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Facile synthesis of isoquinolines and isoquinoline *N*-oxides *via* a copper-catalyzed intramolecular cyclization in water†

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A highly efficient method for the facile access of isoquinolines and isoquinoline *N*-oxides *via* a Cu(I)-catalyzed intramolecular cyclization of (*E*)-2-alkynylaryl oxime derivatives in water has been developed. This protocol was performed under simple and mild conditions without organic solvent, additives or ligands. By switching on/off a hydroxyl protecting group of oximes, the selective N–O/O–H cleavage could be triggered, delivering a series of isoquinolines and isoquinoline *N*-oxides, respectively, in moderate to high yields with good functional group tolerance and high atom economy. Moreover, the practicality of this method was further demonstrated by the total synthesis of moxaverine in five steps.

With the pressing need for the sustainability of human society, more environmentally acceptable processes have been playing an increasingly important role in the chemical industry, especially in the manufacture of fine chemicals and pharmaceuticals.[1] In 1998, the twelve principles of green chemistry were put forward by Anastas and Warner. Among the twelve principles, safer and green solvents have been recognized as one of the most important and indispensable elements in the current chemical society.[2,3] Compared with the commonly toxic and highly volatile solvents, some green and sustainable solvents such as supercritical fluids,[4] ionic liquids,[5] and water,[6] have been intensively studied from the beginning of the 21st century. It is noteworthy that water as a green and sustainable reaction medium has received increasing attention from the synthetic community.[7] However, the study of organic chemical reactions in water is still in its infancy, and most organic synthesis still needs to be achieved in strictly dry organic solvents, especially when these systems involve transition metal catalysis.[8] Therefore, the development of diverse and practical approaches by the use of water as a reaction medium in organic synthetic chemistry is more desirable.

Isoquinolines and their derivatives, one of the most important nitrogen-containing heterocycles, have attracted tremendous attention in recent years owing to their widespread occurrence in many natural products,[9] pharmaceuticals,[10] organic materials,[11] and chiral ligands.[12] Due to their versatile applications, a plethora of synthetic strategies have been developed to construct these functionalized heterocyclic compounds under different transition-metal-catalyzed systems,[13] especially the simplest and most direct intramolecular cyclization. In 2009, Zhang and co-workers reported an interesting work involving the product selectivity control reactions to afford isoquinolines and isoquinolin-1(2*H*)-ones by simple subtle structure modification of *ortho*-alkynylaryl aldehyde oxime derivatives.[14] Subsequently, Li,[15] Harrity,[16] Shi[17] and others[18] disclosed a rhodium(III), platinum(0), silver(I) and gold(I)-catalyzed intramolecular cyclization reaction using the same or analogous starting materials for the synthesis of isoquinolines and their derivatives, respectively. However, despite these significant advances made in accessibility of isoquinolines and their derivatives, some challenging issues still remain in terms of the use of toxic organic solvents, precious metal catalysts, harsh reaction conditions, which lead to poor atom economy and are inconsistent with the principles of green chemistry. Therefore, the development of more efficient and environment-friendly methods for the assemble of functionalized isoquinolines and their derivatives is of great significance but extremely challenging. As part of our continuing studies on green chemistry,[19] combined with our interest in the development of new synthetic methods for the construction of nitrogen-containing heterocycles based on oxime compounds,[20] we herein present an unprecedented strategy for the synthesis of

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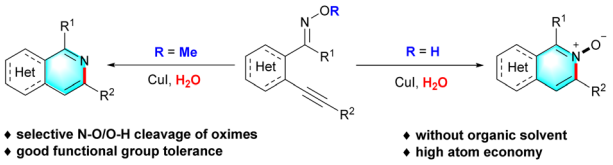
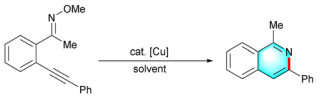


Scheme 1 Synthesis of isoquinolines and isoquinoline *N*-oxides.

isoquinoline and their derivatives in water *via* a copper-catalyzed cyclization reaction of (*E*)-2-alkynylaryl oxime derivatives. Interestingly, the reaction could be performed in the absence of organic solvent, additives or ligands, and enabled the formation of isoquinolines and isoquinoline derivatives respectively by the selective N–O/O–H cleavage of oximes in the same reaction system (Scheme 1).

