˚C) were predominantly used in

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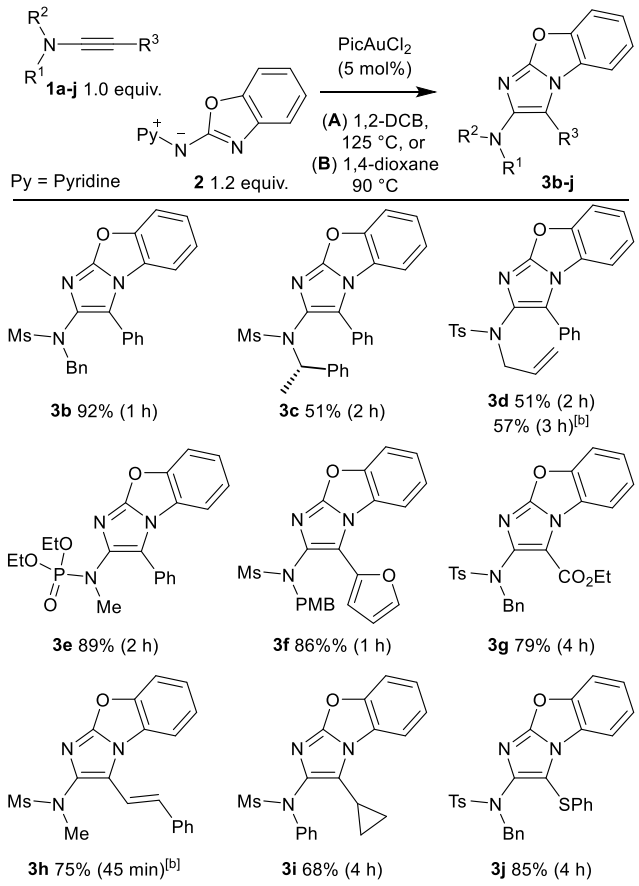


[a] Using conditions **A** and at 0.2 mmol scale at [0.1 M] relative to **1** unless otherwise specified. Yields of isolated product after flash chromatography. [b] Using conditions **B**.

Scheme 2. Synthesis of fused imidazo[2,1-*b*]-benzoxazoles and -benzothiazoles across different ynamides[a]

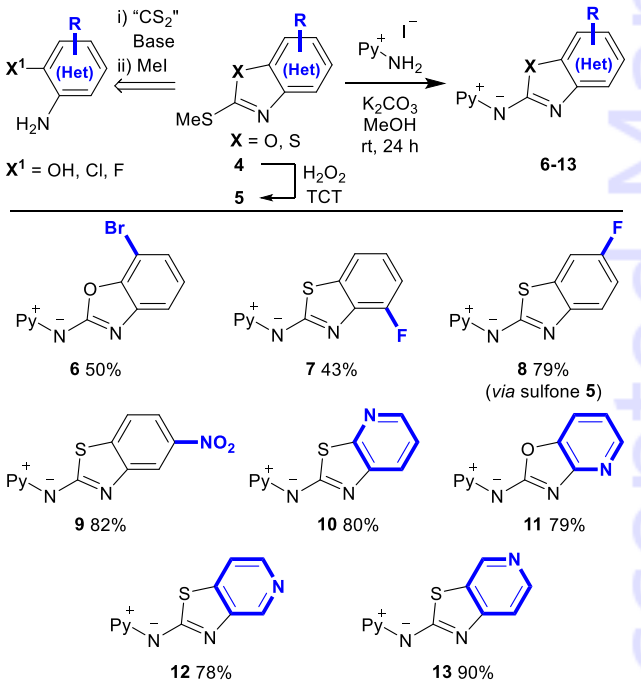
order to achieve faster conversion with reactions generally complete within 4 h.

