An Approach to Highly Functionalized Quinolines and Isoquinolines via a Gold-Catalyzed Benzannulation

Biswajit Panda, Jhuma Bhadra, Tarun K. Sarkar*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India
E-mail: tksr@chem.iitkgp.ernet.in

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Abstract: The $AuCl_3$-catalyzed benzannulation of pyridine-containing oxo-alkynes with external as well as internal alkynes proceeds under mild conditions, and a variety of quinoline and isoquinoline derivatives are produced in good to excellent yields. The reaction proceeds through the formation of aza-isobenzopyrylium auric ate complexes as evident from trapping experiments.

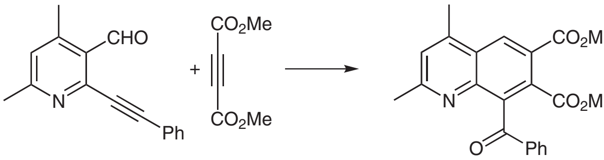
Key words: gold, catalysis, benzannulation, quinolines, isoquinolines

Transition-metal-catalyzed electrophilic activation of alkynes towards intramolecular addition of heteronucleophiles has attracted considerable attention as a useful method for the preparation of heterocyclic compounds.[1] In particular, it has been found that $AuCl_3$ catalyzes the formation of C–C and C–O bonds thus behaving as an effective Lewis acid catalytic system.[2] One of the early examples of such reactions include benzannulation between *o*-alkynylbenzaldehydes and alkynes as developed extensively by the research groups of Yamamoto, Dyker, and others.[3] Surprisingly, use of hetero analogues like pyridine-containing oxo-alkynes in these reactions has not been documented,[4] although the latter may offer an environmentally benign and atom economic route to highly functionalized quinoline and isoquinoline derivatives.

Quinolines and isoquinolines are widespread in the alkaloid family and generally constitute important structural motifs in pharmaceuticals, agrochemicals, or even dyestuffs.[5] In view of their substantial applicability, the syntheses of these species are extensively studied topics.[6,7] However, in spite of their common properties and much research on their preparation, a synthetic methodology based on a single concept that is applicable to both ring systems remains relatively underdeveloped.[8,9] In connection with our ongoing work on transition-metal-catalyzed organic transformations,[10] we now report for the first time the homogeneous gold-catalyzed benzannulation between pyridine-containing oxo-alkynes with both external as well as internal alkynes thereby producing highly functionalized quinolines and isoquinolines in good to excellent yields.

For our initial study we selected the oxo-alkyne **1a**, readily available from the corresponding 2-chloro-3-pyridinecarboxaldehyde via a Sonogashira coupling. When **1a** (0.5 mmol) was subjected to the benzannulation reaction[3a] with dimethyl acetylene dicarboxylate (DMAD, 1.5 mmol) in the presence of $AuCl_3$ (3 mol%) in 1,2-dichloroethane (1.5 mL) at 80 °C, only traces of **2a** were formed (entry 1, Table 1). This failure could be attributed to polymerization of DMAD (Michael acceptor) in the presence of **1a** (Michael donor).[11] After some experimentation we were able to find that working under dilute conditions and at ambient temperature allowed obtention of **2a** in high yield (entry 2, Table 1).

Table 1 Reaction of **1a** with DMAD under Various Catalytic Systems[a]



1a **2a**

Entry	Catalytic system	Yield of **2a** (%)[b]
1	$AuCl_3$	trace[c]
2	$AuCl_3$	89
3	AuCl	57
4	$AuCl(PPh_3)$	0
5	$AuCl(PPh_3)/AgOTf$	64
6	$AuCl_3/Ph_3P$	7
7	$PtCl_2$	0

[a] All reactions were performed using **1a** (0.2 mmol) and DMAD (0.4 mmol) in the presence of catalyst (3 mol%) in DCE (4 mL) at r.t. for 24 h.

[b] Isolated yield, average of two runs.

[c] The reaction was performed using **1a** (0.5 mmol) and DMAD (1.5 mmol) in the presence of $AuCl_3$ (3 mol%) in DCE (1.5 mL) at 80 °C for 2 h.

