

One-Pot Synthesis of Benzene-Fused Medium-Ring Ketones: Gold Catalysis-Enabled Enolate Umpolung Reactivity

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Supporting Information

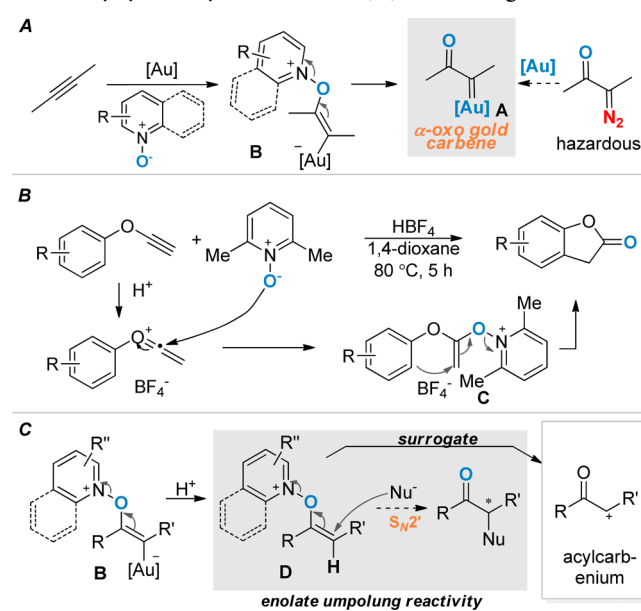
ABSTRACT: Enolate umpolung reactivities offer valuable and potentially unique alternatives over the enolate counterparts for the construction of ubiquitous carbonyl compounds. We disclose here that *N*-alkenoxypyridinium salts, generated readily upon gold-catalyzed additions of protonated pyridine *N*-oxide to *C*–*C* triple bonds of unactivated terminal alkynes, display versatile enolate umpolung chemistry upon heating and react with tethered arene nucleophiles in an *S_N2'* manner. In a synthetically efficient one-pot, two-step process, this chemistry enables expedient preparation of valuable benzo-fused seven-/eight-membered cyclic ketones, including those of *O*-/*N*-heterocycles, from easily accessible aryl-substituted linear alkyne substrates. The reaction yields can be up to 87%.

We have recently developed an intermolecular oxidative gold catalysis, which permits facile and general access to α -oxo gold carbene intermediates (e.g., **A**) from benign and readily available alkynes instead of hazardous α -diazo ketones (Scheme 1A).¹ Mechanistically, the carbene formation commences with a cationic Au(I)-promoted addition of a pyridine/quinoline *N*-oxide to a *C*–*C* triple bond to afford the gold-substituted *N*-alkenoxypyridinium intermediate **B**, which would in turn heterolytically fragment the weak *N*–*O* bond to arrive at **A**. Based on this oxidative approach, a variety of versatile synthetic methods^{1b–g,2} have been developed.

Our early intramolecular work in 2009,³ 2011,⁴ and 2013^{1d} showed that the initial adducts related to **B**, where *SR*₂ or *NR*₃ replaces the *N*-heteroarene, do not always undergo fragmentation to form α -oxo gold carbenes of type **A** but instead proceed through more facile alternative processes. Other studies utilizing the intermolecular strategy shown in Scheme 1A have also revealed alternative reaction pathways undertaken by **B**,^{2c,e} or related other metal intermediates,⁵ where the metal-attached *C*(*sp*²) reacts with tethered nucleophiles without the involvement of the α -oxo metal carbene intermediate **A**. Importantly, Hashmi⁶ showed that the related *N*-alkenoxypyridinium intermediate **C**, generated from electron-rich and activated phenoxyethyne in the presence of *HBF*₄, is also electrophilic at the terminal alkene end despite without metal substitution, and its subsequent cyclization renders benzofuranones (Scheme 1B). Gong⁷ earlier reported a related metal-free oxidation.

