Alkynyl Thioethers in Gold-Catalyzed Annulations To Form Oxazoles
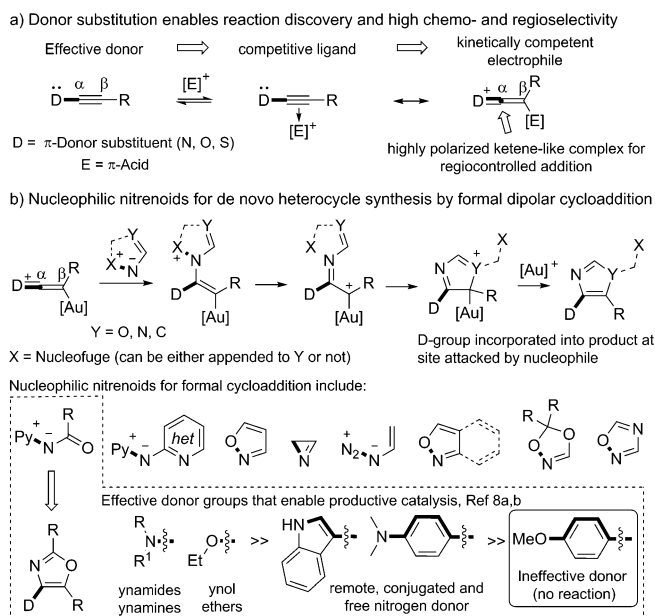
Raju Jannapu Reddy, Matthew P. Ball-Jones, and Paul W. Davies*

Abstract: *Non-oxidative, regioselective, and convergent access to 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, thus leading to complementary regioselective outcomes and addressing the limitations of using ynamides.*

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, thus 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 atom 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] thus allowing intermolecular access to α-imino gold carbene-type reactivity for heterocycle synthesis (Scheme 1b).[8,9] Such reactions, which 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 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

[*] Dr. R. J. Reddy, M. P. Ball-Jones, Dr. P. W. Davies
School of Chemistry, University of Birmingham
Birmingham (UK)
E-mail: p.w.davies@bham.ac.uk

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

route to trisubstituted oxazoles, which provides the structural and functional-group diversity needed across the 2-, 4-, and 5-positions, remains unrealized.[16]

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, thus proving complementary to donor-enabled approaches.

The reaction of the alkynyl thioether **1a** and aminide **2a** (Table 1) showed that conversion into the oxazole **3** was possible at 125°C in 1,2-dichlorobenzene (1,2-DCB; see the Supporting Information for a survey of reaction conditions and pyridine-modified aminides). No reaction was seen without catalyst, with dichloro(pyridine-2-carboxylato)gold being 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] thus contradicting the predicted outcome if sulfur were acting as a π-donor substituent.

Effective reaction was seen with alkyl and aryl substitution at sulfur (Table 1, 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 regioselectiv-

Table 1: Scope of the reaction with respect to the alkynyl thioethers.[a]

Entry	1	R	R^1	t [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	SiPr	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$_2$Et	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. Yields of the isolated regioisomers with the ratio determined by ^{1}H NMR analysis. [b] PicAuCl$_2$ (10 mol%).

ities across the *S*-alkyl and *S*-aryl series (entries 6–10). The sulfur substituent is critical, and the internal alkynes **4a/b** did not react (entries 11 and 12).

