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Au(III)-Catalyzed Tandem Amination–Hydration of Alkynes: Synthesis of α-(*N*-2-Pyridonyl)ketones

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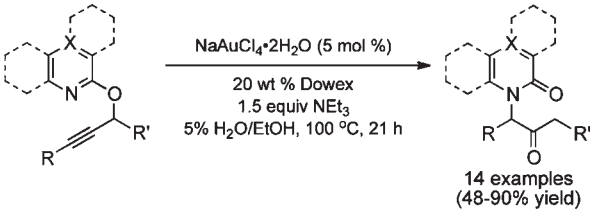
ABSTRACT



A new Au(III)-catalyzed tandem amination–hydration reaction has been discovered, leading to the formation of α-(*N*-2-pyridonyl)ketones and heterocyclic analogues in good to excellent yields (14 examples, 48–90%). This reaction demonstrates the unusual use of a heterocyclic sp^2 nitrogen nucleophile in a gold-catalyzed 6-*endo-dig* cyclization. The tandem process allows rapid access to α-(*N*-2-pyridonyl)ketones, making them a convenient building block for the synthesis of more complex *N*-alkyl pyridone targets.

Gold catalysis has emerged as a powerful method for activating alkynes toward the addition of external nucleophiles.[1] These reactions benefit from the reduced oxophilicity of gold cations relative to other transition metals and the preference for alkyl-gold complexes to undergo protodeauration rather than β-hydride elimination.[2] Such characteristics allow for high functional group tolerance and present an ideal platform for selective amination of alkynes.[3]

First reported by Utimoto in 1987,[4] both inter- and intramolecular gold-catalyzed hydroaminations have been demonstrated.[5] However, heterocyclic sp^2 nitrogens have rarely been utilized as nucleophiles in these reactions, as the resulting products would be unstable cationic nitrogen species. Recent attempts to overcome this limitation have encountered yield-limiting isomerizations[6] or the migration of nonconventional groups.[7]

2-Propargyloxypyridines **1** present an ideal system in which to explore the addition of such nucleophiles to a gold-activated alkyne, given the proximity of the nucleophilic sp^2 pyridine nitrogen and the ability of the cationic intermediate to undergo tautomerization–rearrangement to give *N*-alkyl pyridones (Scheme 1). The prevalence of *N*-alkyl pyridones in both natural products[8] and pharmacologically relevant targets[9] renders the gold-assisted amination significant. In addition, while several methods have been reported for initiating direct *O*- to *N*-alkyl migration in 2-alkoxypyridine systems,[10]

(1) For recent reviews, see: (a) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, *5*, 675–691. (b) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, *5*, 692–706. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239–3265. (d) Hashmi, S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (e) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325.

(2) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903 and references therein.

(3) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, *20*, 4555–4563.

(4) Fukuda, Y.; Utimoto, K.; Nozaki, H. *Heterocycles* **1987**, *25*, 297–300.

(5) Representative examples: (a) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627–630. (b) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349–3352.

(6) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284–2287.

(7) (a) Seregin, I. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2006**, *128*, 12050–12051. (b) Seregin, I. V.; Schammel, A. W.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 3433–3436.

(8) Representative examples: (a) Camptothecin alkaloids: Wall, M. E.; Wani, M. C. *J. Ethnopharmacol.* **1996**, *51*, 239–253. (b) Lupin alkaloids: Gray, D.; Gallagher, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2419–2423. (c) Mappicine: Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215–1217.

(9) Representative examples: (a) Huffman, J. W.; Lu., J.; Hynd, G.; Wiley, J. L.; Martin, B. R. *Bioorg. Med. Chem.* **2001**, *9*, 2863–2870. (b) Parlow, J. J.; Kurumbail, R. G.; Stegeman, R. A.; Stevens, A. M.; Stallings, W. C.; South, M. S. *J. Med. Chem.* **2003**, *46*, 4696–4701.

