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A Direct Route into Fused Imidazo-diazines and Imidazo-pyridines Using Nucleophilic Nitrenoids in a Gold-Catalyzed Formal [3 + 2]-Dipolar Cycloaddition

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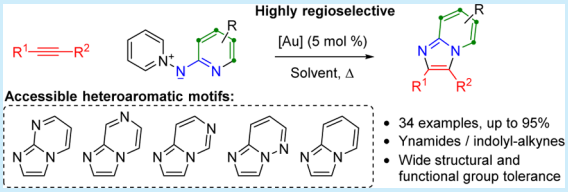
Supporting Information

ABSTRACT: Pyridinium *N*-(heteroaryl)aminides can be employed as robust and practical synthetic equivalents of nucleophilic 1,3-*N*,*N*-dipoles in a formal cycloaddition onto electron-rich alkynes under gold catalysis. Convergent and regioselective access to five types of imidazo-fused heteroaromatics is provided from the appropriate aminide. The efficient transformation accommodates significant structural variation around the aminide, ynamide, or indolyl-alkyne reactants and tolerates sensitive functional groups.



Heteroaromatic structures based on a diazine or pyridine fused across the 1,2-bond of an imidazole have widespread use: as important motifs in the pharmaceutical sector, where their derivatives feature in several current treatments and show extensive clinical activity against a range of disease targets,[1] as organic materials,[2] and as synthetic precursors to other nitrogen-heterocycles; for instance, the imidazo[1,2-*a*]pyrimidine is a masked form of the 2-amino-imidazole motif found in bioactive natural products (Figure 1).[3]

A number of methods have therefore been developed to prepare these scaffolds, and those that assemble the imidazole ring around the accessible aminodiazine or 2-aminopyridine precursors are quite prevalent: Substitution and condensation approaches with preformed electrophilic reagents, such as α-halocarbonyls or 1,3-dicarbonyl derivatives,[4] are complemented by transition-metal-catalyzed methods that allow the direct use of simpler, more-robust, precursors, such as terminal alkynes.[5] With many of these powerful methods having either underlying mechanistic similarities and/or precursors in common, their products often have closely related substitution patterns, especially around the imidazole core. Here we report a mechanistically distinct entry into imidazo[1,2]diazine and imidazo[1,2-*a*]pyridine structures from readily accessible and modifiable precursors. The route offers significant flexibility to access these important heteroaromatic frameworks with unexplored and/or otherwise challenging substitution patterns.

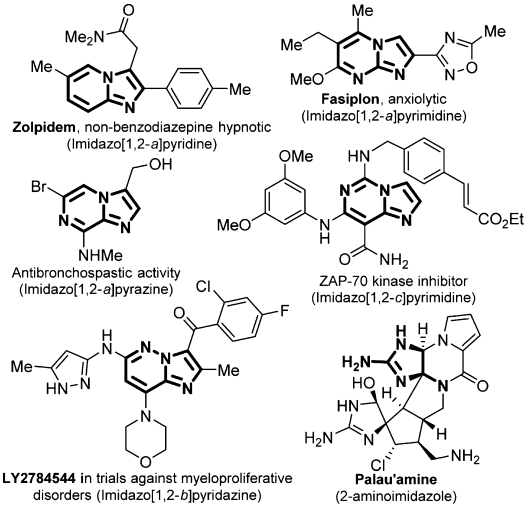


Figure 1. Examples of pharmaceuticals and biologically active compounds based around imidazo-diazine/-pyridine scaffolds.

Our group previously disclosed an intermolecular oxazole synthesis involving a formal [3 + 2]-dipolar cycloaddition between a gold-activated triple bond and an *N*-nucleophilic 1,3-*N*,*O* dipole equivalent.[6] Intrigued by the new patterns of retrosynthetic logic offered by the *umpolung* nucleophilic nitrogen-based dipole character, we questioned whether imidazole moieties could be similarly constructed from a gold activated triple-bond **C**/**D** using a *N*-nucleophilic 1,3-*N*,*N* dipole **A** (Figure 2).[7,8] We considered that pyridinium *N*-(heteroaryl)aminides **B** (heteroaryl = diazines or pyridine) would be potentially attractive as the synthetic equivalents to **A**. Alvarez-Builla et al. have established that aminides **B** are robust and readily accessed from commonly available α-halogenated diazines and pyridines.[9]

By analogy to the oxazole reaction,[6] a successful outcome would reveal the desired 1,3-*N*,*N* dipole character of aminides **B** in a stepwise fashion (Scheme 1, showing the imidazo[1,2-*a*]pyrimidine series): Activation of the triple bond **D** followed by intermolecular nucleophilic attack from **B** could form **E**.[7,8,10] The desired product follows cyclization with elimi-

