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Construction of Oxadiazepines via Lewis Acid-Catalyzed Tandem 1,5-Hydride Shift/Cyclization

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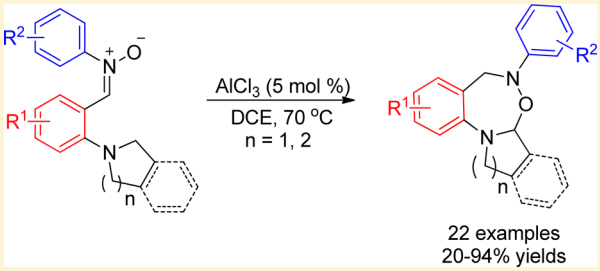
Supporting Information

ABSTRACT: Expeditious access to oxadiazepines via 1,5-hydride shift/cyclization of pyrrolidine- or tetrahydroisoquinoline-containing nitrones has been developed. With 1,3-dipole nitrones serving as the hydride acceptors, this transformation was promoted by a Lewis acid, providing access to structurally diverse oxadiazepines in good yields. A one-pot process for in situ nitrone formation, a 1,5-hydride shift, and ring cyclization was also realized.



INTRODUCTION

The direct and selective functionalization of relatively inert C−H bonds, particularly C(sp^3)-H bonds, has become an active field in fundamental organic chemistry because of its atom- and step-economy.[1] Such transformation not only provides access to structurally diverse complex molecules but also forges new C−C and/or C−X (X = O, N, etc.) bonds without prefunctionalization. Although transition-metal-catalyzed C−H bond functionalization has made tremendous progress in the past few decades, the internal redox process allowing for C−H bond functionalization mostly catalyzed by Brønsted or Lewis acids has recently attracted considerable interest.[2]

In the vast majority of cases, Michael acceptors as electrophilic fragments play an important role in the internal redox process;[3] meanwhile, alkynes,[4] aldehydes,[5] and iminium ions[6] were also employed in this process. In general, this transformation undergoes a 1,5-hydride shift to an electrophilic moiety followed by ring-closure, resulting in the formation of six-membered heterocycles in most cases. Only a limited number of reports provide access to larger membered rings, which are still perceived as a challenging issue in modern organic synthesis. In 2010, Zhang and co-workers reported a Au(I)-catalyzed domino cyclization/1,5-hydride shift/cyclization reaction for the synthesis of furan-fused tetrahydroazepines.[7] In 2011, Seidel's group developed a new redox-neutral process that resulted in the formation of seven-membered indole-fused benzazepines from commercially available materials.[8] In the internal redox process, the formation of seven-membered heterocycles was still rare. Thus, the development of novel methodologies for the rapid construction of seven-membered rings initiated by a 1,5-hydride shift is highly desirable.

As a part of our program aimed at developing redox-neutral reaction cascades to realize C−H bond functionalization at the α position to a nitrogen atom, numerous N-aryl pyrrole derivatives have been prepared via a 1,5-hydride shift/isomerization process.[9] Conversely, 1,3-dipolar cycloaddition reactions between nitrones and electron-deficient alkenes have been intensely studied over the past few decades, providing access to structurally diverse isoxazolidines.[10] To date, there are no reports that apply nitrone as a hydride acceptor to a 1,5-hydride shift/cyclization sequence. In this paper, we present an example for the rapid construction of oxadiazepines using nitrone as a hydride acceptor. This extends the scope and efficiency of hydride shift-initiated cyclization reactions.

RESULTS AND DISCUSSION

We evaluated the 1,5-hydride shift/cyclization reaction of pyrrolidine-containing nitrones with various Brønsted and Lewis acids (10 mol %) as catalysts. The requisite nitrone **1a** for the model reaction was readily prepared by the reaction of 2-(pyrrolidin-1-yl)benzaldehyde with *N*-phenylhydroxylamine.[11] The results are summarized in Table 1. When using *p*-TsOH·H_2O as a Brønsted acid catalyst, the reaction took place smoothly to give desired product **2a** in 80% yield after 2 h at 70 °C (Table 1, entry 3). In contrast, the reaction catalyzed by other Brønsted acids (e.g., $PhCO_2H$, CF_3CO_2H, or DPP) gave the desired product in much lower yields (Table 1, entries 1, 2, 4, respectively). We then examined the catalytic efficiency of some Lewis acids (Table 1, entries 5−8). The results revealed that $AlCl_3$ was the best Lewis acid catalyst to give the product in 85% yield (Table 1, entry 8). Notably, when $Cu(OTf)_2$ was employed as a catalyst, no reaction was observed (Table 1, entry 6). Furthermore, different solvents were evaluated, and DCE was found to be the best solvent for this reaction, enabling reaction completion at 70 °C within 1.5 h. Other solvents, such as toluene, MeCN, 1,4-dioxane, THF, and EtOAc, could also give satisfactory results (Table 1, entries 9, 10, 12−14, respectively).

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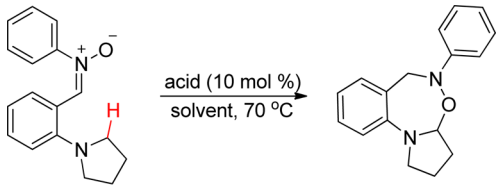
Table 1. Evaluation of the Acid Catalysts and Solvents[a]



1a 2a

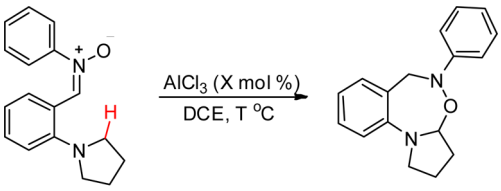
entry	acid	solvent	time (h)	yield (%)[b]
1	$PhCO_2H$	DCE	12	23
2	CF_3CO_2H	DCE	10	20
3	p-TsOH·H_2O	DCE	2	80
4	DPP	DCE	8	33
5	$Sc(OTf)_3$	DCE	13	55
6	$Cu(OTf)_2$	DCE	24	trace
7	$Zn(OTf)_2$	DCE	15	61
8	$AlCl_3$	DCE	1.5	85
9	$AlCl_3$	toluene	1.5	75
10	$AlCl_3$	MeCN	1.5	74
11	$AlCl_3$	EtOH	1.5	13
12	$AlCl_3$	1,4-dioxane	1.7	76
13	$AlCl_3$	THF	1.5	71
14	$AlCl_3$	EtOAc	1.5	78

[a]Reaction conditions: **1a** (0.3 mmol), acid (10 mol %), solvent (3.0 mL), 70 °C. [b]Isolated yield of the product.

However, when the protic solvent EtOH was employed as a solvent, the product was only obtained in 13% yield (Table 1, entry 11).

Upon further investigation of the reaction temperature and catalyst loading (Table 2), it was found that higher product yield

Table 2. Effects of Temperature and Catalyst Loading[a]



1a 2a

entry	T (°C)	X	time (h)	yield (%)[b]
1	25	10	24	40
2	50	10	2	76
3	70	10	1.5	85
4	85	10	1	80
5	70	5	2	84
6	70	1	18	62

[a]Reaction conditions: **1a** (0.3 mmol), $AlCl_3$ (X mol %), DCE (3.0 mL), T °C. [b]Isolated yield of the product.

was achieved at 70 °C (Table 2, entry 3) in contrast to the other temperatures under other identical reaction conditions. When the catalyst loading was decreased to 5 mol %, the product yield was identical to that of 10 mol % catalyst loading (Table 2, entry 5). When the catalyst loading was further decreased to 1 mol %, the product was obtained in only 62% yield after 18 h (Table 2, entry 6). Finally, the optimized reaction conditions were determined as follows: DCE as solvent, 5 mol % $AlCl_3$ as catalyst, reaction temperature at 70 °C.