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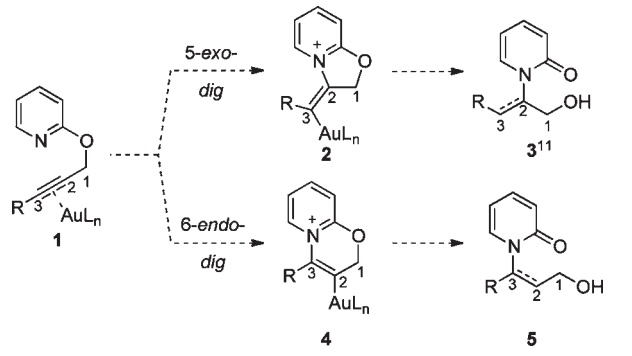
Scheme 1. Predicted Pathways for Au(III)-Catalyzed Addition

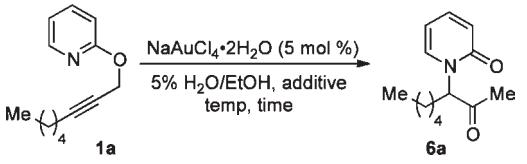


to our knowledge only one system to date enables direct alkyne functionalization.[11]

We originally predicted that cyclization of pyridine **1** would proceed in a 5-*exo*-*dig* manner to give intermediate **2**, given the prevalence of 5-*exo*-*dig* cyclizations in gold-catalyzed alkynyl additions.[2] Pyridinium ion **2** could then rearrange to *N*-alkenyl pyridone **3**, as has been previously observed in our laboratory (Scheme 1).[11] Alternatively, if intramolecular addition occurred in the less common 6-*endo*-*dig* fashion, the pyridone product **5** would display *N*-alkylation at the distal position (carbon 3).[12] Formation of either product would demonstrate the successful addition of a heterocyclic sp^2 nitrogen nucleophile to an activated alkyne. As such, efforts to develop this transformation were undertaken.

Pursuant to numerous examples of gold-catalyzed alkyne amination, $NaAuCl_4{\bullet}2H_2O$ was selected as a catalyst and aqueous EtOH was utilized as the solvent for preliminary studies (Table 1).[2,13] Initial efforts, however, were unsuccessful, as treatment of pyridine **1a** with 5 mol % $NaAuCl_4{\bullet}2H_2O$ at room temperature gave only starting material (entry 1). Given that nitrogen bases have been observed to increase the catalytic efficiency of Au(III), NEt_3 was explored as an additive.[14] Again, no reaction was observed at ambient temperature; however, when the reaction was warmed to 40 °C, unexpected α-(*N*-2-pyridonyl)-ketone **6a** was isolated exclusively, albeit in only 11% yield (entries 2 and 3). The formation of ketone **6a** from 2-propargyloxypyridine **1a** occurs via a 6-*endo*-*dig* cyclization and results in the addition of heteroatoms to both ends of the alkyne. The formation of a viscinally substituted product is unusual, given that the majority of other known gold-catalyzed double additions to alkynes proceed to give products with geminal substitution patterns.[15]

Table 1. Reaction Optimization



entry	concn (M)	additive	temp (°C)	time (h)	yield (%)[a]
1	0.12	–	rt[b]	24	NR[c]
2	0.12	1.0 equiv NEt_3	rt[b]	24	NR[c]
3	0.12	1.0 equiv NEt_3	40	72	11
4	0.24	1.0 equiv NEt_3	80	72	28
5	0.95	1.0 equiv NEt_3	80	21	15
6	0.95	1.5 equiv NEt_3	80	21	63
7	0.95	0.30 equiv $MeSO_3H$	80	21	30
8	0.95	20 wt % Dowex	80	21	48
9	0.95	1.5 equiv NEt_3 20 wt % Dowex	80	21	75
10	0.95	1.5 equiv NEt_3 20 wt % Dowex	90	21	82
11	0.95	1.5 equiv NEt_3 20 wt % Dowex	100	21	89

[a] Isolated yield. [b] rt = room temperature. [c] NR = no reaction.

