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Cu^{II}-Catalyzed Coupling with Two Ynone Units by Selective Triple and Sigma C−C and C−H Bond Cleavages

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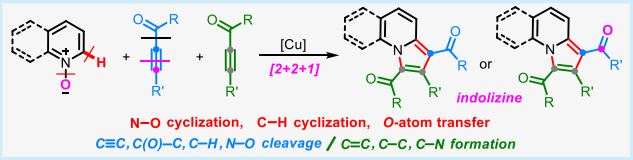
ABSTRACT: We report a new copper-catalyzed [2 + 2 + 1] annulation process through the selective cleavage of sigma and triple C−C and C−H bonds using two ynone units. This new methodology involves breaking multiple chemical bonds in a single operation, including C≡C, C−C, C−H, and N−O. These high-value adducts lead to a diverse collection of synthetically challenging trisubstituted indolizines by the simultaneous engagement of different bond-breaking events and show excellent fluorescence in green aqueous solutions.



Arguably, one of the greatest challenges in synthetic chemistry is the selective breaking and reassembly of inert chemical bonds.[1] In this fascinating field, carbon−carbon bonds represent the most fundamental linkages in organic molecules. The selective C−C bond cleavage is highly challenging owing to the inherent strength of sigma and multiple carbon−carbon bonds and the difficult-to-control site-selectivity, yet such processes have a profound impact on chemical synthesis.[2,3] Indeed, the cleavage of C−C and C=C bonds has evolved in the past decade, resulting in an ever-growing impetus in the functionalization of strained and unstrained molecules.[2] However, the selective cleavage of triple C≡C bonds is poorly established and remains one of the major research challenges arising from the larger dissociation energy (>200 kcal/mol) compared with C−C sigma bonds (∼85 kcal/mol) as well as the precarious electrophilic reactivity of systems.[3] Although methods including stoichiometric organometallic reactions,[4a,b] alkyne metathesis,[4c−e] oxidative cleavage,[4f−h] and metal-catalyzed strategies[4i−k] have been developed, the C≡C bond cleavage is regarded as a unique activation mode that allows access to elusive motifs and highly versatile building blocks.

Ynones feature two types of versatile and conjugated functional moieties, namely, C=O and C≡C bonds, and have been delivered as multipurpose intermediates in the synthesis of structurally complex organic architectures, including in the construction of value-added motifs.[5] In recent years, increasing endeavors to develop the cleavage of carbon−carbon bonds in ynones have been launched, albeit generating a limited number of cases. In this domain, the groups of Dong,[6] Cheng,[7] and Zhang[8] described the functionalization of C−C(CO) bonds (Scheme 1A). With regard to the more challenging triple C≡C bond cleavage owing to the weaker polarization, there are far fewer results, generally delivering linear molecules.[9−13] Likewise, the appealing and challenging synergistic merger of C−H functionalization[14] with C≡C bond cleavage is in infancy.

In this context, herein, we report a new copper-catalyzed [2 + 2 + 1] annulation process through the selective cleavage of sigma and triple C−C and C−H bonds using two ynone units (Scheme 1B). The method accomplishes C−H functionalization through a cascade C−H activation, C−C dissociation, nucleophilic cyclization, and oxidative aromatization.

The following features of our findings are noteworthy:[1] the unprecedented three-component domino transformation involving selective sigma and triple C−C and C−H bond scissions;[2] the productive merger of C≡C, C(O)−C, and C−H cleavages with the concomitant highly orchestrated assembly of C−C, C=C, and C−N bonds with high selectivity; (3) the formal 1,3-O atom transfer; and (4) the concise assembly of diversely trisubstituted indolizines, which are key structural motifs in a large number of bioactive products and functional molecules and typically require multistep synthesis with highly functionalized reagents (Scheme 1C).[15,16]

Our investigation began with an examination of the relevant reaction parameters by reacting isoquinoline *N*-oxide **1a** with two symmetric phenyl-substituted ynone units **2a**. A representative summary of the experimental results is presented in Table 1. After extensive optimization, we were delighted to find that using $Cu(OAc)_2$ as a catalyst and toluene as a solvent at 100 °C successfully generated the desired product **3aa** (entry 1). A solvent screen showed that PEG-200

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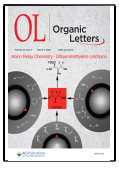

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Scheme 1. Strategies for C−C and C≡C Cleavage of Ynones

