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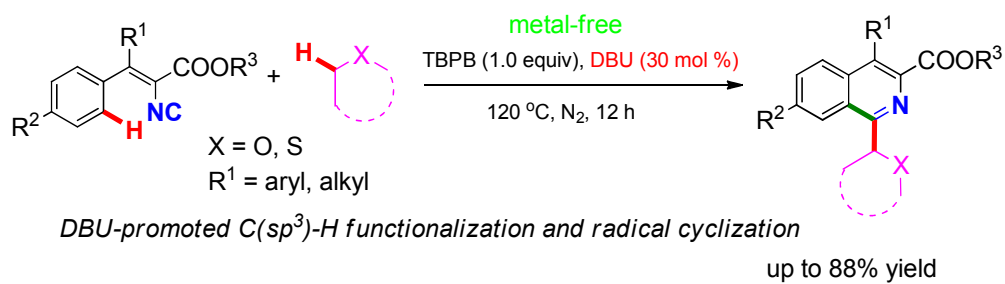


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ARTICLE TYPE

DBU-promoted cyclization of vinyl isocyanides with ethers via functionalization of C(sp³)-H bond for the synthesis of isoquinolines

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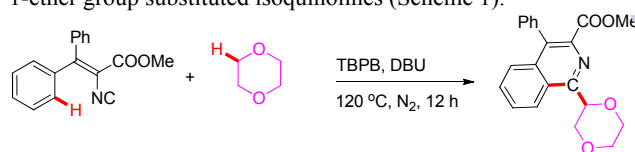
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A DBU-promoted cascade functionalization of C(sp³)-H bond adjacent to oxygen and radical cyclization reaction of vinyl isocyanides was developed. The reaction was carried out without use of any metal catalyst or photoredox catalysis, which provides an easy access to multi-functionalized isoquinolines.

Selective C-H bond functionalization has become an active research topic in organic chemistry and emerged as a powerful tool to construct complex molecules, due to high atom-economy and alleviating the need for prefunctionalized substrates.¹ Direct functionalization of relatively unreactive C(sp³)-H bonds, especially the C(sp³)-H bonds adjacent to a heteroatom, is of high value in organic synthesis, as functionalized ethers and amines widely exist in natural products and bioactive compounds.³ In recent years, a number of C(sp³)-H bond functionalization and cross-dehydrogenative coupling (CDC) of ethers and alcohols have been developed to construct ethers and alcohol derivatives.⁴ Tu and other groups have developed cascade C(sp³)-H bond functionalization and addition reaction of several alkenes⁵ and alkynes⁶ affording hydroalkylation products. Recently, Ji group explored a metal-free functionalization of C(sp³)-H bond of ethers and a 1,2-aryl migration cascade process resulting in α -aryl- β -oxyalkylated carbonyl ketones with good yields.⁷ However, metal-free functionalization of C(sp³)-H bond of ethers and followed by intermolecular or intramolecular cyclization reactions remains great challenge and less explored.⁸

Isonitriles belong to an important class of organic intermediates, which could directly construct heterocycles with high efficiency.^{9,10} For example, cyclization of 2-alkenylphenylisocyanide has been used as a key step for the total synthesis of aspidophytine.¹¹ Recently, radical initiated cyclization of aryl isonitriles has been well developed and several radical precursors,¹² including ethers and alcohols,¹³ have been developed to construct substituted phenanthridines. However, cyclization of vinyl isonitriles to synthesize substituted isoquinolines was less explored and only few examples were reported. Recently, Xu group developed a manganese-catalyzed oxidative radical cascade reaction of vinyl isocyanides for the synthesis of aryl isoquinolines with boronic acids as aryl radical precursor.¹⁴ Yu group reported light-promoted cyclization reactions of vinyl isocyanides with diaryliodonium salts or Umemoto's trifluoromethylation reagent.¹⁵ Studer group developed a method for synthesis of 1-trifluoromethylated

isoquinolines via radical trifluoromethylation of isonitriles.¹⁶ However, pre-functionalized substrates, transition metals and light condition are usually needed for these transformations. Furthermore, functionalization of C(sp³)-H bond adjacent to oxygen atom has never been explored to trigger the cyclization of vinyl isocyanides. So, development of simple metal-free radical cyclization of vinyl isocyanides with ethers and alcohols becomes high desirable. Herein, we would like to report a facile metal-free functionalization of C(sp³)-H bond adjacent to oxygen and subsequently cyclization reaction of vinyl isocyanides affording 1-ether group substituted isoquinolines (Scheme 1).