With the optimized conditions in hand, the substrate scope of the 1,5-hydride shift/cyclization process was evaluated. The influence of substituted phenyl groups linked to the pyrrolidine on the reaction outcome was examined first (Scheme 1). Both electron-donating and -withdrawing substituents on the benzene ring were tolerated in the reaction, affording corresponding products **2b–g** in 46–92% yields. Notably, when the strong electron-withdrawing group NO_2 was introduced to the benzene ring, the corresponding product **2h** was obtained in only 20% yield. Next, the reaction with different N-aryl-substituted nitrones was evaluated. Nitrones bearing electron-rich and -poor aryl substitutions were well-tolerated, affording oxadiazepines **2i–p** in good to excellent yields (60–94% yields). For example, the reaction of phenyl-substituted substrate **1k** provided cyclization product **2k** in 61% yield. The structure of oxadiazepine **2o** was further confirmed by X-ray crystallography (see Supporting Information for details).

To broaden the generality of this methodology, we examined the tetrahydroisoquinoline-containing nitrones as the reaction substrates instead of pyrrolidine-containing nitrones. As shown in Scheme 2, reactions of tetrahydroisoquinoline-containing nitrones **1q–v** proceeded smoothly, providing access to the corresponding oxadiazepines **2q–v** in 62–75% yields.

To test the idea that the nitrone formation, 1,5-hydride shift, and ring cyclization could take place through a one-pot process, we examined the reaction of 2-(pyrrolidin-1-yl)benzaldehydes **3** with *N*-arylhydroxylamines **4** under the optimal reaction conditions (Scheme 3). To our delight, three transformations (nitrone formation, 1,5-hydride shift, and ring cyclization) occurred successfully in a one-pot manner to afford the desired oxadiazepines in good yields (51–82% yields). Meanwhile, we also evaluated the substrate scope with regard to the other amine moiety, such as piperidine and morpholine, but disappointingly, no reaction was observed.

The proposed mechanism is illustrated in Scheme 4. According to the FMO analysis, the coordination between Lewis acid and nitrone lowered the LUMO energy of the nitrone, consequently decreasing the energy between the HOMO of the C–H bond and the LUMO of the nitrone, prompting the [1,5]-hydride shift and affording the imminium ion intermediate **B**. Then, intramolecular electrophilic attack by an oxygen anion on imminium ion intermediate **B** provides desired cyclized product **2a.**

■ CONCLUSIONS

In conclusion, by using the 1,3-dipole nitrones as the hydride acceptors, we have developed a novel internal redox process based on 1,5-hydride shift/cyclization of pyrrolidine- or tetrahydroisoquinoline-containing nitrones. This protocol provides access to structurally diverse oxadiazepines in good to excellent yields. Furthermore, the in situ nitrone formation, 1,5-hydride shift, and ring cyclization could take place through a one-pot process, affording the corresponding oxadiazepines in good yields. The exploration of new internal redox processes using other 1,3-dipoles as hydride acceptors to produce seven-membered rings is ongoing in our laboratory.

■ EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded on an ACF* 300Q spectrometer. Low- and high-resolution mass spectra (LRMS and HRMS) were recorded in electron impact mode. The mass analyzer type used for the HRMS measurements was TOF. Reactions

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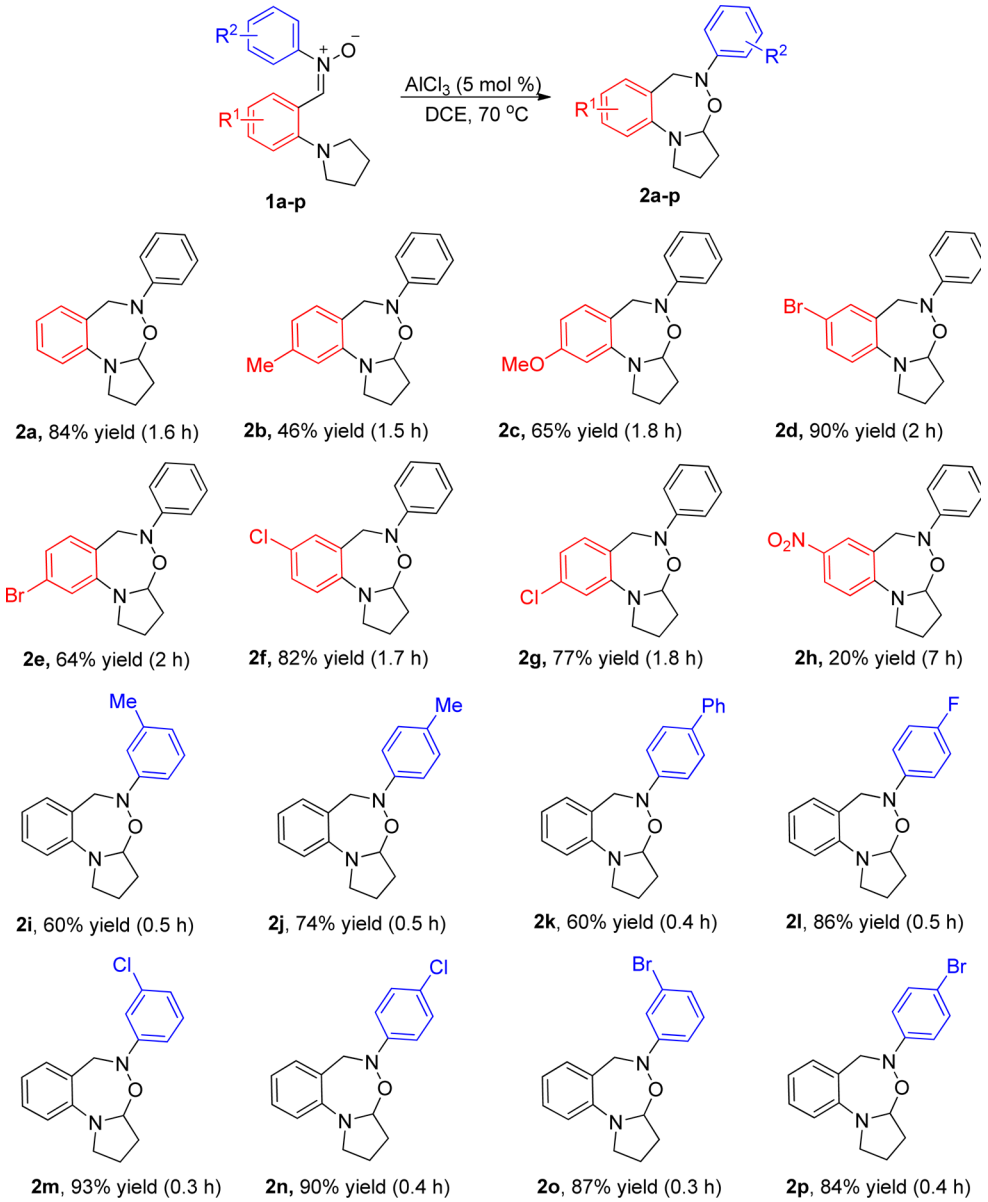
Scheme 1. Substrate Scope of Pyrrolidine-Containing Nitrones[a]



[a]Reaction conditions: **1** (0.3 mmol), $AlCl_3$ (5 mol %), DCE (3.0 mL), 70 °C. Isolated yields of the products.

were monitored by TLC on silica gel 60 F254 plates. Column chromatography was carried out on silica gel (200−300 mesh).

Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br s = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

General Procedure for Synthesis of Substituted 2-Pyrrolidin Nitrones 1a−p. To a solution of *N*-phenylhydroxylamine **4** (1.2 equiv) in EtOH was added 2-(pyrrolidin-1-yl)benzaldehyde **3** (1.0 equiv). The mixture was stirred at 70 °C in the dark until complete consumption as monitored by TLC. The reaction was cooled to room temperature, diluted with water, and extracted with DCM. The combined organic layer was washed with saturated NaCl solution and dried over Na_2SO_4. The solvents were removed under reduced pressure and purified by flash chromatography to give the desired products **1a−p**.

*(E)-N-Phenyl-1-(2-(pyrrolidin-1-yl)phenyl)methanimine Oxide (**1a**).* The general procedure was performed with 2-(pyrrolidin-1-yl)benzaldehyde (640 mg, 3.67 mmol) and *N*-phenylhydroxylamine (480 mg, 4.40 mmol) in EtOH (10 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 5:1) to give compound **1a** (0.42 g, 43% yield) as a yellow solid. Mp 75−76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, J = 7.8 Hz, 1H), 8.12 (s, 1H), 7.80 (d, J = 6.9 Hz, 2H), 7.53−7.40 (m, 3H), 7.35 (t, J = 7.5 Hz, 1H), 7.08−6.98 (m, 2H), 3.27 (t, J = 6.3 Hz, 4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.5, 133.1, 131.5, 129.6, 129.2, 128.9, 121.7, 121.4, 120.4, 115.9, 53.1, 25.3; HRMS (ESI) exact mass calcd for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.1497, found 267.1496.

*(E)-1-(4-Methyl-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1b**).* The general procedure was performed with 4-methyl-2-(pyrrolidin-1-yl)benzaldehyde (207 mg, 1.09 mmol) and *N*-phenylhydroxylamine (143 mg, 1.31 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 5:1) to give compound **1b** (0.12 g, 41% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, J = 8.1 Hz, 1H), 8.08 (s, 1H), 7.78 (d, J = 7.2 Hz, 2H), 7.52−7.40 (m, 3H), 6.85 (d, J = 8.1 Hz, 1H), 6.81 (s, 1H), 3.24 (t, J = 6.3 Hz, 4H), 2.36 (s, 3H), 1.93 (t, J = 6.5 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 149.5, 142.2, 133.0, 129.5, 129.2, 128.7, 121.7, 121.5, 119.0, 116.8, 53.1, 25.3, 22.2; HRMS (ESI)

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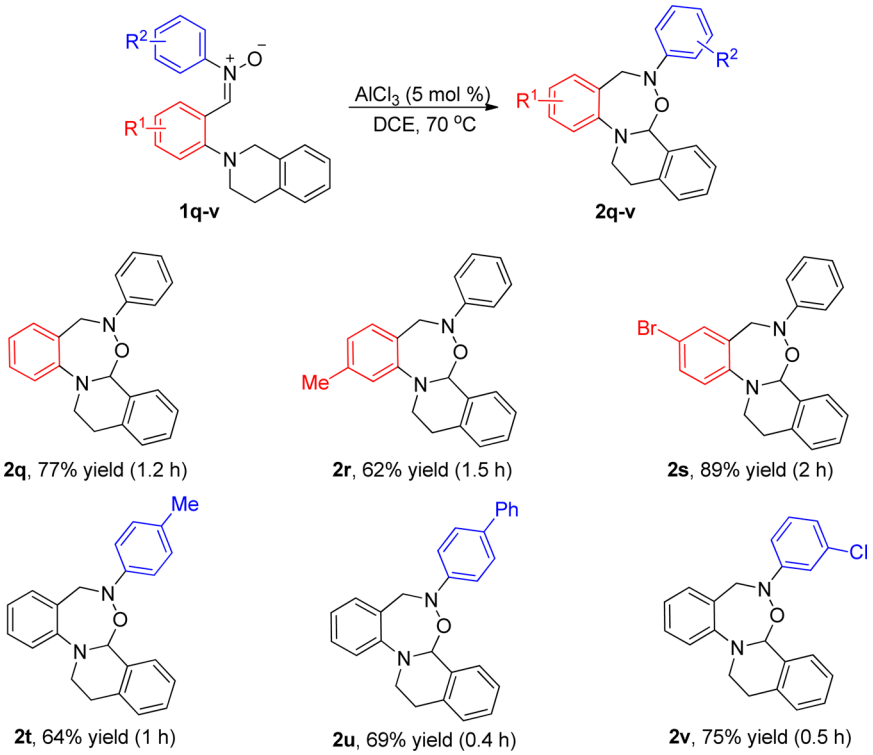
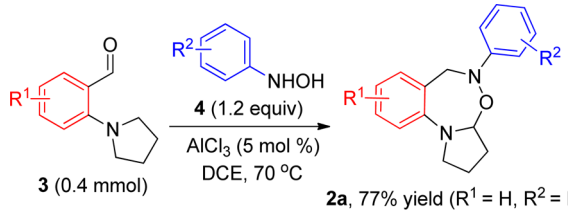
Scheme 2. Substrate Scope of Tetrahydroisoquinoline-Containing Nitrones[a]



[a]Reaction conditions: **1** (0.3 mmol), $AlCl_3$ (5 mol %), DCE (3.0 mL), 70 °C. Isolated yields of the products.

Scheme 3. One-Pot Reactions of 2-(Pyrrolidin-1-yl)benzaldehydes 3 with *N*-Arylhydroxylamines 4



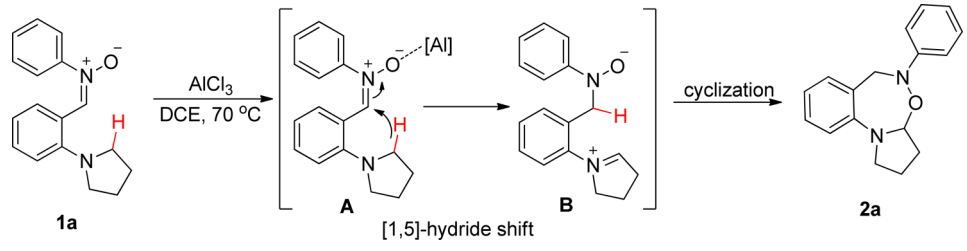
exact mass calcd for $C_{18}H_{20}N_2ONa$ $[M + Na]^+$ 303.1473, found 303.1480.

*(E)-1-(4-Methoxy-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1c**).* The general procedure was performed with 4-methoxy-2-(pyrrolidin-1-yl)benzaldehyde (186 mg, 0.907 mmol) and *N*-phenylhydroxylamine (118 mg, 1.09 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 2:1) to give compound **1c** (0.20 g, 73% yield) as a yellow solid. Mp 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.28 (d, J = 8.7 Hz, 1H), 8.03 (s, 1H), 7.76 (d, J = 7.5 Hz, 2H), 7.46−7.40 (m, 3H), 6.56 (d, J = 8.7 Hz, 1H), 6.49 (s, 1H), 3.84 (s, 3H), 3.28−3.23 (m, 4H), 1.95−1.90 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.6, 151.7, 148.8, 131.0, 129.6, 129.13, 129.07, 128.6, 121.1, 113.3, 104.4, 101.1, 55.1, 52.4, 24.9; HRMS (ESI) exact mass calcd for $C_{18}H_{20}N_2O_2Na$ $[M + Na]^+$ 319.1422, found 319.1429.