Given the unique structure and potential utility of ketone **6a**, optimization studies were pursued. Increasing the concentration, temperature, and amount of NEt_3 were found to improve the reaction efficiency, affording product **6a** in up to 63% yield after 21 h (entries 4–6). After additional attempts to optimize these variables led to no further improvement in yield, a Brønsted acidic additive was evaluated as an alternative. Previous reports suggest that many gold-catalyzed reactions are enhanced by Brønsted acids, as they generally aid in protodeauration.[16] When the reaction was performed in the presence of $MeSO_3H$, TLC analysis indicated significant formation of pyridone **6a**; however, when the crude residue was concentrated *in vacuo*, rapid decomposition of the product was observed (entry 7). To circumvent this problem, acidic Dowex resin was employed, as it could be easily removed prior to concentration (entry 8). While the yield of product **6a** initially decreased in the presence of Dowex relative to that observed with NEt_3, when both additives (NEt_3 and Dowex) were employed

(10) (a) Lanni, E. L.; Bosscher, M. A.; Ooms, B. D.; Shandro, C. A.; Ellsworth, B. A.; Anderson, C. E. *J. Org. Chem.* **2008**, *73*, 6425–6428. (b) Yeung, C. S.; Hsieh, T. H. H.; Dong, V. M. *Chem. Sci.* **2011**, *2*, 544–551. (c) Rodrigues, A.; Lee, E. E.; Batey, R. A. *Org. Lett.* **2010**, *12*, 260–263.

(11) Tasker, S. Z.; Brandsen, B. M.; Ryu, K.-A.; Snapper, G. S.; Staples, R. J.; DeKock, R. L.; Anderson, C. E. *Org. Lett.* **2011**, *13*, 6224–6227.

(12) Addition to the distal position of the alkyne has been observed in Au-catalyzed reactions of propargylic esters; see: Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750–2752.

(13) (a) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443–446. (b) Arcadi, A.; Di Giuseppe, S.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715–2720. (c) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, *4*, 610–618.

(14) Ritter, S.; Horino, Y.; Lex, J.; Schmalz, H. G. *Synlett* **2006**, 3309–3313.

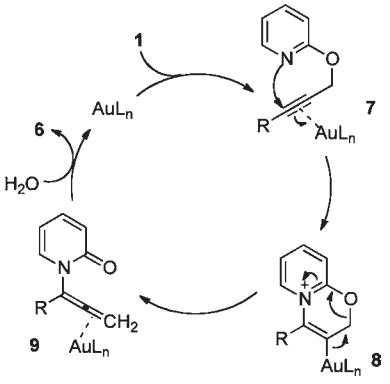
(15) (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415–1418. (b) Antoniotti, S.; Genin, E.; Michelet, V.; Genet, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976–9977. (c) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489–4492. (d) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279–282.

(16) Hashmi, A. S. K. *Catal. Today* **2007**, *122*, 211–214 and references therein.

simultaneously, pyridone **6a** could be isolated in up to 89% yield (entries 9–11). It is believed that NEt_3 may act as a ligand for Au(III); however, given that superstoichiometric NEt_3 is optimal, the amine may also play a role in buffering the reaction. Gold-catalyzed reactions requiring both a basic site for nucleophilic addition and an acidic environment for successful protodeauration are precedented.[16] At this point, other low molecular weight alcohols and different amounts of water (0%–10%) were evaluated as solvents, but no improvement in yield was observed (see Supporting Information). Reactions performed in the presence of one or both additives (NEt_3 and/or Dowex), but in the absence of $NaAuCl_4{\bullet}2H_2O$, resulted in the isolation of only starting material, confirming that Au(III) is playing a central role in catalyzing these reactions.[16]

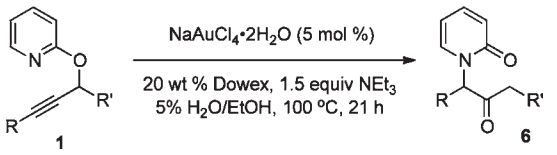
It is proposed that ketone **6a** forms via the mechanism shown in Scheme 2. Initial alkyne coordination to the metal center, followed by nucleophilic addition of the pyridine nitrogen in a 6-*endo*-*dig* manner, would provide vinyl-gold intermediate **8**. In a similar system, Tanaka concluded that coordination of nitrogen to the gold center was likely followed by inner-sphere C–N bond formation.[5b] This suggests that, in the present case, the pyridine nitrogen may act as a directing group. Elimination of gold would then give allenamide **9**. Subsequent hydration of the allene can then proceed via acid-accelerated, secondary catalytic activity of the gold complex or by a direct acid-promoted hydration.[17] Further mechanistic studies are currently underway in our laboratory.