We envisioned that the metal-less *N*-alkenoxypyridinium **D** of general scope could be generated from typical unactivated

Scheme 1. (A) Generation of α -Oxo Gold Carbenes via Oxidative Gold Catalysis; (B) Hashmi's Work Using Electron-Rich Alkynyl Phenyl Ethers; and (C) Our Design



alkynes via sequential gold-promoted formation of **B** and its subsequent protodeauration (Scheme 1C). It is surmised that such a species might offer a new range of versatile reactivities complementary to the chemistry featuring oxidatively generated and highly reactive α -oxo gold carbenes (i.e., **A**). In particular, it is anticipated that **D** could react with nucleophiles in an *S_N2'* manner and, as such, behave as a surrogate of highly reactive and little utilized acylcarbenium ions⁸ and display novel enolate umpolung reactivities. Notably, approaches to achieving enolate umpolung have been reported but are limited in scopes and utilities.⁹ Herein, we disclose our preliminary results in this regard, which reveals facile oxidative constructions of benzene-fused seven-/eight-membered alkenones from readily available linear arylalkyne substrates. Medium-ring ketones of these types are synthetically useful and often prepared via ring expansion or from diazo substrates,¹⁰ both of which, however, could require

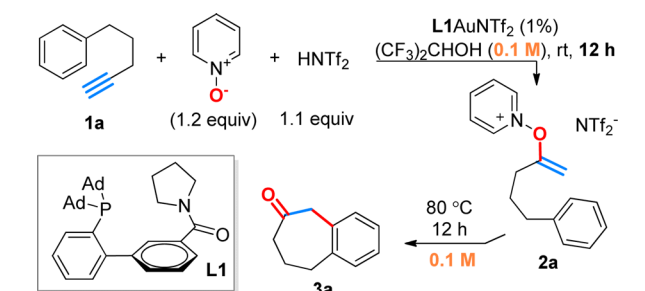
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multisteps and/or necessitate the use of hazardous diazo compounds.

At the outset, we employed 5-phenylpent-1-yne as the substrate for the preparation of the desired *N*-alkenoxy-pyridinium salt **2a** (Table 1). Moreover, we surmised that **2a** might

Table 1. Initial Reaction Discovery and Condition Optimization



entry	deviation from the initially optimized conditions ^a	yield	
		first step	overall
1	–	90%	71%
2	Ph ₃ P as ligand	84% ^b	–
3	IPr as ligand	79% ^b	–
4	JohnPhos as ligand	27% ^b	–
5	(2,6- ^t Bu ₂ C ₆ H ₃ O) ₃ P as ligand	18% ^b	–
6	CF ₃ CH ₂ OH as solvent	90%	57%
7	DCE as solvent	79% ^b	35%
8	CH ₃ CN as solvent	61%	–
9	THF as solvent	trace	–
10	4-methylpyridine <i>N</i> -oxide instead	86%	30% ^c
11	2-bromopyridine <i>N</i> -oxide instead	72%	25%
12	2-ethoxypyridine <i>N</i> -oxide instead	48%	–
13	quinoline <i>N</i> -oxide instead	98%	48% ^d
14	HOTf as acid	90%	71%
15	pyridine <i>N</i> -oxide (1 equiv) and Tf ₂ NH (1.2 equiv) instead	N.R.	–
16	[1a] = 1.0 M and 0.5 mol % L1AuNTf ₂ , 1 h for the 1 st step; 90 °C and 3 h for the 2 nd step	98%	75% ^e (70% ^f)

^aReactions run in vials; yields as determined by ¹H NMR. ^bReaction time: 24 h; no alkyne left. ^c35% of the pyridinium intermediate remained. ^d26% of methyl ketone formed. ^e~77% NMR obtained by using 5 mol % of Ph₃PAuNTf₂. ^fIsolated yield.