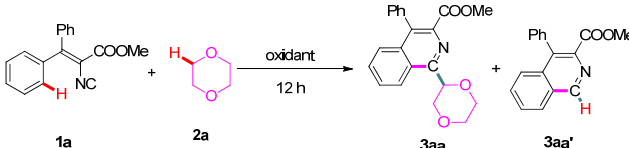
DBU-promoted radical cyclization of vinyl isocyanides no transition-metal no photoredox catalysis

Scheme 1 Metal-free radical cyclization reaction.

The initial reaction of methyl 2-isocyano-3,3-diphenylacrylate (**1a**) was carried out by using 2.0 equiv of DTBP as the oxidant in 1,4-dioxane (**2a**) under nitrogen atmosphere at 120 °C affording the expected product **3aa** in very poor yield after 12 h (36%, entry 1, Table 1). Then, 30% H₂O₂ in water was tried for this reaction, and no obvious improvement was found (entry 2). It was noticeable that the reactions with other oxidants, such as BPO, TBPA and TBPB, gave dramatically increased chemical yields (entries 3-5). TBPB was the best oxidant and 65% yield was found. Running the reaction in air gave a lower yield of **3aa**, which disclosed that the reaction has to be done under inert atmosphere (48% yield, entry 6). The by-product methyl 4-phenylisoquinoline-3-carboxylate (**3aa'**) was also detected from these reactions. To improve the chemoselectivity, several metal catalysts were tried in the reaction. However, even worse chemoselectivity and lower chemical yields were found (entries 7-11). Interestingly, when some organic bases, including DMAP (entry 14) and DBU (entry 15), as well as inorganic base *t*-BuOK (entry 12) and K₂CO₃ (entry 13) were used as catalysts for this reaction, excellent chemoselectivities were obtained. In particular, the reaction in the presence DBU only gave the desired product **3aa** with higher yield (72%, entry 15). Increasing the temperature to 130 °C or decreasing the temperature to 90 °C resulted in a little bit lower chemical yields (entries 16 and 17). Finally, the

loading amount of oxidant and DBU was investigated, which showed that 1.0 equiv of TBPB and 30% mol of DBU was the best reaction conditions (entries 18-21).

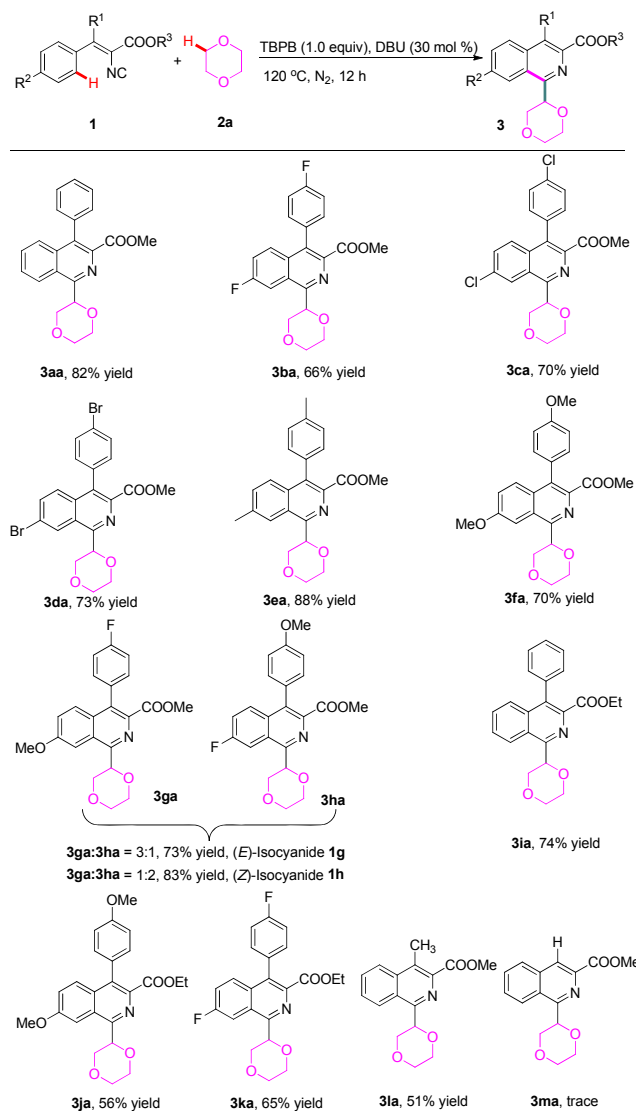
Table 1 Optimization of the reaction conditions for the reaction of methyl 2-isocyano-3,3-diphenylacrylate **1a** and 1,4-dioxane **2a**^a



