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Silver-Assisted [3 + 2] Annulation of Nitrones with Isocyanides: Synthesis of 2,3,4-Trisubstituted 1,2,4-Oxadiazolidin-5-ones

Xuanyu Shen, Andrey Shatskiy, Yan Chen, Markus D. Kärkäs,* Xiang-Shan Wang, and Jian-Quan Liu*

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ABSTRACT: A silver-assisted method for [3 + 2] annulation of nitrones with isocyanides has been developed. The developed protocol allows access to a variety of 2,3,4-trisubstituted 1,2,4-oxadiazolidin-5-one derivatives as single diastereomers in good to excellent yields using silver oxide as the catalyst and molecular oxygen as the terminal oxidant. A plausible mechanism involving a nucleophilic addition/cyclization/protodeargentation/oxidation pathway is proposed on the basis of experimental results.

INTRODUCTION

Nitrones and isocyanides constitute multifaceted building blocks in organic synthesis and have been extensively implemented in the construction of nitrogen-based heterocyclic compounds.[1,2] Thus far, several remarkable reaction manifolds have been realized. Among these, the [3 + 2] dipolar cycloaddition reaction represents a powerful strategy to access five-membered heterocyclic compounds owing to its simplicity and atom efficiency.[3,4] In contrast, [3 + 1] and [3 + 1 + 1] cycloaddition reactions of nitrones with isocyanides to assemble heterocycles have rarely been utilized.[5−8]

Only a handful of reports detailing the cycloaddition manifolds of nitrones with isocyanides have been disclosed (Figure 1a). For example, the Zhu, Zeeh, and Lorke groups have demonstrated that nitrones can undergo [3 + 1] cycloaddition with isocyanides to afford four-membered 4-imino-1,2-oxazetidine motifs.[6] Furthermore, a proposed [3 + 3] cycloaddition process involving nitrones and α-metalated isocyanides to produce five-membered 2-imidazolidinones was recently reported.[8] Also, Xu and co-workers realized that isocyanoacetates could react with nitrones to produce polysubstituted pyrroles in the presence of commercially available copper salts through a [3 + 1 + 1] cycloaddition manifold.[7] Luzyanin and co-workers have also described a metal-mediated strategy in which nitrones react with palladium-bound isocyanides to provide carbene complexes (Figure 1b).[9] Despite the number of synthetic methodologies that have been realized,[10] the development of new and efficient methods that rely on easily available starting materials are of great value. As a continuation of the recently witnessed reports on isocyanide-involving reaction manifolds,[11] we have explored silver-mediated manifolds involving isocyanides.[12] Here, we disclose a silver-assisted [3 + 2] annulation reaction of nitrones with isocyanides for the assembly of 1,2,4-oxadiazolidin-5-ones and the subsequent decarboxylative process for accessing amidines, which are vital motifs in pharmaceuticals and natural products.[13] The developed methods display broad substrate scope and are conducted under mild reaction conditions (Figure 1c).

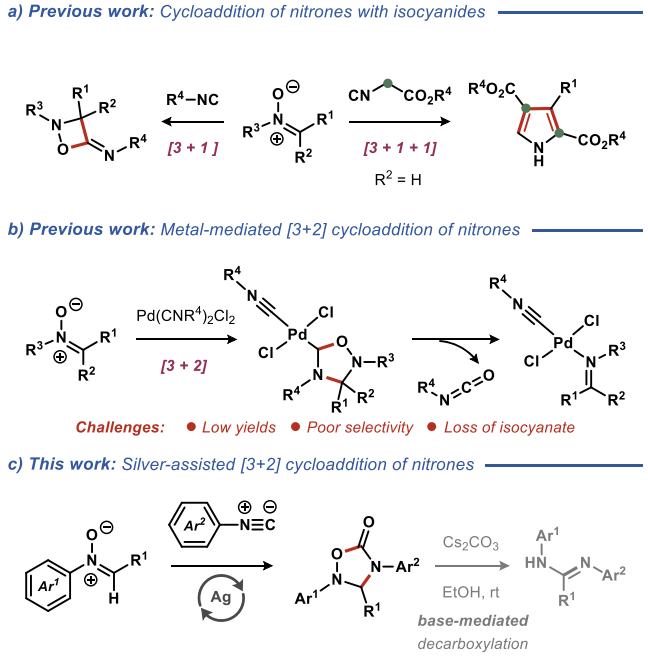

Figure 1. Annulation reactions of isocyanides with nitrones.