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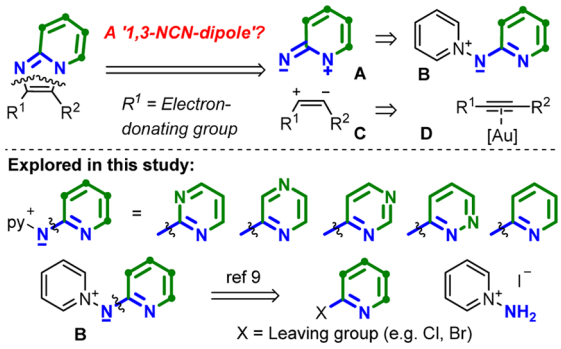
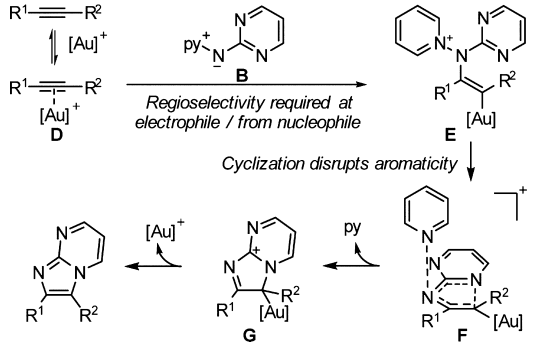
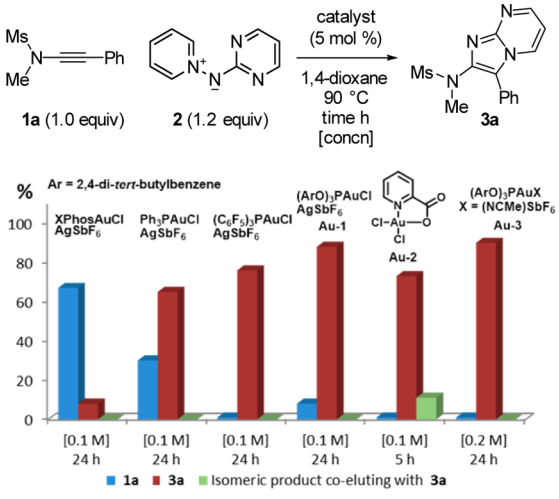


Figure 2. Proposed reactivity concept invoking *N*-nucleophilic 1,3-*N*,*N*-dipole equivalents for an imidazole-forming process.

Scheme 1. Proposed Process for the Desired Transformation



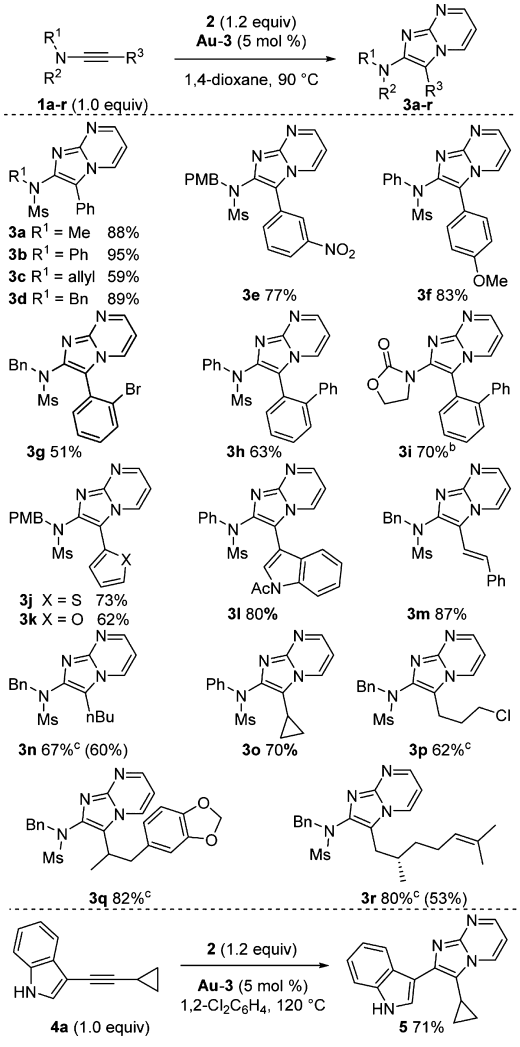
Scheme 2. Effect of Different Gold Catalysts on the Reaction of an Ynamide with Pyridinium *N*-(2-Pyrimidinyl)aminide



nation of pyridine and then deaurative aromatization of **G**. Our putative mechanism in the oxazole series involves a (pseudo)-bishetero-4π-electrocyclization where elimination of pyridine is considered near-synchronous with cyclization and triggered as the substituents approach alignment. This is shown idealized as **F** where the N−N bond is perpendicular to the developing 4π system.[11] Questions from the outset of the project were related to whether the conjugated nitrogens in **B** would be sufficiently nucleophilic for the intermolecular process, and with what regioselectivity, and how replacing a C═O bond with an aromatic C═N bond would affect cyclization.