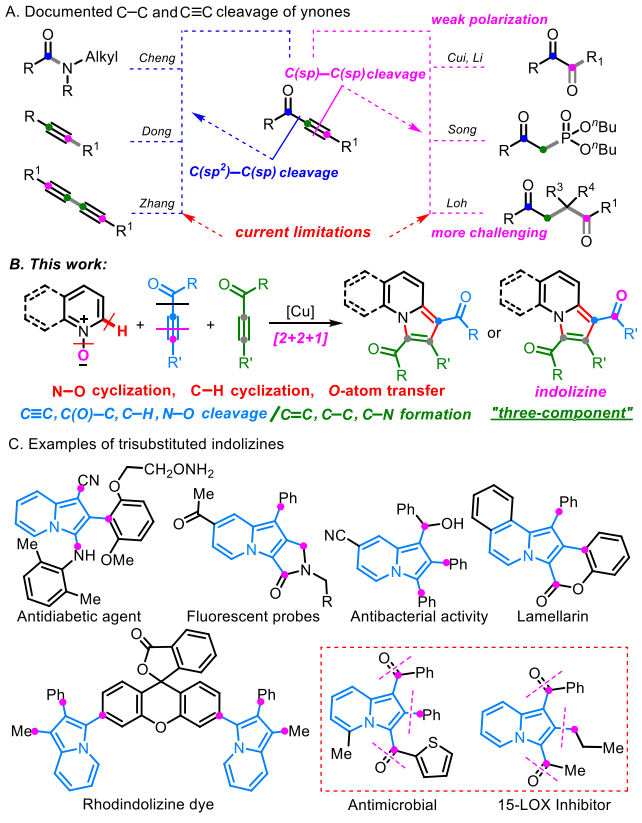
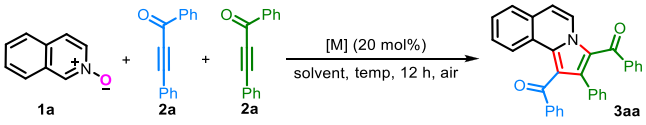


Table 1. Optimization of the Reaction Conditions[a]



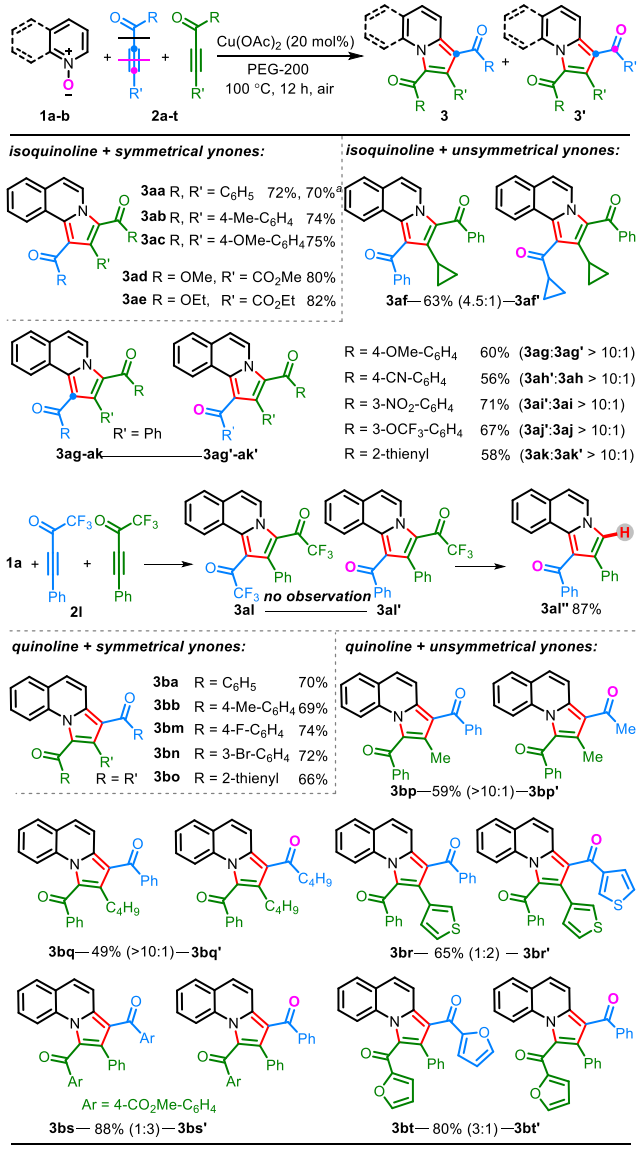
entry	[M]	solvent	temp (°C)	yield (%)[b]
1	$Cu(OAc)_2$	toluene	100	32
2	$Cu(OAc)_2$	1,4-dioxane	100	37
3	$Cu(OAc)_2$	DCE	100	53
4	$Cu(OAc)_2$	H_2O	100	53
5	$Cu(OAc)_2$	PEG-200	100	77 (72)[c]
6	$Cu(acac)_2$	PEG-200	100	30
7	CuBr	PEG-200	100	52
8	$CuSO_4·5H_2O$	PEG-200	100	59
9[d]	$Cu(OAc)_2$	PEG-200	100	22
10	$Cu(OAc)_2$	PEG-200	90	67
11	$Cu(OAc)_2$	PEG-200	110	73
12		PEG-200	100	trace

