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Cite this: DOI: 10.1039/c2cc33706a

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Copper-catalyzed direct oxidative annulation of *N*-iminopyridinium ylides with terminal alkynes using O_2 as oxidant†‡

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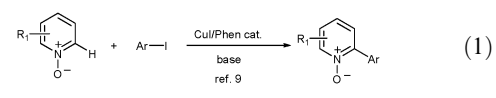
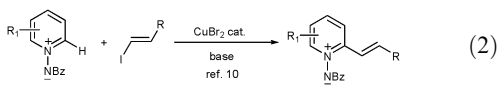
Received 23rd May 2012, Accepted 28th June 2012
DOI: 10.1039/c2cc33706a

The aerobic direct dehydrogenative annulation of *N*-iminopyridinium ylides with terminal alkynes leading to pyrazolo[1,5-*a*]pyridine derivatives has been developed.

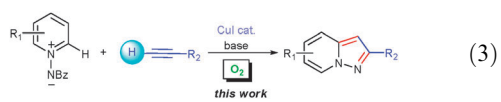
Pyridine moieties are key structural units and exist widely in a large number of natural products, functional materials, pharmaceuticals, and ligands.[1] The search for efficient and convergent modifications of pyridine derivatives through direct C–H functionalization presents a direct and atom-economic process for the synthesis of pyridine-containing compounds, and therefore has attracted considerable attention.[2–9] In the past decades, the Rh,[2] Ru,[3] Pd,[4] Ir,[5] Ni,[6] Zr,[7] Ln,[8] and Ag[9] catalyzed C–H functionalization of pyridines have been significantly developed. In comparison to these transition metal catalysts, C–H functionalization of pyridine derivatives with inexpensive Cu catalysts has rarely been reported,[10,11] even though Cu was the first transition metal shown to promote C–H arylation.[12,13] Recently, Daugulis and coworkers have disclosed the novel CuI/phen catalyzed arylation reaction of pyridine *N*-oxide (eqn (1)).[10] The first $CuBr_2$ catalyzed direct alkenylation of *N*-iminopyridinium ylides was reported by Charette's group (eqn (2)).[11]



(1)



(2)



(3)

As coupling partners, terminal alkynes have been widely employed in Sonogashira couplings.[14] However, the catalytic dehydrogenative coupling of C_{sp^2}–H with terminal alkynes still remains a challenging issue,[15] due to the difficulties of avoiding the dimerization of terminal alkynes under oxidative conditions.

Recently, Su and coworkers realized the first Cu-catalyzed direct alkynylation of an aromatic C–H bond with terminal alkynes.[15c] We envisioned that the direct alkynylation of pyridine derivatives could be achieved by appropriate oxidative Cu-catalysis. Herein, we report the first aerobic oxidative dehydrogenative annulation of *N*-iminopyridinium ylides with terminal alkynes *via* direct alkynylation. The significance of the present finding is threefold: (1) this method provides a novel copper catalysts for the C–H activation of pyridine derivatives with alkynes; (2) natural, inexpensive, and environmentally friendly molecular oxygen[16] was used as the oxidant making this method very simple and practical and (3) this relatively inexpensive Cu-catalysts provides an efficient and straightforward approach to pyrazolo[1,5-*a*]pyridine derivatives, which are important components of pharmaceutically active compounds.[17]

Under our hypothesis, the investigation was initially started with the reaction between pyridinium ylide **1a** and phenylethyne **2a** in a Cu/O_2 catalytic system. The direct alkynylation product was not detected, but a trace amount of the dehydrogenative annulation product **3a** was obtained when CuI (10 mol%) was employed as the catalyst (Table S1, ESI‡). The yield was slightly promoted to 27% on addition of 10 mol% Ag_2CO_3 (Table S1, ESI‡). After screening different parameters (see ESI‡), **3a** was obtained in 74% yield under the optimized conditions (CuI 10 mol%, Ag_2CO_3 10 mol%, DABCO 2.0 equiv., O_2). The 20% yield under air indicated the importance of O_2 in this transformation (see ESI‡).