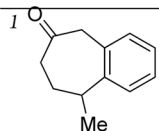
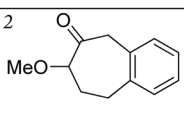
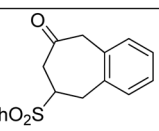
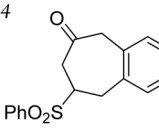
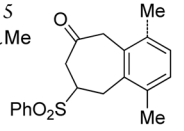
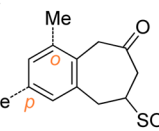
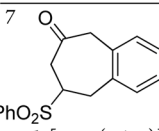
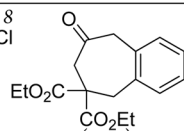
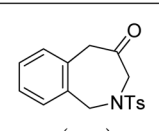
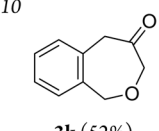
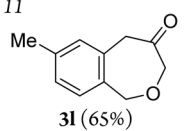
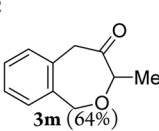
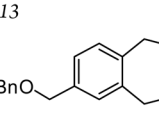
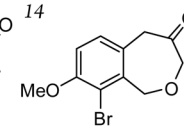
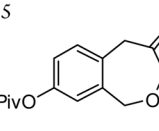
undergo Friedel–Crafts-type cyclization to deliver the benzene-fused cycloheptenone **3a**. After considerable effort on condition discovery and optimization, we were indeed able to implement both transformations in a two-step, one-pot process.

With the initially optimized conditions, **3a** was formed in a good 71% overall yield (entry 1). The reaction conditions, as shown in the equation in Table 1, include the use of **L1** as the most effective ligand, hexafluoroisopropanol as the optimal solvent, and cheap and commercially available pyridine *N*-oxide as the oxidant. The first step proceeded smoothly at ambient temperature in 12 h, affording **2a** in 90% NMR yield; the second step required heating at 80 °C for 16 h. Notably, **2a** is a stable species and was isolated in 88% yield and fully characterized. It needs to be pointed out that intermediates of this type has rarely been isolated before.¹¹ Dissolving **2a** in (CF₃)₂CHOH and heating the solution at 80 °C again afforded **3a** in 75% NMR yield, which is comparable to the estimated yield of the second step in the one-pot process (i.e., ~79%). This result confirms that in the one-pot reaction, the remaining gold catalyst, the excess

oxidant, and its protonated form did not interfere the desired cyclization. The ligand **L1** was previously developed by us as a bifunctional ligand for gold-catalyzed highly efficient addition of carboxylic acid to alkynes.¹² Indeed, other typical ligands including PPh₃, JohnPhos, IPr, and (2,6-^tBu₂C₆H₃O)₃P all fared worse than **L1** in terms of reaction rate and efficiency (entries 2–5). The reaction solvent turned out to be critical for both steps. While CF₃CH₂OH is equally effective in the first step, the yield of the cyclization is lower (entry 6). Other solvents such as DCE, CH₃CN, and THF are less or not conducive to the initial gold catalysis (entries 7–9). The replacement of pyridine *N*-oxide with substituted ones led to poor yields (entries 10–12). In the case of quinoline *N*-oxide (entry 13), though the first step was more efficient, the cyclization turned out to be inferior, and moreover, the corresponding methyl ketone was formed in 26% yield. This side product, also observed with other *N*-oxides albeit to a much less extent (<8%), is likely formed upon nucleophile attack at the C2 of the quinoline ring followed by rearomatization. TfOH was as efficient an acid as HNTf₂ (entry 14). It is interesting, though, that little **2a** was detected when the acid HNTf₂ was used in excess to the oxidant in the gold catalysis step (entry 15), which can be attributed to the much decreased concentration of the nucleophilic free oxidant. Finally, the conditions could be further improved by running the first step at a higher initial concentration (i.e., 1 M), which permitted the use of only 0.5 mol % of the gold catalyst while offering a near quantitative yield in only 1 h, and the second step at 90 °C, which allowed the completion of the cyclization in a much shorter 3 h (entry 16). As such, the overall one-pot process afforded **3a** in 75% NMR and 70% isolated yield. Of note, with 5 mol % Ph₃PAuNTf₂ as the gold catalysis, the overall yield is comparable. Gagosz et al. have demonstrated that a related one-step gold catalysis via a gold-containing intermediate of type **B** enables efficient oxidative cyclization of 3-arylpropynes, but reported that no **3a** was formed from **1a** by using their protocol, even in the presence of MsOH,^{2c} highlighting the complementary nature of our umpolung approach.

