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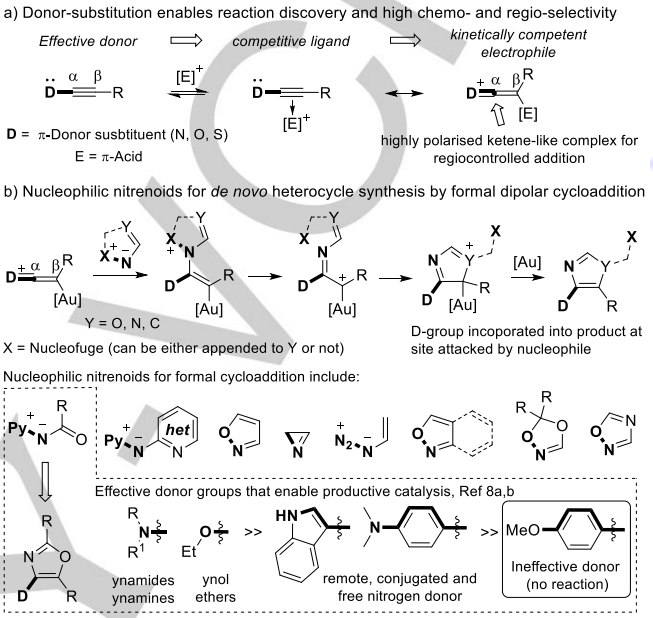
Alkynyl thioethers in gold-catalyzed annulations to form oxazoles

Raju Jannapu Reddy, Matthew P. Ball-Jones and Paul W. Davies*

Abstract: Non-oxidative, regioselective and convergent access into densely-functionalized oxazoles is realized in a functional-group tolerant manner using alkynyl thioethers. Sulfur terminated alkynes provide access to reactivity previously requiring strong donor-substituted alkynes such as ynamides. Sulfur does not act in an analogous donor-fashion in this gold-catalyzed reaction, leading to complementary regioselective outcomes while limitations from the use of ynamides are overcome by the synthetically useful thioether substituent.

Compared to other heteroatom-substituted alkynes, alkynyl thioethers are remarkably little explored in intermolecular late transition metal-catalysis despite being readily accessed and robust.[1-2] Ynamides, in contrast, are privileged substrates: In π-acid catalysis their donor nature aids metal-alkyne coordination and affords highly-polarized electrophiles, providing the high chemo- and regioselectivity required for the discovery of efficient intermolecular reactions (Scheme 1a).[3-4] As the resulting inclusion of a donor-nitrogen limits the utility of the products, retaining the reactivity profile of these transformations whilst accessing more flexible and readily-elaborated substitution patterns would be desirable. The value of sulfur-substituted compounds[5] coupled with progress in C-C and C-heteroatom bond-formation from C-S bonds,[6] renders alkynyl thioethers appealing alternatives to ynamides. Indeed the ketenethionium pathway (Scheme 1a) from alkynyl thioethers has recently been invoked in proton-catalyzed reactions with nitriles[2g,h] and gold-catalyzed reactions with sulfides.[2i]

Ynamides enabled the discovery of formal [3+2]-dipolar cycloadditions with nucleophilic nitrenoids[7] allowing intermolecular access to α-imino gold carbene-type reactivity for heterocycle synthesis (Scheme 1b).[8-9] Such reactions that do not depend on ynamides are scarce.[8b,h] A strong donor alkyne substituent proved critical in the formation of oxazoles using *N*-acyl pyridinium *N*-aminides as even electron-rich alkynes such as anisole-derivatives did not react (Scheme 1b, inset).[8a,b] Oxazoles are valuable synthetic intermediates[10-11] and structural components in bioactive natural products,[12] agrochemicals,[13] ligands,[14] and functional materials.[15] Despite recent advances, a single modular and convergent route into trisubstituted oxazoles that provides the structural and functional group diversity needed across the 2-, 4-, and 5-positions remains unrealised.[16]



Scheme 1. Donor substituent dictated reactivity and regioselectivity in π-acid catalysis, and its application in enabling new cycloaddition reactions.

Following our interest in the use of gold catalysis with sulfides[17] we report here on the reactivity of alkynyl thioethers with nucleophilic nitrenoids to prepare oxazoles. Importantly, the regioselectivity is not consistent with a controlling ketenethionium species. The sulfur group plays an alternative role in enabling reactivity, proving complementary to donor-enabled approaches.

