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Single-Step Approach toward Nitrones via Pyridinium Ylides: The DMAP-Catalyzed Reaction of Benzyl Halides with Nitrosoarenes

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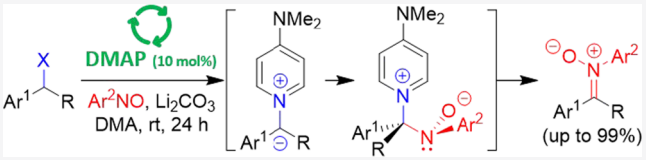
ABSTRACT: A single-step approach is reported for the preparation of nitrones from benzyl halides and nitrosoarenes via pyridinium ylides, utilizing 4-dimethylaminopyridine (DMAP) catalyst and mild reaction conditions (Li_2CO_3, dimethylacetamide, and room temperature). The reaction provides both keto- and aldonitrones in high yields with a wide scope for benzyl halides and nitrosoarenes. In the same reaction system, 2-methyl-2-nitrosopropane, which does not have an aryl group, also affords the corresponding *N*-*tert*-butyl nitrones from primary benzyl bromides that have an electron-withdrawing group. As an application of the reaction, methyl 2-bromo-2-phenylacetate was used to prepare the corresponding isoxazolidine by a sequential one-pot synthesis.



INTRODUCTION

Nitrones have been actively studied and are potent neuroprotective agents due to the radical scavenging effect of their 1,3-dipole structure.[1] The well-known neuroprotective nitrones α-phenyl-*N*-*tert*-butylnitrone (PBN)[1a] and NXY-059[1b] are shown in Figure 1. PBN has been used as a positive control to

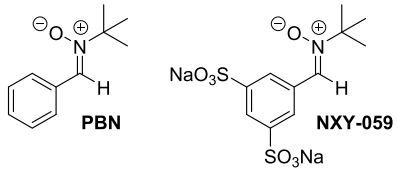


Figure 1. Neuroprotective nitrones.

evaluate the effects of reactive oxygen species (ROS) scavenging in multiple medicinal chemistry papers.[1c−f] NXY-059, which is derived from the structure of PBN, is the first nitrone to reach clinical trials for the treatment of acute ischemic stroke.

Nitrones are essential intermediates in the preparation of biologically active heterocycles such as isoxazolidines, isoxazolines, imidazolidin-4-ones, and β-lactams via various chemical transformations.[2] Nitrones are particularly useful compared to other 1,3-diopoles or corresponding imines primarily because they are relatively stable and easy to handle despite their prompt reactivity. Owing to the biological and chemical significance of nitrones, there are many reports of oxidative or reductive approaches used to synthesize nitrones by starting from hydroxylamines,[3] secondary amines,[4] imines,[5] and nitro compounds.[6] Moreover, alternative methods to prepare nitrones have been developed,[2,7] such as condensation of *N*-arylhydroxylamines with ketones,[7a] cross-coupling of oximes with arylboronic acids,[7b,c] and metal-free *N*-arylation of oximes with diaryliodonium salts.[7d,e]

Recently, we reported metal-free aerobic oxidation of aryl α-halo esters to aryl α-keto esters using 4-dimethylaminopyridine (DMAP) catalyst with Li_2CO_3 in dimethylacetamide (DMA).[8] By applying this catalytic system, we expected to effectively synthesize nitrones from nitroso compounds with benzyl halides, abundant chemical species that are readily available. Diverse strategies to provide nitrones starting from nitroso compounds have been reported. They include (i) a $P(NMe_2)_3$-mediated reaction with 1,2-dicarbonyls,[9a] (ii) a gold-catalyzed reaction with electron-deficient alkynes,[9b] (iii) a solvent-free silica gel-promoted reaction with diazooxindoles,[9c] (iv) a proline-based organocatalytic reaction with α,β-unsaturated aldehydes at the γ-position,[9d] (v) a proline-mediated reaction with benzaldehydes,[9e] (vi) a reaction with sulfones,[9f] (vii) a coupling reaction with *N*-nosylhydrazones,[9g] and (viii) a 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP)-catalyzed reaction with aryl acetic acid esters.[9h] Nevertheless, there was no reaction method for preparing nitrones directly from nitrosoarenes using benzyl halides. Of the eight examples given above, only reactions (vi) and (vii) reported protocols applicable to the synthesis of both keto- and aldonitrones.

A classic way to synthesize nitrones from nitroso compounds that was not mentioned above is Kröhnke oxidation, which involves the following three steps: conversion of primary or

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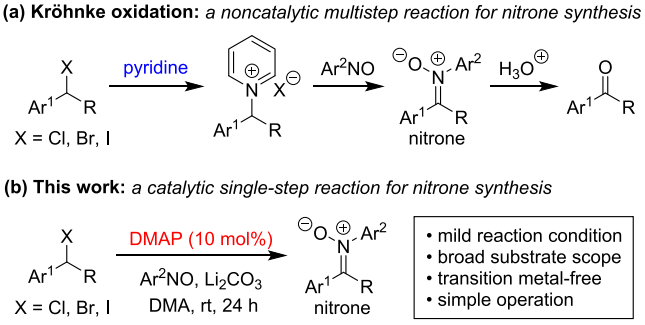
secondary halides into pyridinium salts, synthesis of nitrones from pyridinium salts with nitrosoarenes, and hydrolysis of nitrones to aldehydes or ketones (Scheme 1a).[10] To prepare

Scheme 1. Comparison between Kröhnke Oxidation and the Reaction Reported in This Work



nitrones, Kröhnke oxidation can of course be applied, but this multistep sequential reaction theoretically requires at least 1.0 equiv of pyridine. Kröhnke did not mention a detailed general protocol for preparing pyridinium salts from the corresponding halides, as his method was focused on starting with pyridinium salts. However, in recently reported examples of Kröhnke oxidation, benzyl bromides were reacted with 4.0 equiv of 4-methylpyridine in dimethyl sulfoxide (DMSO) at room temperature[11a] and benzyl iodides were reacted with excess pyridine as a solvent at 100 °C.[11b] Therefore, we thought that our previously reported catalytic pyridinium ylide system could simplify the process of Kröhnke oxidation and reduce the waste of resources. Herein, we report the DMAP-catalyzed direct synthesis of keto- and aldonitrones from corresponding benzyl halides and nitrosoarenes (Scheme 1b). The reactions were carried out under mild reaction conditions (Li_2CO_3, DMA, and room temperature).

