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N_2H_4–H_2O Enabled Umpolung Cyclization of *o*-Nitro Chalcones for the Construction of Quinoline *N*-Oxides

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Cite This: *Org. Lett.* 2021, 23, 595–600 Read Online

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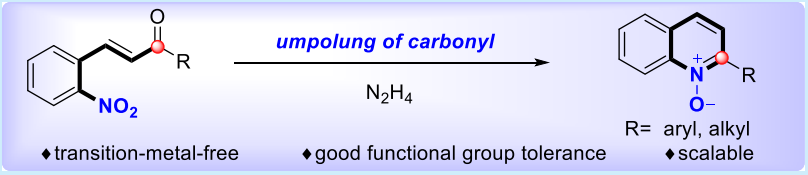

ABSTRACT: Umpolung is a unique strategy which converts the property of an atom into the opposite one. An efficient and general method for the construction of quinoline *N*-oxides via umpolung of carbonyl groups was developed from ortho-nitro chalcones and hydrazine in basic conditions. The strategy is transition-metal free and has good functional group tolerance, environmental friendliness, as well as mild reaction conditions with nitrogen gas as the byproduct.

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N-Oxide compounds are an important class of heterocyclic compounds which are widely found in natural products and bioactive molecules.[1] Among them, quinoline *N*-oxides have unique properties and widespread applications as organocatalysts,[2] the directing groups in C–H activations,[3] as well as the core skeletons of alkaloid Aurachins A;[4] in addition, they are also very important oxidants in gold-catalyzed reactions (Figure 1).[5]

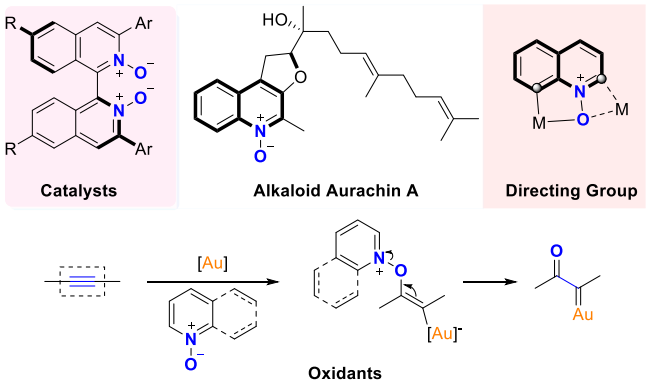
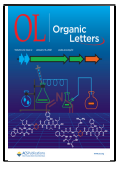


Figure 1. Selected examples of important compounds containing quinoline *N*-oxides.

Despite their importance in chemistry, interestingly, efficient methods for the synthesis of quinoline *N*-oxides are rather rare. There are three main synthetic strategies for the construction of quinoline *N*-oxides (Scheme 1A): (1) oxidation of quinolines;[6] (2) reductive cyclization of 2-nitrochalcones;[7] and (3) carbanion and nitro cyclization under redox-neutral conditions.[8] The first one needs elevated temperature under oxidative conditions; therefore, this strategy is not compatible with sensitive functional groups (Scheme 1Ai).[6] For the second one, the nitro group of 2-nitrochalcone is reduced to hydroxylamine which further cyclizes to obtain quinoline *N*-oxide under a reductive system (Scheme 1Aii).[7] For the third one, the nitro group is attacked by an *in situ* generated carbanion to form quinoline *N*-oxides under the redox-neutral conditions (Scheme 1Aii),[8] which lacks broad substrate scope. Given the importance of quinoline *N*-oxides, it becomes highly desirable to develop a general and efficient strategy to access versatile quinoline *N*-oxides.

The carbonyl group has been extensively studied in contemporary organic synthesis. The positively polarized carbonyl carbon is a versatile reaction site for various nucleophilic reagents, and such nucleophilic attacks can further derive many other chemical reactions. Umpolung of a carbonyl group to a nucleophilic carbon atom has greatly expanded the diversity of carbonyl-compound-involved transformations. For example, the reaction of aldehydes with 1,3-dithiol can lead to an electrophilic thioacetal,[9] which could consequently deprotonate with organolithium reagents to form a carbanion. Benzoin condensation is another typical umpolung reaction in which CN^- attacks the carbonyl group of aldehyde, and subsequent hydrogen transfer results in a nucleophilic intermediate which further attacks another aldehyde to lead to an α-hydroxy ketone.[10] Later, the N-heterocyclic carbene (NHC) was developed to achieve a similar reaction.[11] In 2015,

