C–H Activation

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Metal-Free Oxidation/C(sp^3)–H Functionalization of Unactivated Alkynes Using Pyridine-*N*-Oxide as the External Oxidant**

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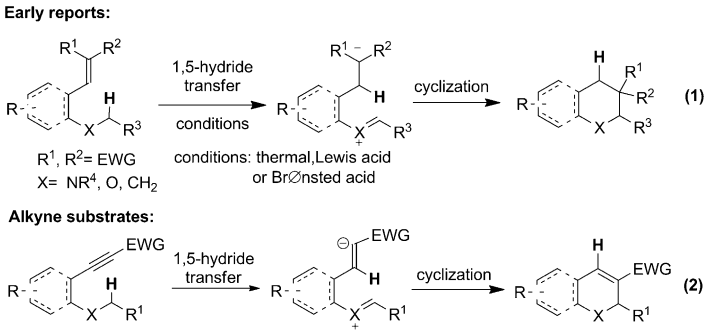
The direct and selective functionalization of the C(sp^3)–H bond has broad synthetic potential owing to the ubiquity of this bond in organic compounds, but it's transformation still remains challenging.[1] In recent years, a 1,5-hydride transfer/cyclization strategy giving a rapid buildup of molecular complexity has drawn increased attention.[2] Electron-deficient alkenes[3] were used as the most typical hydride acceptors under various conditions [Scheme 1, Eq. (1)] in the early reports, although there were a few examples that deal with

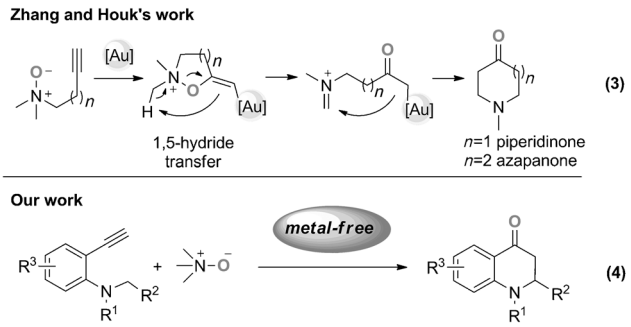


Scheme 1. C(sp^3)–H functionalization by hydride transfer/cyclization sequences, EWG = electron-withdrawing group.

imines[4] or aldehydes.[5] Once efficient C(sp^3)–H functionalization of activated alkynes were demonstrated, the 1,5-hydride transfer/ring-closure strategy became established in the research area of alkynes [Scheme 1, Eq. (2)].[6] For unactivated alkyne substrates, Ru,[7,8b] Pt,[8] Pd,[9] and Au[10] were found to be the practical catalysts.

Recently, the rapid development of α-oxo gold carbene species generated through oxidation of alkynes[11] provides a feasible new pathway for C(sp^3)–H functionalization. Zhang, Houk and co-workers[12] have recently identified a mechanism involving concerted 1,5-hydride/oxygen transfer/cyclization to realize the formation of piperidinones and azapanones [Scheme 2, Eq. (3)]. Despite these breakthroughs using gold catalysis, there is interest in seeking metal-free routes to these transformations, not only because these metals are often expensive and environmentally hazardous, but also residual metallic impurities are an important issue, especially in pharmaceutical industry. Herein, we report a metal-free oxidation/C(sp^3)–H functionalization of unactivated terminal alkynes, yielding 2,3-dihydroquinolin-4(1*H*)-ones as potential precursor to 4-quinolone [Scheme 2, Eq. (4)], which is an important structural motif of clinically used antibacterial drugs.[13] To our knowledge, this finding is the first example involving unactivated alkynes that does not require the participation of a gold complex.[14]

On the basis of Zhang's pioneering work,[15] we initially investigated an oxidation/C–H functionalization cascade using 2-ethynylaniline derivative **1a** as a substrate in the presence of 5 mol% [PPh_3AuNTf_2] (NTf_2 = bis(trifluoromethylsulfonyl)amide) 2.0 equivalents MsOH (methanesulfonic acid), and pyridine-*N*-oxide **2a** (in CH_2Cl_2, at 30 °C; Table 1, entry 1). After the complete consumption of **1a** in 12 h, the desired 2,3-dihydroquinolin-4(1*H*)-one **4a** was successfully isolated in only 17% yield, meanwhile a byproduct **4b** was isolated (only in 15% yield). We suspected that the trace amount of H_2O in solvent probably led to the formation of **4b** through the competing hydroamination/hydrolysis reaction of alkynes.[16] The yield of **4a** was improved to 35% by using **2b** as the oxidant (Table 1, entry 2). Surprisingly, the reaction also proceeded to give **4a** in the absence of the gold complex without a significant decrease in the yield (Table 1, entry 3 vs entry 2).