Initially, (*E*)-1-(2-(phenylethynyl)phenyl)ethanone *O*-methyl oxime **1a** was selected as model substrate for the optimization of reaction conditions (Table 1). When **1a** was reacted in the presence of 10 mol% CuI in water at 80 °C under an air atmosphere, 1-methyl-3-phenylisoquinoline **2a** was obtained in 92% yield (entry 1). Prolonging the reaction time led to a slightly higher yield (95%) (entry 2). In the absence of a copper catalyst, no product was observed (entry 3), which indicating that copper catalyst played an important role for the transformation. Subsequently, screening of other copper salts, including CuBr, CuCl, $CuBr_2$ and $Cu(OAc)_2$, showed that CuI was the best catalyst for the reaction (entries 4–7). Moreover, we observed the reaction temperature had great impact on the reaction. Decreasing the temperature to 70 °C led to lower yield (entry 8). Further optimization of solvents revealed that water was more efficient than other solvents, such as 1,4-dioxane, toluene, EtOH and AcOH (entries 9–12). Based on these results, the optimal reaction conditions were established as follows: **1a** (0.5 mmol), CuI (10 mol%), H_2O (2 mL) at 80 °C for 15 h in air.

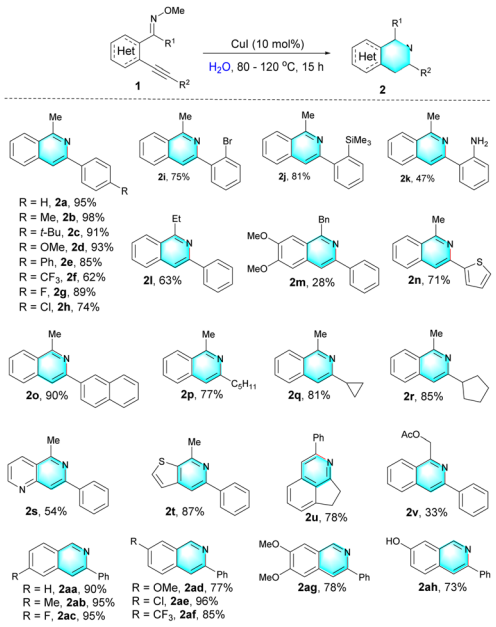
Table 1 Optimization of the reaction conditions[a]



Entry	[Cu]	Solvent	Time (h)	Yield[b] (%)
1	CuI	H_2O	12	91
2	CuI	H_2O	15	95
3	—	H_2O	15	NR
4	CuBr	H_2O	15	73
5	CuCl	H_2O	15	46
6	$CuBr_2$	H_2O	15	43
7	$Cu(OAc)_2$	H_2O	15	NR
8[c]	CuI	H_2O	15	48
9	CuI	1,4-Dioxane	12	87
10	CuI	Toluene	12	28
11	CuI	EtOH	12	65
12	CuI	AcOH	12	Trace

[a] Reaction condition: **1a** (0.5 mmol), [Cu] (10 mol%), and solvent (2 mL) at 80 °C in a sealed tube, and reaction time as specified. [b] Isolated yields. [c] 70 °C.

Table 2 Substrate scope for the synthesis of 1,3-disubstituted isoquinolines[a,b]



[a] Reaction condition: **1** (0.5 mmol), CuI (10 mol%), and H_2O (2 mL), at 80–120 °C for 15 h in a sealed tube. [b] Isolated yield.