Scheme 2. Proposed Mechanism for the Tandem Amination–Hydration of 2-Propargyloxypyridines **1**



Under the optimized reaction conditions a variety of substituted 2-propargyloxypyridines **1** were evaluated in the amination–hydration reaction (Table 2). The method proved to be robust with respect to both alkyl and aryl substituted substrates (entries 1–4). While attenuated yields have previously been observed in sterically crowded

Table 2. Formation of *N*-Alkyl Pyridones **6**



entry	substrate	R	R′	product	yield (%)[a]
1	**1a**	*n*-pentyl	H	**6a**	89
2	**1b**	CH_2CH_2Ph	H	**6b**	81
3	**1c**	Cy	H	**6c**	76
4	**1d**	Ph	H	**6d**	82
5	**1e**	$(CH_2)_2OTIPS$	H	**6e**	84
6	**1f**	CH_2OTIPS	H	**6f**	–
7	**1g**	Et	Me	**6g**	75
8	**1h**	*n*-butyl	$CH_2CH(CH_3)_2$	**6h**	53

[a] Isolated yields. Mean values from multiple experiments (±3%).

systems,[10c] cyclohexyl- and phenyl-substituted substrates **1c** and **1d** revealed no such decrease in reactivity, yielding pyridones **6c** and **6d** in 76% and 82% yields, respectively (entries 3 and 4). Conversely, inclusion of a silyl ether was met with mixed results. While silyl ether **1e** underwent clean conversion to pyridone **6e** in 84% yield, homologue **1f** was found to decompose, giving only 2-pyridone, under the reaction conditions (entries 5 and 6). The failure of silyl ether **1f** to undergo the amination–hydration reaction may be due to its ability to form an α,β-unsaturated gold–carbene complex upon β-elimation of the silyl ether, as recently observed in an analogous platinium-catalyzed system.[18]

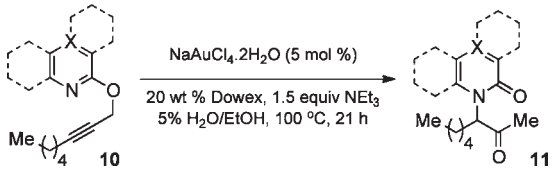
More complex ketones can also be prepared in this way if substitution is included at the propargylic position of alkyne **1**. For example, subjecting α-methyl and α-isobutyl pyridines **1g** and **1h** to the reaction conditions affords the corresponding extended ketones in 75% and 53% yields, respectively (entries 7 and 8).