*(E)-1-(5-Bromo-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1d**).* The general procedure was performed with 5-bromo-2-(pyrrolidin-1-yl)benzaldehyde (200 mg, 0.79 mmol) and *N*-phenylhydroxylamine (103 mg, 0.95 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 6:1) to give compound **1d** (0.23 g, 83% yield) as a yellow solid. Mp 93−94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.31 (d, J = 2.1 Hz, 1H), 8.04 (s, 1H), 7.81−7.72 (m, 2H), 7.53−7.43 (m, 3H), 7.39 (dd, J = 8.7, 2.1 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 3.24 (t, J = 6.3 Hz, 4H), 1.94 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 150.2, 133.4, 131.9, 130.2, 129.8, 128.8, 122.4, 120.3, 119.8, 115.9, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{18}N_2OBr$ $[M + H]^+$ 345.0602, found 345.0605

*(E)-1-(4-Bromo-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1e**).* The general procedure was performed with 4-bromo-2-(pyrrolidin-1-yl)benzaldehyde (150 mg, 0.593 mmol) and *N*-phenylhydroxylamine (78 mg, 0.712 mmol) in EtOH (3 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 5:1) to give compound **1e** (0.13 g, 64% yield) as a yellow solid.

Scheme 4. Proposed Reaction Mechanism



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Mp 146−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.06 (d, J = 9.0 Hz, 1H), 8.03 (s, 1H), 7.81−7.75 (m, 2H), 7.53−7.42 (m, 3H), 7.15−7.09 (m, 2H), 3.28 (t, J = 6.3 Hz, 4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 149.4, 132.3, 129.9, 129.8, 129.3, 125.6, 123.2, 121.7, 119.8, 119.0, 53.0, 25.5; HRMS (ESI) exact mass calcd for $C_{17}H_{18}N_2OBr$ $[M + H]^+$ 345.0602, found 345.0610.

*(E)-1-(5-Chloro-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1f**).* The general procedure was performed with 5-chloro-2-(pyrrolidin-1-yl)benzaldehyde (230 mg, 1.05 mmol) and *N*-phenylhydroxylamine (137 mg, 1.26 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 5:1) to give compound **1f** (0.17 g, 54% yield) as a yellow solid. Mp 139−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (d, J = 2.4 Hz, 1H), 8.08 (s, 1H), 7.83−7.74 (m, 2H), 7.54−7.44 (m, 3H), 7.29 (dd, J = 2.4, 8.7 Hz, 1H), 6.93 (d, J = 8.7 Hz, 1H), 3.25 (t, J = 6.3 Hz, 4H), 1.96 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ, 148.9, 131.7, 131.2, 129.9, 129.3, 128.1, 125.8, 122.5, 121.7, 117.2, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{18}N_2OCl$ $[M + H]^+$ 301.1108, found 301.1115.

*(E)-1-(4-Chloro-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1g**).* The general procedure was performed with 4-chloro-2-(pyrrolidin-1-yl)benzaldehyde (220 mg, 1.05 mmol) and *N*-phenylhydroxylamine (137 mg, 1.26 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 7:1) to give compound **1g** (0.22 g, 70% yield) as a yellow solid. Mp 138−139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, J = 8.4 Hz, 1H), 8.02 (s, 1H), 7.79−7.71 (m, 2H), 7.50−7.41 (m, 3H), 6.99−6.87 (m, 2H), 3.27 (t, J = 6.3 Hz, 4H), 1.94 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 149.3, 136.9, 132.2, 129.8, 129.3, 121.6, 120.0, 119.2, 115.9, 52.9, 25.5; HRMS (ESI) exact mass calcd for $C_{17}H_{17}N_2ONaCl$ $[M + Na]^+$ 323.0927, found 323.0937.

*(E)-1-(5-Nitro-2-(pyrrolidin-1-yl)phenyl)-N-phenylmethanimine Oxide (**1h**).* The general procedure was performed with 5-nitro-2-(pyrrolidin-1-yl)benzaldehyde (220 mg, 1 mmol) and *N*-phenylhydroxylamine (131 mg, 1.2 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 3:1) to give compound **1h** (0.18 g, 57% yield) as a yellow solid. Mp 178−180 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.48 (s, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.95−7.86 (m, 2H), 7.60−7.48 (m, 3H), 6.92 (d, J = 9.3 Hz, 1H), 3.54 (t, J = 6.3 Hz, 4H), 1.92 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 148.0, 135.6, 131.7, 129.8, 129.1, 125.9, 125.5, 121.4, 120.7, 114.6, 113.7, 51.4, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{17}N_3O_3Na$ $[M + Na]^+$ 334.1168, found 334.1175.

*(E)-1-(2-(Pyrrolidin-1-yl)phenyl)-N-(m-tolyl)methanimine Oxide (**1i**).* The general procedure was performed with 2-(1-pyrrolidinyl)-benzaldehyde (200 mg, 1.14 mmol) and *N*-(*m*-tolyl)hydroxylamine (168 mg, 1.37 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate =10:1) to give compound **1i** (213 mg, 66% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, J = 7.8 Hz, 1H), 8.06 (s, 1H), 7.62 (s, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.37−7.24 (m, 3H), 7.04−6.94 (m, 2H), 3.24 (t, J = 6.3 Hz, 4H), 2.42 (s, 1H), 1.92 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.5, 139.5, 133.1, 131.5, 130.4, 128.9, 128.8, 122.6, 121.4, 120.4, 118.7, 115.9, 53.1, 25.3, 21.5; HRMS (ESI) exact mass calcd for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1648, found 281.1644.

*(E)-1-(2-(Pyrrolidin-1-yl)phenyl)-N-(p-tolyl)methanimine Oxide (**1j**).* The general procedure was performed with 2-(1-pyrrolidinyl)-benzaldehyde (200 mg, 1.14 mmol) and *N*-(*p*-tolyl)hydroxylamine (168 mg, 1.37 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 6:1) to give compound **1j** (0.15 g, 47% yield) as a yellow solid. Mp 114−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (d, J = 7.8 Hz, 1H), 8.08 (s, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.36−7.22 (m, 3H), 7.06−6.93 (m, 2H), 3.24 (t, J = 6.3 Hz, 4H), 2.41 (s, 3H), 1.93 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 147.2, 139.8, 132.5, 131.4, 129.7, 128.8, 121.6, 121.5, 120.5, 115.9, 53.1, 25.3, 21.2; HRMS (ESI) exact mass calcd for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1648, found 281.1651.

*(E)-N-([1,1′-Biphenyl]-4-yl)-1-(2-(pyrrolidin-1-yl)phenyl)-methanimine Oxide (**1k**).* The general procedure was performed with 2-(1-pyrrolidinyl)benzaldehyde (250 mg, 1.43 mmol) and *N*-([1,1′-biphenyl]-4-yl)hydroxylamine (317 mg, 1.71 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 15:1) to give compound **1k** (397 mg, 81% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (d, J = 7.8 Hz, 1H), 8.17 (s, 1H), 7.87 (d, J = 8.4 Hz, 2H), 7.72−7.57 (m, 4H), 7.52−7.30 (m, 4H), 7.08−6.98 (m, 2H), 3.28 (t, J = 6.3 Hz, 4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 148.5, 142.7, 139.9, 132.9, 131.6, 129.1, 128.9, 128.1, 127.9, 127.3, 122.1, 121.4, 120.5, 116.0, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1805, found 343.1806.