RESULTS AND DISCUSSION

To optimize the reaction conditions, we performed the synthesis of nitrone **3aA** from secondary benzyl bromide **1ab** and nitrosobenzene **2A** under our previously optimized conditions[8] (Table 1). The DMAP catalyst with an excess of **2A** (5.0 equiv) successfully gave **3aA** (entry 1: yield, 93%; E/Z ratio, 93/7), but pyridine did not function well as a catalyst under the same conditions (entry 2: yield, 21%; E/Z ratio, 81/19). According to the literature[10,12] and our previously reported work,[8] pyridine catalysts form pyridinium salts with **1ab** by a substitution reaction and the salts generate pyridinium ylides under mildly basic conditions. The results of entries 1 and 2 indicate that the higher nucleophilicity of DMAP in comparison to pyridine is a key factor in the successful synthesis of nitrone **3aA**. The highest yield and E/Z selectivity (entry 3: yield, 98%; E/Z ratio, 94/6) were obtained when less **2A** (2.0 equiv) was used, rather than in entry 1 (5.0 equiv). However, further reducing the concentration of **2A** (1.2 equiv) or Li_2CO_3 (1.0 equiv) was not effective (entry 4: yield, 89%; E/Z ratio, 89/11; entry 5: yield, 88%; E/Z ratio, 90/10). In entries 1−5, only trace amounts of ethyl 2-oxo-2-phenylacetate, the aerobic oxidation product of **1ab**,[8] were observed by ^{1}H nuclear magnetic resonance (NMR). In addition, when the reactions were carried out under Ar, the yields of **3aA** were not significantly improved. This is probably because substrate **1ab** reacts predominantly with the nitrosobenzene (**2A**) dissolved in the same DMA solvent rather than with the O_2 in air. It was confirmed that nitrone **3aA** was not observed in the absence of a pyridine catalyst or base (entries 6 and 7).

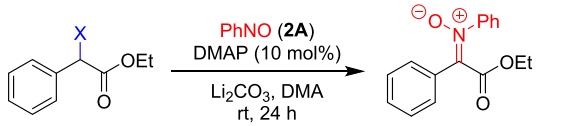
Table 1. Optimization of Reaction Conditions[a]

entry	**2A** (equiv)	pyridine cat.	Li_2CO_3 (equiv)	yield (%)[b]
1	5.0	DMAP	2.0	93 (93/7)
2	5.0	pyridine	2.0	21 (81/19)
3	2.0	DMAP	2.0	98 (94/6)
4	1.2	DMAP	2.0	89 (89/11)
5	2.0	DMAP	1.0	88 (90/10)
6	2.0		2.0	0
7	2.0	DMAP		0

[a]Reaction conditions: To a 0.2 M solution of **1ab** (0.2 mmol, 1.0 equiv) in DMA (1.0 mL) were added **2A**, the catalyst (0.02 mmol, 10 mol %), and Li_2CO_3 at room temperature, and the mixture was stirred for 24 h. [b]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. In parentheses are E/Z ratios.

Using the optimal reaction conditions, the reaction scope of halides (X) in the substrates was evaluated (Table 2). In the

Table 2. Scope of Halide Compatibility[a,b]



1aa X = Cl
1ab X = Br
1ac X = I

3aA X = Cl 90%[c] *E*/*Z* 93/7
X = Br 95% *E*/*Z* 94/6
X = I 68% *E*/*Z* 93/7

[a]Reaction conditions: see entry 3 in Table 1. [b]Isolated yield. [c]K_2CO_3 (2.0 equiv) was used.

synthesis of nitrone **3aA** from phenyl α-halo esters **1aa−c**, chloride (**1aa**: yield, 90%; E/Z ratio, 93/7) and bromide (**1ab**: yield, 95%; E/Z ratio, 94/6) were effective leaving groups, but iodide was not (**1ac**: yield, 68%; E/Z ratio, 93/7). The reaction scope of aryls (Ar) and other functional groups (R) was also examined using various benzyl bromides **1b−n** (Table 3). As a result of changing the Ar groups, sterically hindered 1-naphthyl **1b** showed a very low yield (**3bA**, 19%), while less hindered 2-naphthyl **1c** gave a relatively good yield (**3cA**, 81%). 4-OMe, an electron-donating group (EDG), resulted in a reduced yield (**3dA**, 62%), but the electron-withdrawing groups (EWGs) 4-Br and 4-CO_2Et smoothly provided the corresponding nitrones (**3eA**, 87%; **3fA**, 99%). Nitrones **3a−fA**, prepared from ethyl α-bromoarylacetates, exhibited E/Z ratios ranging from 89/11 to 95/5.

As a result of changing the R groups (Table 3), methyl ester **1g** and cyclic amide **1h** successfully afforded the corresponding ketonitrones (**3gA**, yield: 94%, E/Z ratio: 89/11; **3hA**, yield: 98%, E/Z ratio: 95/5), but ketone **1i** did not (**3iA**, yield: 44%, E/Z ratio: 97/3), despite modification of the optimized reaction conditions. Reports of the unsatisfactory result with **3iA** can also be found in prior literature.[9a] Isolated yields of **3gA** from nitrosobenzene (**2A**) with methyl 2-oxo-2-phenyl-

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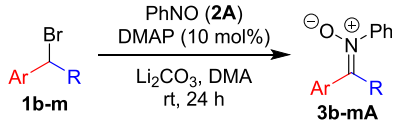
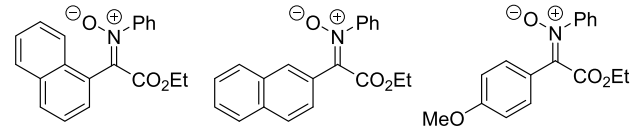
Table 3. Scope of Aryls and Other Functional Groups[a,b]