With the optimized conditions in hand, we further studied the substrate scope of this Cu(I) catalyzed intramolecular cyclization reaction, and the experimental results were displayed as follows (Table 2). First, the (*E*)-2-alkynylaryl ketone *O*-methyl oximes **1** bearing electron-donating substituents (*p*-Me, *p*-^{t}Bu, *p*-OMe, and *p*-Ph) proceeded well in this reaction, affording the corresponding products (**2b–2e**) in good to excellent yields. The structure of **2e** was confirmed by X-ray crystallography analysis (CCDC 2095902, see the ESI† for details). While substrates possessing electron-withdrawing groups (**1f–1i**) showed lower reactivity than those with electron-rich groups, delivering the desired isoquinolines in 62–89% yields. Other functional groups, such as TMS (**1j**) and NH_2 (**1k**) groups, were also tolerated under standard conditions, allowing for efficient synthesis of isoquinolines. In particular, the isoquinoline product **2k** could be utilized as a bidentate ligand.[21] 1-Ethyl-3-phenylisoquinoline **2l** and 1-benzyl-3-phenylisoquinoline **2m** were obtained in 28% and 63% yield, respectively. Substrates **1n–1t** bearing thienyl, naphthyl, *n*-pentyl, cycloprophyl, cyclopentyl and pyridyl groups were also applicable to this transformation, producing the corresponding products **2n–2t** in moderate to good yields. Especially, this strategy was demonstrated to be efficient for the construction of polycyclic isoquinoline **2u**. And, *N*-acetoxyl imine **1v** was successfully converted to isoquinolines **2v** in acceptable yield, which expanded the diversity of this method. In addition, the 3-phenylisoquinolines **2aa–2ah** were also obtained in 73–96% yields.

Interestingly, the reaction of (*E*)-2-alkynylaryl oximes **3** (Table 3) is quite different under standard reaction conditions, providing various 3-phenylisoquinoline *N*-oxide **4** as products.

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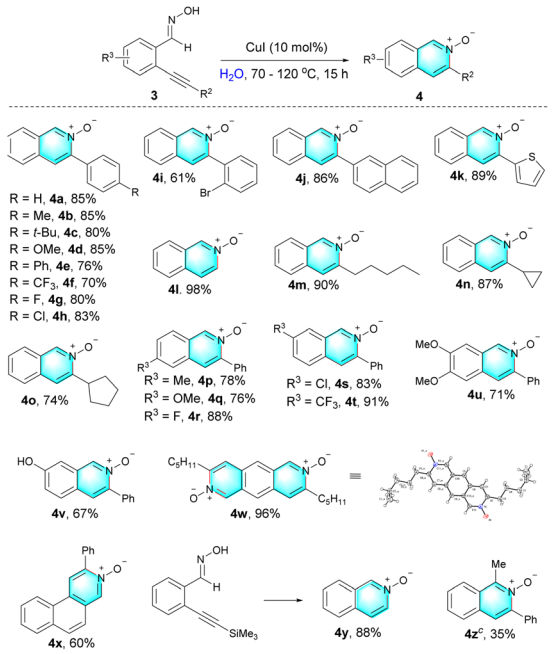
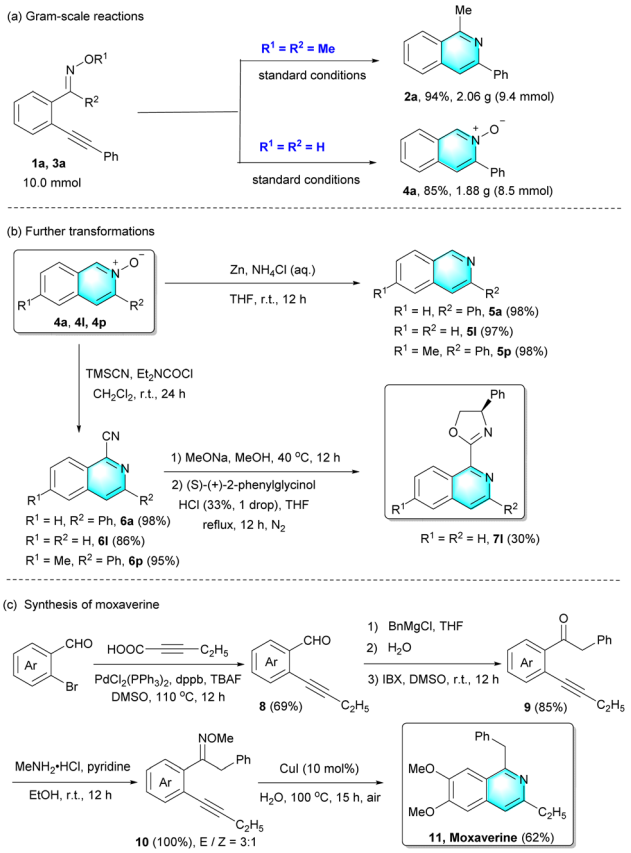
Table 3 Substrate scope for the synthesis of 3-substituted isoquinoline *N*-oxides[a,b]