We then studied this reaction in 1,2-dichloroethane with different gold catalysts. AuCl catalyzes this reaction though the yield is low (Table 1, entry 3), whereas other gold(I) catalysts, for example, $AuCl(PPh_3)$ (entry 4, Table 1) is completely inactive. Only when $AuCl(PPh_3)$ was combined with AgOTf, the system catalyzes the reaction and gave the desired product in moderate yield (entry 5, Table 1). As expected combination of $AuCl_3$ with Ph_3P

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gives traces of the desired product (Table 1, entry 6). Triphenylphosphine might react with $AuCl_3$ to destroy its catalytic activity or Lewis acidity.[3h] At this stage we were also interested to use other carbophilic Lewis acids, such as $PtCl_2$[3e] which is known to catalyze the same kinds of reactions, sometimes with even higher efficiency. However, when **1a** was exposed to DMAD in 1,2-dichloroethane in the presence of $PtCl_2$ (Table 1, entry 7), no traces of **2a** could be detected from ^1H NMR of the crude product.

We then applied this methodology to a series of pyridine-containing oxo-alkynes, and the results are presented in Table 2. As can be seen from Table 2 (entries 1–5), electron-rich auric ate complexes (cf. **7**, vide infra) formed from oxo-alkynes **1a–d**[12] react effectively with electron-poor dienophiles to yield variously substituted quinolines **2a–e** in high yield. Notably, the reaction times are short when a strong electron donor, such as a *p*-dimethylanilino group, is attached to the acetylenic end of the oxo-alkyne as in entry 2, whereas the reactions are sluggish (entries 3 and 5) when a long carbon chain dangles from the acetylenic end due possibly to steric reasons in the transition state of the reaction.

Table 2 $AuCl_3$-Catalyzed Benzannulation of Pyridine-Containing Oxo-Alkynes with Alkynes[a]

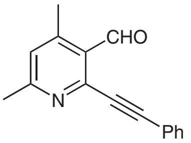
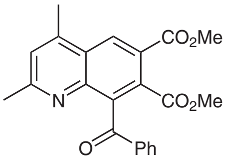
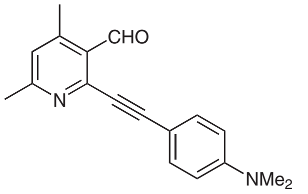
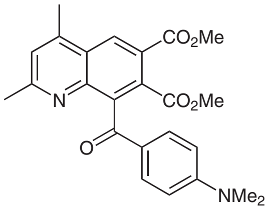
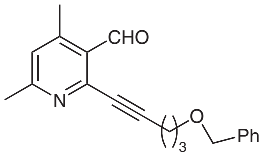
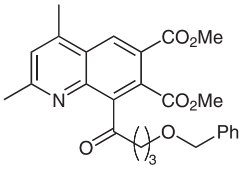
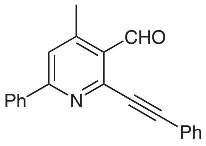
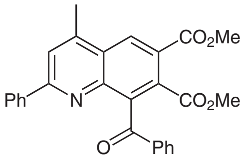
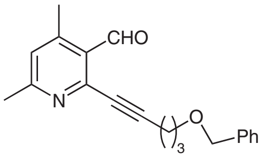
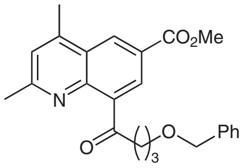
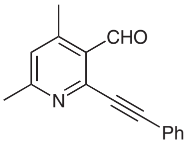
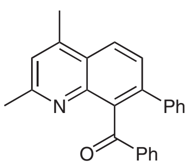
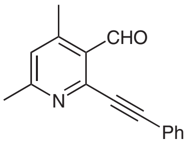
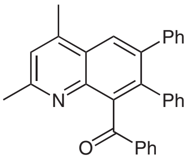
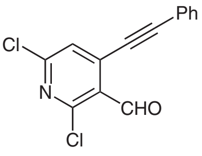
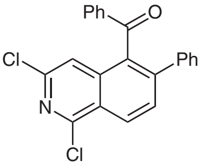
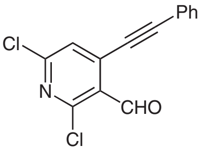
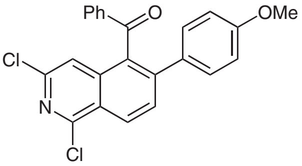
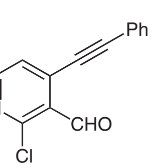
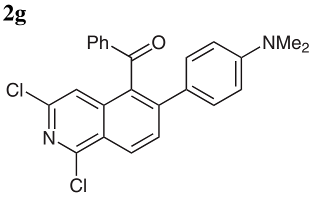
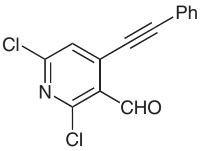
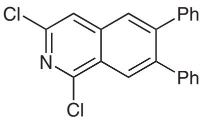
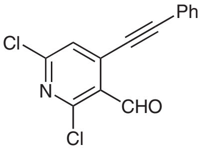
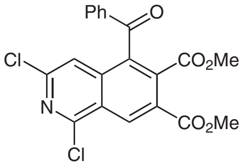
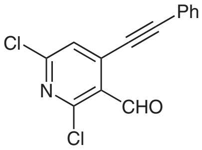
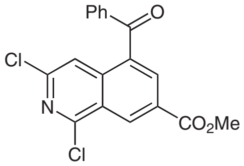
Entry	Oxo-alkyne	Product	Yield (%)[b]
1	 **1a**	 **2a**	89
2	 **1b**	 **2b**	83[c]
3	 **1c**	 **2c**	79[d]
4	 **1d**	 **2d**	92
5	 **1c**	 **2e**	76[d]
6	 **1a**		0[e]