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.50 mmol), catalyst (20 mol %), solvent (2.0 mL), *T* (°C, oil bath), 12 h, air. [b]^{1}H NMR yields. [c]Isolated yield in parentheses. [d]Ar atmosphere.

was optimal and afforded the desired product in 72% yield (entry 5). A high yield using the H_2O system should be noted (entry 4). Interestingly, other Cu(I) and Cu(II) catalysts, including $Cu(acac)_2$, CuBr, and $CuSO_4·5H_2O$, showed no beneficial effect on the reaction (entries 6−8). Importantly, using anaerobic conditions, the desired transformation was dramatically inhibited, leading to **3aa** in only 22% yield (entry 9), which confirmed the critical role of oxygen. Furthermore, changes in the reaction temperature to either a higher or a lower level did not increase the reaction efficacy (entries 10 and 11). Importantly, in the absence of a Cu catalyst, this sequential C−C, C≡C, and C−H cleavage protocol was completely shut down (entry 12). Further details of the reaction optimization are summarized in the Supporting Information (SI).

Having established the optimal reaction conditions, we next evaluated the generality of this C−C, C≡C, and C−H cleavage protocol. As shown in Scheme 2, a wide range of

Scheme 2. Substrate Scope of Ynones



[a]1.0 mmol scale.

ynone partners were found to be competent by reacting with both isoquinoline and quinoline *N*-oxides (**1a**, **1b**), delivering the desired products in 49−88% yields. With regard to the carbonyl fragment of ynones, in addition to alkoxy groups (**3ad**, **3ae**), various substituents on the aromatic ring were well compatible, including electron-donating groups, such as methyl (**3ab**) and methoxy groups (**3ac**, **3ag**), as well as electron-withdrawing groups, such as cyano (**3ah′**), nitro (**3ai′**), trifluoromethoxy (**3aj′**), fluoro (**3bm**), bromo (**3bn**) and ester

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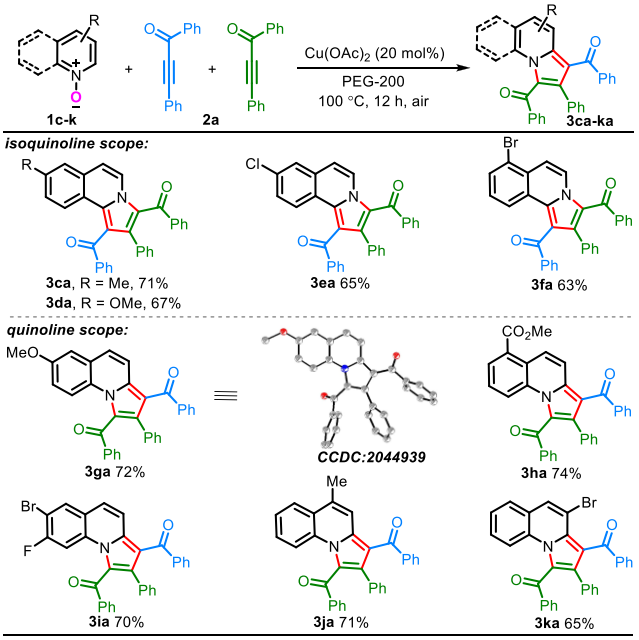
groups (**3bs′**). Interestingly, when the CF_3-containing substrate **2l** was subjected to the reaction, the corresponding trisubstituted product was further converted into the deacylation adduct **3al″** in 87% yield because the CF_3 group enhanced the electrophilicity of carbonyl carbon followed by the attack of water. Notably, heterocyclic arenes such as thienyl (**3ak**, **3bo**) and furyl (**3bt**) are also well compatible. Next, the alkynyl fragment, namely, the R′ moiety, was investigated. We were delighted to find that a broad array of different functional groups were tolerated, including alkoxy (**3ad**, **3ae**), cyclopropyl (**3af**), diversified arene (**3bb**, **3ac**, **3bm**, **3bn**), alkyl (**3bp**, **3bq**), and heteroarene groups (**3bo**, **3br**), to forge structurally diversified indolizines. When the reaction was performed on a 1.0 mmol scale, **3aa** was obtained in 70% yield.

