Synthetic Methods

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Intermolecular and Selective Synthesis of 2,4,5-Trisubstituted Oxazoles by a Gold-Catalyzed Formal [3 + 2] Cycloaddition**

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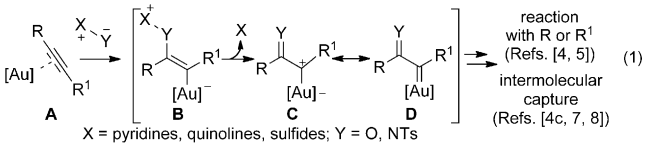
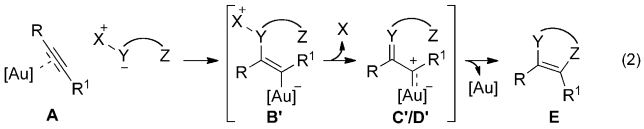
The generation and subsequent evolution of metal-stabilized carbocation/carbenoid reactivity patterns from C–C π systems is central to π-acid catalysis.[1] Following the formation of α-oxo/imido organogold species by intramolecular atom-transfer processes onto alkynes,[2,3] such intermediates [Eq. (1), **B**–**D**, Ts = toluene-4-sulfonyl] have very recently been accessed by intermolecular attack of an O- or N-nucleophilic oxidant[4] or nitrene equivalent[5] to an electrophilically activated π system [Eq. (1), **A**→**B**]. The intermediates are quenched by the reaction with a functionality contained within the alkyne starting material (at R or R^1),[4,5] a [3 + 3] sigmatropic rearrangement at **B**,[6] or by further reaction with a nucleophilic oxidant[4c,7] or nitrile[8] in the absence of faster intramolecular processes. Though elimination of the delivery system [Eq. (1), **B**→**C**/**D**] may not proceed as a distinct step,[4] the overall reactivity patterns observed are reminiscent of electrophilic α-oxo-metal carbenoids (**C**/**D**), and thus allow C–C triple bonds to be perceived of as simpler and direct alternatives to extensively used α-oxo-diazo compounds.



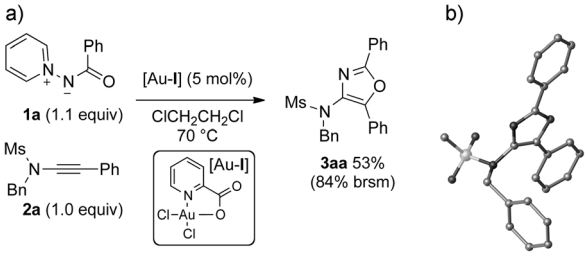
(1)

However, the introduction of functionality adjacent to the electrophilic organogold center in such processes offers wider opportunity for the design of efficient transformations. We questioned whether the intermolecular nucleophilic attack on **A**, which initiates the organometallic intermediate, could simultaneously install the means to quench it [Eq. (2)]. The resulting gold-catalyzed intermolecular cycloaddition across the π system would, as far as we are aware, be unprecedented.[9]



(2)

Conjugated N-ylides were selected to achieve the required two-center reactivity. While robust pyridine-N-aminides, such as **1a** (Y–Z = N–C=O), are established as 1,3-C,N dipoles incorporating the pyridine group,[10] an alternate reactivity as an N-nucleophilic 1,3-N,O-dipole equivalent would emerge under the proposed catalytic regime. Gratifyingly, aminide **1a** reacted with ynamide **2a** in the presence of the dichloro(pyridine-2-carboxylato)gold(III) precatalyst[11] ([Au-**I**]) to afford the cycloaddition product oxazole **3aa** as a single regioisomer alongside recovered starting material (Scheme 1). Single-crystal X-ray diffraction confirmed the structure of **3aa** and hence the regioselectivity of the intermolecular cycloaddition.[12]



Scheme 1. a) Formal cycloaddition of ynamide **2a** with the robust 1,3-N,O-dipole equivalent **1a**. b) Crystal structure of **3aa**; hydrogen atoms omitted for clarity. Bn = benzyl, brsm = based on recovered starting material, Ms = methanesulfonyl.