Site-specific nickel-catalyzed cross-coupling with MeMgBr saw conversion of the thio-oxazoles **3/3′** into the known and separable methyl oxazoles **5a/5a′** or **5b**, thus confirming preferential formation of 5-thio-oxazoles in the annulation (Scheme 2).[19,20] X-ray diffraction subsequently
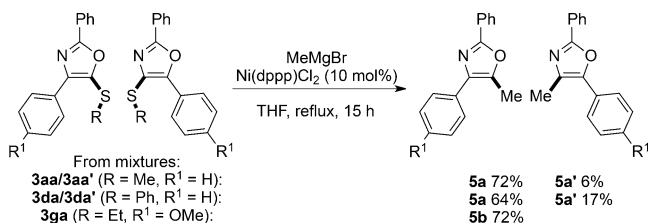
Scheme 2. Nickel-catalyzed Kumada cross-coupling of thioether substituted oxazoles. dppp = 1,3-bis(diphenylphosphino)propane, THF = tetrahydrofuran.
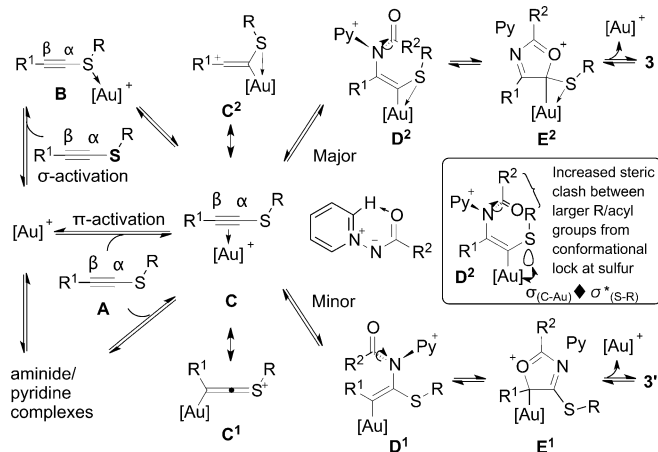
confirmed the structures of **3aa** and **3ga** (see the Supporting Information).[21] These first nickel-mediated Kumada-type couplings with 5-thioether oxazoles[22] demonstrate the value of the thioether handle, in this case providing substitution patterns which are not directly accessible from the annulation (see **4b** in Table 1).

The reactivity of alkynyl thioethers was evaluated across functionalized *N*-acyl aminides (**2**, Scheme 3; accessible from carboxylic acids or esters in one step[23]). Broad functional-group and structural tolerance was seen, with incorporation of electron-rich and electron-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 (0.2 to 3.0 mmol scale).
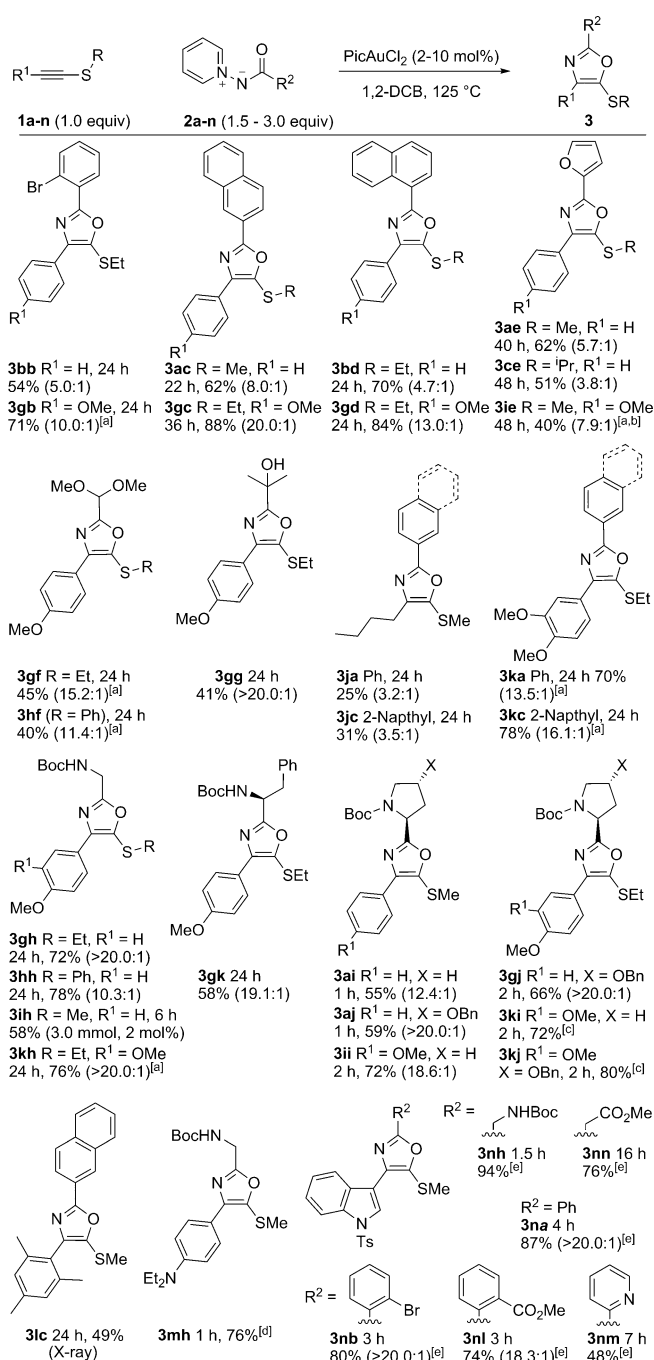
Scheme 3. Intermolecular formal [3+2] dipolar cycloaddition of alkynyl thioethers with *N*-acyl pyridinium *N*-aminides. PicAuCl$_2$ (5 mol%) unless otherwise mentioned. Shown are the yields of the isolated regioisomers with the ratio determined by ^{1}H NMR analysis. [a] PicAuCl$_2$ (10 mol%). [b] 2.0 equiv. of **2**. [c] Reaction carried out on 0.4 mmol scale. [d] 0.5 mmol scale. [e] 3.0 equiv. of **2**. Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.