Received: December 16, 2020
Published: December 30, 2020



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https://dx.doi.org/10.1021/acs.orglett.0c04162
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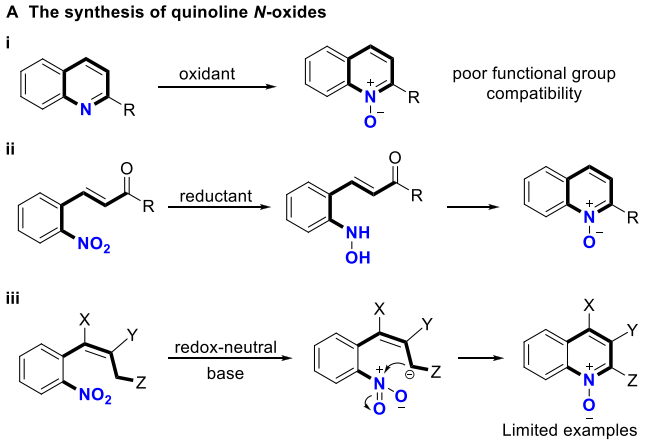
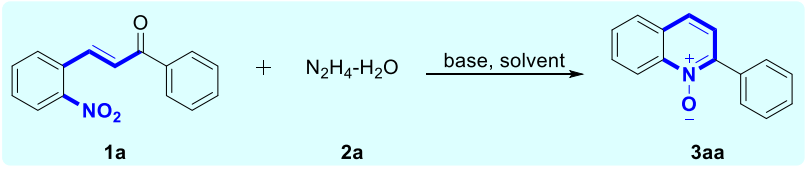
Scheme 1. Quinoline *N*-Oxide Synthesis



the Deng group reported a novel strategy for the synthesis of chiral amines based on the umpolung reaction of aldehydes with benzylamines, followed by nucleophilic addition of the *in situ* generated aza-allyl anion to the α,β-unsaturated systems.[12] The Wolff−Kishner reduction is a classic reaction which involves a deoxygenation process of the carbonyl group to lead to a methylene moiety.[13] The mechanism also reflected the polarity reversal of the carbonyl group. Li and co-workers reported a Rh-catalyzed umpolung reaction with aldehydes as carbanion equivalents to react with ketones to render tertiary alcohols. Subsequently, the same group used these masked alkyl carbanions to achieve cross-coupling reactions with aryl ethers, aryl halides, etc.[14] However, the efficiency of the aforementioned transformations is also often predicated on expensive and toxic metals. Herein, we conceived a transition-metal-free strategy by umpolung reaction of the carbonyl group (Scheme 1B): (1) hydrazone is formed between hydrazine and the carbonyl group in basic conditions, and (2) after the deprotonation and the double-bond migration, a carbanion results, which intramolecularly attacks the nitro group, eventually obtaining quinoline *N*-oxide. This reaction features mildness, environmental benignity, good functional group tolerability, broad substrate scope, as well as scalability and would provide an efficient and general strategy for the construction of 2-substituted quinoline *N*-oxides.

Under our conception, the general potential of the envisioned process was first investigated on model substrate 2-nitrochalcone (**1a**) with hydrazine hydrate (**2a**) in Table 1. Initially, $NaHCO_3$ (1 equiv) was used as the base to examine the reaction in the EtOH. To our delight, the expected product **3aa** was obtained albeit in low yield (entry 1). Base screening suggested that NaOH was the optimal one (entries 2−4). The NaOH was prepared as an aqueous solution (entries 4−14). Interestingly, the reaction went smoothly at 70 °C to produce the desired cyclic product **3aa** in 50% yield (entry 6). Solvent screening suggested that the protic solvents had poor efficiency, while the ether solvents were superior ones. Among them, THF was the optimal one to deliver **3aa** in 70% yield (entry 12). We were rather happy to find that after decreasing the amount of base, reaction time, as well as the amount of hydrazine hydrate the yield of 2-phenylquinoline 1-