Though [3 + 2] cycloadditions across C–C π systems are widely employed for the preparation of other heterocycles, their application toward 1,3-oxazoles is extremely limited.[13] This is seemingly due to poor chemoselectivity in the formation and application of the required 1,3-N,O-dipole equivalent, acyl nitrenes, for instance by thermal or photochemical decomposition of acyl azides in the presence of alkynes.[14,15] A copper-catalyzed cycloaddition–fragmentation–cyclization cascade affords 2,5-disubstituted oxazoles from terminal alkynes and acyl azides.[16] Similarly convergent one-step or one-pot methods to prepare functionalized 1,3-oxazoles are rare,[8] and often require the use of highly reactive species with consequent structural limitations.[17] Instead, these important motifs for bioactive molecules, ligand frameworks, and materials are most commonly pre-

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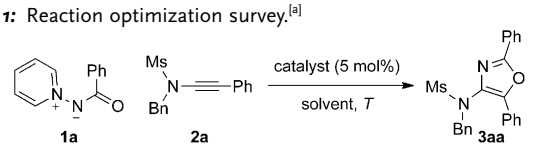
pared by intramolecular cyclization[18] or elaboration around an oxazole core.[19]

The novel reactivity of the aminide as a potentially controllable N-acyl nitrene equivalent to form oxazoles was studied (Table 1). No product was observed in the absence of

Table 1: Reaction optimization survey.[a]



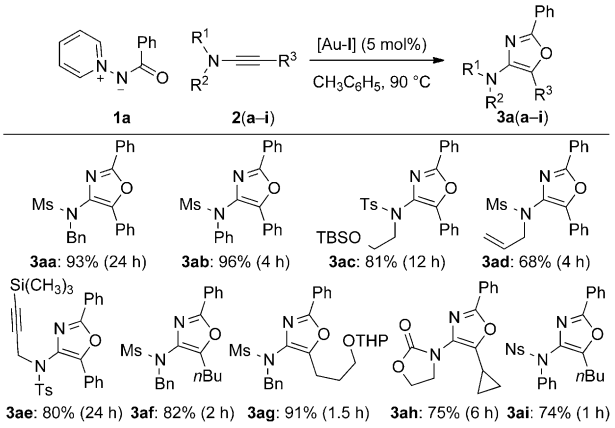
Entry	Catalyst	**1a** [equiv]	Solvent	*T* [°C]	**3aa** (**2a**) [%][b]
1	–	1.1	$ClCH_2CH_2Cl$	70	0 (>95)
2	*para*-TsOH	1.1	$ClCH_2CH_2Cl$	70	0 (>95)
3	$[Ph_3PAuSbF_6]$[c]	1.1	$ClCH_2CH_2Cl$	70	53 (47)
4	$[Ph_3PAuNTf_2]$	1.1	$ClCH_2CH_2Cl$	70	37 (57)
5	$AuBr_3$	1.1	$ClCH_2CH_2Cl$	70	59 (34)
6	$Na[AuCl_4]$	1.1	$ClCH_2CH_2Cl$	70	40 (57)
7	[Au-**I**]	1.5	$ClCH_2CH_2Cl$	70	79 (6)
8	[Au-**I**]	2	$ClCH_2CH_2Cl$	70	65 (22)
9	[Au-**I**]	1.5	$CH_3C_6H_5$	90	95 (0)
10	$[Ph_3PAuOTf]$[c]	1.5	$CH_3C_6H_5$	90	61 (14)
11	–	1.5	$CH_3C_6H_5$	90	0 (94)
12	–	1.5	$CH_3C_6H_5$	110	0 (>95)
13	–	1.5	*ortho*-xylene	140	3 (86)

[a] Reaction conditions: **1a** (as shown), **2a** (0.1 mmol, 1 equiv), catalyst (5 mol%), solvent (0.1 M), 24 h. [b] Yields and ratios calculated by ^{1}H NMR spectroscopy against a known quantity of an internal standard. [c] Prepared in situ by adding equimolar quantities of $[Ph_3PAuCl]$ and the appropriate Ag^I salt. [Au-**I**] = dichloro(pyridine-2-carboxylato)gold(III), Ts = toluene-4-sulfonyl.

a gold catalyst at 70 °C, either with or without Brønsted acid (Table 1, entries 1 and 2). Cationic gold(I) complexes and gold tribromide (Table 1, entries 3–5) were similarly effective to [Au-**I**], though sodium tetrachloroaurate was slightly less active (Table 1, entry 6). The use of 1.5 equivalents of **1a** saw improved conversion, though a further increase was not beneficial (Scheme 1 vs. Table 1, entries 7 and 8). Switching to a less polar solvent at higher temperature resulted in nearly quantitative formation of the desired product using robust air-stable [Au-**I**] (Table 1, entry 9) with a less clean reaction observed using a cationic gold species (Table 1, entry 10). Even at significantly higher temperatures thermal reactions saw only trace amounts of oxazole identified (Table 1, entries 11–13).

A range of functionalized ynamides were treated with aminide **1a** under the optimized reaction conditions (Scheme 2).[20] Benzyl, aryl, and alkyl substituents at the nitrogen atom were all well-tolerated, as was a tethered silyl ether (**3aa**–**3ac**). Oxazole **3ad** was prepared in good yield, given the propensity of N-allyl ynamides to undergo a thermal Claisen rearrangement.[21] Excellent chemoselectivity for the ynamide π system occurred in the presence of an alkene (**3ad**) or even an alkyne (**3ae**).

