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Gold-Catalyzed Synthesis of 3-Acylimidazo[1,2-*a*]pyridines *via* Carbene Oxidation

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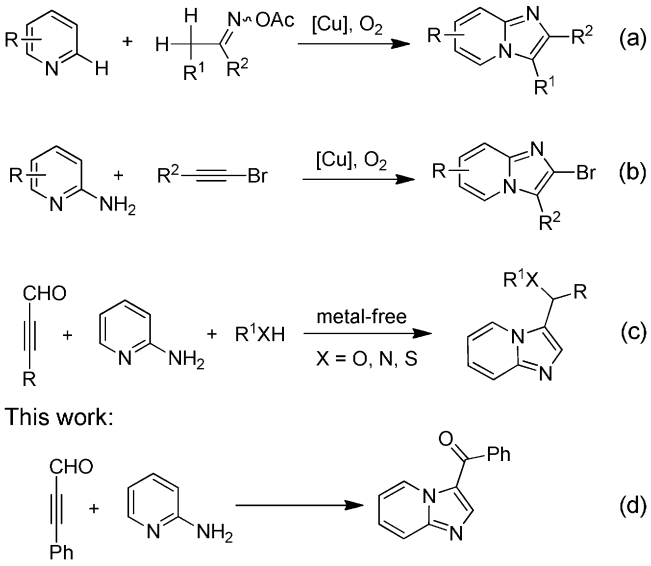
Abstract: A convenient gold-catalyzed strategy for the synthesis of imidazo[1,2-*a*]pyridine derivatives has been developed *via* gold carbene complexes. This transformation opens a new synthetic route to a variety of 3-carbonyl-substituted imidazo[1,2-*a*]pyridines using air as oxidant affording the products in good yields.

Keywords: carbene oxidation; gold catalysis; imidazo[1,2-*a*]pyridines; propiolaldehyde; pyridin-2-amines

The imidazo[1,2-*a*]pyridine nucleus is arguably one of the most significant heterocycles in that it is found in numerous drugs and bioactive molecules.[1] Among the drug molecules zolpidem, alpidem, zolimidine, olprinone, saripidem and necopidem have been considered as attractive synthetic targets because of their biological activities and synthetic challenges.[2] Thus, it is not surprising that imidazo[1,2-*a*]pyridines have received special attention by chemists of different specialties to provide selective synthetic access to the enormous variety of structural features typical of this class.[3] Historically, the synthesis of these compounds has been extensively investigated for more than a century. Recently, numerous facile and straightforward syntheses of different types of imidazo[1,2-*a*]pyridine derivatives have been reported in the literature.[4] Among a variety of new synthetic transformations, transition metal-catalyzed reactions, with metals such as palladium,[5] copper,[6] silver,[7] and iron[8] have proven to be a powerful and useful tool for the synthesis of imidazo[1,2-*a*]pyridines.

Recently, Jiang et al. have reported a convenient copper-catalyzed intermolecular oxidative conversion of pyridine (Scheme 1a)[9] or 2-aminopyridine (Scheme 1b)[10] to imidazo[1,2-*a*]pyridines; Mantellini et al. have reported an efficient solvent- and catalyst-free transformation for the synthesis of imidazo-[1,2-*a*]pyridines;[11] our group has also developed a novel multicomponent reaction to form imidazo-[1,2-*a*]pyridine derivatives (Scheme 1c).[12] As part of our continuing interest in the synthesis of imidazo[1,2-*a*]pyridines, herein we develop a new and facile gold-catalyzed protocol to construct 3-carbonyl-substituted imidazo[1,2-*a*]pyridines *via* a gold[13] carbene oxidation (Scheme 1d).

Initially, we have optimized the conditions for the reaction between 3-phenylpropiolaldehyde **1a** and pyridin-2-amine **2a**, and the results are summarized in Table 1. Substrates **1a** (0.5 mmol), **2a** (0.7 mmol), and AcOH (5 mol%) were stirred for 0.5 h. Then various gold salts were examined. When substrates **1a** and **2a** were treated with AuCl in dioxane at room tempera-



Scheme 1. Synthesis of imidazo[1,2-*a*]pyridines.