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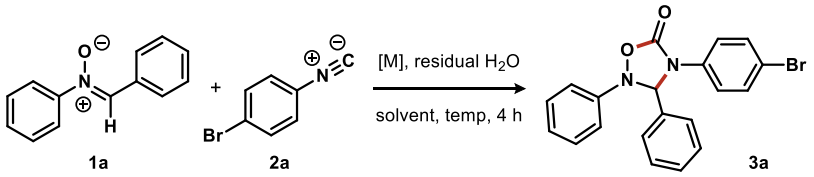
Table 1. Optimization of the Reaction Conditions[a,b]



entry	[M]	solvent	temp (°C)	yield (%)[b]
1	Ag_2O	DMF	80	76
2	AgOAc	DMF	80	42
3	Ag_2CO_3	DMF	80	74
4	AgOTf	DMF	80	<5[c]
5	$AgBF_4$	DMF	80	<5[c]
6	CuI	DMF	80	<5[c]
7	$Pd(OAc)_2$	DMF	80	<5[c]
8	**Ag_2O**	**1,4-dioxane**	**80**	**91**
9	Ag_2O	toluene	80	76
10	Ag_2O	CH_3CN	80	53
11	Ag_2O	EtOH	80	<10[c]
12	Ag_2O	1,4-dioxane	40	38
13		1,4-dioxane	80	<5[c]

[a]Reaction conditions: all reactions were carried out with **1a** (0.55 mmol), **2a** (0.5 mmol), catalyst (10 mol %) in the solvent (2.0 mL) under air for 4 h. [b]Yield are of isolated **3a** after purification by column chromatography. [c]Yield determined by ^1H NMR analysis of the reaction mixture using CH_2Br_2 as the internal standard.

RESULTS AND DISCUSSION

N-Benzylideneaniline oxide (**1a**) and 1-bromo-4-isocyanobenzene (**2a**) were selected as model substrates for the optimization of the [3 + 2] annulation reaction. To our delight, conducting the reaction in DMF at 80 °C in the presence of Ag_2O (10 mol %) afforded the desired product 4-(4-bromophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3a**) in a 76% isolated yield after merely 4 h (Table 1, entry 1). Screening of other silver salts, including AgOAc, Ag_2CO_3, AgOTf, $AgBF_4$, and other metal precursors, such as CuI and $Pd(OAc)_2$, showed that Ag_2CO_3 and Ag_2O displayed the best reactivity while AgOAc proved to be less efficient and the other metal catalysts were inactive (Table 1, entries 2–7). Next, switching to 1,4-dioxane greatly increased the yield of annulation adduct **3a** to 91% (Table 1, entry 8). The use of aprotic or polar solvents, such as toluene and MeCN, had a negative effect on the reaction and delivered **3a** in diminished yields (Table 1, entries 9 and 10) while employing the protic solvent EtOH nearly inhibited the reaction (Table 1, entry 11). Decreasing the reaction temperature from 80 to 40 °C led to a significantly diminished yield of the desired product (Table 1, entry 12). A control experiment established that a silver catalyst is required for the reaction to proceed (Table 1, entry 13). Furthermore, the annulation affords product **3a** as a single diastereomer as confirmed by single-crystal X-ray diffraction analysis (CCDC 1915298, see Scheme 1).