[a] Reaction condition: **3** (0.5 mmol), CuI (10 mol%), and H_2O (2 mL), at 70–120 °C for 15 h in sealed tube. [b] Isolated yield. [c] 50 °C.



Scheme 2 Gram-scale reactions (a), further transformations (b) and synthesis of moxaverine (c).

The structure of **4a** was characterized by X-ray crystallography analysis (CCDC 2128901, see the ESI† for details). Substrates possessing either electron-donating (**3b–3e**, **3p–3q**, and **3u**) or electron-withdrawing groups (**3f–3i**, and **3r–3t**) all underwent well in this system, producing the corresponding products in moderate to excellent yields. A series of important functional groups attached on the triple bond, including naphthyl (**3j**), thienyl (**3k**), *n*-pentyl (**3m**), cycloprophyl (**3n**), cyclopentyl (**3o**) groups, were also well tolerant, affording the desired products in 74–90% yields. The terminal alkyne (**3l**) and internal alkyne (the TMS substituent) (**3y**) gave the same product. Hydroxyl group (**3v**) was also compatible with the standard reaction conditions. Arene-fused nitrocycles **4w** and **4x** could also be obtained using this method, and the formula of **4w** was established by X-ray crystal structure analysis (CCDC 2142641, see the ESI† for details). *o*-Alkynylaryl ketoxime **3z** was also found to be tolerated in this reaction, and the corresponding product **4z** were also obtained in a 35% yield at 50 °C.

To investigate the practicality of this method, gram-scale reactions and further transformations were carried out (Scheme 2). On a 10.0 mmol scale, the desired isoquinoline **2a** and isoquinoline *N*-oxide **4a** were isolated in 94% and 85% yield, respectively. Subsequently, treating isoquinoline *N*-oxides with ammonium chloride solution of zinc, isoquinoline *N*-oxides (**4a**, **4l**, and **4p**) could be converted into the corresponding isoquinolines **5a**, **5l** and **5p** in excellent yields. Furthermore, the reaction of **4a**, **4l**, and **4p** with TMSCN took place at room temperature, providing the desired cyanoisoquinolines **6a**, **6l** and **6p** in 86–98% yields. More importantly, chiral ligand **7l** could be further successfully prepared in a moderate yield from cyanoisoquinolines **6l**.

On the other hand, this Cu(I)-catalyzed intramolecular cyclization could also be applied to the synthesis of isoquinoline alkaloid moxaverine **11** (Scheme 2(c)), which is employed as a famous drug to treat functional gastrointestinal disorders. Initially, the commercially available 6-bromoveratraldehyde and 2-pentynoic acid were used to synthesize the internal alkyne **8** with palladium catalysis. The internal alkyne **8** reacting with benzylmagnesium chloride was converted to the product containing alcohol functionality, which was then oxidized to the intermediate product **9**. Further transformation of ketone to oxime derivative **10** underwent well, albeit the two configurations ($E/Z = 3:1$) could not be completely purified. Finally, moxaverine **11** was easily prepared in 62% yield by employing this novel cyclization.

In order to further understand the reaction mechanism, some control experiments (Scheme 3) were conducted. Firstly, the reaction of the *Z*-isomer of oxime ethers **1b** (Scheme 3(i)) did not take place to give product **2a** under the standard condition. Subsequently, we found that the reaction of *E*-oxime ethers could be carried out under N_2 atmosphere to yield the desired heterocycle **2a** in 96% yield (Scheme 3(ii)), showing that oxygen might not be involved in the intramolecular cyclization reaction. The addition of TEMPO (Scheme 3(iii)) did not prevent the reaction, which indicates that the reaction might not proceed *via* a radical pathway. Finally, the reaction of (*E*)-1-(2-