Table 1. Optimization of the reaction conditions.[a]

1a **2a** **3a**

Entry	Catalyst	Solvent	Temp. [°C]	Yield [%][b]
1	AuCl	dioxane	r.t.	32
2	$AuCl_3$	dioxane	r.t.	26
3	Ph_3PAuCl	dioxane	r.t.	49
4	$Ph_3PAuCl/AgSbF_6$	dioxane	r.t.	81
5	$Ph_3PAuCl/AgOTf$	dioxane	r.t.	66
6	$Ph_3PAuCl/AgBF_4$	dioxane	r.t.	58
7	$Ph_3PAuCl/AgOAc$	dioxane	r.t.	51
8	$Ph_3PAuCl/AgSbF_6$	DMF	r.t.	72
9	$Ph_3PAuCl/AgSbF_6$	DMSO	r.t.	70
10	$Ph_3PAuCl/AgSbF_6$	DMA	r.t.	65
11	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	r.t.	86
12	$Ph_3PAuCl/AgSbF_6$	CH_3CN	r.t.	71
13	$Ph_3PAuCl/AgSbF_6$	THF	r.t.	76
14	$Ph_3PAuCl/AgSbF_6$	$ClCH_2CH_2Cl$	r.t.	80
15	$Ph_3PAuCl/AgSbF_6$	toluene	r.t.	55
16	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	50	59
17	$Ph_3PAuCl/AgSbF_6$	CH_2Cl_2	80	17
18	–	CH_2Cl_2	r.t.	–

[a] *Reaction conditions:* **1a** (0.5 mmol), **2a** (0.7 mmol), catalyst (3 mol%), solvent (3.0 mL), room temperature to 80 °C.
[b] GC yields.

ture for 12 h and the desired product was formed in 32% yield (Table 1, entry 1). A 26% yield was obtained when $AuCl_3$ was used as the catalysts (Table 1, entry 2). Interestingly, a moderate yield was formed using Ph_3PAuCl as catalyst (Table 1, entry 3). Stimulated by these results, we attempted to test Ph_3PAuCl with several of silver salts as co-catalyst (Table 1, entries 4–7). Various Ag salts, such as $AgSbF_6$, AgOTf, $AgBF_4$ and AgOAc, were employed. To our delight, the desired product **3a** was produced in 86% yield in the presence of PPh_3AuCl with $AgSbF_6$ as co-catalyst. The effects of solvents were next examined (Table 1, entries 9–15). Among the solvents, we were delighted to find that the experiments performed in CH_2Cl_2 gave good yields. Other media, such as DMF, DMSO, DMA, CH_3CN, THF, $ClCH_2CH_2Cl$, and toluene, afforded lower yields. We next attempted to improve the yield by adjusting the temperature. Unfortunately, the yield decreased gradually on increasing the temperature from room temperature to 80 °C (Table 1, entries 16 and 17). The result clearly indicated that the reaction was sensitive to temperature variations. Finally, control experiments showed that no product was formed in the absence of $Ph_3PAuCl/AgSbF_6$ (Table 1, entry 18).

After achieving the optimized reaction conditions, we next investigated the reactions between various substituted propiolaldehydes (**1a–1c**) and pyridin-2-amines (**2a–2h**) (Table 2). Aldehyde **1a** was used to explore the scope of the pyridin-2-amines. As expected, the desired imidazo[1,2-*a*]pyridine derivatives were formed in good yields. The results indicated that the substrate was compatible with a range of substituents in all positions on the pyridine ring of the pyridin-2-amine. The halo groups (chloro, bromo) remained unaffected under our optimized reaction conditions. Notably, the reaction also performed very well using a multiply substituted pyridin-2-amine (3,5-dibromo-4-methylpyridin-2-amine) as substrate. Encouraged by these initial results, the substrate scope of this transformation was next tested using different substituted propiolaldehydes. Interestingly, the reaction was found to be very general using oct-2-ynal (**1b**) as a substrate, and the corresponding products (**3i–3m**) were formed in moderate to good yields. To our delight when the substrate propiolaldehyde **1c** was examined the desired product **3n** was obtained in moderate yield under the optimized reaction conditions. These results indicate that the catalytic system is applicable to both aryl- and alkyl-substituted as well as terminal propiolaldehydes.