Next, the optimal reaction conditions were adopted on a variety of nitrones and aryl isocyanides to investigate the generality of the protocol (Scheme 1). A collection of diversely functionalized nitrones underwent annulation with aryl isocyanides to deliver the corresponding product **3** in good to excellent yields. For example, para-substituted arene motifs bearing electron-donating or electron-withdrawing moieties were tolerated in the annulation with 1-bromo-4-isocyanobenzene (**2a**) to produce the corresponding products (**3b**–**3g**) in high yields. Similarly, ortho-, meta-, and disubstituted substrates were also well tolerated, affording products **3h**–**3n** in good to high yields. Gratifyingly, common functional groups including alkyl, alkoxy, halogen, cyano, and trifluoromethyl were all effective. A more elaborate substrate (**1p**) with a potentially sensitive alkyne moiety could also be successfully converted to product **3p** (72%), illustrating the compatibility of the developed method. Heteroaryl nitrones including 2-furyl and 2-thienyl were also evaluated, delivering the corresponding adducts **3t** and **3u** with high efficiency. Furthermore, subjecting the fused aromatic (**1v**) or alkyl (**1w** and **1x**) nitrones to isocyanide **2a**, afforded the desired products **3v**–**3x** in good to excellent yields. The protocol also tolerated a wide variation of substituents on the arene ring on the isocyanides (**2y**–**2ad**), efficiently delivering a set of diverse oxadiazolidinones (**3y**–**3ad**) in high yields. The applicability of the annulation protocol was highlighted through a gram-scale reaction of *N*-benzylideneaniline oxide (**1a**) and 1-bromo-4-isocyanobenzene (**2a**). The reaction was performed on a 10 mmol scale and proceeded smoothly to give product **3a** (3.26 g, 83%) even when decreasing the amount of the catalyst to 5 mol % (Scheme 1).

We further explored the application of the synthesized oxadiazolidinones. Intriguingly, subjecting **3a**, **3y**, **3z**, **3ab**, and **3ac** to Cs_2CO_3 (2.0 equiv) triggered extrusion of CO_2 to give amidines **4a**–**4e** in up to 92% yield (Scheme 2). Compared to Anderson's reaction conditions,[10d] no reaction occurred using compound **3** even when extending the reaction time to 24 h. Therefore, the developed protocol undoubtedly represents a more general and practical methodology to access amidines, complementing the existing ones.

A series of mechanistic experiments was performed to gain insights into the reaction mechanism (Scheme 3). The key step is clearly to derive the source of the carbonyl oxygen that is incorporated in oxadiazolidinone **3**. Therefore, experiments were carried out with **1c** and **2a** under the optimized reaction conditions with the addition of 2.0 equiv of $H_2{}^{18}O$ (Scheme 3a). In the presence of $H_2{}^{18}O$, the reaction between **1c** and **2a** only provides [^{16}O]-**3c**; albeit with a decreased yield.[14] This