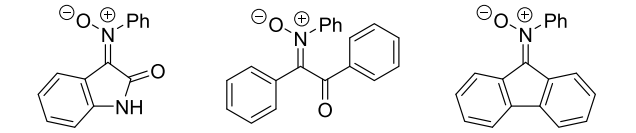


ketonitrone



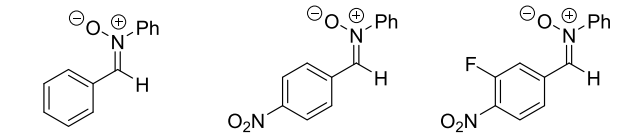
3bA 19% *E*/*Z* 95/5 **3cA** 81% *E*/*Z* 89/11 **3dA** 62% *E*/*Z* 94/6

3eA 87% *E*/*Z* 92/8 **3fA** 99% *E*/*Z* 90/10 **3gA** 94% *E*/*Z* 89/11



3hA 98% *E*/*Z* 95/5 **3iA** 44%[c,d] *E*/*Z* 97/3 **3jA** 73%

aldonitrone



3kA 25%[e] *Z*/*E* >99/1 **3lA** 57%[e] *Z*/*E* >99/1 **3mA** 85%[e] *Z*/*E* >99/1

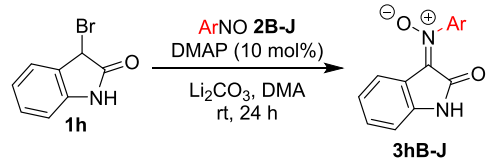
[a]Reaction conditions: see entry 3 in Table 1. [b]Isolated yield. [c]DMAP (20 mol %) was used. [d]Na_2CO_3 (2.0 equiv) was used. [e]Cs_2CO_3 (1.0 equiv) was used.

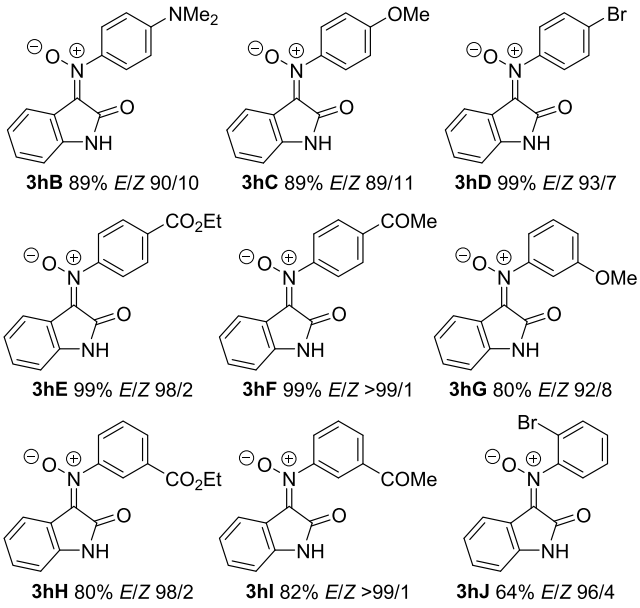
acetate and methyl 2-phenylacetate were reported, respectively, as 85% (E isomer)[9a] and 87% (E/Z ratio: 95/5).[9h] Our protocol gave **3gA** in a higher yield (94%) but considering the E/Z ratio (89/11), the mole fractions of the *E* isomer in the three results were similar. In addition, our method showed a similar result (yield: 98%, E/Z ratio: 95/5) compared to the known method (yield: 95%, E isomer) of preparing **3hA** by copper-catalyzed coupling between isatin oxime and $PhB(OH)_2$.[7c] Interestingly, 9-bromofluorene (**1j**) without a carbonyl resulted in a higher yield than we expected (**3jA**, 73%). In other studies, isolated yields of **3jA** from the corresponding sulfone and *N*-nosylhydrazone were 92%[9f] and 84%,[9g] respectively. Compared to these results, **3jA** was afforded in a lower yield (73%) here. However, our method has the advantage that **3jA** was prepared directly from commercially available 9-bromo-9*H*-fluorene (**3j**) without further chemical transformations. The very high yield of oxindole **3hA** (98%) and the unexpectedly high yield of fluorene **3jA** (73%) were attributed to the use of cyclic substrates to minimize steric hindrance.

As expected, benzyl bromide (**1k**), a primary halide without an EWG, showed a very low yield (**3kA**, 25%) due to the relatively high pK_a value of the pyridinium salt produced through a substitution reaction between **1k** and DMAP. Thus, 4-NO_2-benzyl bromides **1l** and **1m** were examined as substrates in the presence of Cs_2CO_3 base (1.0 equiv) and the corresponding aldonitrones were obtained in increased yields (**3lA**, 57%; **3mA**, 85%). Primary benzyl bromides **1k**−**m** provided the corresponding aldonitrones **3l**−**nA** with a very high Z/E ratio (>99/1). Considering the reported procedures to prepare aldonitrones using sulfones[9f] and *N*-nosylhydrazones,[9g] it is a limitation that only primary benzyl bromides containing EWGs showed moderate yields.

3-Bromoindolin-2-one (**1h**) was chosen as a substrate for further investigation of the substituent scope of nitrosoarenes **2** because **1h** can generate a very important nitrone containing an oxindole structure (Table 4).[7a,c,e] Nitrosobenzenes with all

Table 4. Scope of Nitrosoarene Compatibility[a,b]





3hB 89% *E*/*Z* 90/10 **3hC** 89% *E*/*Z* 89/11 **3hD** 99% *E*/*Z* 93/7

3hE 99% *E*/*Z* 98/2 **3hF** 99% *E*/*Z* >99/1 **3hG** 80% *E*/*Z* 92/8

3hH 80% *E*/*Z* 98/2 **3hI** 82% *E*/*Z* >99/1 **3hJ** 64% *E*/*Z* 96/4

[a]Reaction conditions: see entry 3 in Table 1. [b]Isolated yield.

of the 4-substituents tested smoothly produced the corresponding nitrones **3hB**−**F**, but substrates with EDGs tended to result in slightly lower yields (**3hB**, 89%; **3hC**, 89%) than substrates with EWGs (**3hD**, 99%; **3hE**, 99%; **3hF**, 99%). Nitrosobenzenes **2G**−**I**, which have 3-substituents, gave the corresponding nitrones **3hG**−**I** in good yields (**3hG**, 80%; **3hH**, 80%; **3hI**, 82%). However, the presence of a 2-Br substituent, which can cause steric hindrance, led to a significantly reduced yield (**3hJ**, 64%). Nitrones **3hB**−**J**, prepared from **1h**, showed E/Z ratios ranging from 89/11 to >99/1.