Strikingly, the unsymmetrical ynones unexpectedly delivered the desired products via the exclusive cleavage of the C≡C bond (**3ag**–**3ak**, **3bp**–**3bq**, >10:1 rr) or the formation of O-transfer products from C(O)–C dissociation (**3ah′**–**3aj′**); however, some examples (**3br**–**3bt**) gave a mixture of two separable regioisomers.

Next, we investigated the substrate scope of the *N*-oxide component. As shown in Scheme 3, a broad range of functional

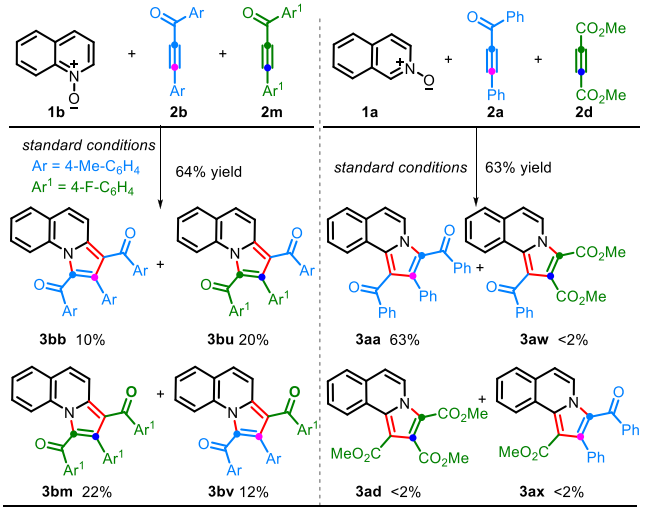
Scheme 3. Substrate Scope of *N*-Oxides



groups with diverse electronic properties, such as methyl (**3ca**), methoxy (**3da**, **3ga**), and chloro (**3ea**), and including highly valuable handles for further transformation, such as bromo (**3fa**), ester (**3ha**), and polyhalogenated moieties (**3ia**), were all found to be successfully accommodated in this newly established C–C, C≡C, and C–H cleavage protocol. Gratifyingly, when the sensitive pyridine ring was modified with electron-donating (**3ja**) and electron-withdrawing groups (**3ka**), this chemistry still worked smoothly to construct the desired products in 71 and 65% yields. The structure of **3ga** was unambiguously confirmed by the X-ray crystallographic analysis. However, in the current stage, the simple pyridine *N*-oxide was not compatible, probably due to the more stable aromatic system.

Encouraged by the reaction performance of both symmetrical and unsymmetrical ynones, we next sought to examine the highly challenging incorporation of two different ynones, which theoretically could lead to four regioisomers (Scheme 4). Indeed, subjecting aryl-ynones **2b** and **2m** to the reaction

Scheme 4. Coupling of Two Different Ynones



with quinoline *N*-oxide **1b** provided a mixture of **3bb**, **3bm**, **3bu**, and **3bv** in a 1:2:2:1 ratio, albeit in a 64% total yield. In contrast, the reaction of phenyl-ynone **2a** and ester-ynone **2d** with isoquinoline *N*-oxide **1a**, furnished only one product, **3aa**, and no other regioisomers (**3ad**, **3aw**, **3ax**) were detected, providing the basis for the development of highly selective C–C, C≡C, and C–H cleavage protocols with different ynone units.

To demonstrate the utility of annulation products obtained in this C–C, C≡C, and C–H cleavage protocol, we focused on the photophysical property. These unique trisubstituted indolizines showed high fluorescence in aqueous solutions, which renders them promising for fluorescence imaging in living cells. (See the SI.)

To shed light on the reaction mechanism, we performed a number of experiments (Scheme 5). First, upon treatment with radical scavengers, such as butylated hydroxytoluene (BHT), TEMPO, or 1,1-diphenylethylene (DPE), no obvious decrease in the reaction efficiency took place, which rules out the radical pathway (Scheme 5A). Second, by omitting Cu^{II} from the system, the C2–C–H alkenylation occurred, delivering the diketone **4** along with a minor amount of monoketone **5** (Scheme 5B). Next, compound **4** was employed to react with ynone **2a** and successfully afforded **3ba** in 82% yield (Scheme 5C). Moreover, compound **5** also proved to be competent to give **3ba** in 87% yield; however, it was practically unreactive in the absence of Cu^{II} (Scheme 5D). These experimental results provide strong evidence supporting **4** and **5** as key intermediates. Finally, isotope-labeling experiments employing ynone ^{18}***O*-2r** as the reaction partner led to the product ^{18}***O*-3br′** as well as ^{18}***O*-3br** (Scheme 5E), which shows that the O atom of *N*-oxide successfully moved into the desired indolizine in a 1,3-shift. (See the SI for details.)

