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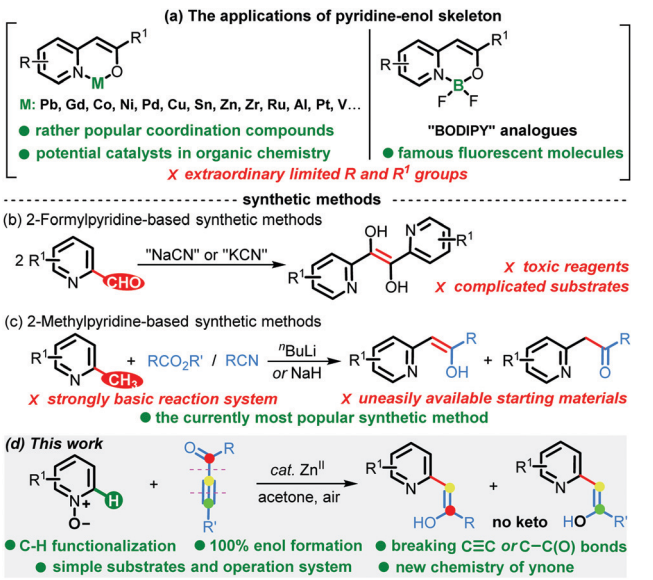
Zinc-catalyzed C–H alkenylation of quinoline *N*-oxides with ynones: a new strategy towards quinoline-enol scaffolds†

Yan Hu,[a] Jiang Nan,[a]* Xue Gong,[b] Jiawen Zhang,[a] Jiacheng Yin[a] and Yangmin Ma*[a]

A zinc-catalyzed C–H alkenylation of quinoline *N*-oxides with ynones has been developed to rapidly assemble a broad collection of valuable quinoline-enol organic architectures. Uncommonly, this novel reaction involves C–H functionalization, and N–O, C–C and C≡C bond cleavage in one operation, and leads exclusively to the formation of an enol rather than a keto product. Application of the enols generated was highlighted by further derivative transformation and preparation of a series of "BODIPY" analogues with high quantum yields (up to 86%).

Pyridine-enol scaffolds, featuring N,O-chelated fragments, have always drawn considerable attention as an appealing class of bidentate ligands and have been extensively employed in various chemical disciplines.[1] Pyridine-enol scaffolds can coordinate with a wide variety of metals to generate adducts with prominent photophysical characteristics, and even as potential catalysts for use in catalytic synthesis (Scheme 1a, left).[2] Alternatively, they can react with boron compounds to form chelated boron dipyrromethenes (BODIPYs). The latter are fluorescence-emitting molecules with sharp absorption and emission spectra, large Stokes shifts, and high quantum yields (Scheme 1a, right).[3] To date, however, only two efficient and applicable approaches for the syntheses of the organic skeleton are available:[4] (i) CN^- salts-promoted dimerization of 2-formylpyridines (Scheme 1b)[5] and (ii) condensation of 2-methylpyridines with esters or nitriles towards pyridine-enols (Scheme 1c).[6] Despite their practicality, typically these two approaches encounter unamiable reaction systems, such as toxic or strongly basic reagents (*e.g.* ^{n}BuLi), and are restricted to substrates that are not easily accessible and architecturally finite pyridine-enol molecules. Accordingly, enhancement of the efficiency of synthetic methods that allow simple and common building blocks under mild reaction conditions is remarkably alluring.

In terms of simple starting materials and greater reaction efficiency, exploiting direct C–H functionalization provides the most powerful and succinct platform for synthesizing pyridine-enol units because additional operations for preparing complicated substrates are avoided.[7] Conversely, in recent years, ynone compounds have been widely utilized as multipurpose synthetic intermediates to reconstruct new C–C bonds, especially *via* C(O)–C dissociation.[8] The appealing and challenging synergistic merger of C–H functionalization with C(O)–C dissociation (and the even more challenging cleavage of the C≡C bond of ynones) is in its infancy.[9] In our ongoing efforts in quinoline chemistry,[10] we herein report a Lewis acid-catalyzed C–H functionalization of quinoline *N*-oxides with ynones through a simple reaction system. In this protocol, exclusive enol formation was observed instead of keto formation. Most



Scheme 1 Applications and synthetic approaches for pyridine-enol scaffolds.