Motifs found in bioactive compounds and natural products, such as peptidic oxazoles[24] derived from aminides **2h–k** and (3-indolyl)oxazoles[12] derived from the alkynyl thioether **1n**, are readily prepared. The alkynyl thioether **1j** gave 5-thioethers **3ja/c** as the major isomers, thus 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 atom (an inversion of regioselectivity compared to ynamides) is rationalized by a stabilizing Au−S interaction in the development of vinyl gold carbenoid $\mathbf{D^2}$, an interaction which is carried through into the to aurated heterocycle $\mathbf{E^2}$ (Scheme 4). Three-membered metal–S dative interactions
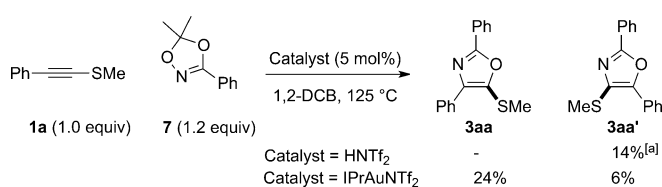

Scheme 4. Proposed mechanistic rationale for the observed regioselectivity.

Scheme 5. Regiodivergent synthesis of thio-oxazoles using either gold or protic catalysis. [a] Yield of the material isolated after column chromatography, with further **3aa′** contaminated with dioxalane **7**. Tf = trifluoromethanesulfonyl.

inverted regioselectivity relative to the heteroatom, thus 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.

are known,[2c,d] though stabilizing hyperconjugative $\sigma_{C\text{-}Au}$ to $\sigma^*_{C\text{-}S}$ interactions ($\mathbf{D^2}$ 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 $\mathbf{C^2}$) is reinforced by more-electron-donating groups at R^1. The aminide nitrogen atom reconfigures as the nucleofuge is extruded with cyclization, thus requiring the acyl group to move up toward the aurated carbon atom. The lower regioselectivities seen with larger acyl (**3gc** vs. **3gd**, Scheme 3) or sulfur substituents are consistent with the conformations imposed in $\mathbf{D^2}$. To maintain the S–Au interactions the sulfur substituent is positioned toward the approaching aminide, thus causing repulsive interactions.[26]

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 **1a** and **2a** in the presence of Tf$_2$NH. Using the dioxazole **7**[8i,m] in place of **2a** led to the formation of **3aa′** and no trace of **3aa** (Scheme 5). In the presence of a cationic Au^I catalyst **3aa** was formed as the major isomer, thus 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.

In summary, broad functional-group and structural tolerance allows 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, and the sulfur is required for reactivity but gives

Conflict of interest

The authors declare no conflict of interest.

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