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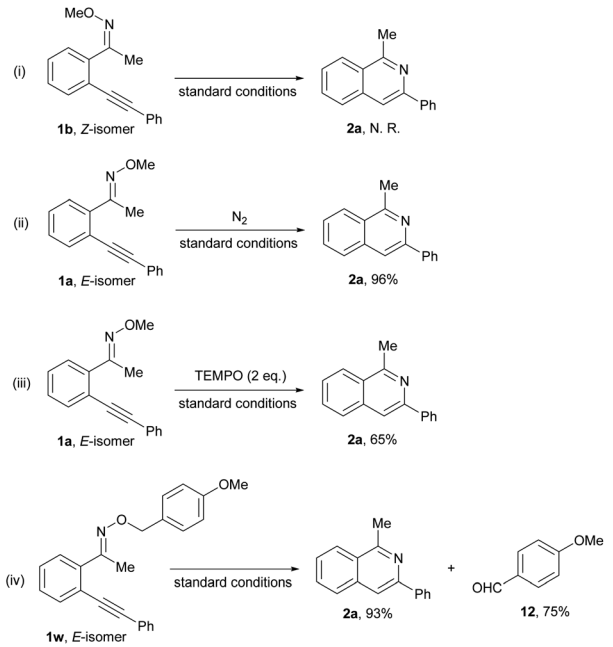
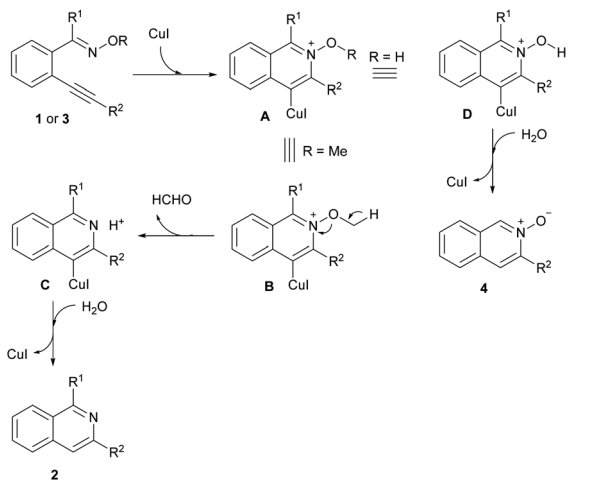


Scheme 3 Control experiments (i–iv).

(phenylethynyl)phenyl)ethanone *O*-(4-methoxybenzyl) oxime ether **1w** (Scheme 3(iv)) was conducted under the standard reaction conditions, and we found that the corresponding product **2a** and *p*-anisaldehyde **12** could be produced in 93% and 75% yield, respectively, which shows that the methoxy on the N atom might convert to formaldehyde.

Based on the above results and the previous work,[14,17,18] a possible reaction pathway is proposed for the formation of isoquinolines **2** and isoquinoline *N*-oxides **4** (Scheme 4). Initially, *ortho*-alkynylaryl oxime derivatives **1** or **3** were easily converted to intermediates **A** by a Cu(I)-catalyzed intramolecular cyclization. When R^1 is a methyl group, the cleavage of the N–O bond could give the intermediate **C** with the losing of one molecular of CH_2O. The subsequent protonation of intermediate **C** would afford the isoquinolines **2**. When R^1 is a hydrogen atom, the cleavage of the O–H bond of intermediate **D** could afford the isoquinoline *N*-oxides **4** with the assistance of one molecule of H_2O.



Scheme 4 Plausible mechanism.

In conclusion, we have developed an environment-friendly cyclization reaction for the synthesis of isoquinolines and isoquinoline *N*-oxides by selective N–O/O–H cleavage of oximes. This reaction featured in the use of green solvent, high atom economy, broad substrate scope and good functional group tolerance. The diversity of isoquinoline derivatives has been realized by subtle structure modification under mild reaction conditions with simple operations. More importantly, Moxaverine could be efficiently prepared in five steps employing this new method. Further investigations of the reaction mechanism and applications are ongoing in our lab.

Conflicts of interest

There are no conflicts to declare.

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