[a] Key Laboratory of Chemical Additives for China National Light Industry, College of Chemistry and Chemical Engineering, Shaanxi University of Science and Technology, Xi'an 710021, China. E-mail: nanjiang@sust.edu.cn

[b] College of Bioresources Chemical and Materials Engineering, Shaanxi University of Science and Technology, Xi'an 710021, China

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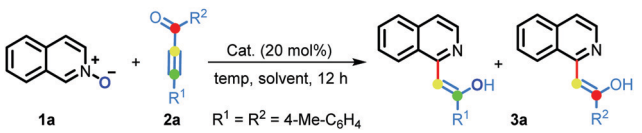
importantly, this newly established methodology involves breaking multiple chemical bonds in a single operation, including C≡C, C–C, C–H, and N–O bonds (Scheme 1d).

We commenced our studies with isoquinoline *N*-oxide **1a** and ynone **2a** as model substrates to explore the optimal reaction conditions. Gratifyingly, the highly selective C1–H functionalization of *N*-oxide was realized upon exposure to the common $Cu(OTf)_2$ catalyst, which afforded the enol molecule **3a** as an exclusive isomer in 42% yield (Table 1, entry 1). Other Lewis acids, such as $Zn(OTf)_2$, $Zn(OAc)_2{\cdot}2H_2O$, $ZnCl_2$, and $Mg(NTf)_2$, also proved to be viable (Table 1, entries 2–5). $Zn(OAc)_2{\cdot}2H_2O$ appeared preferential and provided 52% yield (Table 1, entry 3). The absence of a catalyst hampered this protocol, and delivered only 8% yield of **3a** (Table 1, entry 6). Further attempts with a series of solvents revealed that acetone was the optimum choice (Table 1, entries 7–11), which led to the isolated target product in 65% yield. Changing the reaction temperature did not promote this conversion further. However, an increased temperature was relatively beneficial (Table 1, entries 12 and 13), which also implied that this class of enol structure was could tolerate heat. Unfortunately, reducing the catalyst load resulted in an obviously diminished output (Table 1, entry 14). More detailed information on reaction optimization is shown in ESI.†

The substrate scope of this developed C–H alkenylation reaction was investigated according to the reaction conditions stated above (Scheme 2). A wide range of symmetrical ynones with various substituents, including methyl (**2a**), methoxyl (**2c**), chloro (**2d**), fluoro (**2e**), cyano (**2f**), trifluoromethyl (**2g**) and bromo (**2h**) groups at the *meta* or *para* sites of the phenyl ring, were employed to react with **1a**. They smoothly generating the anticipated isoquinoline-enol derivatives in moderate-to-good yields. The absolute molecular structure of **3c** was elucidated unambiguously by X-ray diffractometry (CCDC 2049499†). A widely applicable heterocyclic fragment, such as the 2-thiophene precursor **2i**, was also involved in this procedure. Furthermore, this conversion could be extended to the alkyl substrate (**2j**, **2k**, and **2l**) and gave rise to **3j**, **3k**, and **3l**. In addition, unsymmetrical ynones also underwent this transformation appropriately. Among them, all the biaryl-substituted reagents (**2n–p**) afforded almost equal amounts of two regioselective enol compounds and the phenyl–methyl ynone (**2m**), but with relatively high selectivity (5 : 1), which is consistent with the latter reaction mechanism proposed.