In addition, primary benzyl bromides **1l**−**o** were reacted with 2-methyl-2-nitrosopropane (**2K**) to synthesize *N*-*tert*-butyl aldonitrones that are frequently observed in neuroprotective agents (Table 5). In the same reaction system using DMAP as a catalyst, the corresponding *N*-*tert*-butyl aldonitrones **3l**−**oK** were successfully produced in moderate yields (52−71%) and very high Z/E ratios (>99/1). Unfortunately, **2K** did not provide ketonitrones due to high steric hindrance.

As we have reported, pyridinium salt **4a** was isolated (82%) from the reaction of **1ab** (1.1 equiv) with DMAP (1.0 equiv)

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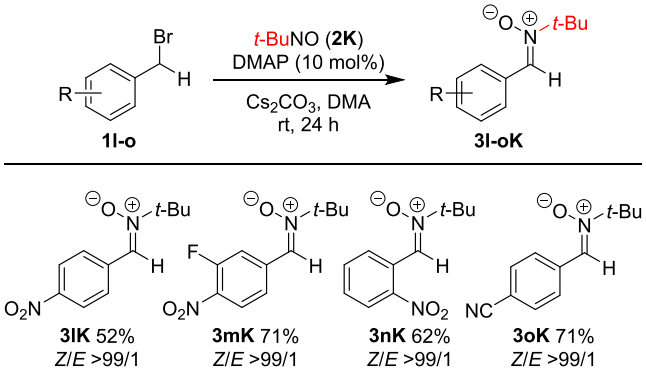
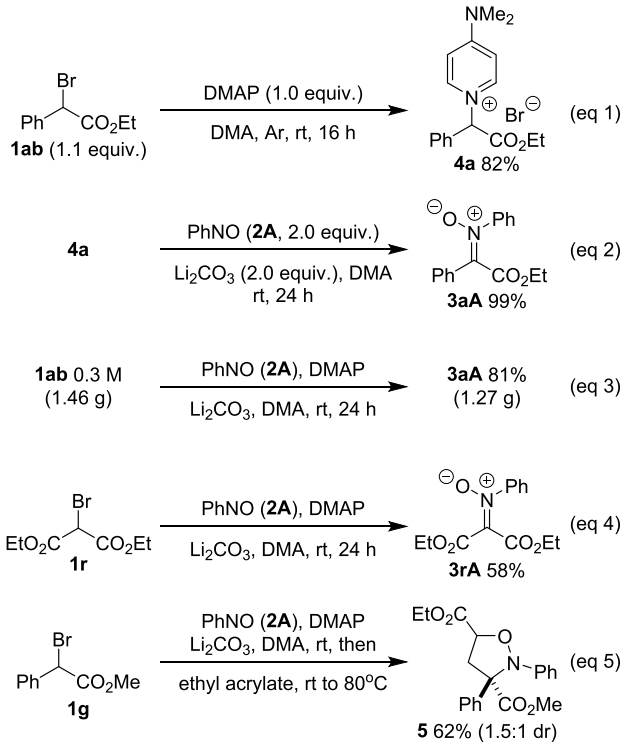
Table 5. Scope of 2-Methyl-2-nitrosopropane (2K) Compatibility[a,ba]



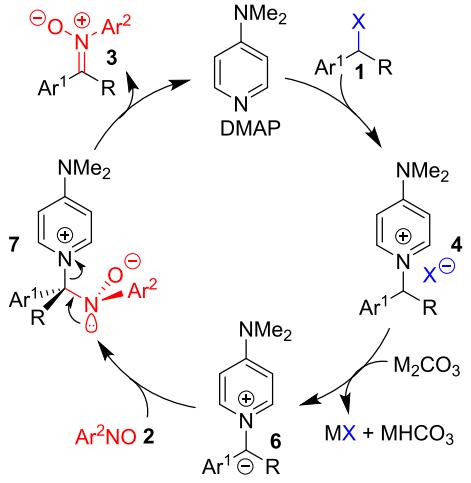
[a]Reaction conditions: To a 0.2 M solution of **1l−o** (0.2 mmol, 1.0 equiv) in DMA (1.0 mL) were added **2K** (0.4 mmol, 2.0 equiv), the catalyst (0.02 mmol, 10 mol %), and Cs_2CO_3 (1.0 mmol, 1.0 equiv) at room temperature, and the mixture was stirred for 24 h. [b]Isolated yield.

in DMA (eq 1).[8] It was reacted under Ar to prevent the formation of ethyl 2-oxo-2-phenylacetate, an aerobic oxidation product of **1ab**. In the presence of **2A** (2.0 equiv) and Li_2CO_3 (2.0 equiv), nitrone **3aA** was synthesized from **4a** and isolated in 99% yield (eq 2). The same reaction strategy was employed for a gram-scale synthesis of nitrone **3aA** (eq 3). Although the yield declined to 81%, the potential for industrial mass production remains. Despite the absence of aryl groups, it was confirmed that diethyl bromomalonate (**1r**) also afforded the corresponding ketonitrone **3rA** in 58% yield (eq 4). As an application of the developed method, a one-pot reaction of a heterocycle was performed under mild reaction conditions. Sequential addition of nitrosobenzene (**2A**) and ethyl acrylate to benzyl bromide **1g** afforded 3,5-substituted isoxazolidine **5** in 62% yield as a 1.5:1 mixture of diastereomers (eq 5).



Based on the above results (eqs 1[8] and 2) and Kröhnke's report,[10] a plausible mechanism was proposed (Scheme 2).

Scheme 2. Proposed Mechanism



The DMAP catalyst substitutes a halide of substrate **1** to form pyridinium salt **4**. A carbonate abstracts the benzylic hydrogen of **4** to generate a pyridinium ylide **6**. Then, ylide **6** reacts with nitrosoarene **2** to provide nitrone **3** through intermediate **7**. The regenerated DMAP then undergoes the catalytic cycle again. Upon removal of DMAP from **7**, the major isomer seems to prefer a *trans*-relationship between Ar^1 and Ar^2 to minimize the electronic repulsion between O atoms (R═ carbonyls) or the steric hindrance between aryls (R═H). On the basis of the abovementioned experimental results, successful catalysis may require the following essential features: (i) the electrophilicity of halide **1** must be suitable for the reaction with DMAP; (ii) the pK_a value of pyridinium salt **4** must enable generation of ylide **6**; and (iii) the Ar^1, Ar^2, and R must be small enough to avoid steric hindrance.