Scheme 2. Oxidation/C(sp^3)–H functionalization of unactivated alkynes under gold(I) and metal-free conditions.

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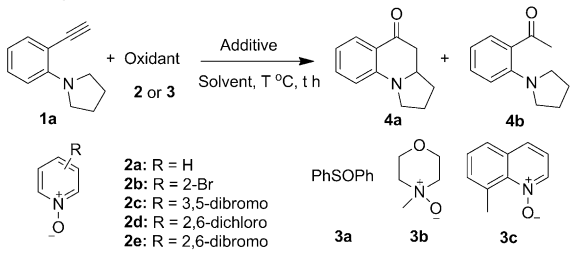
Table 1: Optimization of reaction conditions.[a]



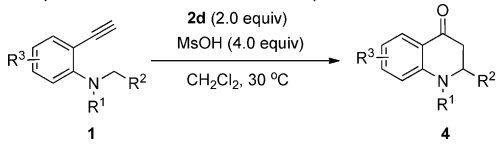
Entry	Cat.[b]	Oxide	Additive	Solvent	*t* [h]	Yield [%][c] 4a	4b
1	[Au]	**2a**	MsOH	CH_2Cl_2	12	17	15
2	[Au]	**2b**	MsOH	CH_2Cl_2	12	35	18
3	–	**2b**	MsOH	CH_2Cl_2	12	28	13
4	–	**3a**	MsOH	CH_2Cl_2	12	–	75
5	–	**3b**	TFA[d]	CH_2Cl_2	3	–	93
6	–	**3c**	MsOH	CH_2Cl_2	3	40	13
7	–	**3c**	MsOH[e]	CH_2Cl_2	3	53	18
8	–	**2c**	MsOH[e]	CH_2Cl_2	3	53	–
9	–	**2c**	TFA[e]	CH_2Cl_2	24	trace	–
10	–	**2c**	TfOH[e]	CH_2Cl_2	24	12	–
11	–	**2c**	MsOH[e]	EtOAc	24	45	–
12	–	**2c**	MsOH[e]	MeCN	24	20	15
13	–	**2c**	MsOH[e]	Toluene	24	trace	–
14	**–**	**2d**	**MsOH[e]**	**CH_2Cl_2**	**3**	**72**	**–**
15	-	**2e**	MsOH[e]	CH_2Cl_2	3	64	–
16	-	**2d**	–	CH_2Cl_2	48	–	–

[a] Unless indicated otherwise, reactions of **1a** (0.2 mmol), **2**, or **3** (0.4 mmol) and additive (0.4 mmol) were carried out in 2 mL solvent at 30 °C, best result highlighted in bold. [b] [Au] = [$Ph_3PAuNTf_2$]. [c] Yield of isolated product. [d] Under the same conditions, **1a** would not be consumed when using MsOH. [e] 4.0 equivalents were used.

This finding prompted us to develop a metal-free procedure. Thus, a range of sulfoxide and *N*-oxides were examined as external oxidants (Table 1, entries 4–8). Phenyl sulfoxide (**3a**) and *N*-methyl morphine-*N*-oxide (**3b**) led to exclusive production of **4b**. The yield of **4a** was improved to 53 % in the presence of 4.0 equivalents of MsOH when 8-methylquinoline-*N*-oxide (**3c**) was employed (Table 1, entry 7). 3,5-Dibromopyridine-*N*-oxide **2c** turned out to work better than **3c** on account of it suppressing the formation of **4b**. Both TFA and TfOH failed to give a decent yield (Table 1, entries 9, 10). Of the solvents used, CH_2Cl_2 was found to be the solvent of choice (Table 1, entries 11–14). Another two different substituted pyridine-*N*-oxides **2d** and **2e** were then investigated (Table 1, entries 14, 15), and the yield was substantially improved to 72 % when **2d** was used. Moreover, the starting substrate was recovered almost quantitatively even after 48 h in the absence of MsOH (Table 1, entry 16), clearly demonstrating the significant nature of MsOH towards activation of alkynes.[17]

With the optimized conditions in hand, we investigated the generality of this metal-free method (Table 2). The Brønsted acid promoted reaction tolerated a range of 2-ethynylanilines bearing either of electron-withdrawing, neutral, or electron-donating substituents on the benzene ring (Table 2, entries 1–9), affording the products in 48–84 % yields. Notably, 2-ethynylanilines with biologically active fluorine-based substituents underwent the reaction cleanly

Table 2: Scope for the metal-free oxidation/C–H functionalization.[a]