*(E)-N-(4-Fluorophenyl)-1-(2-(pyrrolidin-1-yl)phenyl)methanimine Oxide (**1l**).* The general procedure was performed with 2-(1-pyrrolidinyl)benzaldehyde (200 mg, 1.14 mmol) and 4-chlorophenylhydroxylamine (173 mg, 1.37 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 7:1) to give compound **1l** (181 mg, 56% yield) as a yellow solid. Mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (d, J = 7.8 Hz, 1H), 8.07 (s, 1H), 7.80 (dd, J = 9.0, 4.8 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.17 (t, J = 8.4 Hz, 2H), 7.06−6.95 (m, 2H), 3.26 (t, J = 6.3 Hz, 4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 150.6, 132.9, 131.7, 128.8, 123.6 (d, J = 9.0 Hz), 120.6, 116.2 (d, J = 7.5 Hz), 115.9, 53.2, 25.3; HRMS (ESI) exact mass calcd for $C_{17}H_{18}FN_2O$ $[M + H]^+$ 285.1398, found 285.1404.

*2-(3-Phenyl-2,5-dihydro-1H-pyrrol-1-yl)benzaldehyde (**1m**).* The general procedure was performed with 2-(1-pyrrolidinyl)benzaldehyde (250 mg, 1.43 mmol) and *N*-(3-chlorophenyl)hydroxylamine (245 mg, 1.71 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **1m** (265 mg, 62% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, J = 7.8 Hz, 1H), 8.07 (s, 1H), 7.84 (s, 1H), 7.70−7.65 (m, 1H), 7.45−7.30 (m, 3H), 7.01 (t, J = 7.8 Hz, 2H), 3.26 (t, J = 6.3 Hz, 4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 135.1, 133.3, 131.9, 130.3, 129.8, 128.8, 122.5, 121.1, 120.5, 119.8, 116.1, 114.7, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{17}ClN_2O$ $[M + H]^+$ 301.1102, found 301.1100.

*(E)-N-(4-Chlorophenyl)-1-(2-(pyrrolidin-1-yl)phenyl)methanimine Oxide (**1n**).* The general procedure was performed with 2-(1-pyrrolidinyl)benzaldehyde (200 mg, 1.14 mmol) and 4-chlorophenylhydroxylamine (196 mg, 1.37 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 5:1) to give compound **1n** (306 mg, 89% yield) as a yellow solid. Mp 142−143 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (d, J = 8.1 Hz, 1H), 8.09 (s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.03 (t, J = 8.1 Hz, 2H), 3.26 (t, J = 6.3 Hz, 4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 147.9, 135.5, 133.1, 131.8, 129.4, 128.8, 123.0, 121.2, 120.5, 116.1, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{18}ClN_2O$ $[M + H]^+$ 301.1102, found 301.1105.

*(E)-N-(3-Bromophenyl)-1-(2-(pyrrolidin-1-yl)phenyl)methanimine Oxide (**1o**).* The general procedure was performed with 2-(1-pyrrolidinyl)benzaldehyde (250 mg, 1.43 mmol) and *N*-(3-bromophenyl)hydroxylamine (295 mg, 1.71 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **1o** (181 mg, 37% yield) as a yellow solid. Mp 104−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (d, J = 7.8 Hz, 1H), 8.07 (s, 1H), 8.00 (s, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.36 (t, J = 8.1 Hz, 2H), 7.03 (t, J = 8.1 Hz, 2H), 3.28 (t, J = 6.3 Hz, 4H), 1.97 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 133.4, 132.8, 131.9, 131.0, 130.5, 128.8, 125.3, 122.8, 120.9, 120.4, 120.3, 116.0, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{18}BrN_2O$ $[M + H]^+$ 345.0597, found 345.0592.

*(E)-N-(4-Bromophenyl)-1-(2-(pyrrolidin-1-yl)phenyl)methanimine Oxide (**1p**).* The general procedure was performed with 2-(1-pyrrolidinyl)benzaldehyde (200 mg, 1.14 mmol) and *N*-(4-bromobenzyl)hydroxylamine (256 mg, 1.37 mmol) in EtOH (4 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 8:1) to give compound **1p** (243 mg, 62% yield) as a yellow solid. Mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (d, J = 7.8 Hz, 1H), 8.10 (s, 1H), 7.70 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 7.8 Hz, 1H), 7.03 (t, J = 8.1 Hz, 2H), 3.26 (t, J = 6.3 Hz,

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4H), 1.95 (t, J = 6.3 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 148.4, 133.1, 132.4, 131.8, 128.8, 123.5, 123.3, 121.2, 120.5, 116.1, 53.2, 25.4; HRMS (ESI) exact mass calcd for $C_{17}H_{18}BrN_2O$ $[M + H]^+$ 345.0597, found 345.0597.

General Procedure for Synthesis of Substituted 2-Tetrahydroisoquinoline Nitrones 1q−v. To a solution of *N*-phenylhydroxylamine **4** (1.2 equiv) in EtOH was added 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde **3** (1.0 equiv). The mixture was stirred at 70 °C in the dark until complete consumption as monitored by TLC. The reaction was cooled to room temperature, diluted with water, and extracted with DCM. The combined organic layers were washed with saturated NaCl solution and dried over Na_2SO_4. The solvents were removed under reduced pressure and purified by flash chromatography to give the desired products **1q−v**.

*(E)-1-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)phenyl)-N-phenylmethanimine Oxide (**1q**).* The general procedure was performed with 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (300 mg, 1.26 mmol) and *N*-phenylhydroxylamine (165 mg, 1.52 mmol) in EtOH (5 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **1q** (237 mg, 57% yield) as a yellow solid. Mp 140−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (d, J = 7.8 Hz, 1H), 8.38 (s, 1H), 7.80−7.70 (m, 2H), 7.48−7.38 (m, 3H), 7.31−7.03 (m, 6H), 4.24 (s, 2H), 3.34 (t, J = 5.7 Hz, 2H), 2.98 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 149.6, 134.7, 134.2, 131.7, 131.4, 129.8, 129.3, 129.1, 129.0, 126.7, 126.4, 126.2, 125.2, 123.8, 121.8, 119.5, 55.3, 52.4, 29.5; HRMS (ESI) exact mass calcd for $C_{22}H_{21}N_2O$ $[M + H]^+$ 329.1654, found 329.1660.

*(E)-1-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)-4-methylphenyl)-N-phenylmethanimine Oxide (**1r**).* The general procedure was performed with 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-4-methylbenzaldehyde (300 mg, 1.20 mmol) and *N*-phenylhydroxylamine (156 mg, 1.434 mmol) in EtOH (5 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate =30:1) to give compound **1r** (241 mg, 59% yield) as a yellow solid. Mp 139−141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, J = 8.1 Hz, 1H), 8.36 (s, 1H), 7.85−7.70 (m, 2H), 7.52−7.36 (m, 3H), 7.25−7.15 (m, 3H), 7.14−7.01 (m, 3H), 4.24 (s, 2H), 3.34 (t, J = 5.7 Hz, 2H), 3.01 (t, J = 5.7 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 149.5, 142.5, 134.8, 134.2, 131.5, 129.6, 129.2, 129.1, 128.9, 126.6, 126.5, 126.2, 124.6, 122.5, 121.8, 120.2, 55.3, 52.5, 29.7, 22.2; HRMS (ESI) exact mass calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1805, found 343.1804.