CONCLUSIONS

In summary, we have developed a catalytic single-step approach toward nitrone construction that shortens Kröhnke's multistep procedure by exploiting DMAP. In the reaction of diverse benzyl halides, the strong nucleophilicity of DMAP enables the production of the corresponding ylides that react with electrophilic nitroso species. When nitrones are produced, DMAP is regenerated and then undergoes the catalytic cycle again. A neuroprotective skeleton, *N-tert*-butylnitrone, was also accessible in the developed reaction system, and a privileged scaffold, isoxazolidine, was prepared through the corresponding nitrone by a sequential one-pot reaction. Our new organocatalytic system with mild reaction conditions provides a simple and effective method to synthesize nitrones directly from benzyl halides and nitrosoarenes.

EXPERIMENTAL SECTION

General. All reagents and solvents from commercial sources were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using precoated silica gel 60 F254 plates (Merck) and a UV light detector (254 nm). Flash column chromatography was performed over silica gel (70−230 mesh) purchased from Merck. Melting points (mp) were measured in open capillary tubes by means of a Büchi B-540 instrument without correction. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a

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Varian VNMRS500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) and referenced to residual solvent or tetramethylsilane (TMS). Gas chromatography−high-resolution mass spectrometry (GC−HRMS) was performed on JEOL JMS-AX 505wA and JEOL JMS-HX/HX 110A magnetic sector high-resolution mass spectrometers.

Preparation of Benzyl Halides 1. All substrates **1** except ethyl 2-bromo-2-(naphthalen-1-yl)acetate (**1b**), ethyl 2-bromo-2-(naphthalen-2-yl)acetate (**1c**), ethyl 2-bromo-2-(4-methoxyphenyl)acetate (**1d**), ethyl 4-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (**1f**), and 3-bromoindolin-2-one (**1h**) were commercially available. Substrates **1b−d**, **1f**, and **1h** were prepared by literature procedures.[8,13]

Preparation of Nitroso Compounds 2. Nitrosobenzene (**2A**), *N*,*N*-dimethyl-4-nitrosoaniline (**2B**), and 2-methyl-2-nitrosopropane (**2K**) were commercially available. 1-Methoxy-4-nitrosobenzene (**2C**), 1-bromo-4-nitrosobenzene (**2D**), ethyl 4-nitrosobenzoate (**2E**), 1-(4-nitrosophenyl)ethan-1-one (**2F**), 1-methoxy-3-nitrosobenzene (**2G**), ethyl 3-nitrosobenzoate (**2H**), 1-(3-nitrosophenyl)ethan-1-one (**2I**), and 1-bromo-2-nitrosobenzene (**2J**) were prepared by literature procedures.[9a,14]

Representative Procedure for Nitrones 3. To a 0.2 M solution of benzyl bromide (**1ab**, 0.2 mmol, 48.5 mg, 1.0 equiv) in *N*,*N*-dimethylacetamide (DMA, 1.0 mL) were added nitrosobenzene (**2A**, 0.4 mmol, 42.8 mg, 2.0 equiv), 4-dimethylaminopyridine (DMAP, 0.02 mmol, 2.4 mg, 10 mol %), and Li_2CO_3 (0.4 mmol, 29.6 mg, 2.0 equiv) at room temperature. After 24 h, the reaction mixture was diluted with EtOAc (30 mL) and washed with brine (30 mL × 3). The extract was dried over anhydrous $MgSO_4$. After filtration of the solid, the solvent in the filtrate was removed in vacuo, and the residue was purified by silica gel column chromatography (10−30% EtOAc/*n*-hexane) to give the corresponding nitrones **3aA**.

Gram-Scale Procedure for Nitrone 3aA. To a 0.3 M solution of ethyl α-bromophenylacetate (**1ab**, 97%, Sigma-Aldrich; MW, 243.10 g/mol, 5.84 mmol, 1.46 g, 1.0 equiv) in anhydrous *N*,*N*-dimethylacetamide (DMA, 99.8%, Sigma-Aldrich, 20 mL) were added nitrosobenzene (**2A**, >97%, Sigma-Aldrich; MW, 107.11 g/mol, 11.7 mmol, 1.25 g, 2.0 equiv), 4-dimethylaminopyridine (DMAP, ≥99.0%, Sigma-Aldrich; MW, 122.17 g/mol, 0.58 mmol, 71.0 mg, 10 mol %), and Li_2CO_3 (≥99.0%, Sigma-Aldrich; MW, 73.89 g/mol, 11.7 mmol, 865 mg, 2.0 equiv) at room temperature. After 24 h, the reaction mixture was diluted with EtOAc (0.9 L) and washed with brine until DMA was removed. Particularly, during the first washing process with brine, the product can migrate to the aqueous layer with DMA. If the product is present in the aqueous layer after checking by TLC, it must be extracted again with EtOAc. The extract was dried over anhydrous $MgSO_4$. After filtration of the solid, the solvent in the filtrate was removed in vacuo, and the residue was purified by silica gel column chromatography (10−30% EtOAc/*n*-hexane) to give nitrone **3aA** (yield: 1.27 g, 81%; yellow solid).

Assignment of Diastereomeric Ratios and Configurations. Diastereomeric ratios were determined by integration of appropriate signals in ^{1}H NMR spectra of isolated product mixtures. When the minor isomer could not be distinguished even after enlarging the ^{1}H NMR spectrum, the isomeric ratio was recorded as >99/1. In all cases, no attempt was made to separate isomers. Configurations of nitrones **3** were determined as E or Z according to the literature studies.[7c,e,9a,h]

*(E)-2-Ethoxy-2-oxo-N,1-diphenylethan-1-imine oxide (**3aA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 51.0 mg, 95%; yellow solid; mp 67−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22−8.16 (m, 2H), 7.58−7.40 (m, 8H), 4.04 (q, J = 7.1 Hz, 2H), 0.94 (t, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ163.9, 148.4, 140.8, 130.9, 130.1, 129.2, 128.6, 128.4, 124.4, 123.4, 62.4, 13.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NO_3$ 270.1130; found: 270.1136.