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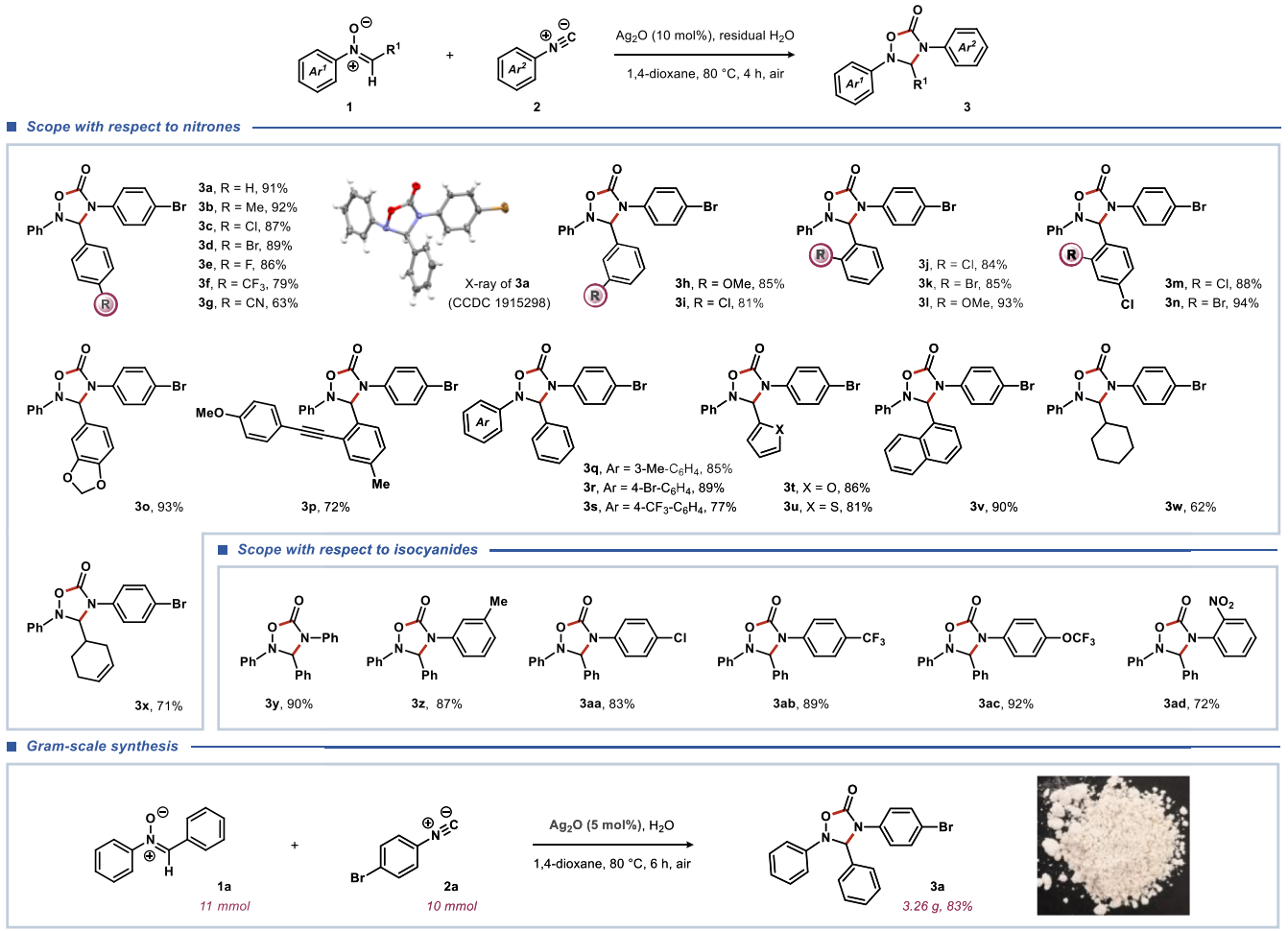
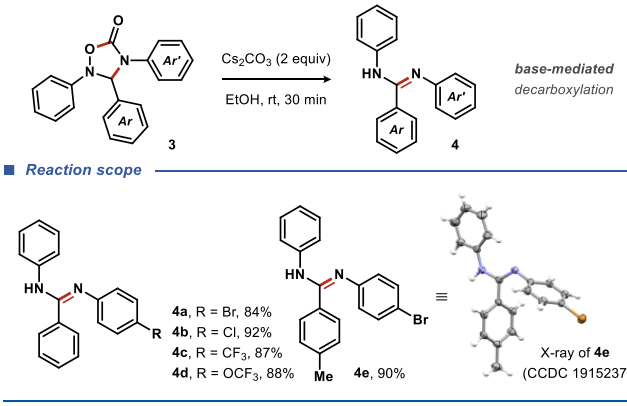
Scheme 1. Silver-Assisted Synthesis of Oxadiazolidinones[a]

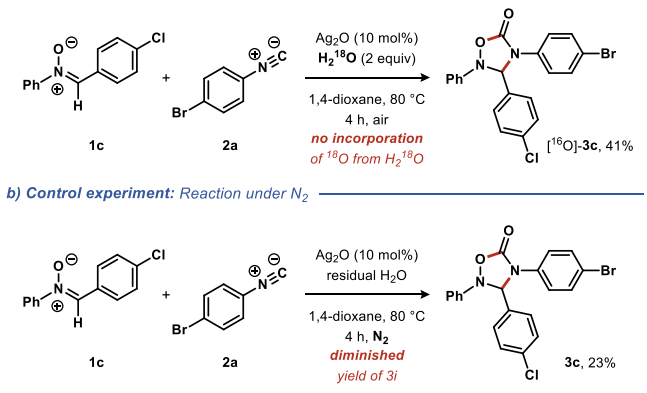


[a]All reactions were carried out with **1a** (0.55 mmol), **2a** (0.5 mmol), and Ag_2O (10 mol %) in 1,4-dioxane (2.0 mL) at 80 °C under air for 4 h. Yields are of isolated products after purification by column chromatography. Products were isolated as single diastereomers.