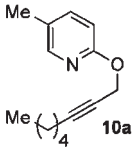
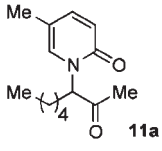
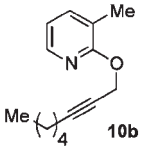
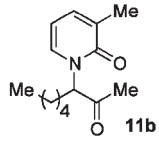
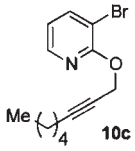
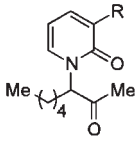
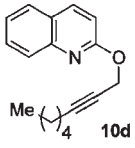
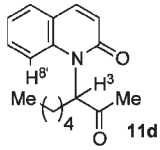
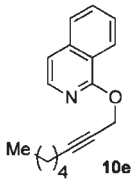
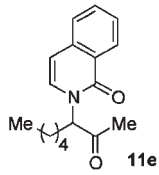
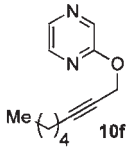
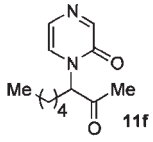
Extension of the tandem amination–hydration to the synthesis of *N*-heterocyclic analogues **11** also proceeded in good to excellent yields (Table 3). Methyl-substituted substrates **10a** and **10b** gave the corresponding ketones in 68% and 80% yields, respectively (entries 1 and 2). Bromopyridine **10c** also underwent rearrangement, affording product **11c** in 70% yield; however in this case, the dehalogenated pyridone **6a** was also observed (entry 3). Sterically encumbered quinoline **10d** and isoquinoline **10e** also reacted smoothly to give the corresponding ketones **11d** and **11e** in excellent yields (entries 4 and 5). By contrast, however, pyrazine **10f** reacts sluggishly, giving only 48% yield of product **11f** after 21 h (entry 6). This attenuated reactivity is thought to be a result of unproductive gold coordination to the nitrogen at the 4-position of the pyrazine.

(17) (a) Cramer, P.; Tidwell, T. T. *J. Org. Chem.* **1981**, *46*, 2683–2686. (b) Rafizadeh, K.; Yates, K. *J. Org. Chem.* **1984**, *49*, 1500–1506. (c) Smadja, W. *Chem. Rev.* **1983**, *83*, 263–320.

(18) Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 689–691.

Table 3. Formation *N*-Alkyl Heterocycles **11**



entry	substrate	product	yield (%)[a]
1	 **10a**	 **11a**	68
2	 **10b**	 **11b**	80
3	 **10c**	 **11c**: R = Br **6a**: R = H	**11c** (R= Br): 70 **6a** (R=H): 21
4	 **10d**	 **11d**	86
5	 **10e**	 **11e**	90
6	 **10f**	 **11f**	48

[a] Isolated yields. Mean values from multiple experiments (±3%).

Hindered rotation around the C−N bond in these systems serves to generate transitory axial chirality.[19] In the case of 2-quinolone **11d**, the hindered C−N bond rotation can be observed clearly by ^{1}H NMR, where no signal for methine proton H-3 is observed at room temperature in $CDCl_3$ and the signal for quinolone proton H-8′ is broad and lacks evidence of spin coupling (Table 3, entry 4). As the temperature is increased, the H-3 signal becomes evident at ∼5.9 ppm and enhanced splitting can be observed in the H-8′ resonance.[20] Computational studies conducted at the B3LYP/6-31G(d) level of theory predict the barrier to rotation around the C−N bond in 2-quinolone **11d** to be 13.98 kcal/mol (ΔG_{calc}).[21,22] Given these results, substituted quinolone analogues are expected to exhibit enhanced rotameric stability and are therefore being evaluated in our laboratory.

In summary, we have developed a method for the conversion of 2-propargyloxypyridines **1** and heterocycles **10** into a new class of α-(*N*-2-pyridonyl)ketones and heterocyclic analogues in good to excellent yields. By exploiting the bench stability and alkynophilicity of $NaAuCl_4•2H_2O$, an unprecedented tandem amination−hydration of an alkyne by a heterocyclic sp^2 nitrogen nucleophile has been accomplished. Studies directed at an asymmetric variant of this reaction are currently underway in our laboratory.

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Supporting Information Available. Representative experimental procedures, additional optimization studies, computational studies, ^{1}H and ^{13}C NMR spectra for all new compounds, and VT and 2D NMR spectra for 2-quinolone **11d**. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Kumarasamy, E.; Jesuraj, J. L.; Omlid, J. N.; Ugrinov, A.; Sivaguru, J. *J. Am. Chem. Soc.* **2011**, *133*, 17106–17109.

(20) For full variable temperature NMR studies, see Supporting Information.

(21) For full compuational studies and references, see Supporting Information.

(22) Comparable studies on BINOL have shown its barrier to rotation to be 37.8 kcal/mol. See: Meca, L.; Reha, D.; Havlas, Z. *J. Org. Chem.* **2003**, *68*, 5677–5680.