According to the previously discussed results and literature precedents,[17] a tentative mechanism for this unprecedented C–C, C≡C, and C–H cleavage protocol is proposed (Scheme 6). The reaction is initiated by a [3 + 2] cyclization

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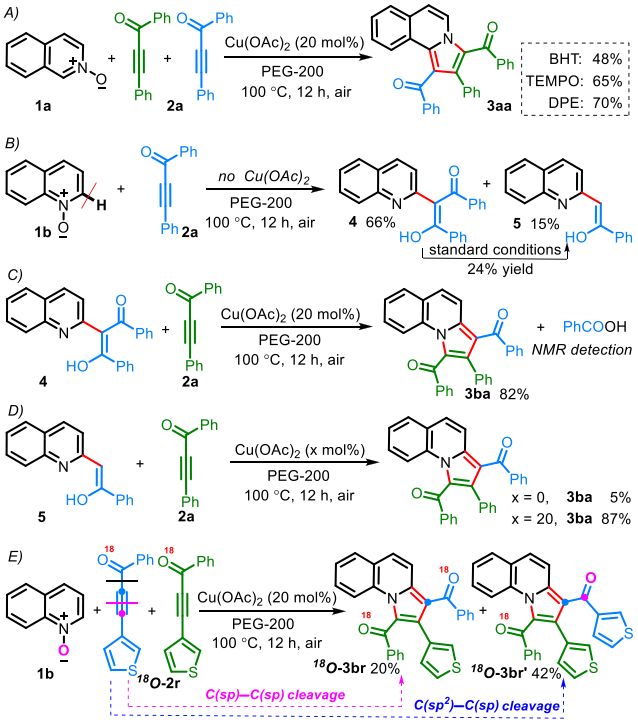
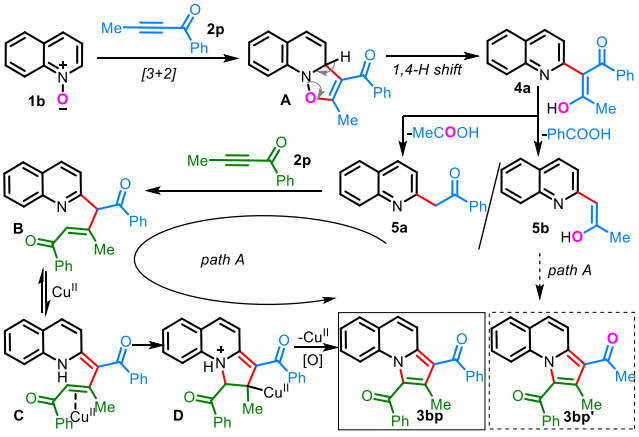
Scheme 5. Mechanistic Studies



Scheme 6. Proposed Mechanism



between *N*-oxide **1b** and ynone **2p** to give the five-numbered product **A**. Subsequently, the formed isoxazoline undergoes N−O ring-opening and a 1,4-proton shift to produce enol-bonded product **4a**, which undergoes C−C bond cleavage via the retro-Claisen reaction to furnish **5a** or **5b**. The Michael addition adduct **B** is formed from the reaction of **5a** with the second unit of ynone **2p**, followed by nucleophilic addition to give **D**, driven by the acidity of Cu^{II}. Finally, a sequential 1,3-proton shift/oxidation occurs, leading to the construction of indolizine **3bp** and the concomitant regeneration of Cu^{II}. The alternative O-transfer product **3bp′** is obtained from **5b** via the analogous pathway.

In conclusion, a new copper-catalyzed process through the selective cleavage of sigma and triple C−C and C−H bonds using two ynone units has been developed. The method represents the first example of a three-component coupling combining C−H activation with C−C and C≡C bond cleavages in a single chemical operation and serves as a direct entry into very useful indolizine scaffolds. Mechanistic studies support a domino process involving a cascade C−H activation, C−C cleavage, nucleophilic cyclization, and oxidative aromatization. Further studies on the utility and applications of this new methodology to unreactive bonds are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00371.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 2044939 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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