Entry	Oxidant (equiv)	Catalyst (mol %)	Temp (°C)	Yield (%) ^d (3aa/3aa')
1	DTBP (2.0) ^e	-	120	36/1 ^b
2	H ₂ O ₂ (2.0) ^f	-	120	31/24 ^b
3	BPO (2.0) ^g	-	120	63/15 ^b
4	TBPA (2.0) ^h	-	120	41/3 ^b
5	TBPB (2.0) ⁱ	-	120	65/2 ^b
6	TBPB (2.0)	-	120	48/2 ^{i, b}
7	TBPB (2.0)	CuBr (20)	120	30/25 ^c
8	TBPB (2.0)	Cu ₂ O (20)	120	55/5 ^c
9	TBPB (2.0)	Cu(OAc) ₂ (20)	120	32/11 ^c
10	TBPB (2.0)	Mn(OAc) ₃ ·2H ₂ O (20)	120	42/40 ^c
11	TBPB (2.0)	MnCl ₂ (20)	120	40/27 ^c
12	TBPB (2.0)	<i>t</i> -BuOK (30)	120	68/1 ^c
13	TBPB (2.0)	K ₂ CO ₃ (30)	120	46/1 ^c
14	TBPB (2.0)	DMAP (30)	120	54/0 ^c
15	TBPB (2.0)	DBU (30)	120	72/0 ^c
16	TBPB (2.0)	DBU (30)	90	70
17	TBPB (2.0)	DBU (30)	130	64
18	TBPB (1.0)	DBU (30)	120	82
19	TBPB (3.0)	DBU (30)	120	53
20	TBPB (1.0)	DBU (10)	120	75
21	TBPB (1.0)	DBU (50)	120	80

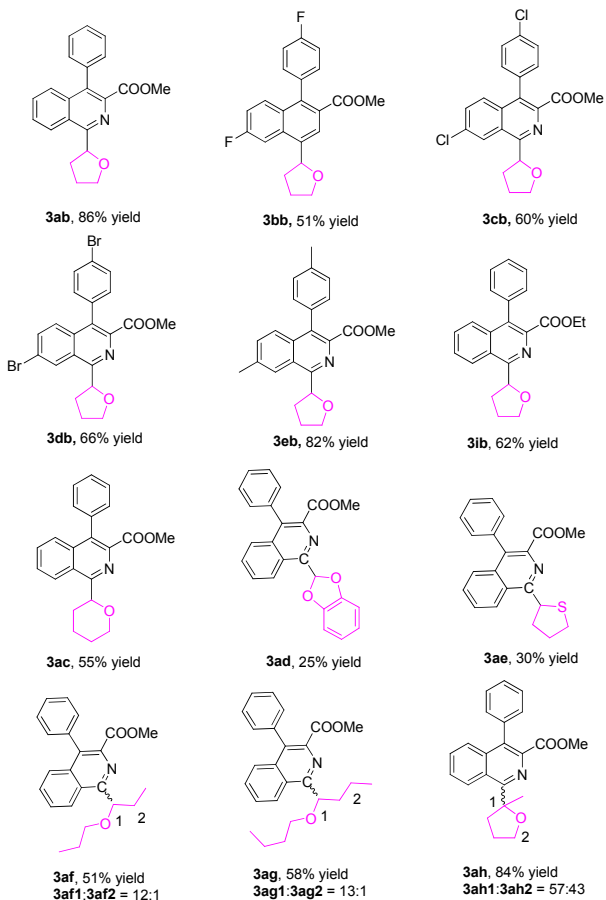
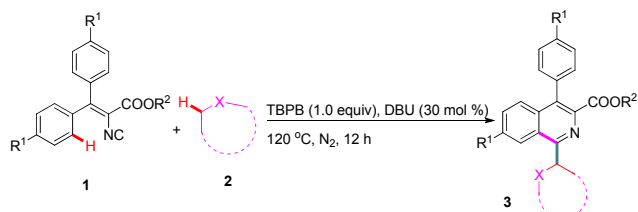
^a Reaction condition: **1a** (0.2 mmol), 1,4-dioxane **2a** (2.0 mL), oxidant, 12 h, N₂ atmosphere. ^b Yield determined by ¹H NMR with CH₂Br₂ as the internal label. ^c Yield determined by ¹H NMR after column chromatography isolation. ^d Isolated yield based on **1a**. ^e DTBP: di-*tert*-Butyl peroxide. ^f 30% H₂O₂ in water. ^g BPO: Benzoyl peroxide. ^h TBPA: *tert*-Butyl peracetate. ⁱ TBPB: *tert*-Butyl peroxybenzoate. ^j Under air.