Scheme 2. Application of Oxadiazolidinones to the Synthesis of Amidines through CO_2 Extrusion



Scheme 3. Mechanistic Investigations



implies that O_2 is the oxygen source in this reaction. Meanwhile, a decreased yield of product **3c** was obtained when carrying out the reaction under N_2, highlighting that O_2 is necessary for the reaction to proceed efficiently (Scheme 3b).

Based on the results from the described experiments and related literature precedents,[2,15] a plausible mechanism was proposed (Scheme 4). Initially, isocyanide **2** coordinates to the silver center, generating silver intermediate **A**.[16] Then, it is believed that nitrone **1** attacks complex **A**, producing intermediate **B**. This species presumably undergoes rapid intramolecular cyclization to generate the five-membered cyclized cationic intermediate **C**.[17] Subsequent protodeargentation of intermediate **C** produces **D**, which is oxidized by O_2,[18] delivering product **3** with the regeneration of water and completing the catalytic cycle. Thus, the protodeargentation

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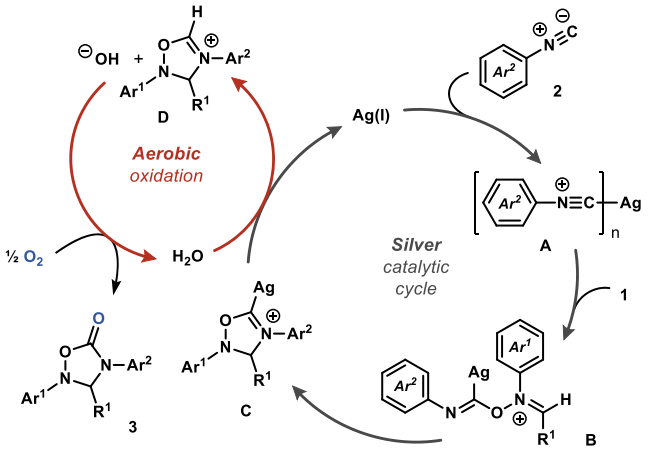
Scheme 4. Proposed Reaction Mechanism for the Formation of Oxadiazolidinone 3



step can be initiated by residual water present in the solvent or air (cf. Scheme 1).

CONCLUSIONS

In summary, we have developed a silver-assisted protocol for [3 + 2] annulation between isocyanides and nitrones, providing a convenient approach for the construction of 2,3,4-trisubstituted 1,2,4-oxadiazolidin-5-ones in good to excellent yields. The reaction mechanism is proposed to proceed through a nucleophilic addition/cyclization/proto-deargentation/oxidation pathway. Finally, base-promoted decarboxylation of the prepared oxadiazolidinones at ambient temperature is also described, providing a convenient protocol for the direct assembly of amidine compounds.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial suppliers and used without treatment, unless otherwise indicated. The products were purified by column chromatography on silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian NMR spectrometer at 400 and 101 MHz, respectively. NMR spectra for compounds **3a**−**3ad** were recorded in $CDCl_3$, while compounds **4a**−**4e** displayed spectra containing signals from multiple tautomeric forms and geometrical isomers; however, good quality NMR spectra for these compounds were obtained in $CDCl_3$ upon the addition of a small amount of D_2SO_4. Mass spectra were recorded on a BRUKER Autoflex III Smartbeam MS-spectrometer. High-resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) methods.

General Procedure for Synthesis of 1,2,4-Oxadiazolidin-5-ones (with 3a as an Example). A 10 mL Schlenk flask equipped with a magnetic stir bar was charged with a mixture of **1a** (108 mg, 0.55 mmol), **2a** (90 mg, 0.5 mmol), and 1,4-dioxane (2.0 mL). Then, Ag_2O (12 mg, 10 mol %) was added and the mixture was stirred at 80 °C in an oil bath until substrate **2a** was consumed as indicated by thin layer chromatography (TLC) (about 4 h). The resulting mixture was concentrated and the residue was taken up in CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (silica gel; petroleum ether/ethyl acetate 10:1) afforded **3a** as a white solid (179 mg, 91%).