With the optimal conditions (cf. Table 1, entry 16) in hand, we then set out to explore the scope of the novel umpolung chemistry in the context of constructing benzene-fused seven-membered ketones. As shown in Table 2, a methyl (entry 1), a methoxy (entry 2), or a sulfonyl (entry 3) substitution at the propylene tether between the phenyl ring and the C–C triple bond were readily allowed, and the corresponding benzene-fused heptenones were formed in fair to good yields. Considering the two-step nature of the oxidative cyclization, the average single step yields in these cases are still near or exceeding 80%. In entry 3, the sulfonyl substrate was easily prepared via propargylation of deprotonated (phenethylsulfonyl)benzene. This flexible access to the aryl alkynes enabled expedient examination of the impact of a methyl substituent at different positions of the benzene ring. As shown in entries 4–6, these reactions proceeded smoothly and efficiently. In the case of an *ortho*-Me (entry 5), an inseparable minor isomer was formed, the structure of which was assigned based on NMR spectra and correlation to a later case (*vide infra*). In the case of a *meta*-Me, no regioselectivity was detected, consistent with the low steric demand of an unsubstituted alkene end (entry 6). With a moderately deactivating *p*-Cl on the benzene ring, the desired product **3h** was isolated in a poor 19% yield, while the major product was the corresponding methyl ketone, despite the high yielding of the initial gold catalysis (~94%). This result, while consistent with the Friedel–Crafts nature of the cyclization, indicates that the

Table 2. Formation of Benzene-Fused Seven-Membered Ketones: Reaction Scopes^{a,b}

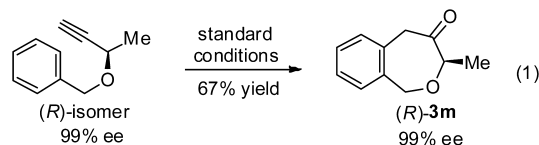
		
3b (77%) (1 st step: 1.5 h)	3c (67%) (1 st step: 1.5 h)	3d (62%) (1 st step: 12 h)
		
3e (78%) (1 st step: 12 h)	3f (70%, 3.8/1) (1 st step: 12 h)	3g (78%, <i>o/p</i> = 1:1) (1 st step: 12 h)
		
3h [19% (36% ^c)] (1 st step: 12 h; 2 nd step: 24 h)	3i (58%) (1 st step: 2.5% Au, 24 h; 2 nd step: 4 h)	3j (57%) (1 st step: 6 h; 2 nd step: 4 h and 100 °C)
		
3k (52%) (1 st step: 2.5 h; 2 nd step: 7 h and 100 °C)	3l (65%) (1 st step: 3 h; 2 nd step: (1 st step: 8 h; 2 nd step: 4.5 h and 100 °C, 20% pyridine)	3m (64%) (1 st step: 8 h; 2 nd step: 4.5 h and 100 °C, 20% pyridine)
		
3n (48%) (1 st step: 4 h; 2 nd step: 8 h and 100 °C)	3o (57%) 1 st step: 7 h; 2 nd step: 10 h and 100 °C)	3p (51%) (1 st step: 4 h; 2 nd step: 8 h and 100 °C, 20% pyridine)

^aTypical reaction conditions: (i) Pyridine *N*-oxide (1.2 equiv), HNTf₂ (1.1 equiv), L1AuNTf₂ (0.5 mol %), (CF₃)₂CHOH (1 M), rt, 3 h; (ii) (CF₃)₂CHOH (0.1 M), 90 °C, 3 h. ^bIsolated yield. ^cYield of the corresponding methyl ketone **3h'**.