*(E)-2-Ethoxy-1-(naphthalen-1-yl)-2-oxo-N-phenylethan-1-imine oxide (**3bA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 12.1 mg, 19%; yellow solid; mp 114−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1H), 7.94−7.91 (m, 1H), 7.76−7.73 (m, 1H), 7.69 (dd, J = 7.1, 1.2 Hz, 1H), 7.65−7.61 (m, 2H), 7.59−7.49 (m, 6H), 4.04 (q, J = 7.1 Hz, 2H), 0.94 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.4, 148.7, 133.7, 130.8, 130.4, 129.2, 129.0, 128.0, 127.1, 126.4, 125.3, 124.7, 123.3, 62.2, 13.6 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}NO_3$ 320.1287; found: 320.1285.

*(E)-2-Ethoxy-1-(naphthalen-2-yl)-2-oxo-N-phenylethan-1-imine oxide (**3cA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 51.7 mg, 81%; yellow solid; mp 106−108 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03−9.02 (m, 1H), 8.00 (dd, J = 8.8, 1.9 Hz, 1H), 7.94−7.87 (m, 2H), 7.85−7.82 (m, 1H), 7.58−7.49 (m, 4H), 7.47−7.44 (m, 3H), 4.08 (q, J = 7.1 Hz, 2H), 0.95 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.0, 148.5 134.2 132.8, 130.2 129.5, 129.3, 129.2, 128.0, 127.9 126.6 124.9 123.5 62.5, 13.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}NO_3$ 320.1287; found: 320.1283.

*(E)-2-Ethoxy-1-(4-methoxyphenyl)-2-oxo-N-phenylethan-1-imine oxide (**3dA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 37.1 mg, 62%; yellow solid; mp 76−79 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29−8.22 (m, 2H), 7.55−7.47 (m, 2H), 7.46−7.40 (m, 3H), 7.00−6.95 (m, 2H), 4.02 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 0.92 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.1, 161.4, 148.3, 140.6, 130.6, 129.9, 129.1, 123.5, 121.7, 113.8, 62.4, 55.4, 13.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}NO_4$ 300.1236; found: 300.1233.

*(E)-1-(4-Bromophenyl)-2-ethoxy-2-oxo-N-phenylethan-1-imine oxide (**3eA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 60.6 mg, 87%; yellow solid; mp 96−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17−8.05 (m, 2H), 7.61−7.58 (m, 2H), 7.52−7.42 (m, 5H), 4.03 (q, J = 7.2 Hz, 2H), 0.92 (t, J = 7.2 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.6, 148.4, 139.9, 131.7, 130.3, 130.1, 129.2, 128.0, 125.0, 123.3, 62.6, 13.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{16}H_{15}BrNO_3$ 348.0235; found: 348.0231.

*(E)-2-Ethoxy-1-(4-(ethoxycarbonyl)phenyl)-2-oxo-N-phenylethan-1-imine oxide (**3fA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 67.6 mg, 99%; yellow solid; mp 64−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27−8.21 (m, 2H), 8.15−8.11 (m, 2H), 7.56−7.50 (m, 2H), 7.48−7.43 (m, 3H), 4.40 (q, J = 7.1 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.7, 163.5, 148.4, 140.0, 133.1, 131.9, 130.4, 129.5, 129.2, 128.5, 123.3, 62.6, 61.3, 14.3, 13.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{19}H_{20}NO_5$ 342.1341; found: 342.1344.

*(E)-2-Methoxy-2-oxo-N,1-diphenylethan-1-imine oxide (**3gA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 48.0 mg, 94%; yellow solid; mp 86−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16−8.11 (m, 2H), 7.53−7.43 (m, 8H), 3.56 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.5, 148.4, 140.5, 130.9, 130.2, 129.2, 128.6, 128.5, 124.4, 123.2, 53.0 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO_3$ 256.0974; found: 256.0978.

*(E)-2-Oxo-N-phenylindolin-3-imine oxide (**3hA**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 46.9 mg, 98%; orange solid; mp 195−196 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.27 (d, J = 7.4 Hz, 1H), 7.60−7.47 (m, 5H), 7.40 (td, J = 7.7, 1.3 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 160.4, 146.9, 141.5, 135.0, 132.8, 130.7, 129.3, 124.7, 124.4, 122.3, 118.9, 110.3 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}N_2O_2$ 239.0821; found: 239.0818.

*(E)-2-Oxo-N,1,2-triphenylethan-1-imine oxide (**3iA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 24.0 mg, 44%; yellow solid; mp 138−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26−8.19 (m, 2H), 7.74−7.70 (m, 2H), 7.49 (ddt, J = 7.8, 7.1, 1.3 Hz, 1H), 7.46−7.43 (m, 3H), 7.37−7.32 (m, 4H), 7.26−7.20 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 191.2, 147.5, 136.6, 134.2, 131.0, 130.4, 130.0, 129.5, 129.3, 129.0, 128.9, 128.8, 128.7, 128.5, 127.8, 124.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{20}H_{16}NO_2$ 302.1181; found: 302.1185.

*N-Phenyl-9H-fluoren-9-imine oxide (**3jA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 39.8 mg, 73%; yellow solid; mp 184−185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (ddd, J =

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7.6, 1.3, 0.7 Hz, 1H), 7.70−7.67 (m, 1H), 7.65−7.62 (m, 1H), 7.62−7.58 (m, 3H), 7.55−7.51 (m, 2H), 7.49 (td, J = 7.5, 1.3 Hz, 1H), 7.42 (td, J = 7.6, 1.2 Hz, 1H), 7.23 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (ddd, J = 8.0, 7.4, 1.1 Hz, 1H), 5.89 (dt, J = 8.0, 0.8 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.1, 145.5, 139.3, 139.1, 132.4, 131.2, 130.8, 130.4, 130.2, 129.2, 128.9, 127.3, 127.1, 123.9, 120.2, 119.7 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}NO$ 272.1075; found: 272.1072.