General Procedure for Synthesis of Amidines (with 4a as an Example). A 10 mL Schlenk flask equipped with a magnetic stir bar was charged with a mixture of **3a** (197 mg, 0.5 mmol) and Cs_2CO_3 (325 mg, 1 mmol, 2.0 equiv). Then, EtOH (2.0 mL) was added and the mixture was stirred at room temperature until substrate **3a** was consumed as indicated by TLC (about 30 min). The resulting mixture was concentrated and the residue was taken up in CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the crude product by column chromatography (silica gel; petroleum ether/ethyl acetate 10:3) afforded **4a** as a white solid (147 mg, 84%).

*4-(4-Bromophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3a**).* The product was obtained in a 91% yield (179 mg). White solid; mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.47 (m, 2H), 7.45−7.43 (m, 3H), 7.41−7.36 (m, 4H), 7.24−7.19 (m, 5H), 6.11 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.0, 149.1, 135.2, 134.7, 132.2, 130.2, 129.5, 129.4, 127.1, 125.9, 122.4, 118.8, 117.4, 86.3; HRMS (APCI) m/z: calcd for $C_{20}H_{16}BrN_2O_2$ [M + H]$^+$, 395.0390; found, 395.0370.

*4-(4-Bromophenyl)-2-phenyl-3-(p-tolyl)-1,2,4-oxadiazolidin-5-one (**3b**).* The product was obtained in a 92% yield (187 mg). White solid; mp 138−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 6H), 7.25−7.19 (m, 7H), 6.07 (s, 1H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.0, 149.1, 140.4, 134.7, 132.2, 132.15, 130.0, 129.4, 127.1, 125.8, 122.5, 118.7, 117.4, 86.3, 21.3; HRMS (APCI) m/z: calcd for $C_{21}H_{18}BrN_2O_2$ [M + H]$^+$, 409.0552; found, 409.0531.

*4-(4-Bromophenyl)-3-(4-chlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3c**).* The product was obtained in a 87% yield (186 mg). White solid; mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42−7.38 (m, 8H), 7.26−7.16 (m, 5H), 6.08 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.8, 148.8, 136.3, 134.4, 133.7, 132.4, 129.6, 129.5, 128.6, 126.2, 122.6, 119.1, 117.5, 85.6; HRMS (APCI) m/z: calcd for $C_{20}H_{15}BrClN_2O_2$ [M + H]$^+$, 429.0005; found, 429.0017.

*3,4-Bis(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3d**).* The product was obtained in a 89% yield (209 mg). White solid; mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.4 Hz, 2H), 7.42−7.35 (m, 6H), 7.25−7.16 (m, 5H), 6.07 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.8, 148.8, 134.4, 134.2, 132.6, 132.4, 129.5, 128.9, 126.2, 124.6, 122.6, 119.2, 117.5, 85.7; HRMS (APCI) m/z: calcd for $C_{20}H_{15}Br_2N_2O_2$ [M + H]$^+$, 472.9500; found, 472.9471.

*4-(4-Bromophenyl)-3-(4-fluorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3e**).* The product was obtained in a 86% yield(177 mg). White solid; mp 150−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49−7.45 (m, 2H), 7.41−7.37 (m, 4H), 7.24−7.18 (m, 4H), 7.16−7.10 (m, 3H), 6.10 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 85.7, 116.5 (d, $J_{(F-C)}$ = 21.9 Hz), 117.5, 119.1, 122.7, 126.1, 129.2 (d, $J_{(F-C)}$ = 8.5 Hz), 129.5, 131.1 (d, $J_{(F-C)}$ = 3.2 Hz), 132.3, 134.4, 148.8, 153.8, 163.6 (d, $J_{(F-C)}$ = 248.9 Hz); HRMS (APCI) m/z: calcd for $C_{20}H_{15}BrFN_2O_2$ [M + H]$^+$, 413.0301; found, 413.0300.