To gain further insight into the mechanism, a series of control experiments was carried out to determine the source of oxygen atom.

Firstly, the reaction was run in the presence of $H_2{}^{18}O$. The product **3a** was formed, while **3a′** was not detected by GC-MS (Scheme 2).

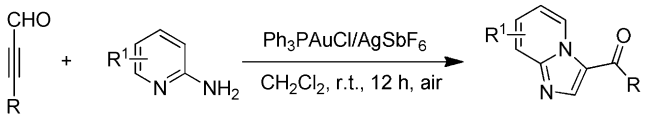
Secondly, a trace of **3a** was formed and most of intermediate **A** was detected by GC-MS when the reaction was run under nitrogen protection (Scheme 3).

Finally, the reaction was carried out using intermediate **A** as a substrate under anhydrous conditions. The product **3a** was obtained in 89% GC yield (Scheme 4). All these results demonstrated that oxygen atom (C=O) comes from the air rather than H_2O.

On the basis of previous reports[14] and the experiment results, a possible old-catalyzed mechanism has been postulated as shown in Scheme 5. AcOH-promoted intermolecular dehydration of **1a** and **2a** has occurred to give intermediate **A** which is followed by coordination of the gold(I) species to generate the intermediate **B**. Then an intramolecular 5-*exo-dig* cyclization has taken place to form the carbene complex **C** which underwent carbene oxidation with oxygen metathesis to generate the desired product.

In summary, we have developed a novel gold-catalyzed transformation for the formation of C–C and C=O bonds *via* the oxidation of gold carbene complexes. It provides an efficient synthetic route to prepare 3-carbonyl-substituted imidazo[1,2-*a*]pyridines, a common structural motif in natural products and

Table 2. Gold-catalyzed synthesis of imidazo[1,2-*a*]pyridines.[a]



1 **2** **3**

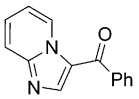
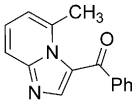
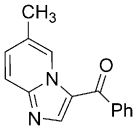
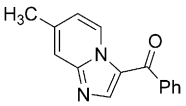
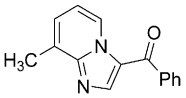
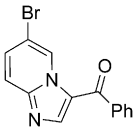
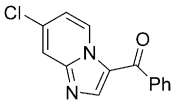
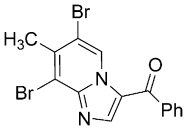
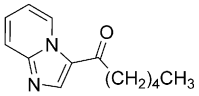
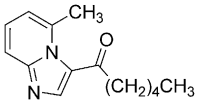
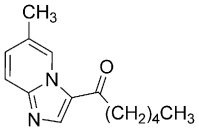
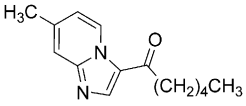
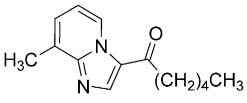
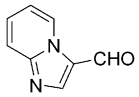
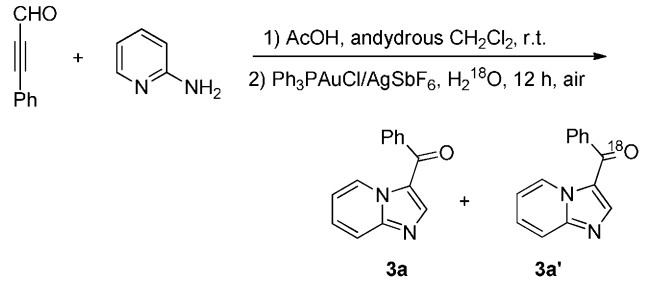
Entry	**1** (R =)	2 (R^1 =)	Product	Yield [%]
1	**1a** (Ph)	**2a** (H)	**3a** 	77
2	**1a** (Ph)	**2b** (6-CH_3)	**3b** 	72
3	**1a** (Ph)	**2c** (5-CH_3)	**3c** 	78
4	**1a** (Ph)	**2d** (4-CH_3)	**2d** 	75
5	**1a** (Ph)	**2e** (3-CH_3)	**3e** 	70
6	**1a** (Ph)	**2f** (5-Br)	**3f** 	73
7	**1a** (Ph)	**2g** (4-Cl)	**3g** 	73
8	**1a** (Ph)	**2h** (3-Br, 4-CH_3, 5-Br)	**3h** 	72
9	**1b** [$(CH_2)_4CH_3$]	**2a** (H)	**3i** 	70
10	**1b** [$(CH_2)_4CH_3$]	**2b** (6-CH_3)	**3j** 	68
11	**1b** [$(CH_2)_4CH_3$]	**2c** (5-CH_3)	**3k** 	74
12	**1b** [$(CH_2)_4CH_3$]	**2d** (4-CH_3)	**3l** 	75
13	**1b** [$(CH_2)_4CH_3$]	**2e** (3-CH_3)	**3m** 	70