*(E)-1-(5-Bromo-2-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)-N-phenylmethanimine Oxide (**1s**).* The general procedure was performed with 5-bromo-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (300 mg, 0.95 mmol) and *N*-phenylhydroxylamine (124 mg, 1.14 mmol) in EtOH (5 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 4:1) to give compound **1s** (189 mg, 49% yield) as a yellow solid. Mp 178−179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, J = 2.1 Hz, 1H), 8.33 (s, 1H), 7.80−7.70 (m, 2H), 7.54 (dd, J = 2.1, 8.4 Hz, 1H), 7.49−7.42 (m, 3H), 7.25−7.15 (m, 3H), 7.09 (d, J = 8.7 Hz, 2H), 4.23 (s, 2H), 3.33 (t, J = 5.7 Hz, 2H), 2.98 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 149.3, 134.3, 134.0, 131.7, 131.3, 130.1, 129.4, 129.2, 129.0, 126.8, 126.4, 126.3, 125.7, 121.7, 121.1, 117.1, 55.1, 52.3, 29.3; HRMS (ESI) exact mass calcd for $C_{22}H_{20}BrN_2O$ $[M + H]^+$ 407.0754, found 407.0753.

*(E)-1-(2-(3,4-Dihydroisoquinolin-2(1H)-yl)phenyl)-N-(p-tolyl)-methanimine Oxide (**1t**).* The general procedure was performed with 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (237 mg, 1 mmol) and *N*-(*p*-tolyl)hydroxylamine (147 mg, 1.2 mmol) in EtOH (5 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **1t** (109 mg, 32% yield) as a yellow solid. Mp 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.44 (d, J = 7.8 Hz, 1H), 8.37 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.26−7.15 (m, 7H), 7.13−7.04 (m, 1H), 4.25 (s, 2H), 3.35 (t, J = 5.7 Hz, 2H), 2.99 (t, J = 5.7 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 147.3, 139.9, 134.7, 134.2, 131.6, 130.9, 129.7, 129.1, 128.9, 126.6, 126.4, 126.2, 125.2, 123.7, 121.5, 119.4, 55.3, 52.4, 29.5, 21.2; HRMS (ESI) exact mass calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1805, found 343.1808.

*(E)-N-([1,1′-Biphenyl]-4-yl)-1-(2-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)methanimine Oxide (**1u**).* The general procedure was performed with 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (300 mg, 1.26 mmol) and *N*-([1,1′-biphenyl]-4-yl)hydroxylamine (279 mg, 1.52 mmol) in EtOH (5 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 8:1) to give compound **1u** (450 mg, 88% yield) as a yellow solid. Mp 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (d, J = 7.8 Hz, 1H), 8.44 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 7.5 Hz, 2H), 7.52−7.32 (m, 4H), 7.30−7.14 (m, 5H), 7.14−7.06 (m, 1H), 4.26 (s, 2H), 3.36 (t, J = 5.7 Hz, 2H), 3.00 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 148.5, 142.8, 139.8, 134.7, 134.2, 131.0, 131.3, 129.2, 129.1, 128.1, 127.9, 127.3, 126.7, 126.5, 126.2, 123.8, 122.1, 119.5, 55.3, 52.5, 29.5; HRMS (ESI) exact mass calcd for $C_{28}H_{25}N_2O$ $[M + H]^+$ 405.1961, found 405.1967.

*(E)-N-(3-Chlorophenyl)-1-(2-(3,4-dihydroisoquinolin-2(1H)-yl)-phenyl)methanimine Oxide (**1v**).* The general procedure was performed with 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)benzaldehyde (300 mg, 1.26 mmol) and *N*-(3-chlorophenyl)hydroxylamine (216 mg, 1.52 mmol) in EtOH (5 mL). The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1) to give compound **1v** (235 mg, 51% yield) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (d, J = 7.8 Hz, 1H), 8.34 (s, 1H), 7.82 (s, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.50−7.32 (m, 3H), 7.29−7.13 (m, 5H), 7.12−7.04 (m, 1H), 4.24 (s, 2H), 3.35 (t, J = 5.7 Hz, 2H), 2.98 (t, J = 5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 135.2, 134.6, 134.1, 132.1, 131.8, 130.3, 129.9, 129.2, 129.1, 126.7, 126.4, 126.3, 124.9, 123.8, 122.7, 119.8, 119.6, 55.5, 52.4, 29.4; HRMS (ESI) exact mass calcd for $C_{22}H_{19}ClN_2O$ $[M + H]^+$ 363.1259, found 363.1255.

General Procedure for Synthesis of Oxadiazepines 2 Catalyzed by $AlCl_3$. To a solution of substituted nitrones **1** (0.3 mmol) in dichloroethane (3 mL) was added $AlCl_3$ (5 mol %) to the reaction flask, and the reaction was stirred at 70 °C. The reaction was monitored by TLC until complete consumption. Then, the solvent was concentrated. The reaction mixture was purified by flash chromatography (petroleum ether/ethyl acetate = 10:1−20:1) to obtain the desired products **2**.

***2a**, Eluent: Petroleum Ether/Ethyl Acetate (300:1).* Yellow solid, 84% yield (67 mg); mp 78−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 4H), 7.12 (d, J = 7.8 Hz, 2H), 7.00−6.87 (m, 3H), 4.95 (d, J = 6.3 Hz, 1H), 4.74 (AB, J = 15.9 Hz, 1H), 4.68 (AB, J = 15.9 Hz, 1H), 3.60−3.35 (m, 2H), 2.40−2.15 (m, 3H), 2.05−1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 147.8, 130.7, 129.0, 128.2, 121.1, 120.6, 116.1, 115.8, 95.3, 62.1, 50.1, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{19}N_2O$ $[M + H]^+$ 267.1497, found 267.1493.

***2b**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* White solid, 46% yield (39 mg); mp 125−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, J = 7.8 Hz, 2H), 7.17 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 8.4 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.72 (s, 1H), 4.92 (d, J = 6.9 Hz, 1H), 4.69 (AB, J = 15.6 Hz, 1H), 4.63 (AB, J = 15.6 Hz, 1H), 3.52−3.35 (m, 2H), 2.34 (s, 3H), 2.27−2.12 (m, 3H), 2.00−1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 147.7, 137.9, 130.6, 128.9, 125.6, 121.3, 121.0, 116.5, 116.2, 95.4, 61.7, 50.0, 32.5, 22.9, 21.5; HRMS (ESI) exact mass calcd for $C_{18}H_{20}N_2ONa$ $[M + Na]^+$ 303.1473, found 303.1468.

***2c**, Eluent: Petroleum Ether/Ethyl Acetate (150:1).* Yellow solid, 65% yield (58 mg); mp 73−75 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 7.8 Hz, 2H), 6.88 (t, J = 7.2 Hz, 1H), 6.48−6.40 (m, 2H), 4.92 (d, J = 6.9 Hz, 1H), 4.64 (AB, J = 15.6 Hz, 1H), 4.58 (AB, J = 15.6 Hz, 1H), 3.77 (s, 3H), 3.41−3.32 (m, 2H), 2.28−2.09 (m, 3H), 1.97−1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 149.8, 149.0, 131.7, 129.0, 121.1, 116.2, 104.8, 102.5, 95.4, 61.5, 55.4, 50.0, 32.5, 22.9; HRMS (ESI) exact mass calcd for $C_{18}H_{21}N_2O_2$ $[M + H]^+$ 297.1603, found 297.1598.

***2d**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* Yellow oil, 90% yield (93 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.31−7.22 (m, 3H), 7.04 (d, J = 8.1 Hz, 2H), 6.90 (t, J = 7.2 Hz, 1H), 6.71 (d, J = 8.4 Hz, 1H), 4.87 (d, J = 6.9 Hz, 1H), 4.57 (s, 2H), 3.39−3.28 (m, 2H), 2.33−2.06 (m, 3H), 1.98−1.81 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 146.9, 133.1, 130.9, 130.5, 129.7, 121.6, 117.5, 116.2, 112.7, 95.5,

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62.1, 50.2, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{17}N_2OBrNa$ $[M + Na]^+$ 367.0432, found 367.0422.