N-Alkyl, -benzyl and -allyl substituents are all tolerated (e.g. **3(a-f)**) including a bulky α-methylbenzyl substituent (**3c**) shown to substantially reduce the effectiveness of other gold-catalysed reactions.[11a] The desired intermolecular reaction to afford **3d** outperformed thermal intramolecular aza-Claisen rearrangement of *N*-allyl-ynsulfonamide **1d**, even at 125 °C.[20] *N*-Phosphoryl ynamides react as smoothly as yne-sulfonamides (cf. **3a** and **3e**).[21]

Changing the ynamide C-substituent allows ready access to a variety of C-3 substitution patterns on the heteroaromatic, including electron-rich (**3f**) and electron-poor (**3g**) groups. Though the reactive enynamide **1h** degraded at 125 °C (**3h** formed in 35% yield), the 3-alkenyl-heterocycle **3h** was formed in good yield under the less vigorous reaction conditions (90 °C in 1,4-dioxane). Cyclopropyl-substituted **3i** was obtained in good yield, though other alkyl-substituted ynamides afforded complex mixtures.[22] Thioynamide **1j** reacts smoothly to give the 2-amino-3-thioether products **3j**, bearing a useful thioether group for later derivatisation.[23]

We then sought to explore the wider potential of the formal [3+2]-dipolar cycloaddition by using elaborated aminides **B** to access more varied structural types across the fused tricyclic motif **A**. The reported synthesis of **2** employed substitution of the 2-haloheterocycle with *N*-amino-pyridinium iodide.[13] As chemo- and regio-selectivity issues can render the synthesis of suitably halogenated fused-heterocycles inefficient or impractically lengthy, we also sought a complementary method. To this end, we investigated whether methylthio heterocycles **4** would be suitable precursors as they can be prepared from the readily accessible *o*-halo or *o*-hydroxy aromatic amine motif, by reaction with a CS_2 equivalent followed by *S*-methylation (Scheme 3).[24]

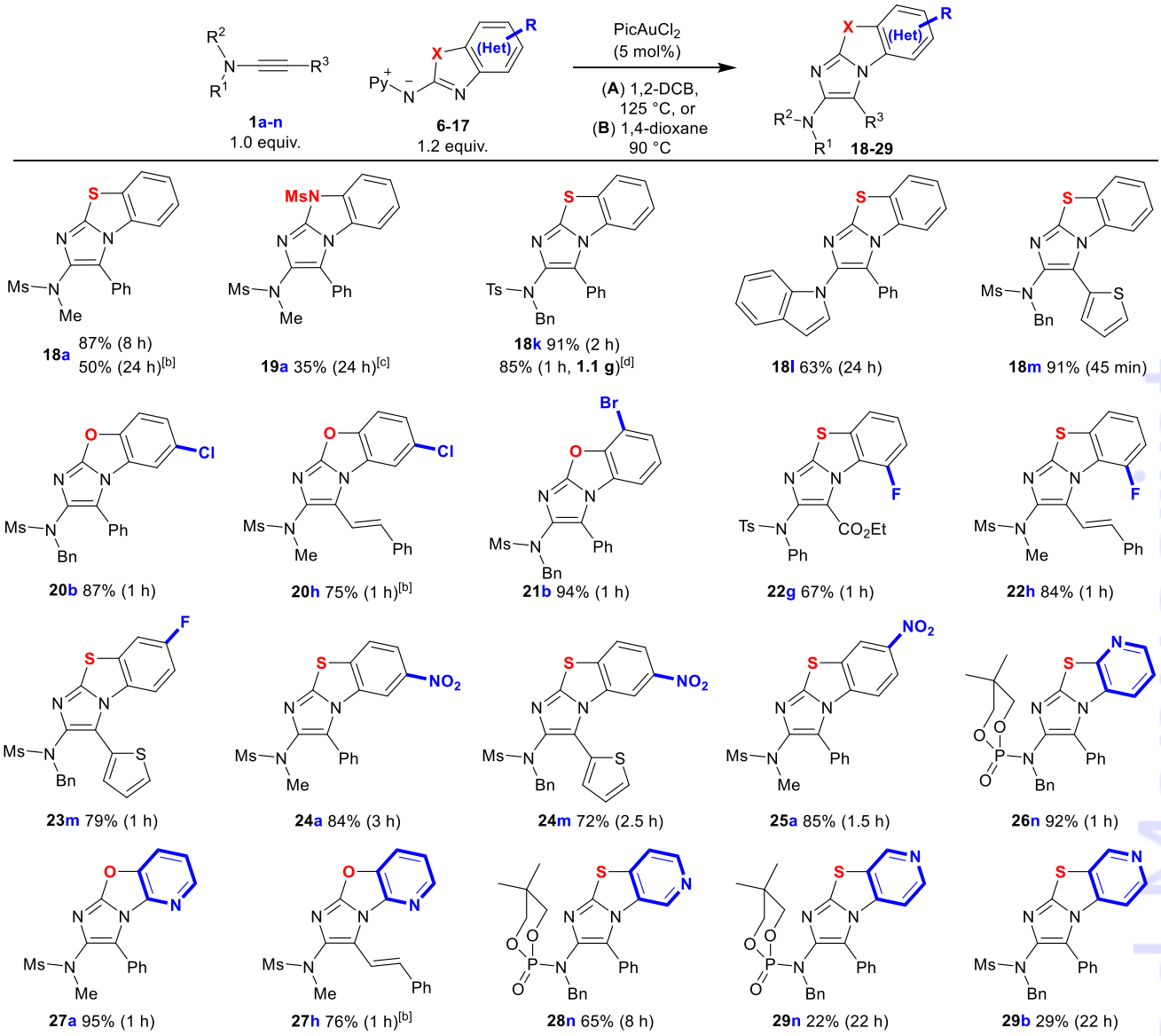
A variety of novel, and functionalised, 2-methylthiobenzo(thio/oxa)zoles and aza-analogues **4** were prepared (see ESI). In most cases, clean reactions occurred with *N*-amino pyridinium iodide and potassium carbonate in methanol, affording a range of new *N*-heteroaryl pyridinium *N*-aminides **6-13** as bench-stable crystalline materials (Scheme 3). While the 7-fluorobenzothiazolyl sulfide **4c** was unreactive, use of its corresponding arylsulfone (**5c**) provided ready access into the desired aminide **8**.