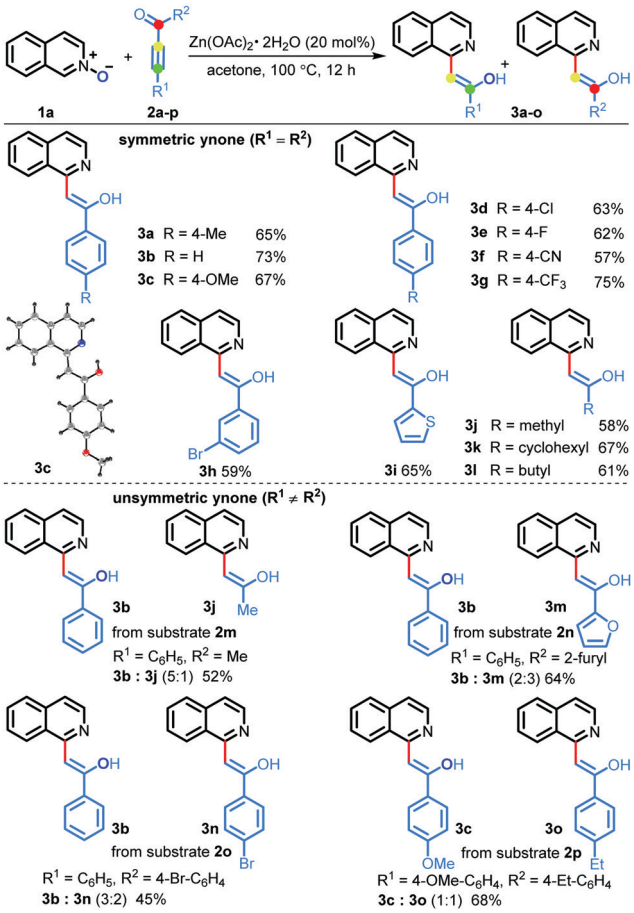
Given the outstanding potential for use of this pyridine-enol bidentate organic framework, we next looked into the reaction scope with respect to *N*-oxides to obtain more diverse molecules. As shown in Scheme 3, an array of substituents, including electron-withdrawing and electron-donating groups, were attached at the isoquinoline and reacted with diphenyl ynone **2b** to furnish the envisioned products **3a′–f′** suitably. Importantly, the bromo substitution was well tolerated (**3a′–b′**), which could permit rapid syntheses of diverse and complicated molecules. Likewise, switching the coupling partner to quinoline *N*-oxide enabled release of the respective adduct **3g′**, and several common functional groups, such as methyl (**3h′**, **3o′**), halogen (**3i′**, **3j′**, and **3n′**), ester (**3k′**), dimethylamino (**3l′**), and methoxyl (**3m′**), moieties embedded at the vacant C3–C7 positions of quinoline were accommodated.

Table 1 Optimization of the reaction conditions[a]