Table 1. Development of Optimized Conditions for 2-Phenylquinoline *N*-Oxide Formation[a]



entry	base (equiv)	solvent (mL)	temp (°C)	time (h)	N_2H_4−H_2O (equiv)	yield[c] (%)
1	$NaHCO_3$ (1)	EtOH (2)	90	5	1.2	15
2	K_3PO_4 (1)	EtOH (2)	90	5	1.2	23
3	K_2CO_3 (1)	EtOH (2)	90	5	1.2	13
4[b]	NaOH (1)	EtOH (2)	90	5	1.2	42
5	NaOH (1)	EtOH (2)	80	5	1.2	48
6	NaOH (1)	EtOH (2)	70	5	1.2	50
7	NaOH (1)	EtOH (2)	60	5	1.2	46
8	NaOH (1)	MeOH (1)	70	5	1.2	10
9	NaOH (1)	MeCN (1)	70	5	1.2	n.r.
10	NaOH (1)	1,4-dioxane (1)	70	5	1.2	66
11	NaOH (1)	Toluene (1)	70	5	1.2	25
12	NaOH (1)	THF (1)	70	5	1.2	70
13	NaOH (1)	THF (1)	70	2	1.2	72
14	NaOH (0.5)	THF (1)	70	2	2.5	94 (85)[d]

[a]Reaction conditions: **1a** (0.2 mmoL), **2a** (0.5 mmoL), and NaOH (0.1 mmoL) in THF (1 mL) at 70 °C heating under an oil bath for 2 h, under nitrogen. [b]NaOH is sodium hydroxide in water with 17 mmoL/mL. [c]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [d]Isolated yield. THF = tetrahydrofuran, n.r. = no reaction.

https://dx.doi.org/10.1021/acs.orglett.0c04162
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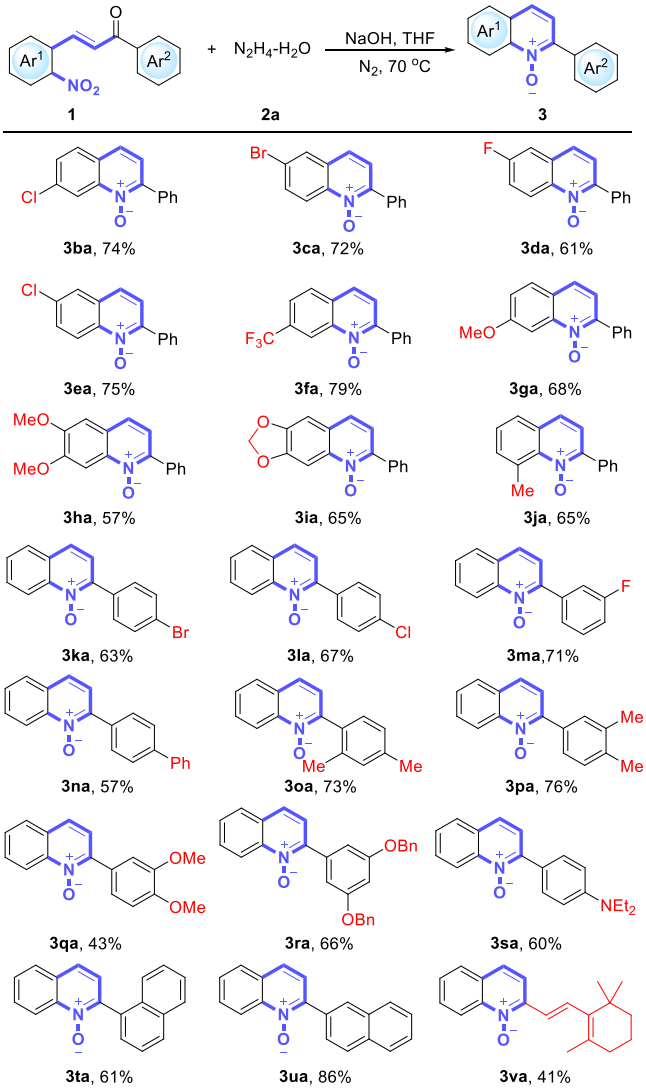
oxide (**3aa**) was subsequently increased to 94% yield (entry 14), which eventually was proven to be the best reaction condition.