Table 2 $AuCl_3$-Catalyzed Benzannulation of Pyridine-Containing Oxo-Alkynes with Alkynes[a] (continued)

Entry	Oxo-alkyne	Product	Yield (%)[b]
7	 **1a**		0[e]
8	 **1e**	 **2f**	86
9	 **1e**	 **2g**	91
10	 **1e**	 **2h**	88
11	 **1e**	 **2i**	72
12	 **1e**		0[e]
13	 **1e**		0[e]

[a] All reactions were performed using oxo-alkyne (0.2 mmol) and alkyne (0.4 mmol) in the presence of $AuCl_3$ (3 mol%) in DCE (4 mL) at r.t., the reraction time being 24 h or otherwise noted.

[b] Isolated yield, average of two runs.

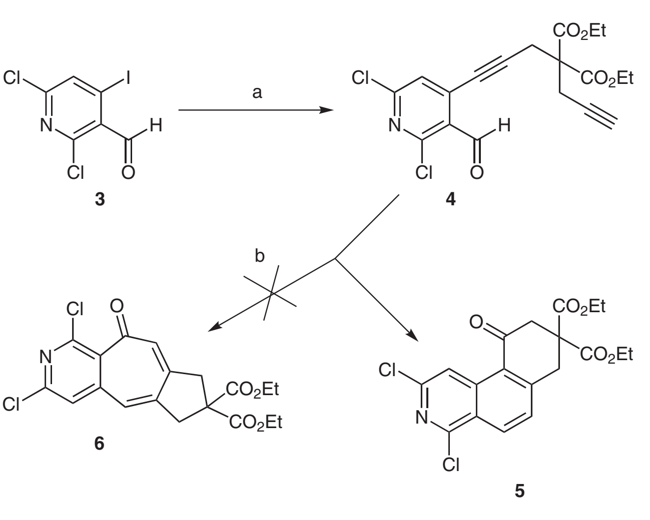
[c] Reaction time was 10 h.

[d] Reaction time was 48 h.

[e] Refluxing the reaction mixture does not give any trace of desired products.

On the other hand **1a** does not react with electron-rich alkynes, such as phenylacetylene or diphenylacetylene (entries 6 and 7). These results indicate that a Diels–Alder-type [4+2] cycloaddition may be operating in these cases. This methodology was further extended for the synthesis of substituted isoquinolines. Thus, as expected electron-poor auric ate complexes (cf. **7**, vide infra) formed from oxo-alkynes, for example, **1e**[12] react nicely with electron-rich alkynes (entries 8–10) to give isoquinolines **2f–h** in high yields. The regioselectivity in entries 5 and 8–10 is in accord with the observation made by Yamamoto et al. in benzenoid systems.[3a] Incidentally, reaction of **1e** with diphenyl acetylene followed a completely different pathway to yield the isoquinoline **2i**; such debenzoylations are known in the literature, although higher yields of products are observed only using $Cu(OTf)_2$.[13] In contrast, reactions of **1e** with electron-poor dienophiles, for example, DMAD or methyl propiolate did not yield any traces of the desired isoquinolines (entries 12 and 13, Table 2).[14]