Under the standard conditions, this reaction exhibited broad substrate scope with respect to terminal alkynes (Table 1). Substrates bearing either electron-donating (*para*-, *meta*-, or *ortho*-substituted) or -withdrawing substituents were well tolerated, leading to the corresponding products in moderate to good yields (Table 1, **3a–3j**). Especially, the attainments of chloro and bromo products with high yields paved a convenient way for the synthesis of more complicated derivatives *via* cross-coupling reactions (Table 1, **3g** & **3h**). The heterocyclic alkynes performed differently in this transformation, which may be due to their distinct in electronic charateristics. For instance, the reaction of **1a** with 2-ethynylpyridine did not lead to the

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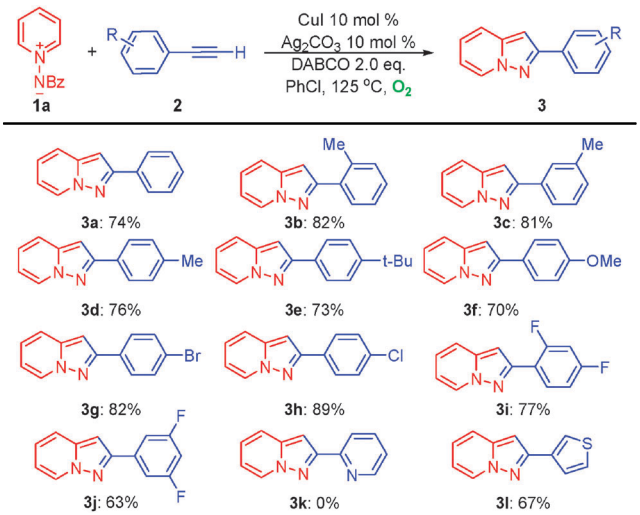
† This article is part of the *ChemComm* 'Emerging Investigators 2013' themed issue.
‡ Electronic supplementary information (ESI) available: See DOI: 10.1039/c2cc33706a

Table 1 The aerobic dehydrogenative annulations of **1a** with different alkynes (**2**)[a,b]

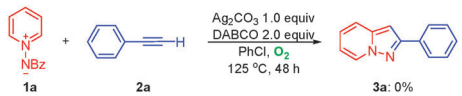


[a] Standard reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), CuI (10 mol%), Ag_2CO_3 (10 mol%), DABCO (0.4 mmol), PhCl (2 mL) under O_2 (1 atm) for 48 h. [b] Isolated yields.

relevant product, while 3-ethynylthiophene afforded the product **3l** in a 67% yield.

This dehydrogenative transformation was then expanded to various *N*-iminopyridinium ylides (Table 2). Moderate yields were obtained under these standard conditions (Table 2). This might be due to the easy decomposition of these ylides. Product **3m** was afforded by the reaction of 4-benzyl pyridinium ylide **1b** with 1-chloro-4-ethynylbenzene **2b** with the oxidization of benzyl to benzoyl under the oxidative conditions (Table 2, entry 1). A mixture of **3p** and **3q** was obtained when *meta*-chloro pyridinium ylide was employed as the substrate (Table 2, entry 4).

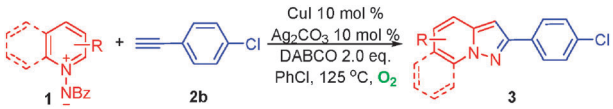
To understand the mechanism, several experiments were carried out. A trace amount of the product **3a** was afforded in the absence of Ag_2CO_3 (Table S1, entry 1) and this reaction could hardly happen in the absence of CuI, even when 1 equiv. amount of Ag_2CO_3 was employed (eqn (4)). We envisioned that copper acetylide **4**, which is generated from the alkyne **2a** with copper under aerobic basic conditions, could be an intermediate in this process. To test this possibility, the reaction of **1a** with **4** was conducted under different conditions.

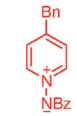
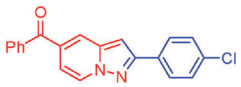
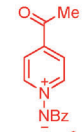
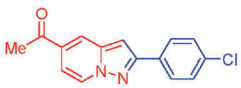
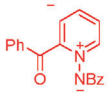
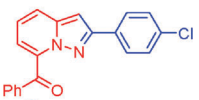
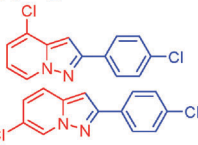
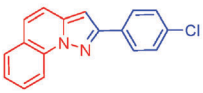


(4)