The reaction of alkynyl thioether **1a** and aminide **2a** showed that conversion into oxazole **3** was possible at 125 °C in 1,2-dichlorobenzene (1,2-DCB) (see Supporting Information for a survey of reaction conditions and pyridine-modified aminides). No reaction was seen without catalyst, with dichloro(pyridine-2-carboxylato)gold superior to other metal salts including cationic gold and Ir(cod)Cl_2.[1c] 5-Methylthio-oxazole **3aa** was favored over 4-methylthio-oxazole **3aa'** in all cases,[18] contradicting the predicted outcome if sulfur were acting as π-donor substituent.

Effective reaction was seen with alkyl and aryl substitution at sulfur (Entries 1-5). Smaller *S*-substituents gave improved conversion and higher regioselectivity. Conjugating the alkyne with a strongly electron-withdrawing group shut down the reaction while an electron-donating substituent saw smooth reactions and excellent regioselectivities across the *S*-alkyl and *S*-aryl series (Entries 6-10). The sulfur substituent is critical; internal alkynes **4a/b** did not react (Entries 11-12).

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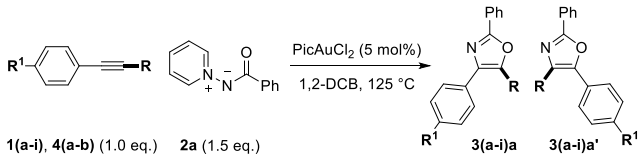
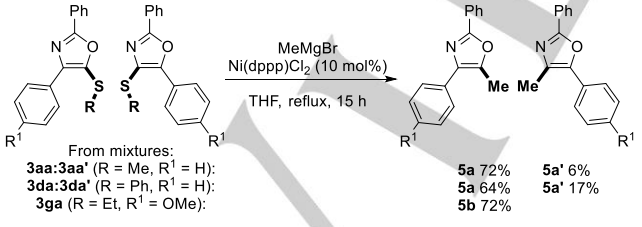


Entry	1	R	R^1	Time /h	3	Yield / % (3:3')
1	**1a**	SMe	H	24	**3aa**	72% (8.4:1)
2	**1b**	SEt	H	24	**3ba**	70% (6.5:1)
3	**1c**	S^{i}Pr	H	24	**3ca**	65% (4.5:1)
4	**1d**	SPh	H	24	**3da**	61% (4.8:1)
5	**1e**	SBn	H	24	**3ea**	51% (6.3:1)
6[b]	**1f**	SMe	CO_2Et	48	**3fa**	-
7	**1g**	SEt	OMe	36	**3ga**	64% (>20:1)
8[b]	**1g**	SEt	OMe	24	**3ga**	78% (>20:1)
9	**1h**	SPh	OMe	24	**3ha**	67% (15:1)
10	**1i**	SMe	OMe	24	**3ia**	73% (>20:1)
11	**4a**	Ph	OMe	48	-	-
12	**4b**	Me	OMe	48	-	-

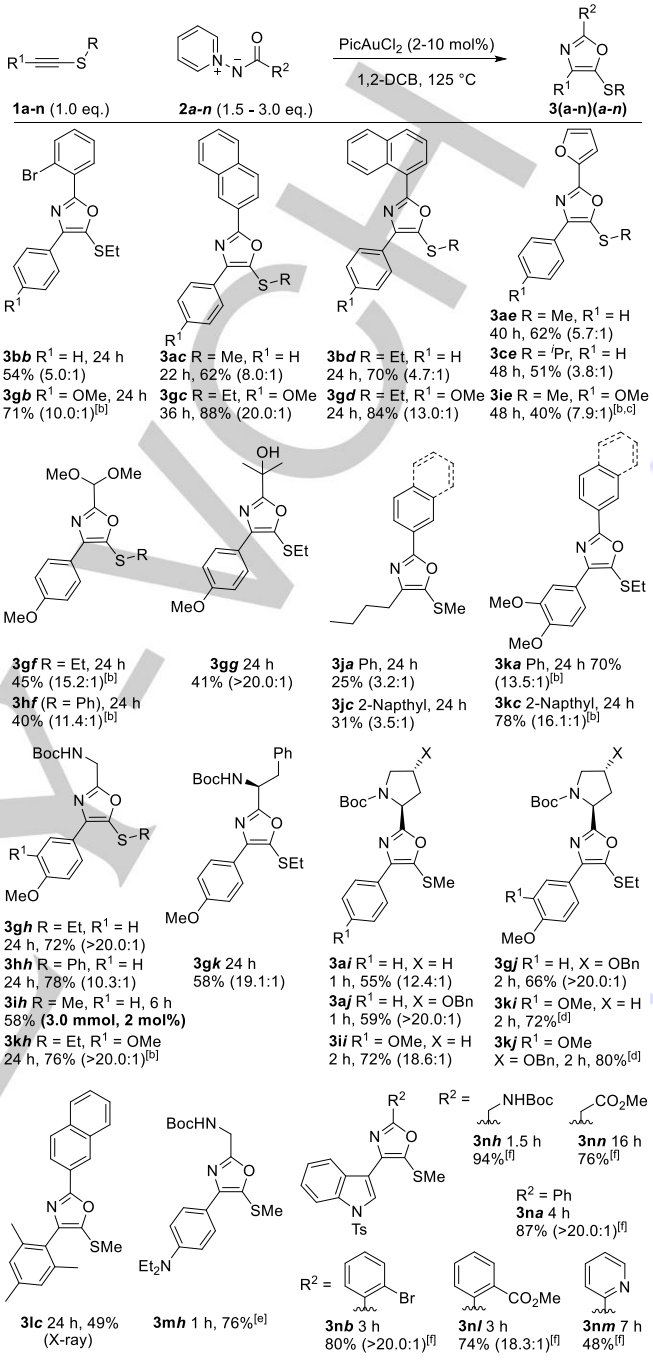
[a] Reactions performed using alkynyl thioether (0.2 mmol) and $PicAuCl_2$ (5 mol%), unless otherwise stated. Isolated yields of regioisomers with the ratio determined by ^1H NMR analysis. [b] $PicAuCl_2$ (10 mol%).