We commenced our study with ynamide **1a** and pyridinium *N*-(2-pyrimidinyl) aminide **2**.[9,12−14] The desired imidazo[1,2-*a*]pyrimidine **3a** was indeed formed on heating with a Au catalyst (see Supporting Information (SI) for the full study of reaction conditions).[15] Despite the number of nucleophilic nitrogens in the starting materials, products, and byproducts, productive catalysis was observed along with an inverse correlation between the conversion and electron-donating ability of the ligand on Au(I) complexes with the phosphite gold complex **Au-1** showing the highest efficacy (Scheme 2). The Au(III) precatalyst **Au-2** was also quite effective with faster conversion but also afforded a side product that coeluted with **3a**.[16] Ultimately, excellent conversion, regioselectivity and yield of **3a** could be obtained using an efficient 1:1.2 ratio of **1a:2** on heating at 90 °C at 0.2 M in 1,4-dioxane with 5 mol % of preformed gold(I) acetonitrile hexafluoroantimonate complex **Au-3**.[6b]

Scheme 3. Gold-Catalyzed Synthesis of Imidazopyrimidines[a]



[a]Unless otherwise specified all reactions are run using ynamide (1.0 equiv), **2a** (1.2 equiv) and **Au-3** (5 mol %) in dioxane (0.2 M) for 3.5−22 h. Yields given from the isolated product after flash chromatography. [b] Yield from recrystallization after chromatography. [c] Reaction run using **Au-2** (5 mol %) with the yields in parentheses being those achieved using **Au-3**. PMB = *p*-methoxybenzyl.

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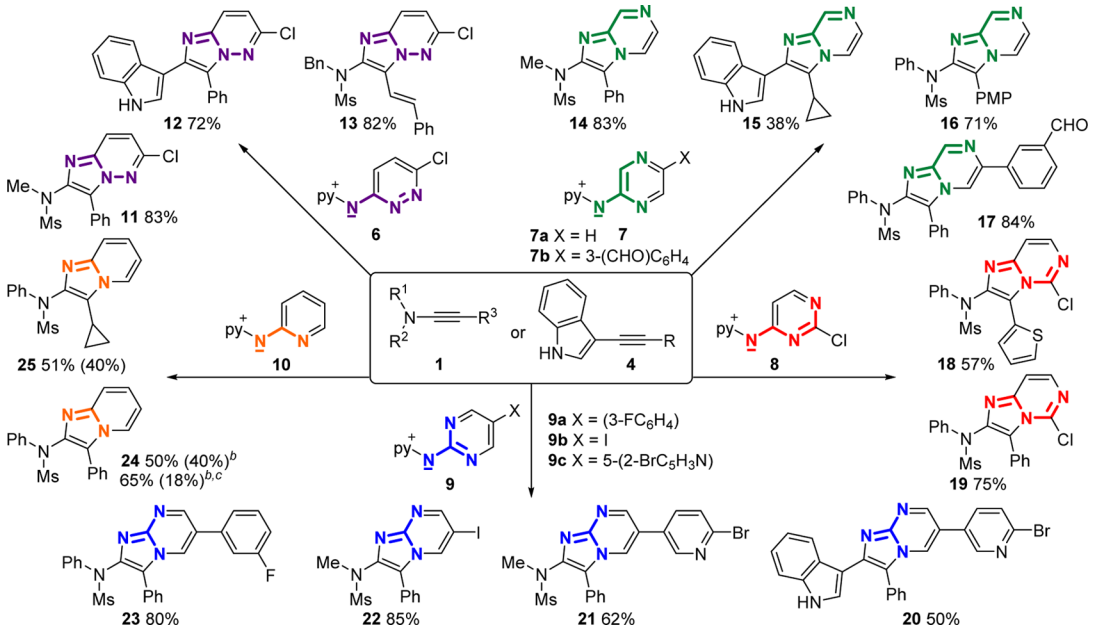
Scheme 4. Preliminary Investigation of the Scope of This Heterocycle Formation by Variation of the Aminide Partner[a]



[a]Reaction conditions: alkyne (1.0 equiv, 0.2 M), aminide (**6**–**10**, 1.2 equiv), and **Au-3** (5 mol %) in either 1,4-dioxane at 90 °C (ynamides **1**) or 1,2-dichlorobenzene at 120 °C (indole-alkynes **4**) unless otherwise specified. Yields of isolated product after flash chromatography. [b] Yields in parentheses refer to recovered starting alkyne. [c] Reaction performed using **Au-2** (5 mol %). PMP = *p*-methoxyphenyl.