With the optimal conditions in hands, the substrate scope of 2-nitrochalcones was investigated for this umpolung reaction (Scheme 2). First, different substituents on Ar^1 rings were explored (**3ba**−**3ia**). Substrates bearing either electron-deficient or electron-rich substituents at the different positions of Ar^1 rings all afforded comparable yields. Under the standard conditions, the halogen (−Cl, −Br, and −F) groups were well compatible, and the position of the substituent did not have much effect on the reaction. When 2-nitrochalcone was substituted with a strong electron-withdrawing group like the trifluoromethyl group on the aromatic ring, the corresponding product **3fa** was obtained in excellent yield. When the substituent on the Ar^1 ring was replaced with an electron-rich group, the yield of the reaction did not decrease significantly (**3ga**−**3ia**). A sterically hindered substrate could also afford a preferable yield (**3ja**). Subsequently, the different substituents on the Ar^2 ring were also investigated. Once again, halogen groups, as well as electron-deficient and electron-rich groups, were all compatible, and the corresponding desired quinoline *N*-oxides (**3ka**−**3sa**) were obtained in decent yields. The 4-phenyl substrate could also render the target product **3na** in modest yield. In addition, when the Ar^2 ring was replaced with a naphthalene ring, both 1-naphthalene and 2-naphthalene were well tolerated, and the corresponding products **3ta** and **3ua** were obtained in good yields. Of note, when Ar^2 is a conjugated olefin which is derived from the violet ketone, the product **3va** was obtained in a medium yield as well.

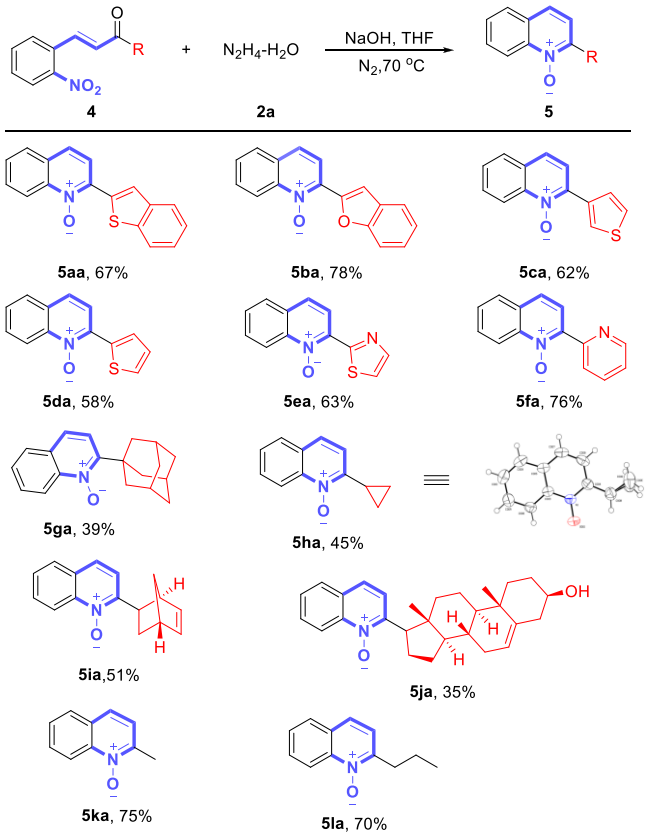
We next surveyed the scope of α,β-unsaturated carbonyl compounds whose R group was heteroaromatic rings or alkyl groups (Scheme 3). To our delight, this transformation has very good substrate scope. In addition to chalcones in which an aromatic substituent was introduced to the 2-position of the final products, heteroaromatic rings were also compatible under the standard conditions, rendering the corresponding 2-heteroaromatic-substituted quinoline *N*-oxides in moderate to excellent yields (**5ba**−**5fa**). Moreover, 2-alkyl-substituted quinoline *N*-oxides could also be smoothly afforded (like adamantane, cyclopropane, and norbornene and so on) (**5ga**−**5la**). The structure of **5ha** was unambiguously demonstrated by X-ray crystallographic analysis. The derivative of the drug molecule pregnenolone was also a competent substrate under

Scheme 2. Substrate Scope of 2-Nitrochalcones[a]



[a]Reaction conditions: **1a** (0.2 mmoL), **2a** (0.5 mmoL), NaOH (0.1 mmoL), in THF (1 mL) at 70 °C heating under an oil bath for 2 h, under nitrogen.