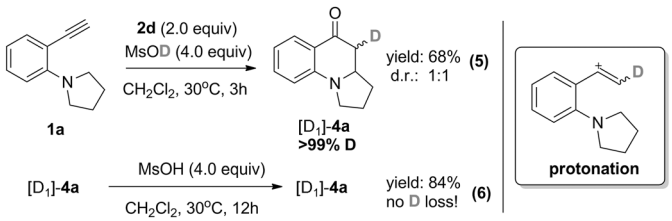
Entry	Substrate	*t* [h]	Product	Yield [%][b]
1	**1b**: R^3 = 4-F	12	**4b**	75
2	**1c**: R^3 = 4-Cl	3	**4c**	71
3	**1d**: R^3 = 4-Br	3	**4d**	65
4	**1e**: R^3 = 4-OCF_3	12	**4e**	84
5	**1f**: R^3 = 4-CF_3	24	**4f**	51
6	**1g**: R^3 = 5-F	12	**4g**	48
7	**1h**: R^3 = 5-CH_3	24	**4h**	56
8	**1i**: R^3 = 5-CF_3	12	**4i**	76
9	**1j**: R^3 = 3-F	2	**4j**	72
10	**1k**	24	**4k**	40
11	**1l**	24	**4l**	50
12	**1m**: R^3 = H	2	**4m**	56
13	**1n**: R^3 = 4-Cl	2	**4n**	42
14	**1o**: R^3 = 4-F	2	**4o**	52
15	**1p**	12	**4p** (30 %) + **4p′**	(25 %)

[a] Unless indicated otherwise, reactions of **1** (0.2 mmol), **2d** (0.4 mmol), and MsOH (0.8 mmol) were carried out in 2 mL CH_2Cl_2 at 30 °C. [b] Yield of isolated product.

(Table 2, entries 1,4–6,8,9). More importantly, a range of substituents including acyclic, cyclic, and unsymmetric variants on the amine moiety were amenable, leading to the formation of the corresponding products in moderate yields (40–56 %; Table 2, entries 10–15, the result in entry 15 was considered as 55 % yield in total). Compared to the reactions exploring **1l** and **1p**, **4l** was produced exclusively, whereas **4p** and **4p′** were obtained in 55 % total yield albeit with indistinctive regioselectivity.[18] In addition, a preliminary enantioselective method was investigated with a chiral phosphoric acid, but with a low enantioselectivity.[19]

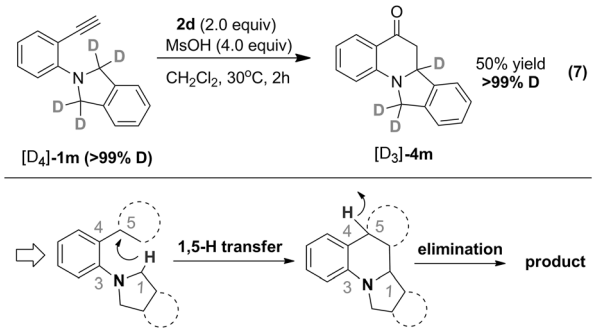
We have endeavored to probe the mechanism of this metal-free route. As part of deuterium-labeling studies, **1a** was added to the reaction under standard conditions except

that 4.0 equivalents of MsOD was employed [Scheme 3, Eq. (5)]. Combined with [D_1]-**4a**'s tolerance of MsOH[20] [Scheme 3, Eq. (6)], the observation of 50% deuterium on



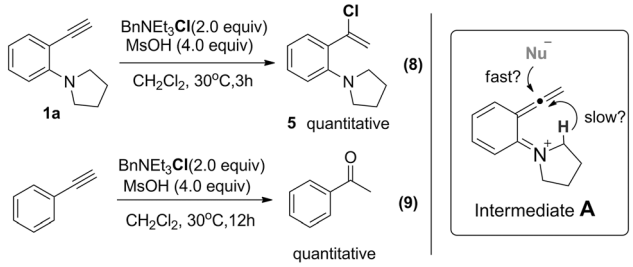
Scheme 3. Deuterium-labeling experiments (1).

[D_1]-**4a**'s ketonic α-position implied that protonation of alkynes occurred in the initial step. Then [D_4]-**1m** which was 100% deuterated at methylene positions adjacent to nitrogen was prepared to trace the potential hydride transfer. The reaction afforded a 50% yield of [D_3]-**4m** with no deuterium at ketonic α-position [Scheme 4, Eq. (7)], which probably went through a hydride-transfer/elimination process.[21]