*(Z)-N,1-Diphenylmethanimine oxide (**3kA**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield: 9.9 mg, 25%; yellow solid; mp 104−106 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.43−8.37 (m, 2H), 7.93 (s, 1H), 7.78 (dd, J = 7.6, 2.1 Hz, 2H), 7.48 (dt, J = 6.4, 3.2 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 149.1, 134.7, 131.0, 130.7, 129.9, 129.2, 129.1, 128.7, 121.8 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{13}H_{12}NO$ 198.0919; found: 198.0920.

*(Z)-1-(4-Nitrophenyl)-N-phenylmethanimine oxide (**3lA**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield: 27.6 mg, 57%; yellow solid; mp 175−176 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 9.0 Hz, 2H), 8.31 (d, J = 9.0 Hz, 2H), 8.08 (s, 1H), 7.83−7.75 (m, 2H), 7.56−7.48 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 148.9, 148.0, 136.2, 132.3, 130.7, 129.4, 129.2, 123.9, 121.7 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{13}H_{11}N_2O_3$ 243.0770; found: 243.0775.

*(Z)-1-(3-Fluoro-4-nitrophenyl)-N-phenylmethanimine oxide (**3mA**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield: 44.2 mg, 85%; yellow solid; mp 160−161 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (dd, J = 12.8, 1.7 Hz, 1H), 8.14 (t, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.95 (d, J = 8.9 Hz, 1H), 7.81−7.74 (m, 2H), 7.57−7.49 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.7 (d, J_{CF} = 264.1 Hz), 148.8, 137.3 (d, J_{CF} = 9.4 Hz), 137.1 (d, J_{CF} = 8.5 Hz), 131.2 (d, J_{CF} = 1.5 Hz), 131.0, 129.5, 126.2 (d, J_{CF} = 2.4 Hz), 124.6 (d, J_{CF} = 4.0 Hz), 121.7, 117.4 (d, J_{CF} = 24.7 Hz) ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{13}H_{10}FN_2O_3$ 261.0675; found: 261.0679.

*(E)-N-(4-(Dimethylamino)phenyl)-2-oxoindolin-3-imine oxide (**3hB**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 50.1 mg, 89%; maroon solid; mp 201−202 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.34 (t, J = 7.7 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.70 (d, J = 8.6 Hz, 2H), 3.01 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 160.7, 152.2, 140.7, 135.8, 133.1, 131.8, 126.0, 124.1, 122.0, 119.9, 110.9, 110.0, 40.3 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}N_3O_2$ 282.1243; found: 282.1248.

*(E)-N-(4-Methoxyphenyl)-2-oxoindolin-3-imine oxide (**3hC**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 47.8 mg, 89%; orange solid; mp 200−201 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.29−8.24 (m, 1H), 7.56−7.53 (m, 2H), 7.38 (td, J = 7.7, 1.3 Hz, 1H), 7.06−7.00 (m, 3H), 6.89 (d, J = 7.7 Hz, 1H), 3.84 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 161.0, 160.6, 141.2, 140.1, 134.6, 132.5, 126.2, 124.5, 122.2, 119.2, 114.1, 110.2, 56.0 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_3$ 269.0926; found: 269.0930.

*(E)-N-(4-Bromophenyl)-2-oxoindolin-3-imine oxide (**3hD**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 62.8 mg, 99%; orange solid; mp 201−203 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.79 (s, 1H), 8.25 (d, J = 7.6 Hz, 1H), 7.76−7.68 (m, 2H), 7.60−7.53 (m, 2H), 7.41 (td, J = 7.7, 1.3 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 160.5, 145.8, 141.6, 135.3, 133.0, 132.3, 126.7, 124.7, 123.8, 122.4, 118.8, 110.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{14}H_8BrN_2O_2$ 316.9926; found: 316.9916.

*(E)-N-(4-(Ethoxycarbonyl)phenyl)-2-oxoindolin-3-imine oxide (**3hE**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 62.1 mg, 99%; orange solid; mp 200−201 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 165.3, 160.5, 149.8, 141.7, 135.5, 133.1, 131.7, 130.3, 125.0, 124.8, 122.4, 118.6, 110.4, 61.6, 14.6 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_4$ 311.1032; found: 311.1033.

*(E)-N-(4-Acetylphenyl)-2-oxoindolin-3-imine oxide (**3hF**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 55.5 mg, 99%; orange solid; mp 196−198 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.81 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 7.42 (t, J = 7.1 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 2.66 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 197.7, 160.5, 149.7, 141.7, 138.3, 135.5, 133.1, 129.4, 125.0, 124.8, 122.4, 118.7, 110.4, 27.4 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_2O_3$ 281.0926; found: 281.0927.

*(E)-N-(3-methoxyphenyl)-2-oxoindolin-3-imine oxide (**3hG**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 42.8 mg, 80%; reddish-orange solid; mp 195−196 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.44−7.38 (m, 2H), 7.19−7.17 (m, 1H), 7.14−7.03 (m, 3H), 6.90 (d, J = 7.8 Hz, 1H), 3.79 (s, 3H). ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 160.3, 159.7, 147.7, 141.5, 135.0, 132.8, 130.2, 124.6, 122.3, 118.8, 116.4, 110.3, 110.1, 56.0 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_3$ 269.0926; found: 269.0928.

*(E)-N-(3-(ethoxycarbonyl)phenyl)-2-oxoindolin-3-imine oxide (**3hH**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 49.6 mg, 80%; reddish-orange solid; mp 195−196 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 8.15−8.07 (m, 2H), 7.92−7.86 (m, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 164.8, 160.2, 146.5, 141.3, 135.1, 132.7, 130.8, 129.6, 128.9, 124.8, 124.5, 122.0, 118.3, 112.3, 110.0, 61.3, 14.2 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}N_2O_4$ 311.1032; found: 311.1027.

*(E)-N-(3-acetylphenyl)-2-oxoindolin-3-imine oxide (**3hI**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 46.0 mg, 82%; orange solid; mp 196−197 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.28 (d, J = 7.6 Hz, 1H), 8.19−8.14 (m, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.90−7.84 (m, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.42 (t, J = 7.7 Hz, 1H), 7.09 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.8 Hz, 1H), 2.62 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 197.5, 160.6, 146.9, 141.6, 137.8, 135.4, 133.1, 130.1, 129.9, 129.1, 124.8, 124.4, 122.4, 118.7, 110.4, 27.3 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{16}H_{13}N_2O_3$ 281.0926; found: 281.0929.