undesired nucleophilic attack at the pyridine ring (*vide supra*) can dominate over the desired cyclization with deactivated arene rings. Notably, with all the sulfone substrates (i.e., entries 3–7), the initial gold catalysis required a much longer 12 h reaction time. With a malonate-derived substrate, the initial gold catalysis was even slower, requiring 24 h in the presence of 2.5 mol % of the gold catalyst, and afforded a lower 84% NMR yield (entry 8). These slow gold catalyses can be attributed to the decreased reactivities of the C–C triple bonds due to induction by the electron-withdrawing substituents. Nevertheless, the umpolung reactions remained mostly efficient.

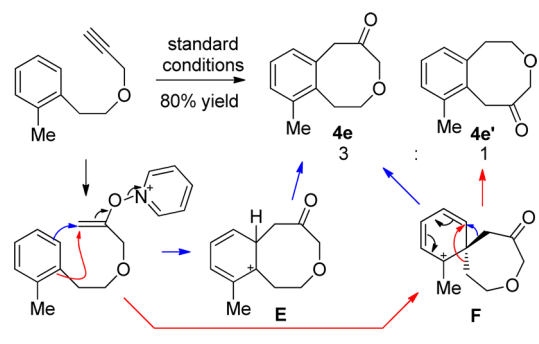
This one-pot oxidative cyclization could be smoothly applied to the readily accessible benzyl propargyl amides and ethers (entries 9–15), thereby affording benzo-fused dihydroazepinones or dihydrooxepinones, some functionalized with benzyl-oxo ether (**3n**), bromo/methoxy (**3o**), or carboxy (**3p**). In these cases, the umpolung step was slow, and a higher temperature, i.e., 100 °C, resulted reasonable reaction times. Notably, in entries

11, 12, and 15, the initial adducts, i.e., the *N*-alkenoxypyridinium salts of type **D**, appeared to decompose under the acidic environment at the elevated temperature. With the buffering of 20 mol % of pyridine, the reactions proceeded smoothly to deliver the anticipated heterocycles in fairly good yields. Extension of the chemistry to phenyl homopropargyl ether, *N*-homopropargylaniline or substrates with electron-rich hetero-aromatic rings such as furan, pyrrole, and indole was not successful. In entries 3, 9, and 10, we also tested Ph₃PAuNTf₂ (5 mol %) instead of L1AuNTf₂ (0.5 mol %), but the gold catalysis was much less efficient, with yields typically <60%. When **Table 2**, entry 12 was performed using the (*R*)-substrate, (*R*)-**3m** was formed without detectable ee erosion (eq 1).



With the success in the formations of benzene-fused seven-membered rings, we then explored the more challenging eight-membered ring formation. Not surprisingly, the reaction of 6-phenylhex-1-yne was poor, and the yield of the cyclization step was ~20%. Much to our delight, the reactions using the easily accessible propargyl ethers as substrates were efficient, affording the dihydrobenzooxocinones in generally good to excellent yields (entries 1–4). Of note are that the unsubstituted product **4a** (entry 1) was formed in a better yield than its seven-membered counterpart (**Table 2**, entry 10), and electron-donating substituents enable further improved reaction efficiencies (entries 2–4).

As shown in **Scheme 2**, with 2-methylphenethyl propargyl ether as the substrate, besides the expected product **4e**, its