Then, the vinyl isocyanides scope of this radical cyclization reaction was examined, and the results are summarized in Scheme 2. Several substituted groups on the aromatic ring, including fluoro (**3ba**), chloro (**3ca**), bromo (**3da**), methyl (**3ea**) and methoxyl (**3fa**) were tolerated in this reaction, and afforded the corresponding 1-ether group substituted isoquinolines in moderate to good yields. It was noticed that the reactions of the substrates with different substituted aromatic rings (**1g** and **1h**) also proceeded smoothly, resulting in the expected product in good chemical yields, but with moderate regioselectivities (**3ga** and **3ha**). The substrates with ethyl ester group at the terminal position of the vinyl group also worked well in the reaction (**3ia-3ka**), resulting in the product with slightly lower yields comparing to those substrates with methyl ester (**3aa**, **3fa** and **3ba**). Finally, when the methyl group, instead of phenyl ring, was used as substituent on the vinyl moiety, it also worked well giving the expected product in 51% yield (**3la**). However, almost no product was observed if there exists a hydrogen atom at this position of vinyl group (**3ma**).



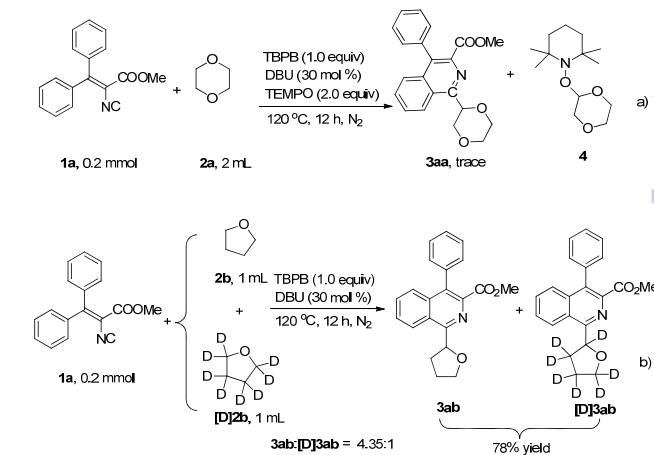
Scheme 2 Cyclization reaction of vinyl isocyanides with 1,4-dioxane **2a**.

Then, various ethers were investigated in this radical cyclization reaction of 2-isocyano-3,3-diphenylacrylate (**1**) (Scheme 3). As shown in Scheme 3, tetrahydrofuran (**2b**) could react well with methyl and ethyl 2-isocyano-3,3-diphenylacrylate (**1a** and **1i**) resulting in the desired product **3ab** and **3ib** (86% and 62% respectively). Fortunately, several substituted vinyl isocyanides could also react well with tetrahydrofuran giving the corresponding product (**3bb-3eb**). Tetrahydropyran and benzo[*d*][1,3]dioxole were also tolerated in this reaction affording the expected substituted isoquinolines with 55% and 25% yield respectively (**3ac** and **3ad**). Tetrahydrothiophene was a suitable substrate for this reaction resulting in expected 1-tetrahydrothiophen substituted product with 30% chemical yield (**3ae**). The reactions with these two linear ethers also proceeded well, affording the corresponding with 51% and 58% yields respectively. The reactions also gave excellent regioselectivity, with the ratio of 12:1 and 13:1 for product **3af** and **3ag**. 2-MeTHF also worked well in this reaction affording the desired product with 84% chemical yield and 57:43 regioselectivity.