***2e**, Eluent: Petroleum Ether/Ethyl Acetate (300:1).* Brown solid, 64% yield (66 mg); mp 153−155 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, J = 7.8 Hz, 2H), 7.17−6.98 (m, 5H), 6.92 (t, J = 7.2 Hz, 1H), 4.94 (d, J = 7.2 Hz, 1H), 4.63 (AB, J = 15.2 Hz, 1H), 4.55 (AB, J = 15.2 Hz, 1H), 3.47−3.35 (m, 2H), 2.35−2.09 (m, 3H), 2.01−1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 149.1, 131.9, 129.1, 127.3, 123.3, 121.9, 121.6, 118.9, 116.3, 95.4, 62.1, 50.2, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{18}N_2OBr$ $[M + H]^+$ 345.0602, found 345.0613.

***2f**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* Yellow oil, 82% yield (74 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.20 (m, 3H), 7.15 (dd, J = 2.4, 8.4 Hz, 1H), 7.05 (d, J = 7.8 Hz, 2H), 6.90 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 4.87 (d, J = 7.2 Hz, 1H), 4.58 (s, 2H), 3.49−3.27 (m, 2H), 2.35−2.13 (m, 3H), 2.01−1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 146.4, 130.3, 130.1, 129.1, 127.9, 125.3, 121.5, 116.9, 116.2, 95.4, 61.9, 50.3, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{17}N_2OClNa$ $[M + Na]^+$ 323.0927, found 323.0938.

***2g**, Eluent: Petroleum Ether/Ethyl Acetate (300:1).* Brown solid, 77% yield (69 mg); mp 131−133 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J = 8.1 Hz, 2H), 7.18 (d, J = 7.8 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 6.97−6.81 (m, 3H), 4.95 (d, J = 7.2 Hz, 1H), 4.66 (AB, J = 15.6 Hz, 1H), 4.58 (AB, J = 15.6 Hz, 1H), 3.46−3.32 (m, 2H), 2.38−2.10 (m, 3H), 2.04−1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 148.9, 133.8, 131.6, 129.1, 126.8, 121.6, 120.3, 116.3, 116.0, 95.4, 61.9, 50.2, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{17}N_2OClNa$ $[M + Na]^+$ 323.0927, found 323.0916.

***2h**, Eluent: Petroleum Ether/Ethyl Acetate (10:1).* Yellow solid, 20% yield (19 mg); mp 158−160 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20−8.08 (m, 2H), 7.30 (t, J = 8.1 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 5.16 (d, J = 7.2 Hz, 1H), 4.74 (AB, J = 15.9 Hz, 1H), 4.56 (AB, J = 15.9 Hz, 1H), 3.54−3.44 (m, 2H), 2.36−2.19 (m, 3H), 2.05−1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 149.7, 131.0, 129.2, 126.9, 126.6, 124.6, 122.5, 116.5, 115.1, 95.6, 62.9, 50.5, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{17}N_3O_3Na$ $[M + Na]^+$ 334.1162, found 334.1164.

***2i**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* White solid, 60% yield (50 mg); mp 70−71 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.02−6.88 (m, 4H), 6.76 (d, J = 7.5 Hz, 1H), 4.95 (d, J = 7.2 Hz, 1H), 4.71 (AB, J = 15.6 Hz, 1H), 4.65 (AB, J = 15.6 Hz, 1H), 3.53−3.40 (m, 2H), 2.37 (s, 3H), 2.30−2.12 (m, 3H), 2.03−1.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 147.8, 138.8, 130.7, 128.9, 128.7, 128.1, 122.2, 120.6, 116.9, 115.8, 113.5, 95.5, 62.6, 50.1, 32.5, 22.9, 21.9; HRMS (ESI) exact mass calcd for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1648, found 281.1642.

***2j**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* Yellow oil, 74% yield (62 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, J = 7.8 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.94 (t, J = 8.4 Hz, 2H), 4.94 (d, J = 7.2 Hz, 1H), 4.64 (s, 2H), 3.55−3.35 (mz, 2H), 2.30 (s, 3H), 2.27−2.12 (m, 3H), 2.04−1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.7, 130.9, 130.7, 129.6, 128.6, 128.1, 120.5, 116.8, 115.7, 95.2, 63.0, 50.0, 32.5, 22.9, 20.7; HRMS (ESI) exact mass calcd for $C_{18}H_{21}N_2O$ $[M + H]^+$ 281.1648, found 281.1644.

***2k**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow oil, 60% yield (62 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.60−7.45 (m, 4H), 7.37 (t, J = 7.5 Hz, 2H), 7.33−7.18 (m, 3H), 7.12 (d, J = 8.7 H, 2H), 6.98−6.83 (m, 2H), 4.93 (d, J = 6.6 Hz, 1H), 4.75 (AB, J = 15.9 Hz, 1H), 4.68 (AB, J = 15.9 Hz, 1H), 3.60−3.33 (m, 2H), 2.33−2.14 (m, 3H), 2.02−1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 147.8, 141.1, 130.7, 128.8, 128.4, 128.2, 127.7, 126.8, 126.7, 120.7, 116.3, 115.8, 95.4, 61.6, 50.1, 32.5, 23.0; HRMS (ESI) exact mass calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1805, found 343.1804.

***2l**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* Yellow oil, 86% yield (73 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.20 (m, 2H), 7.15−7.06 (m, 2H), 6.99 (t, J = 8.7 Hz, 2H), 6.94 (t, J = 8.7 Hz, 2H), 4.95 (d, J = 7.2 Hz, 1H), 4.64 (AB, J = 15.6 Hz, 1H), 4.56 (AB, J = 15.6 Hz, 1H), 3.57−3.32 (m, 2H), 2.36−2.11 (m, 3H), 2.03−1.90 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 156.7, 147.7, 146.6 (d, J = 2.7 Hz), 130.6, 128.2, 120.6, 118.3 (d, J = 7.5 Hz), 115.7 (d, J = 12.0 Hz), 115.3, 95.5, 63.6, 50.0, 32.5, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{18}FN_2O$ $[M + H]^+$ 285.1398, found 285.1398.

***2m**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow solid, 93% yield (84 mg); mp 70−71 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (t, J = 8.7 Hz, 2H), 7.22 (t, J = 8.1 Hz, 1H), 7.13 (s, 1H), 7.01−6.83 (m, 4H), 4.94 (d, J = 6.9 Hz, 1H), 4.74 (AB, J = 15.9 Hz, 1H), 4.69 (AB, J = 15.9 Hz, 1H), 3.56−3.34 (m, 2H), 2.35−2.20 (m, 3H), 2.03−1.92 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 147.5, 134.9, 130.6, 130.0, 128.4, 127.9, 120.8, 120.6, 115.9, 115.7, 113.6, 95.6, 61.2, 50.1, 32.4, 23.0; HRMS (ESI) exact mass calcd for $C_{17}H_{18}ClN_2O$ $[M + H]^+$ 301.1102, found 301.1101.

***2n**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* Colorless oil, 90% yield (81 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 m, 4H), 6.96 (d, J = 8.4 Hz, 2H), 6.88 (t, J = 8.1 Hz, 2H), 4.90 (d, J = 6.9 Hz, 1H), 4.67 (AB, J = 16.2 Hz, 1H), 4.62 (AB, J = 16.2 Hz, 1H), 3.51−3.29 (m, 2H), 2.29−2.10 (m, 3H), 2.00−1.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 147.6, 130.6, 128.9, 128.3, 127.9, 125.9, 120.8, 117.2, 115.8, 95.4, 61.7, 50.0, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{18}ClN_2O$ $[M + H]^+$ 301.1102, found 301.1100.