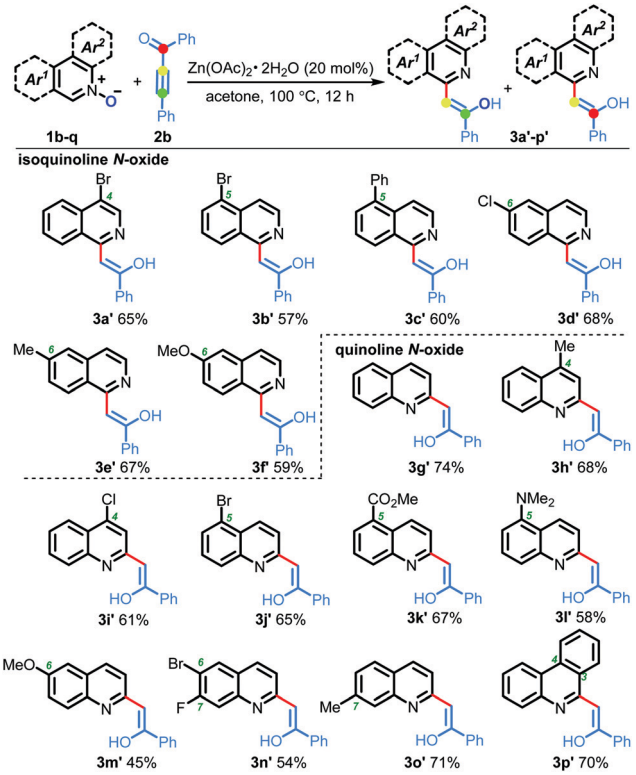


Entry	Catalyst	Solvent	Temp. (°C)	Yield[b] (%)
1	$Cu(OTf)_2$	Toluene	100	42
2	$Zn(OTf)_2$	Toluene	100	45
3	$Zn(OAc)_2{\cdot}2H_2O$	Toluene	100	52
4	$ZnCl_2$	Toluene	100	41
5	$Mg(NTf)_2$	Toluene	100	29
6	—	Toluene	100	8
7	$Zn(OAc)_2{\cdot}2H_2O$	DCE	100	45
8	$Zn(OAc)_2{\cdot}2H_2O$	MeCN	100	47
9	$Zn(OAc)_2{\cdot}2H_2O$	DMF	100	39
10	$Zn(OAc)_2{\cdot}2H_2O$	Acetone	100	65
11	$Zn(OAc)_2{\cdot}2H_2O$	THF	100	58
12	$Zn(OAc)_2{\cdot}2H_2O$	Acetone	80	44
13	$Zn(OAc)_2{\cdot}2H_2O$	Acetone	120	63
14[c]	$Zn(OAc)_2{\cdot}2H_2O$	Acetone	100	48

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (20 mol%) in solvent (2.0 mL) were stirred for 12 h in air. [b] Isolated yields. [c] 10 mol% $Zn(OAc)_2{\cdot}2H_2O$.



Scheme 2 Substrate scope of ynones.



Scheme 3 Substrate scope of the (iso)quinoline *N*-oxides.

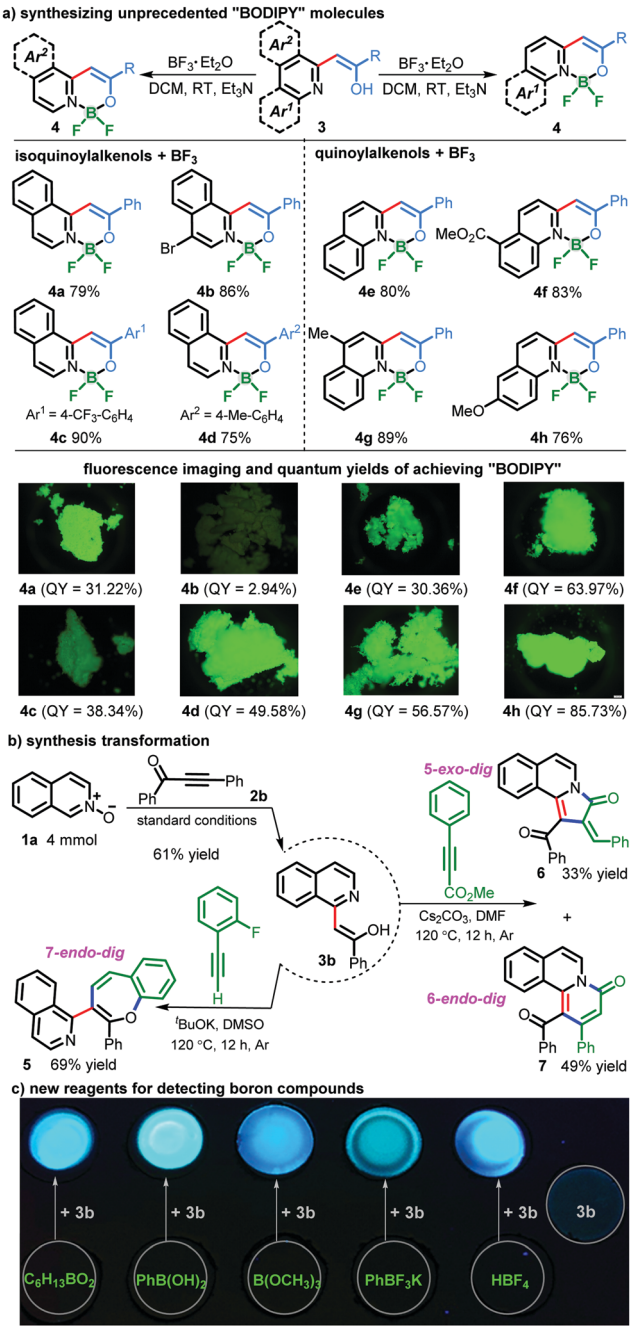
More strikingly, the π-extended precursor **1q** continued to display an appreciable reaction performance for producing the phenanthridine-derived enol **3p′**. However, at the current stage, the pyridine *N*-oxide was not compatible, probably due to its more stable aromatic system.[11]

To showcase the utility of this new transformation, additional experiments on products were conducted on synthetic derivatives and fluorescence properties, as follows:

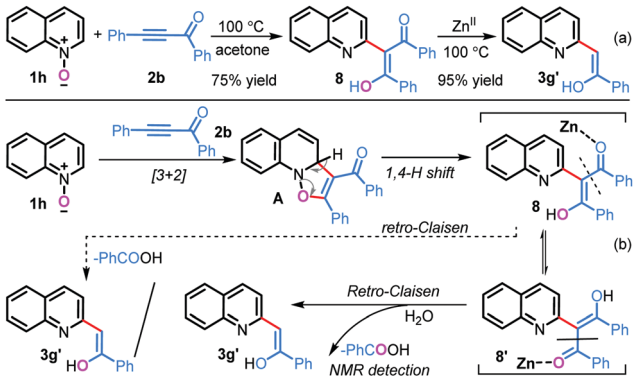
(1) Upon treatment with BF_3 reagent, the enols easily led to the assembly of boron-containing coordination complexes **4a–h** which, to an extent, enriched the scope of the family of BODIPY derivatives (Scheme 4a). This technology was appropriate for diverse substituents on both product components, including bromo (**4b**), trifluoromethyl (**4c**), methyl (**4d**, **4g**), ester (**4f**), and methoxyl (**4h**) groups, and delivered the corresponding boron adducts in good yields. Fluorescence imaging demonstrated that all of these created compounds were bright green and, more remarkably, most had acceptable-to-excellent quantum yields (even up to 86%).

(2) The scale-up catalytic process was found to be viable in terms of productivity with a loading amount of 4.0 mmol, and delivered **3b** in 60% yield (Scheme 4b). Furthermore, several molecules with architecturally more intriguing features were forged *via* further converting products. Relying on the KO^{t}Bu system, product **3b** was treated with 1-ethynyl-2-fluorobenzene, wherein the seven-numbered ether **5** was accessed with exclusive regioselectivity. When adapting methyl 3-phenylpropiolate as a coupling partner, compound **3b** resulted in 33% yield of the five-numbered amide **6** accompanied with 49% yield of the six-numbered amide **7**.

(3) Identification of boron compounds (especially those without fluorescence) is desirable. We attempted to introduce product **3b** for direct treatment with several common boron agents, such as $C_6H_{13}BO_2$(BHpin), $PhB(OH)_2$, $B(OCH_3)_3$, $PhBF_3K$, and HBF_4, using thin-layer chromatography. Delightedly, experimental outcomes illustrated that this type of quinoline-enol structure could detect boron-containing reagents and represented a promising chromogenic agent.



Scheme 4 Large-scale transformation and further derivatization.



Scheme 5 Proposed mechanism.

During implementation of this newly developed methodology, we noted that coupling quinoline *N*-oxide **1h** with diphenyl ynone **2b** without the Zn^{II} catalyst led to the fully substituted enol **8** in 75% yield, which could be effectively converted into the final product **3g′** under standard reaction conditions (Scheme 5a). According to this finding and in combination with the literature,[12] a plausible catalytic pathway could be postulated (Scheme 5b). This conversion originated from the [3+2] cyclization of *N*-oxide with ynone to result in the five-numbered intermediate **A**, followed by 1,4-*H* transfer to yield the ring-opening C2–H alkenyl adduct **8** or its tautomer **8′**. Subsequently, based on the Lewis-acid trait of $Zn(OAc)_2$, a retro-Claisen procedure delivered the title product **3g′** *via* dissociation of the C–C bond, wherein the corresponding carboxylic acid was also observed. Similarly, the tautomer **8′** accounted for the formation of product **3g′** involving O-atom transfer based on the same route.

In summary, a potent and versatile method towards rapidly construction of a pyridine-enol skeleton was disclosed through Zn-catalyzed C–H functionalization of (iso)quinoline *N*-oxides with ynones. In this way, a wide collection of prevalent pyridine-enols bearing bi-coordination function were obtained with good functional-group tolerance. In stark comparison with existing synthetic strategies, this new protocol features a simple substrate-and-reaction system. Notably, this process to the best of our knowledge, represents an extraordinarily infrequent example of merging C–H functionalization with cleavage of C–C bonds and C≡C bonds in a single manipulation.

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Conflicts of interest

There are no conflicts to declare.

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