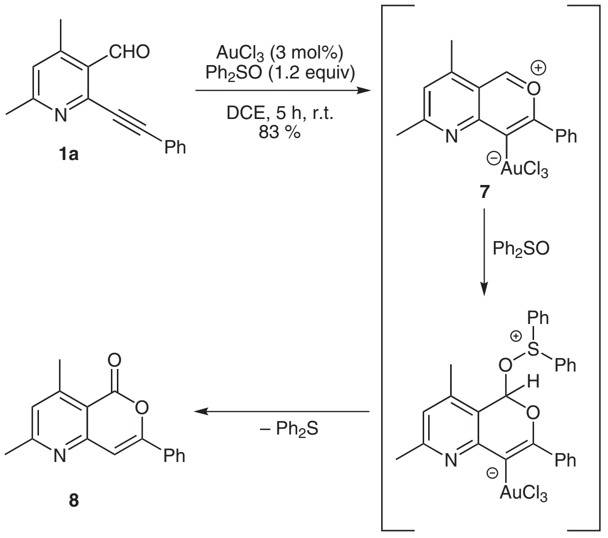
After having success with intermolecular benzannulation reaction on pyridine-containing oxo-alkynes, we then became interested in the intramolecular version of this reaction. Accordingly, the oxo-diyne **4** (Scheme 1) was made via a Sonogashira coupling[15] of 4,4-dicarboethoxy-1,6-heptadiyne with iodo aldehyde **3**, the latter being available from the corresponding acid[16] by esterification (MeI, K_2CO_3, DMF) followed by DIBAL-H reduction. When **4** was treated with $AuCl_3$ (3 mol%) in 1,2-dichloroethane at room temperature, the tricyclic ketone **5** was formed in 92% yield as a white crystalline solid unaccompanied by even traces of the competing [3+2] cycloisomerization product **6**.[17,18]



Scheme 1 *Reagents and conditions*: (a) 4,4-dicarboethoxy-1,6-heptadiyne, $PdCl_2(PPh_3)_2$ (2 mol%), DBMP, MeCN, r.t., 2 h, 56%; (b) $AuCl_3$ (3 mol%), DCE, r.t., 6 h, 92% [DBMP = 2,6-di-*tert*-butyl-4-methylpyridine].

Interestingly, the Thorpe–Ingold effect of the geminally substituted carboethoxy groups which exerts its profound influence in benzenoid systems leading to [3+2]-type products is unable to effect chemoreversal in this case.

Yamamoto et al.[3a] has proposed that the gold-catalyzed benzannulation takes place via the formation of isobenzopyrilium auric ate complexes.[19] Indeed, we were able to detect these species in our case by trapping experiments. Thus when oxo-alkyne **1a** was treated with 3 mol% $AuCl_3$ in the presence of 1.2 equivalents of Ph_2SO at room temperature in 1,2-dichloroethane the aza-isocoumarin derivative **8** was isolated in 83% yield, thereby supporting the formation of isobenzopyrylium complexes of type **7** (Scheme 2).[20]



Scheme 2 Oxidation of aza-isobenzopyrylium auric ate complex

In conclusion, this work shows that highly functionalized quinolines and isoquinolines can be synthesized by a homogeneous gold-catalyzed benzannulation of pyridine-containing oxo-alkynes with substituted alkynes in both inter- and intramolecular fashion.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(4) (a) During the course of our work Organ et al. reported a few reactions of pyridine-containing oxo-alkynes in a flow reactor under heterogeneous conditions, see: Shore, G.; Tsimerman, M.; Organ, M. G. *Beilstein J. Org. Chem.* **2009**, *5*, 35; doi: 10.3762/bjoc.5.35. (b) For a discussion of the merits and demerits of reactions in a flow reactor vis-à-vis reactions in a flask, see: Valera, F. E.; Quaranta, M.; Moran, A.; Blacker, J.; Armstrong, A.; Cabral, J. T.; Blackmond, D. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2478.

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(11) Indeed **1a** was found to react exothermally when brought in contact with DMAD in DCE at a similar concentration.

(12) Oxo-alkynes **1a**–**d** were prepared from the corresponding pyridine-2-chloro aldehydes by Sonogashira coupling; similarly, **1e** was prepared from iodoaldehyde **3** by Sonogashira coupling.

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(14) An alkyne with an aryl and an ester substituent, e.g., $PhC\equiv CCO_2Me$ was found not to react either with the electron-rich oxo-alkyne **1a** or the electron-deficient oxo-alkyne **1e**; presumably in this case the HOMO–LUMO energy difference is too high for both pairs of reactants.

(15) This Sonogashira coupling was unsuccessful (<10%) under the classical conditions [$PdCl_2(PPh_3)_2$/CuI] using a variety of bases such as Et_3N, *i*-Pr_2NH, K_2CO_3, or $NaHCO_3$.

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(18) Even carrying out the reaction at a lower temperature (0–15 °C) did not give any traces of the [3+2] product **6**.

(19) For a discussion and computational analysis regarding [3+2] vs. [4+2] cycloaddition of isobenzopyrylium 1,3-dipoles, see: Straub, B. F. *Chem. Commun.* **2004**, 1726.

(20) We also cannot rule out the possibility of autocatalysis by the oxo-alkynes, as sometimes substrates might coordinate and lead to the formation of even more efficient catalysts, see: Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem. Int. Ed.* **2004**, *43*, 6545.