Scheme 3 Cyclization reaction of vinyl isocyanides with other cyclic esters **2**.

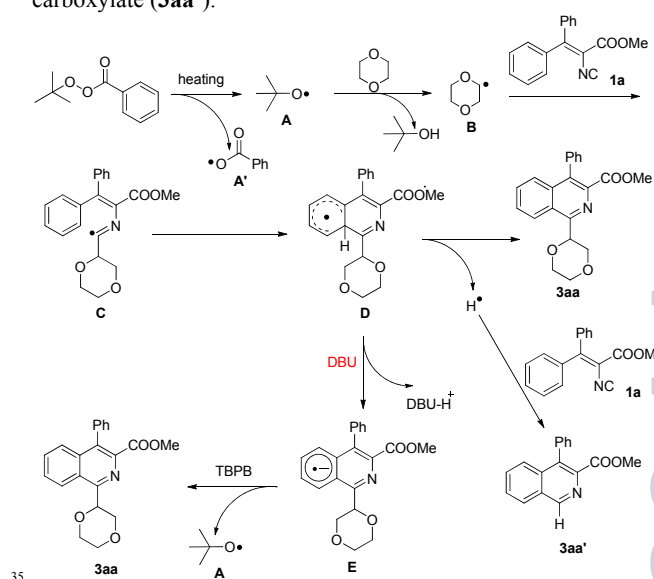
Finally, the studies on the investigation of the reaction mechanism were carried out. When radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction of 1,4-dioxane, the reaction was completely inhibited and no desired cyclic product was observed (Scheme 4a). Only the



Scheme 4 Investigation of reaction mechanism.

coupling product (**4**) with 1,4-dioxane was detected by MS. This result discloses that the reaction proceeds through a radical process. Also, an intermolecular competing kinetic isotope effect (KIE) experiment was conducted with tetrahydrofuran and [D]₄-tetrahydrofuran as starting material (Scheme 4b). An obvious KIE was found with the ratio of 4.35:1 ($k_H:k_D$), which shows that the cleavage of C(sp³)–H bond to form the ether radical may be involved in the rate-determining steps of this procedure.

Based on the above results and previous reports,¹³ a plausible reaction mechanism for this cyclization reaction was supposed (Scheme 5). Firstly, the decomposition of TBPB generates *tert*-butoxy radical intermediate **A** and benzoate radical **A'** under heating, which reacts with 1,4-dioxane to give radical **B** through C(sp³)–H bond cleavage. The intermediate **B** adds to isonitrile **1a** affords the intermediate **C**. Subsequently, the intramolecular radical cyclization of intermediate **C** generates cyclohexadienyl radical **D**. In the presence of DBU, intermediate **D** undergoes the deprotonation to give a radical anion **E**. Finally, radical anion **E** gets oxidized by TBPB to afford the product **3aa** along with a *tert*-butoxyl radical **A** and benzoate anion.^{13b,13c,17} If no DBU is added, intermediate **D** undergoes radical process to give final product **3aa** along with hydrogen radical. Hydrogen radical reacts with **1a** to give the by-product methyl 4-phenylisoquinoline-3-carboxylate (**3aa'**).



Scheme 5 Possible mechanism.

Conclusions

In summary, A DBU-promoted cascade C(sp³)-H bond functionalization of ethers and radical cyclization reaction of vinyl isocyanide was reported. The reaction tolerated a wide range of substrates and could be performed under simple conditions. This reaction involves new C(sp³)-C(sp²) and C(sp²)-C(sp²) bonds formations, which provides a straightforward and atom-economical access to multi-functionalized isoquinolines from readily available starting materials. The current reaction has the limitation on the ether solvent, and only THF and 1,4-dioxane afforded synthetically good yields. This will be further investigated in our future study on this reaction.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data for compound **3** and copies of ¹H and ¹³C NMR spectra]. See DOI: 10.1039/b000000x/

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