[a] *N*-Aminopyridinium iodide (1.00 equiv.), **4** (1.04 equiv.), K_2CO_3 (2.80 equiv.) at [0.1 M]. Yield of isolated product after flash chromatography. TCT = 2,4,6-trichloro-1,3,5-triazine. Py = Pyridine.

Scheme 3. The use of arylthioethers to allow synthesis of functionalised and diverse *N*-(heteroaryl)aminides[a]

Pleasingly, the formal cycloaddition proved to be general across a broad spectrum of *N*-heteroaryl pyridinium *N*-aminides, either prepared from arylthioethers or substitution of halogenated



[a] Using conditions **A** and at 0.2 mmol scale at [0.1 M] relative to **1** unless otherwise specified. Yields of isolated product after flash chromatography. [b] Using conditions **B**. [c] No reaction under conditions **A**. [d] Reaction run at 2.5 mmol scale.

Scheme 4. Novel and functionalised *N*-(heteroaryl)aminides in formal [3+2] dipolar cycloaddition across ynamides.[a]

heterocycles (**14**-**17**, See ESI) (Scheme 4). The attached donor atom impacted substantially on the reactivity of the imidoyl nitrenoid, with both benzothioxazole- and benzimidazole-derived aminides **14**[13] and **15** less reactive than **2**, but still allowing access into imidazo[2,1-*b*]benzothiazole **18a** and imidazo[1,2-*a*]benzimidazole **19a** under the more vigorous reaction conditions.

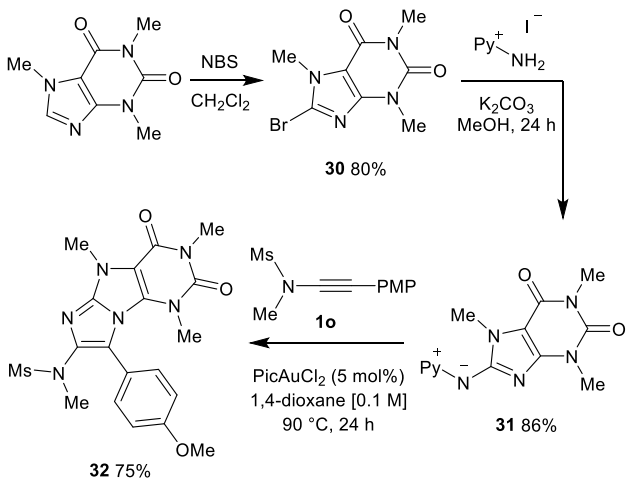
These reactions could be directly scaled-up to prepare more than a gram of imidazo[2,1-*b*]benzothiazole **18k** in high yield. This approach allows ready access into bi-heteroaryl linkages though use of the appropriate alkyne derivative as demonstrated in the use of an *N*-alkynylindole affording 2-(*N*-indolyl)-imidazo-fused system **18l**, or the thiophene **18m**.