***2o**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow solid, 87% yield (90 mg); mp 80−82 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27−7.13 (m, 3H), 7.07 (t, J = 8.1 Hz, 1H), 7.01−6.73 (m, 4H), 4.88 (d, J = 7.2 Hz, 1H), 4.67 (AB, J = 15.9 Hz, 1H), 4.62 (AB, J = 15.9 Hz, 1H), 3.50−3.25 (m, 1H), 2.30−2.07 (m, 3H), 1.98−1.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 147.5, 130.6, 130.3, 128.4, 127.9, 123.5, 123.1, 120.8, 118.5, 115.9, 114.0, 95.7, 61.2, 50.1, 32.4, 23.0; HRMS (ESI) exact mass calcd for $C_{17}H_{18}BrN_2O$ $[M + H]^+$ 345.0597, found 345.0587.

***2p**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow oil, 84% yield (86 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.28 (m, 2H), 7.28−7.13 (m, 2H), 6.98−6.81 (m, 4H), 4.89 (d, J = 6.9 Hz, 1H), 4.68 (AB, J = 15.9 Hz, 1H), 4.62 (AB, J = 15.9 Hz, 1H), 3.50−3.28 (m, 2H), 2.28−2.09 (m, 3H), 1.98−1.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 147.5, 131.8, 130.6, 128.3, 127.8, 120.8, 117.5, 115.8, 113.2, 95.3, 61.2, 49.9, 32.4, 22.9; HRMS (ESI) exact mass calcd for $C_{17}H_{16}BrN_2O$ $[M + H]^+$ 343.0441, found 343.0442.

***2q**, Eluent: Petroleum Ether/Ethyl Acetate (400:1).* Yellow oil, 77% yield (76 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.52−7.10 (m, 12H), 6.96 (t, J = 7.2 Hz, 1H), 5.81 (s, 1H), 4.87 (AB, J = 15.9 Hz, 1H), 4.72 (AB, J = 15.9 HZ, 1H), 3.88−3.74 (m, 1H), 3.55−3.44 (m, 1H), 3.16−3.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 150.2, 136.3, 133.9, 133.3, 130.3, 129.7, 129.1, 128.7, 128.7, 128.5, 126.7, 124.6, 124.1, 121.3, 116.3, 92.2, 62.5, 46.5, 30.4; HRMS (ESI) exact mass calcd for $C_{22}H_{21}N_2O$ $[M + H]^+$ 329.1654, found 329.1645.

***2r**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow oil, 62% yield (64 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49−7.43 (m, 1H), 7.39−7.20 (m, 8H), 7.05 (s, 1H), 6.98 (t, J = 7.2 Hz, 2H), 5.80 (s, 1H), 4.84 (AB, J = 15.6 Hz, 1H), 4.69 (AB, J = 15.6 Hz, 1H), 3.87−3.68 (m, 1H), 3.53−3.42 (m, 1H), 3.20−3.05 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.4, 149.1, 135.9, 134.7, 132.7, 132.3, 130.9, 128.9, 128.8, 128.6, 128.1, 126.4, 124.8, 120.4, 115.1, 114.9, 90.8, 59.7, 58.5 45.8, 29.0; HRMS (ESI) exact mass calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1805, found 343.1803.

***2s**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow oil, 89% yield (108 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, J = 2.4 Hz, 1H), 7.45−7.28 (m, 6H), 7.27−7.20 (m, 1H), 7.15 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 5.74 (s, 1H), 4.80 (AB, J = 15.6 Hz, 1H), 4.60 (AB, J = 15.6 Hz, 1H), 3.78−3.66 (m, 1H), 3.47−3.35 (m, 1H), 3.06 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 149.1, 135.9, 134.7, 132.7, 132.2, 130.9, 128.9, 128.8, 128.6, 128.1, 126.4, 124.8, 120.4, 115.1, 114.9, 90.8, 58.4, 45.8, 29.0; HRMS (ESI) exact mass calcd for $C_{22}H_{20}BrN_2O$ $[M + H]^+$ 407.0754, found 407.0749.

***2t**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow oil, 64% yield (66 mg); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43−6.97 (m, 12H), 5.75 (s, 1H), 4.77 (AB, J = 15.6 Hz, 1H), 4.58 (AB, J = 15.6 Hz, 1H), 3.82−3.67 (m, 1H), 3.48−3.35 (m, 1H), 3.10−2.97 (m, 2H), 2.27 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 148.1, 136.1, 134.1, 133.3, 131.0, 130.3, 129.7, 129.5, 128.6, 128.5, 128.4, 126.5, 124.6, 123.9, 116.8, 91.9, 63.2, 46.5, 30.3, 20.7; HRMS (ESI) exact mass calcd for $C_{23}H_{23}N_2O$ $[M + H]^+$ 343.1805, found 343.1799.

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***2u**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow solid, 69% yield (84 mg); mp 154−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63−7.53 (m, 4H), 7.51−7.37 (m, 4H), 7.37−7.08 (m, 9H), 5.82 (s, 1H), 4.91 (AB, J = 15.9 Hz, 1H), 4.77 (AB, J = 15.9 Hz, 1H), 3.86−3.72 (m, 1H), 3.52−3.45 (m, 1H), 3.11 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 149.4, 141.0, 136.2, 133.9, 133.7, 133.1, 130.3, 129.6, 128.8, 128.7, 128.7, 128.4, 127.7, 126.8, 126.7, 126.6, 124.4, 124.0, 116.4, 92.2, 61.9, 46.5, 30.3; HRMS (ESI) exact mass calcd for $C_{28}H_{25}N_2O$ $[M + H]^+$ 405.1961, found 405.1962.

***2v**, Eluent: Petroleum Ether/Ethyl Acetate (500:1).* Yellow oil, 75% yield (81 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45−7.11 (m, 10H), 7.01 (dd, J = 1.5, 8.1 Hz, 1H), 6.89 (dd, J = 1.2, 7.8 Hz, 1H), 5.77 (s, 1H), 4.87 (AB, J = 15.9 Hz, 1H), 4.71 (AB, J = 15.9 Hz, 1H), 3.82−3.66 (m, 1H), 3.53−3.42 (m 1H), 3.11 (t, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 150.5, 136.2, 134.9, 133.1, 132.7, 130.2, 130.0, 129.4, 128.8, 128.5, 126.7, 124.1, 124.1, 120.8, 115.8, 113.7, 92.5, 61.5, 46.4, 30.2; HRMS (ESI) exact mass calcd for $C_{22}H_{20}ClN_2O$ $[M + H]^+$ 363.1259, found 363.1257.

General Procedure for Synthesis of Oxadiazepines 2 via Reaction of 2-(Pyrrolidin-l-yl)benzaldehydes 3 and *N*-Arylhydroxylamines 4 Catalyzed by Lewis aAcid. To a solution of 2-(pyrrolidin-l-yl)benzaldehydes **3** (0.4 mmol, 1.0 equiv) and *N*-arylhydroxylamines **4** (1.2 equiv) in dichloroethane (4 mL) was added $AlCl_3$ (5 mol %) to the reaction flask, and the reaction was stirred at 70 °C. The reaction was monitored by TLC until complete consumption. The solvent was concentrated. The reaction mixture was purified by flash chromatography to obtain the desired products **2**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01609.

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

CIF file for compound **2o** (CIF)

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Notes

The authors declare no competing financial interest.

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