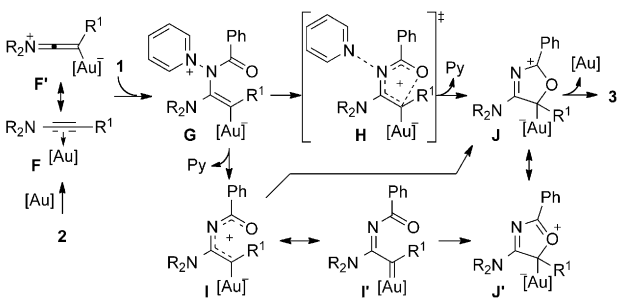
Though developing gold carbenoids are commonly observed to undergo facile 1,2-insertion reactions into adjacent C–H and strained C–C bonds,[1–5] alkyl substituents



Scheme 2. Ynamide scope for the gold-catalyzed oxazole cycloaddition.[a] [a] Reaction conditions: **1a** (1.5 equiv), **2(a–i)** (1.0 equiv), and [Au-**I**] (5 mol%) in toluene (0.1 M) were reacted at 90 °C. Reactions were monitored by TLC and stopped after the time shown in parentheses. Yields refer to isolated product after column chromatography. Ns = 2-nitrobenzenesulfonyl, TBS = *tert*-butyldimethylsilyl, THP = tetrahydropyranyl.

were well tolerated on the ynamide π system in our studies (**3af**–**3ai**). Acid-labile functionality survives the process unscathed (**3ag**). The 4-oxazolidinone-1,3-oxazole **3ah** was formed in good yield despite the potential for ring expansion of the cyclopropane. The reactions of terminal ynamides afforded complex mixtures. The more labile nosyl protecting group on the nitrogen atom of the ynamide was also explored.[22] A 2-nitrobenzenesulfonamide, which is geometrically capable of an intramolecular redox reaction between the nitro group and the gold-activated π system,[23] was employed to test the intermolecular reaction, and the desired oxazole **3ai** was formed in good yield.

The regiochemical outcome of this transformation is consistent with a proposed mechanistic overview in which nucleophilic attack by the aminide occurs adjacent to the nitrogen of a gold-activated ynamide **F**/**F′** to give adduct **G** (Scheme 3).[4c,5,24] Cyclization to **J**/**J′** can be viewed after elimination of pyridine as either a 4π electrocyclization of the extensively delocalized gold-stabilized carbocation **I** or a capture of the electrophilic carbon center in carbenoid **I′** by the acyl oxygen,[25] with both routes assisted by the heteroatom substituent. However, to account for the lack of competing 1,2-insertion reactions, C–O bond formation must be fast, and likely commences with developing carbocationic

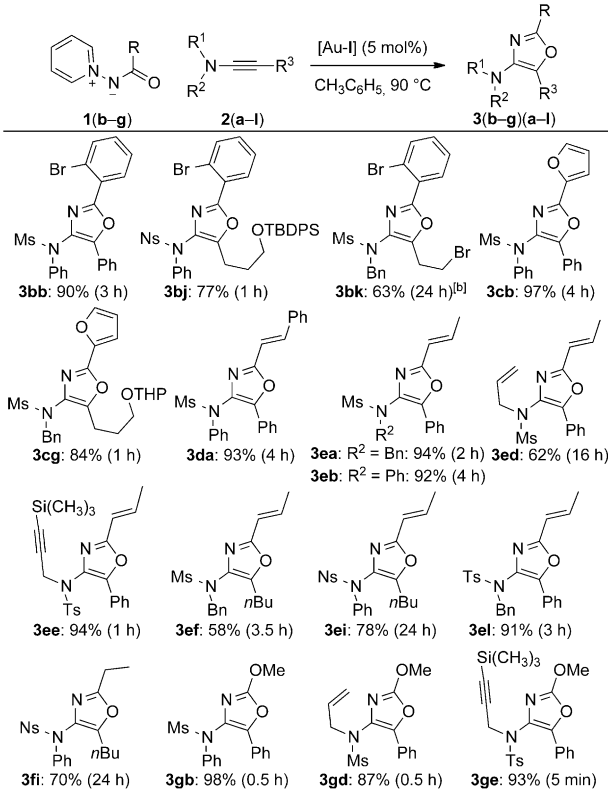


Scheme 3. Proposed mechanism for the formation of 1,3-oxazoles.

character (**G**→**H**→**J**) prior to the complete N–N bond fission. Elimination of the gold-catalyst from **J** then yields oxazole **3**.