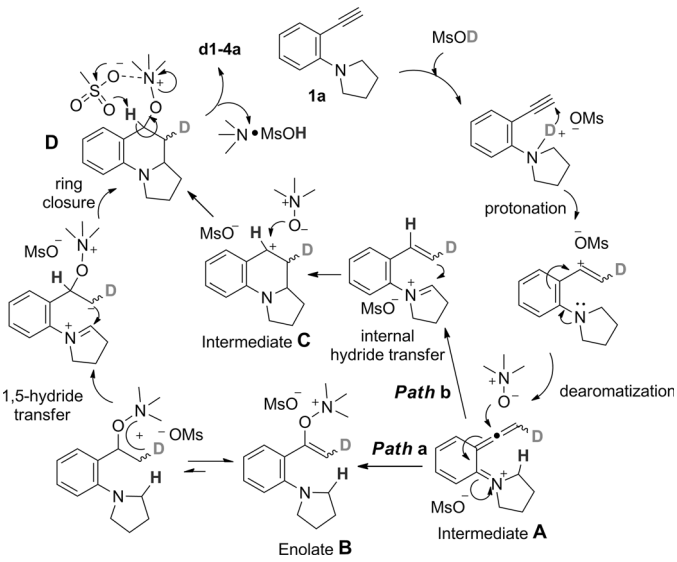


Scheme 4. Deuterium-labeling experiments (2).

Some control experiments were also established. Under optimized conditions, $BnNEt_3Cl$ was chosen as a new nucleophile instead of pyridine-*N*-oxide **2d**, furnishing a simple styrene derivative **5** [Scheme 5, Eq. (8)]. This reaction superficially proceeded through a direct addition of HCl to **1a** whereas complete hydrolysis of phenylacetylene under same conditions was observed [Scheme 5, Eq. (9)], which made us suspect the formation of a nitrogen-involved intermediate **A** via dearomatization. Accordingly, we would like to envisage that pyridine-*N*-oxide attacks intermediate **A** prior to its internal hydride-transfer process, , however, further evidenced for this proposal has not been found.



Scheme 5. Control experiments.



Scheme 6. Reaction mechanism.

On basis of the above observations, a mechanism was proposed (Scheme 6). In the initial step, the basic nitrogen atom tends to capture a proton,[22] which would promote the protonation of alkynes. Intermediate **A** is formed by dearomatization of styrene cation. Afterwards, there are two possible pathways that account for the formation of the final products. In path a, the nucleophilic attack of pyridine-*N*-oxide onto **A** generates enolate **B**, which undergoes a subsequent 1,5-hydride transfer/ring-closure process that is probably promoted by delocalization of **B**, though there is no conclusive evidence. In a final intermediate **D**, the interaction between methanesulfonic anion and pyridine cation would facilitate C–H and N–O bonds cleavage.[21] The above-mentioned rearrangement in intermediate **D** not only rationalizes the formation of corresponding product, but also explains the deuterium loss of [D_3]-**4m** [Scheme 4, Eq. (7)]. In an alternative path b, the hydride of intermediate **A** would migrate preferentially to facilitate the cyclization and the consequential nucleophilic attack of pyridine-*N*-oxide onto benzylic cation **C**. According to our previous control experiments, path a seems to be more likely, while path b cannot be ruled out.

In summary, we have demonstrated the metal-free oxidation/C(sp^3)–H functionalization of unactivated aryl alkynes using pyridine-*N*-oxide as an external oxidant, revealing that the Brønsted acid MsOH plays an extremely important role in promoting this reaction. We have also preliminarily suggested a mechanism in which a key intermediate **A** is identified and two possible pathways are proposed to rationalize the formation of the final products. Further efforts to advance the understanding of the mechanism and investigations focused on high enantioselective process are underway.

Experimental Section

2-Ethynylaniline derivatives **1** (0.2 mmol) and 2,6-dichloropyridine-*N*-oxide **2d** (0.4 mmol) were dissolved in CH_2Cl_2 (1.0 mL) in a dried

test tube. A solution of MsOH (0.8 mmol) in CH_2Cl_2 (1.0 mL) was added to the mixture at 30 °C and the stirring was continued until **1** was consumed completely. Then NEt_3 (0.2 mL) was introduced to the mixture to quench the reaction. After evaporation of all volatiles under vacuum, the residue was purified through column chromatography on silica gel (eluting with petroleum ether/ethyl acetate 20:1) to afford **4**.

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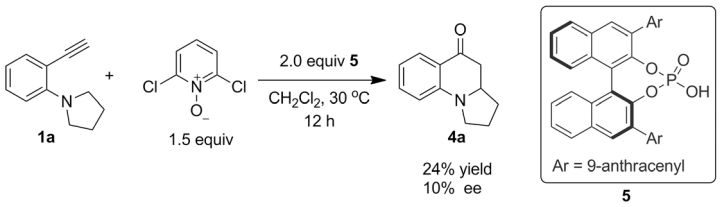
[17] Basic pyridine formed during the reaction neutralizes some of the MsOH, therefore, attempts to realize a catalytic procedure failed.

[18] When the reaction was conducted at lower temperature (−40 °C) for 24 h, **4p** and **4p′** were obtained in 36% and 22% yields, respectively.

[19] Chiral phosphoric acid promoted oxidation/C(sp^3)–H funtionalization:



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