*(E)-N-(2-Bromophenyl)-2-oxoindolin-3-imine oxide (**3hJ**).* Flash column chromatography: 25−100% EtOAc/*n*-hexane; Yield: 40.6 mg, 64%; orange solid; mp 197−199 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 10.84 (s, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.62 (dd, J = 7.8, 1.6 Hz, 1H), 7.58−7.53 (m, 1H), 7.49−7.42 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 160.2, 146.1, 141.9, 135.7, 133.6, 133.4, 131.8, 129.4, 126.4, 125.0, 122.6, 117.9, 116.2, 110.6 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{14}H_{10}BrN_2O_2$ 316.9926; found: 316.9921.

*(Z)-N-tert-Butyl-1-(4-nitrophenyl)methanimine oxide (**3lK**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield: 25.3 mg, 52%; yellow solid; mp 133−135 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.48−8.41 (m, 2H), 8.29−8.23 (m, 2H), 7.70 (s, 1H), 1.64 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.6, 136.7, 128.9, 127.9, 123.7, 72.4, 28.3 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_3$ 223.1083; found: 223.1085.

*(Z)-N-tert-Butyl-1-(3-fluoro-4-nitrophenyl)methanimine oxide (**3mK**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield: 34.2 mg, 71%; pale yellow solid; mp 137−138 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (dd, J = 13.1, 1.8 Hz, 1H), 8.08 (t, J = 8.2 Hz, 1H), 7.84−7.79 (m, 1H), 7.68 (s, 1H), 1.63 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.7 (d, J_{CF} = 263.5 Hz), 137.9 (d, J_{CF} = 9.6 Hz), 136.5 (d, J_{CF} = 8.3 Hz), 127.0 (d, J_{CF} = 1.6 Hz), 125.9 (d, J_{CF} = 2.4 Hz), 124.3 (d, J_{CF} = 3.9 Hz), 117.1 (d, J_{CF} = 24.7 Hz), 72.8, 28.3 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{11}H_{14}N_2O_3$ 241.0944; found: 241.0991.

*(Z)-N-tert-Butyl-1-(2-nitrophenyl)methanimine oxide (**3nK**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield:

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25.3 mg, 62%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.00 (d, J = 8.0 Hz, 1H), 8.18 (s, 1H), 8.03 (dd, J = 8.2, 1.3 Hz, 1H), 7.68 (t, J = 7.7 Hz, 1H), 7.54−7.47 (m, 1H), 1.62 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 147.6, 133.2, 129.7, 129.6, 125.1, 124.8, 124.2, 72.4, 28.2 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{11}H_{15}N_2O_3$ 223.1083; found: 223.1085.

*(Z)-N-tert-Butyl-1-(4-cyanophenyl)methanimine oxide (**3oK**).* Flash column chromatography: 10−25% EtOAc/*n*-hexane; Yield: 28.8 mg, 71%; off-white solid; mp 152−154 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.63 (s, 1H), 1.63 (s, 9H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 134.9, 132.2, 128.6, 127.0, 118.6, 112.6, 72.1, 28.3 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{12}H_{15}N_2O$ 203.1184; found: 203.1184.

*1,3-Diethoxy-1,3-dioxo-N-phenylpropan-2-imine oxide (**3rA**).* Flash column chromatography: 10−30% EtOAc/*n*-hexane; Yield: 30.9 mg, 58%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.49 (m, 1H), 7.49−7.39 (m, 4H), 4.45 (q, J = 7.1 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.3, 158.7, 147.2, 130.9, 129.1, 123.0, 62.7, 62.3, 14.0, 13.7 ppm; HRMS (FAB) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}NO_5$ 266.1028; found: 266.1029.

*5-Ethyl 3-methyl 2,3-diphenylisoxazolidine-3,5-dicarboxylate (**5**).* To a solution of **1** (0.4 mmol) in DMA (2.0 mL) were added the catalyst (4.9 mg, 0.04 mmol), Li_2CO_3 (59.1 mg, 0.8 mmol), and **2A** (0.4 mmol) at room temperature. After stirring for 24 h, ethyl acrylate (85 μL, 0.8 mmol) was added. The reaction mixture was heated to 80 °C using an oil bath, stirred for additional 16 h, diluted with EtOAc (30 mL), and washed with brine (30 mL × 3). The extract was dried over anhydrous $MgSO_4$. After filtration of the solid, the solvent in the filtrate was removed in vacuo, and the residue was purified by silica gel column chromatography (10−25% EtOAc/*n*-hexane) to give the corresponding isoxazolidine **5** as a 1.5:1 mixture of diastereomers. Yield: 88.1 mg, 62%; gummy solid. **Diastereomer A (major)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−6.92(m, 10H), 4.88 (dd, J = 8.8, 5.0 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.67 (dd, J = 12.8, 8.8 Hz, 1H), 3.46 (s, 3H), 2.95 (dd, J = 12.8, 4.9 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H) ppm. **Diastereomer B (minor)**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86−6.92 (m, 10H), 4.76 (dd, J = 8.4, 6.9 Hz, 1H), 4.31−4.23 (m, 2H), 3.58 (dd, J = 12.7, 6.9 Hz, 1H), 3.51 (s, 3H), 2.97 (dd, J = 12.8, 8.4 Hz, 1H), 1.31 (d, J = 14.3 Hz, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.9, 170.6, 170.5, 169.8, 147.0, 146.9, 138.8, 138.3, 138.1, 131.8, 129.1, 128.8, 128.5, 128.4, 128.2, 128.1, 128.1, 127.4, 127.4, 127.1, 124.5, 123.7, 123.1, 120.3, 119.0, 117.7, 78.0, 77.7, 74.8, 74.6, 61.6, 61.5, 52.5, 52.3, 47.7, 46.0, 14.2, 14.1 ppm; HRMS (FAB) m/z: $[M]^+$ calcd for $C_{20}H_{21}NO_5$ 355.1420; found: 355.1420.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00158.

^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra for all products **3** and **5** (PDF)

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Notes

The authors declare no competing financial interest.

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