The scope of this transformation was then explored using different ynamides (Scheme 3).[17] Aminoimidazo[1,2-*a*]-pyrimidines **3** were readily accessed with *N*-methyl, -phenyl, -allyl, -benzyl, and -*p*-methoxybenzyl substituents and either electron-rich or -poor aryl groups at C3 (**3a**–**f**).[18] The presence of sterically bulky *o*-bromobenzene and *o*-biphenyl substituents did not prevent the desired reaction (**3g**–**i**), with the oxazolidinone derivative **3i** afforded in higher yield than the sulfonamide equivalent **3h**. Heteroaryl substituents including 3-indolyl were also well tolerated (**3j**–**3l**). Ynamides with nonaryl substituents were next explored with the C-3 vinyl-substituted heterocycle **3m** prepared in high yield from a conjugated ene-ynamide. Alkylynamides also proved suitable substrates (**3n**–**r**) though yields and separations were deleteriously affected by the formation of side products under the standard conditions. These side products were formed as complex mixtures of isomers but appeared consistent with the group transfer and subsequent C–H insertion pathways previously described under gold-catalyzed oxygen and *N*-sulfonyl nitrene transfer reactions onto alkylynamides.[6,8,13a] As the reactions of alkylynamides were more sluggish than those of arylynamides, the gold(III) species **Au-2** was tested with alkylynamides and resulted in faster reactions as well as increased isolable yields of the products. As a result, structures combining functionalized aliphatic and heteroaromatic moieties can be directly accessed by this method, as demonstrated with the formation of alkyl-chloride, helional and citronellal derivatives **3p**–**3r** in good to high yields, even on gram scale.[19] A preliminary test showed that electron-rich internal alkyne **4** was also a suitable substrate, affording the biaryl linked product **5** in good yield with excellent regioselectivity when run at higher temperature.[6b]

The versatility of this reaction concept was then explored through the use of different aminides (**6**–**10**). Under the standard conditions, direct access into all the structural diazine combinations was possible with imidazo[1,2-*b*]pyridazines (**11**–**13**), -[1,2-*a*]pyrazines (**14**–**17**), and -[1,2-*c*]pyrimidines (**18**–**19**) as well as modified imidazo[1,2-*a*]pyrimidines (**20**–**23**) prepared in good to excellent yields (Scheme 4; see SI for crystal structures of **19** and **23**[20]). Alongside the significant structural generality, the reaction well-tolerated labile electrophilic functional groups such as aldehyde (**17**), 2-bromopyridines (**20**, **21**), and chloropyrimidines (**18**–**19**). In addition, imidazo[1,2-*a*]pyridines (**24**–**25**) could also be prepared in the same manner using **10**.[9] While the structural differences across the diazine family (**2**, **6**–**9**) had little qualitative impact on reactivity, the reactions with **10** were slower, albeit clean with recovery of significant quantities of the starting ynamides. The use of **Au-2** resulted in a less clean reaction but afforded a higher conversion and an improved isolated yield of **24**.

In conclusion, we have revealed the nucleophilic nitrenoid character of readily accessible pyridinium *N*-(heteroaryl)-aminides and employed them as robust and practical synthetic equivalents of 1,3-*N*,*N*-dipoles under gold catalysis. As a result, imidazo-fused heteroaromatics can be formed directly from the aminide and an electron-rich triple bond. These efficient intermolecular reactions show superb regioselectivity with (hetero)aryl-, vinyl-, and alkyl-ynamides as well as 3-alkynyl indoles to access five types of important heteroaromatic scaffolds with new substitution patterns. Effective catalysis is observed despite the number of basic nitrogens in the products and starting materials. The reactions are robust and scalable and accommodate a range of useful functional groups including aldehydes, alkenes, free and acylated indoles, furan, thiophene, nitro, aryl halides, and alkyl chlorides. The products of cycloaddition are formed preferentially even when the ynamide substituents offer alternative reaction pathways from incipient gold-carbenoid intermediate **E** (e.g., suitably tethered reactive π-systems **3b**–**d**, **3h**/**i**, **3q**–**r**), with cleaner reactions obtained using a gold(III) precatalyst in the case of alkylynamides. The mechanism, control factors, and wider utility of this reactivity are under investigation.

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■ ASSOCIATED CONTENT

Supporting Information

Survey of reaction conditions, experimental procedures and characterization, spectral data for all new compounds, NOE experiments for **3a**, and the data for single-crystal X-ray diffraction of **19** and **23** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) The regiochemistry of **3a** was confirmed by NOE coupling; see SI. Full characterization of the minor product has been hampered by coelution with **3a** though MS data confirm it to be an isomer.

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(20) CCDC 1018314 and 1018315 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.