Site-specific Ni-catalyzed cross-coupling with MeMgBr saw conversion of thio-oxazoles **3/3'** into the known and separable methyl oxazoles **5a**/**5a'** or **5b** confirming preferential formation of 5-thio-oxazoles in the annulation (Scheme 2).[19-20] X-Ray diffraction subsequently confirmed the structures of **3aa** and **3ga** (see the Supporting Information).[21] These first nickel-mediated Kumada-type couplings with 5-thioether oxazoles[22] demonstrate the value of the thioether handle, here in preparing substitution patterns that are not directly accessible from the annulation (cf. **4b**, Table 1).



Scheme 2. Nickel-catalyzed Kumada cross-coupling of thioether substituted oxazoles. dppp = 1,3-Bis(diphenylphosphino)propane

The reactivity of alkynyl thioethers was evaluated across functionalized *N*-acyl aminides **2** (accessible from carboxylic acids or esters in one-step[23]). Broad functional group and structural tolerance was seen, with incorporation of electron-



Scheme 3. Intermolecular formal [3+2]-dipolar cycloaddition of alkynyl thioethers with *N*-acyl pyridinium *N*-aminides.[a] [a] $PicAuCl_2$ (5 mol%) unless otherwise mentioned. Isolated yields of regioisomers with the ratio determined by ^1H NMR analysis. [b] $PicAuCl_2$ (10 mol%). [c] 2.0 eq. of **2**. [d] Reaction carried out on 0.4 mmol scale. [e] 0.5 mmol scale. [f] 3.0 eq. of **2**.

-rich and -poor (hetero)aromatics, alkyl chains, acetals, aryl halides, Lewis bases, carbamates, aromatic and aliphatic amines, aromatic or enolisable carboxylic esters, and even a benzylic tertiary alcohol (Scheme 3, 0.2 to 3.0 mmol scale).

Motifs found in bioactive compounds and natural products, such as peptidic oxazoles (**3g*h*-3k*j***)[24] and (3-indolyl)oxazoles

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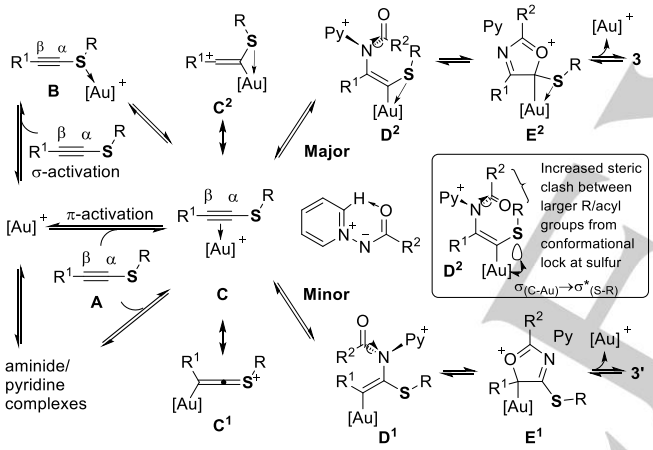
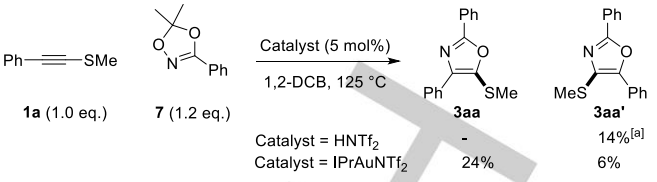
(**3n*a*-3n*n***),[12] are readily prepared. Alkynyl thioether **1j** gave 5-thioethers **3ja**/***c*** as the major isomers, providing 4-alkyl oxazoles. Sterically-congested bi-(hetero)aryl linkages may also be formed as single regioisomers (**3lc**).[21]