Scheme 3. Substrate Scope of 2-Heteroaromatic or Alkyl-Substituted Quinoline *N*-Oxides[a]



[a]Reaction conditions: **4** (0.2 mmoL), **2a** (0.5 mmoL), NaOH (0.1 mmoL), in THF (1 mL) at 70 °C heating under an oil bath for 2 h, under nitrogen atmosphere.

https://dx.doi.org/10.1021/acs.orglett.0c04162
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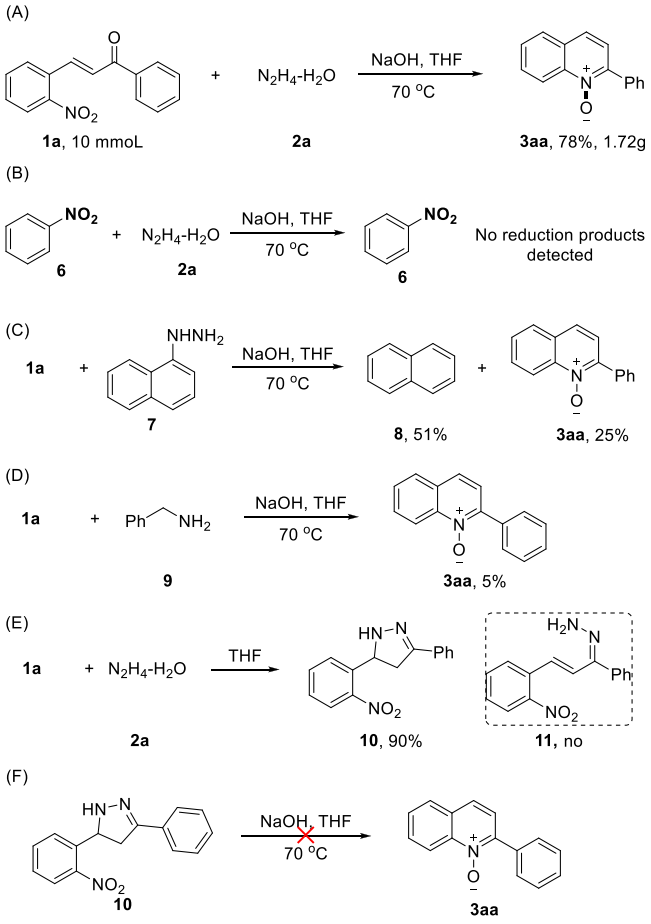
this mild condition (**5ja**), providing the possibility of discovering new bioactive compounds.

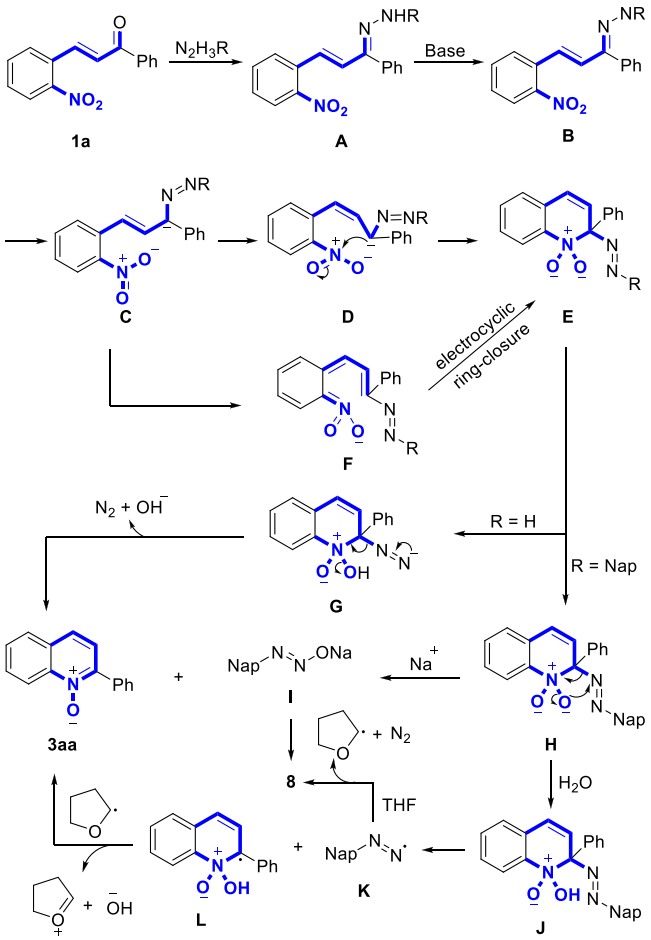
To further demonstrate the practicality of this transformation, a 10 mmol scale reaction smoothly proceeded, and the corresponding quionline *N*-oxide **3aa** was obtained in 78% yield without significant loss of efficiency (Scheme 4A). In order to thoroughly understand the mechanism of this reaction, several control experiments were performed. As we all know, hydrazine is a reductant; however, when nitrobenzene **6** was subjected to our standard reaction conditions, no reductive products were ever detected (Scheme 4B). This result indicated that hydrazine could not be directly reduced into a nitro group in our system. In addition, we found that 1-naphthalene hydrazine (**7**) could also promote this reaction to lead to the formation of naphthalene (**8**) in 51% yield with 25% of desired product **3aa** (Scheme 4C). Inspired by Deng's work, we tried other reagents that could promote the polarity reversal of carbonyl groups.[12] When benzylamine (**9**) was employed in the standard conditions, the quinoline *N*-oxide **3aa** was obtained in a trace amount (Scheme 4D). The result further verified that the reaction between $N_2H_4{-}H_2O$ and the carbonyl group to hydrazone should be the key step for this umpolung reaction. We tried to isolate the intermediate hydrazone; however, the reaction between the hydrazone and the olefin led to five-membered ring **10** in 90% yield, indicating that the hydrazone is more active to react with olefin than the nitro group (Scheme 4E). We further attempted to carry out reaction of **10** under basic conditions and found that no reaction occurred, which further suggested that compound **10** was not the intermediate for this transformation (Scheme 4F).