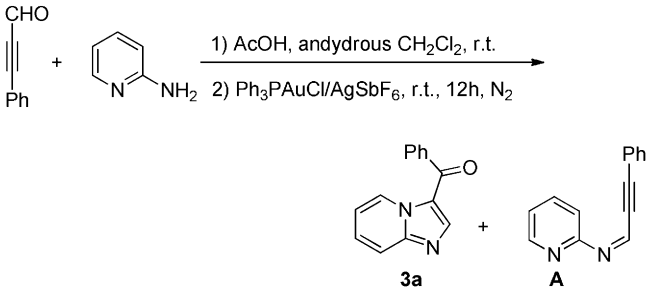
Table 2. (Continued)

Entry	**1** (R=)	2 (R^1=)	Product	Yield [%]
14	**1c** (H)	**2a** (H)	**3n** 	62

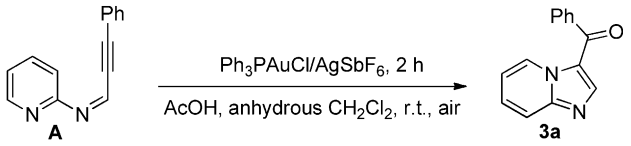
[a] Isolated yields.



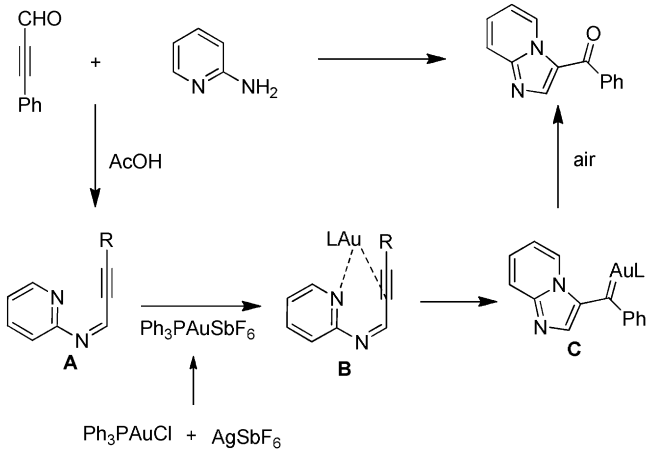
Scheme 2. Control experiment with $H_2{}^{18}O$.



Scheme 3. Control experiment under N_2.



Scheme 4. Control experiment under anhydrous conditions.



Scheme 5. Proposed mechanism.

pharmaceuticals. Moreover, this unprecedented process is applicable to a variety of substituted propiolaldehydes and pyridin-2-amines and it affords highly functionalized imidazo[1,2-*a*]pyridines in moderate to good yields.

Experimental Section

Typical Procedure for the Synthesis of 3a

The mixture of 3-phenylpropiolaldehyde (**1a** 0.5 mmol), pyridin-2-amine (**2a** 0.7 mmol), and AcOH (5 mol%), were stirred in 3 mL dry CH_2Cl_2 for 30 min at room temperature. Then $AuPPh_3Cl$ (3 mol%) and $AgSbF_6$ (3 mol%) were added and the mixture was stirred for 12 h under air. After completion of the reaction (as monitored by TLC), the solution was evaporated to dryness under reduced pressure. Then 10 mL of water were added. The aqueous solution was extracted with diethyl ether (3×10 mL) and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed and the crude product was separated by column chromatography to give the pure product **3a**.

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