The yield was slightly promoted after the addition of Ag^+ (eqn (5) and (6)). Compared with the result in the absence of Ag^+ (20%, entry 7, Table 1), it may be concluded that Ag^+ might assist the formation of the copper acetylide. The addition of DABCO improved the yield significantly (eqn (7)). As we learned, the base plays several roles in this transformation, such as assisting the formation of copper acetylide, the dehydrogenation of substrate **1**, and the expulsion of benzoyl moiety. When a similar reaction was carried out under argon, no corresponding addition product dihydropyridine derivatives was detected (eqn (8)), which may exclude the pathway through Cu-catalyzed addition of terminal

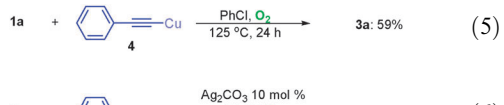
Table 2 The aerobic dehydrogenative annulations of *N*-iminopyridinium ylides (**1**) with **2b**[a]



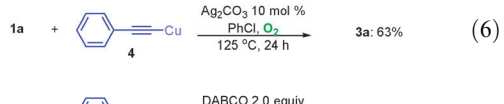
entry	substrate		product		yield (%)[b]
1		1b		3m	42
2		1c		3n	33
3		1d		3o	40
4[c]		1e		3p 3q	54 (1.8:1)
5		1f		3r	82

[a] Standard reaction conditions: **1** (0.2 mmol), **2b** (0.6 mmol), CuI (10 mol%), Ag_2CO_3 (10 mol%), DABCO (0.4 mmol), PhCl (2 mL) under O_2 (1 atm) for 48 h. [b] Isolated yields. [c] The ratio of **3p** and **3q** was determined by ^{1}H NMR.

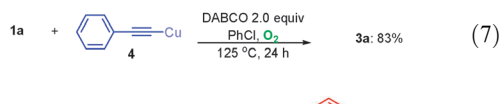
alkynes to pyridinium ylide **1** to form dihydropyridines[18] and followed aromatization. Furthermore, a kinetic isotope effect experiment was carried out to make the mechanism more clear (ESI‡). The kinetic isotope effect (k_H/k_D = 2.2) was observed by comparison with the rates of **1a** and the deuterated ylide [D_5]-**1a**. Meanwhile, the 17% deuterium incorporation at the 3-position suggests the possibility of the protonation process.



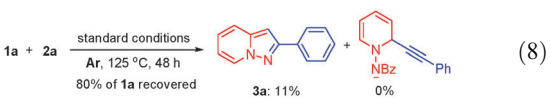
(5)



(6)

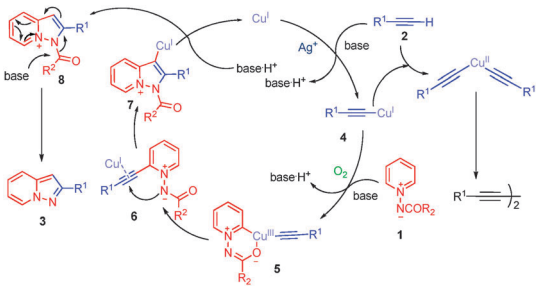


(7)



(8)

On the basis of above results, a proposed mechanism for the reaction is illustrated in Scheme 1. The initial copper acetylide **4** is generated from alkyne **2** with Cu(I) catalyst assisted by Ag_2CO_3 under basic conditions. Subsequently, the oxidative insertion of copper acetylide **4** into the pyridinium ylide **1** forms Cu(III) intermediate **5**[11] *via* C–H bond functionalization. Intermediate **5** undergoes reductive elimination to afford the direct alkynylation intermediate **6**, in which the alkyne can be



Scheme 1 The proposed mechanism for this aerobic dehydrogenative annulations.

activated by copper catalyst. Subsequent 5-*endo* cyclization of **6** *via* the anti-aminocupration of the alkyne attacked by the amido nitrogen generates **7**, which can be converted into **8** *via* a protonation process. Finally, product **3** is afforded *via* the rearomatization of **8**. DABCO assists the expulsion of the benzoyl moiety in this process. We can not exclude that DABCO plays another role of ligand on Cu to facilitate the reaction.[19]

In conclusion, we have demonstrated the aerobic direct dehydrogenative annulations of terminal alkynes for pyrazolo[1,5-*a*]-pyridine derivatives. Further studies to discover the synthetic applications of this reaction are ongoing in our group.

Financial support from National Basic Research Program of China (973 Program 2009CB825300), National Science Foundation of China (No. 21172006), and Peking University are greatly appreciated. We thank Peng Feng in this group for reproducing the results of **3e** and **3m**.

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