On the basis of our observations as well as the reported literature,[12−14,15] a tentative mechanism is proposed (Scheme 5): first, *o*-nitrochalcone **1a** reacts with hydrazine **2a** to form hydrazone **A** *in situ*, and the deprotonation of **A** in basic conditions leads to **B** which quickly tautomerizes into canbanion **C**, the umpolung reaction of the carbonyl group. Carbanion **C** further intramolecularly attacks the nitro group to deliver intermediate **E**. There is also a possible electrocyclic ring-closure path via intermediate **F**. When hydrazine is used, intermediate **E** undergoes proton transfer to obtain intermediate **G** which further renders quinoline *N*-oxide **3aa** after releasing nitrogen gas and hydroxide. When 1-naphthalene hydrazine is used instead, the quinoline *N*-oxide **3aa** is eventually obtained in basic conditions along with the generation of the azo compound **I** (this process could also be called [1,2]-sigmatropic rearrangement); of note, **I** is unstable, which further decomposes into naphthalene alongside one molecule nitrogen.[16] The above control experiment in Scheme 4C verified this process. In addition, the intermediate **G** may also undergo homolysis through the intermediate **J** to obtain radicals **K** and **L**. The radical **K** undergoes the release of nitrogen, and hydrogen transfers from THF to form naphthalene (**8**). Radical **L** is reduced and dehydroxylated to obtain product **3aa**. It is worth mentioning that HO^- would be

Scheme 4. Large-Scale Synthesis and Mechanistic Experiments



Scheme 5. Proposed Mechanism



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Org. Lett. 2021, 23, 595−600

generated during the reaction, so the reaction does not require an equivalent amount of base to obtain a high-yield product (Table 1, entry 14).

In conclusion, we have developed a hydrazine-promoted umpolung reaction of carbonyl groups under transition-metal-free conditions, which undergoes intramolecular nucleophilic cyclization to lead to 2-substituted quinoline *N*-oxides. This reaction features a broad substrate scope, good functional group tolerance, as well as novel mechanism, which might provide more tactics for umpolung reaction of carbonyl groups and nourish carbonyl chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04162.

Experimental procedures and spectral data for all new compounds (PDF)

Accession Codes

CCDC 1992420 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.

■ ACKNOWLEDGMENTS

Financial support from the National Natural Science Foundation (21772046, 2193103) is gratefully acknowledged. We also thank the Instrumental Analysis Center of Huaqiao University for analysis support. G. Zhang thanks the Subsidized Project for Cultivating Postgraduates Innovative Ability in Scientific Research of Huaqiao University.

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https://dx.doi.org/10.1021/acs.orglett.0c04162
Org. Lett. 2021, 23, 595−600