Substitution was well-accommodated at each of the 4-, 5-, 6- and 7-positions across the imidazo[2,1-*b*]benzothiazole and imidazo[2,1-*b*]benzoxazole series on reaction with various ynamides under the standard conditions (Scheme 4). Notably, having the nucleophilic nitrenoid centre in-, or out of- direct conjugation to a strongly withdrawing nitro group had little practical impact (**24a** *vs* **25a**).

The new aminides incorporating pyridine rings **10**-**13** also proved to be effective dipole equivalents allowing rapid access to the fused triheterocyclic scaffolds **26**-**29** under the standard conditions (Scheme 4). In these cases, the reaction profile was significantly altered by the position of the additional aza group. The 4- and 7-aza analogues **11** and **10** reacted smoothly, affording the products **26** and **27** in

excellent yields after one hour. The 5-aza analogue **12** reacted more slowly, requiring 8 h for complete conversion, while the 6-aza analogue **13** reacted sluggishly with relatively low conversion even on prolonged heating. This relative reactivity profile can tentatively be assigned to the ability of the additional basic nitrogen site, in either starting materials or products, to act as a ligand to sequester the active gold species and reduce effective catalyst concentration. Both 5- and 6-positions are more sterically accessible than the *o*-substituted 4- and 7-positions; while the 6-aza group is further activated by the position of the π-donating aminide or imidazole in **13** or **29** respectively.

The applicability of this aminide-based nucleophilic nitrenoid approach to access new heterocyclic motifs was next tested using caffeine as a precursor. Selective bromination at C-2[25] followed by substitution of **30** with *N*-amino-pyridinium iodide generated the aminide **31** in high yield (Scheme 5). As **31** degraded on prolonged heating at elevated temperature, the gold-catalysis was run under the lower temperature conditions affording the densely functionalised cycloaddition adduct **32** in good yield, as apparently the first synthesised example of fused imidazo[1,2-*e*]purine derivatives.



Scheme 5. Rapid elaboration of caffeine into the imidazo[1,2-*e*]purine by a formal cycloaddition approach.

In summary, the valuable *o*-,*o*'-heteroatom-linked *N*-(hetero)aryl imidazole motif can be assembled in short order through a highly regioselective intermolecular formal [3+2]-dipolar cycloaddition reaction. This non-redox approach sees donor heteroatom substituted carbimidoyl nitrenoid reactivity accessed from robust and readily prepared *N*-heteroaryl pyridinium *N*-aminides and is generally applicable to heteroaromatic cores of both established import and untapped potential, as exemplified by its application to access eight different classes of fused tricyclic heteroaromatics. The process employs an efficient 1:1.2 reactant stoichiometry, is practically straightforward, and has been demonstrated on gram scale. The route tolerates substantial structural and functional group elaboration allowing for rapid build-up of structural complexity and molecular diversity. The reactivity and wider applicability of these formal cycloaddition processes is underway in our laboratory.

Experimental Section

Representative formation of aminides from arylthioethers: A mixture of *N*-aminopyridinium iodide (235 mg, 1.06 mmol) and potassium carbonate (411 mg, 2.97 mmol) in methanol [10 mL, 0.1 M] was stirred at room temperature for 30 min until a permanent purple suspension appeared. 2-(Methylthio)thiazolo[5,4-*b*]pyridine (**4e**, 201 mg, 1.10 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 and washed with $NaOH_{(aq.)}$ [2.5M]. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The residue was purified by flash chromatography over silica gel [CH_2Cl_2:methanol (95:5)] affording aminide **10** as a bright yellow solid (194 mg, 0.85 mmol, 80%).

Representative procedure for the formation of *o*-,*o*'-heteroatom-linked *N*-(hetero)aryl imidazoles: A heat gun-dried Schlenk tube under an argon atmosphere was charged with aminide **10** (54.6 mg, 0.24 mmol), dichloro(2-pyridinecarboxylate)gold (4.1 mg, 5 mol%) and ynamide **1n** (71.5 mg, 0.20 mmol) in dry 1,2-dichlorobenzene [0.1 M relative to the ynamide] and the mixture was stirred under argon at 125 °C for 1 h. The reaction mixture was then allowed to cool before being added directly onto a silica gel column and purified by flash chromatography [hexane:ethyl acetate (4:1)] affording **26n** as a white solid (93.3 mg, 0.19 mmol, 92%).

Experimental details and data are in the Supporting Information along with copies of NMR spectra and the crystal structure of **3a**.

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