The favored addition of the nitrenoid β-to the sulfur (an inversion of regioselectivity compared to ynamides) is rationalized by a stabilizing Au–S interaction in the development of vinyl gold carbenoid **D²**, maintained to aurated heterocycle **E²** (Scheme 4). Three-membered metal-C-S dative interactions are known,[2c,d] while stabilizing hyperconjugative σ_{C-Au} to σ^*_{C-S} interactions (**D²** inset) could also be invoked.[25] Sulfur-gold coordination (**B**) may aid formation of a π-activated complex in the presence of other effective ligands to the metal. Ground state perturbation of the alkyne-gold complex with slippage of gold toward sulfur (extreme form **C²**) is reinforced by more electron-donating groups at R^1. The aminide nitrogen reconfigures as the nucleofuge is extruded with cyclisation requiring the acyl group to move up toward the aurated carbon. The lower regioselectivities seen with larger acyl-(**3g*c*** *vs* **3g*d***, Scheme 3) or sulfur-substituents are consistent with the conformations imposed in **D²**. To maintain the S-Au interactions the sulfur substituent is positioned toward the approaching aminide, causing repulsive interactions.[26]



Scheme 4. Proposed mechanistic rationale for the observed regioselectivity.

To rule out a controlling ketenethionium pathway in the gold catalyzed transformation we attempted to access such an intermediate using Brønsted acid catalysis.[2g,h] No reaction was seen between alkynyl thioether **1a** and aminide **2a** in the presence of Tf_2NH. Using dioxazole **7**,[8i,m] in place of **2a** led to the formation of 4-methylthiooxazole **3aa'** and no trace of the 5-methylthio-oxazole **3aa** (Scheme 5). In the presence of a cationic Au(I) catalyst the 5-methylthio-oxazole **3aa** was formed as the major isomer ruling out the nitrenoid's role in switching regioselectivity. These preliminary results show the potential of alkynyl thioethers in regiodivergent heterocycle synthesis by selective application of gold or protic catalysis with nucleophilic nitrenoids.



Scheme 5. Regiodivergent synthesis of thio-oxazoles using gold or protic catalysis. [a] Isolated yield of pure material after column chromatography, with further **3aa'** contaminated with dioxalane **7**.

In summary, broad functional group and structural tolerance allows for convergent and regioselective access into densely substituted oxazoles in the first example of gold catalyzed group-transfer reactions onto alkynyl thioethers. Such alkynes are complementary to strong π-donor substituted-alkynes, the sulfur is required for reactivity but gives inverted regioselectivity relative to the heteroatom, indicating that (metal)ketenethionium-directed pathways invoked in other annulation processes do not apply here Limitations from forming a donor-atom substituted product are addressed by this approach, as demonstrated by the Kumada coupling with 5-thioether-oxazoles.

Acknowledgements

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Keywords: cycloaddition • gold • heterocycles • regioselectivity • sulfur

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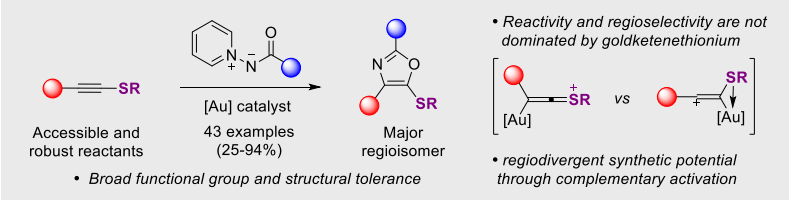

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The first gold catalysed annulations with alkynyl thioethers are reported. This transformation provides ready and convergent access into densely-functionalised 1,3-oxazole motifs. The sulfur substituent is integral to access the desired reactivity and provides a useful synthetic handle for later elaboration. In contrast with recent reports, the reaction is not directed through a ketenethionium pathway.