An alternative mechanism involving the formation of a gold nitrene and an initial chelotropic reaction with the ynamide was ruled out, as a regioisomeric oxazole would be expected.[26] Furthermore, no reaction was seen when complexes established in atom-transfer processes, $[Rh_2(OAc)_4]$, $[Cu(CN)_4]BF_4$, or AgOTf, were used.

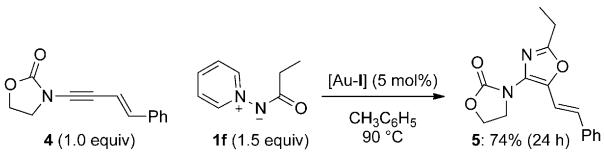
Alongside continued variation of the ynamide, the reaction scope was evaluated with respect to the aminide to vary the 2-substituent in the product oxazoles (Scheme 4). An



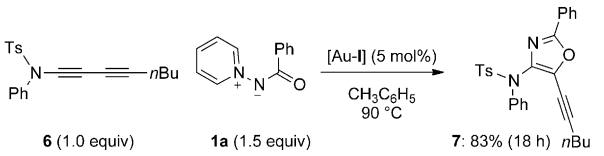
Scheme 4. Scope for the gold-catalyzed oxazole cycloaddition.[a] [a] Reaction conditions: **1**(**b**–**g**) (1.5 equiv), **2**(**a**–**l**) (1.0 equiv) and [Au-**I**] (5 mol%) in toluene (0.1 M) were reacted at 90 °C. Reactions were monitored by TLC and stopped after the time shown in parentheses. Yields refer to isolated product after column chromatography. [b] Contaminated with < 5% of the 5-vinyloxazole from HBr elimination. TBDPS = *tert*-butyldiphenylsilyl.

ortho-bromobenzene group is readily incorporated allowing for future modification (**3bb** and **3bj**). Remarkably, a primary alkyl bromide is also tolerated under these conditions (**3bk**). Straightforward access to a bis-heteroaryl axis is demonstrated by the incorporation of a furyl unit (**3cb** and **3cg**). The same process can be used to prepare valuable 2-vinyl oxazoles (**3da**–**3eb**),[27] including polyunsaturated systems **3ed** and **3ee**. Aliphatic substituents can also be introduced at the 2-position as shown with nosylated compound **3fi**. Heteroatom incorporation at the 2-position was readily achieved using methoxycarbonyl aminide, with excellent yields even with an N-allyl ynamide (**3ga**, **3gd**, and **3ge**).

Ynamides with conjugated π systems reacted predictably in the oxazole synthesis: oxazolidinone-derived enynamide **4** underwent cycloaddition to the 5-vinyl oxazole **5** [Eq. (3)], and the conjugated diynamide **6** reacted cleanly at the π system directly connected to nitrogen atom to give the 5-alkynyloxazole **7** in high yield [Eq. (4)].

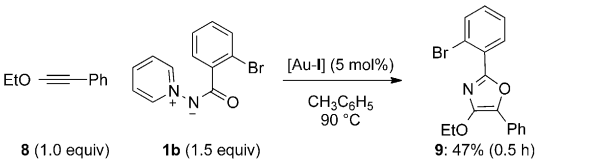


(3)

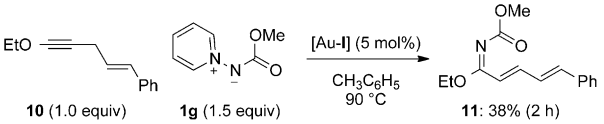


(4)

Preliminary studies indicate that the reaction is not limited to ynamides. 4-Ethoxyoxazole **9** was successfully prepared from ynol ether **8** under the standard reaction conditions [Eq. (5)]. However, ynol ether **10** gave the α,β,γ,δ-unsaturated ethylimidate **11** [Eq. (6)] in keeping with the gold-catalyzed nitrene transfer to alkyl-substituted ynamides[5] and oxidation of alkyl-substituted ynol ethers.[4c] The additional allylic activation of the adjacent methylene group sees 1,2-insertion supplant C–O bond formation.



(5)



(6)

In summary, a regioselective gold-catalyzed intermolecular [3 + 2] cycloaddition across electronically biased π systems is reported. The preparatively straightforward synthesis of highly substituted and functionalized 1,3-oxazoles employs conjugated N-ylides as robust and chemoselective N-nucleophilic N-acyl nitrene/1,3-N,O-dipole equivalents. Strikingly, the reaction is highly chemoselective, and the desired pathway proceeds in preference to several other available processes. Further study into the reactions of ylides with electrophilically activated C–C π systems is ongoing.

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