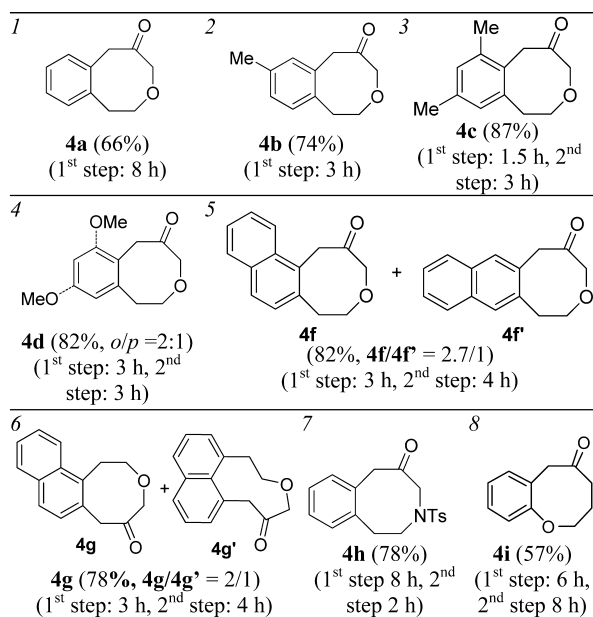
Scheme 2. Proposed Mechanism of the formation of 4e/4e'

structural isomer **4e'** was also isolated. The competitive skeleton rearrangement in this case can be rationalized by invoking the formation of the spirobenzenium **F**, which can be followed by the migration of its alkyl group instead of the acylmethyl group. The occurrence of this reaction pathway could be attributed to the comparable stability of benzenium moieties **F** and the expected cyclization intermediate **E** as a consequence of the *ortho*-methyl group. This rationale could likewise explain the formation of the minor isomer of **3f** (cf. **Table 2**, entry 5).

The reactions with naphthalene-based substrates are interesting. With a 2-naphthyl substrate in entry 5, cyclization to the ring 3-position yielding **4f'** competes with that to the 1-position; another site competition was observed with the 1-naphthyl substrate, where cyclization to the *peri* position en route to a

nine-membered ketone (i.e., **4g'**) was significant (Table 3, entry 6). To our delight, the reaction also permits a one-step

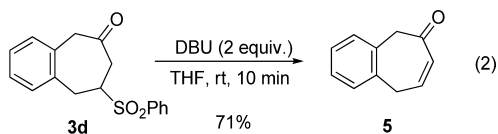
Table 3. Formation of Benzene-Fused Eight-Membered Ketones: Reaction Scopes^{a,b}



^aTypical reaction conditions: (i) pyridine *N*-oxide (1.2 equiv), HNTf₂ (1.1 equiv), **L1**AuNTf₂ (0.5 mol %), (CF₃)₂CHOH (1 M), rt; (ii) (CF₃)₂CHOH (0.1 M), 100 °C, 6 h. ^bIsolated yield.

preparation of the tetrahydrobenzo[*d*]azocinone **4h** from a *N*-propargylsulfonamide (e.g., entry 7). Importantly, the reaction was surprisingly efficient, and the overall yield (i.e., 78%) is better than that of its dihydroazepinone counterpart (57% in Table 2, entry 9). Among the substrates with N or O atoms at other locations of the tether, phenyl bishomopropargyl ether is the only one affording a decent yield (entry 8).

Of interest is that the sulfonyl groups used to enable rapid substrate assembly, as in Table 2, entries 3–7, reside β to the nascent carbonyl group. It is anticipated that they could be eliminated under basic conditions to yield versatile medium-ring conjugated enones.¹³ Indeed, when **3d** was treated with DBU in THF in 10 min, the benzo-fused cycloheptadienone **5** was formed in 71% isolated yield (eq 1). Overall, the sulfonyl group acts as a versatile yet traceless facilitator of the umpolung chemistry.



In conclusion, we have demonstrated that novel *N*-alkenoxypyridinium salts exhibit versatile enolate umpolung reactivities. These intermediates can be readily accessed upon gold-catalyzed addition of protonated pyridine *N*-oxide to C–C triple bonds of unactivated terminal alkynes and easily activated upon heating to react with tethered arene nucleophiles in an S_N2' manner. The significant synthetic value of this approach is demonstrated in this work via expedient one-pot preparation of valuable benzo-fused medium-ring ketones from easily accessible aryl-substituted linear alkynes. This novel strategy possesses the

potential of revolutionizing the enolate umpolung reactivities and offering highly valuable alternatives for the synthesis of various carbonyl compounds. Studies on challenging intermolecular reactions will be next pursued.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02533.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

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