*4-(4-Bromophenyl)-2-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazolidin-5-one (**3f**).* The product was obtained in a 79% yield (182 mg). White solid; mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.44−7.41 (m, 4H), 7.27−7.23 (m, 3H), 7.20−7.18 (m, 2H), 6.18 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.8, 148.9, 139.2, 134.4, 132.5, 132.2, 129.7, 127.6, 126.4, 124.9, 122.4, 122.2, 119.2, 117.5, 85.5; HRMS (APCI) m/z: calcd for $C_{21}H_{15}BrF_3N_2O_2$ [M + H]$^+$, 463.0269; found, 463.0276.

*4-(4-(4-Bromophenyl)-5-oxo-2-phenyl-1,2,4-oxadiazolidin-3-yl)-benzonitrile (**3g**).* The product was obtained in a 63% yield (132 mg). White solid; mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.44−7.40 (m, 4H), 7.28−7.22 (m, 3H), 7.17 (d, J = 8.8 Hz, 2H), 6.17 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.6, 148.7, 140.2, 134.2, 133.1, 132.6, 129.7, 127.9, 126.5, 122.4, 119.4, 117.8, 117.5, 114.3, 85.2; HRMS (APCI) m/z: calcd for $C_{21}H_{15}BrN_3O_2$ [M + H]$^+$, 420.0348; found, 420.0353.

*4-(4-Bromophenyl)-3-(3-methoxyphenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3h**).* The product was obtained in a 85% yield (180 mg). White solid; mp 124−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.32 (m, 5H), 7.25−7.19 (m, 5H), 7.05−7.03 (m, 2H), 6.97−6.95 (m, 1H), 6.07 (s, 1H), 3.80 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 160.3, 153.9, 149.1, 136.7, 134.6, 132.2, 130.5, 129.4, 125.9, 122.4, 119.3, 118.8, 117.3, 115.5, 112.7, 86.2, 55.4; HRMS

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(APCI) m/z: calcd for $C_{21}H_{18}BrN_2O_3$ $[M + H]^+$, 425.0501; found, 425.0509.

*4-(4-Bromophenyl)-3-(3-chlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3i**).* The product was obtained in a 81% yield (173 mg). White solid; mp 161−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.43−7.39 (m, 5H), 7.38−7.33 (m, 2H), 7.25−7.18 (m, 5H), 6.08 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.8, 148.9, 137.4, 135.4, 134.4, 132.4, 130.7, 130.5, 129.6, 127.3, 126.2, 125.2, 122.4, 119.1, 117.4, 85.5; HRMS (APCI) m/z: calcd for $C_{20}H_{15}BrClN_2O_2$ $[M + H]^+$, 429.0005; found, 429.0011.

*4-(4-Bromophenyl)-3-(2-chlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3j**).* The product was obtained in a 84% yield (179 mg). White solid; mp 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 2H), 7.44−7.33 (m, 8H), 7.24−7.21 (m, 3H), 6.70 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.4, 149.3, 134.5, 133.3, 132.4, 132.3, 131.5, 130.5, 129.5, 128.1, 127.9, 126.1, 121.3, 118.6, 117.5, 81.9; HRMS (APCI) m/z: calcd for $C_{20}H_{15}BrClN_2O_2$ $[M + H]^+$, 429.0005; found, 429.0008.

*3-(2-Bromophenyl)-4-(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3k**).* The product was obtained in a 85% yield (200 mg). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.42−7.39 (m, 7H), 7.33−7.29 (m, 1H), 7.25−7.21 (m, 3H), 6.69 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.4, 149.1, 134.4, 133.9, 133.8, 132.3, 131.7, 129.5, 128.8, 128.3, 126.2, 123.2, 121.6, 118.7, 117.9, 84.0; HRMS (APCI) m/z: calcd for $C_{20}H_{15}Br_2N_2O_2$ $[M + H]^+$, 472.9500; found, 472.9504.

*4-(4-Bromophenyl)-3-(2-methoxyphenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3l**).* The product was obtained in a 93% yield (197 mg). White solid; mp 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43−7.35 (m, 7H), 7.30−7.28 (m, 1H), 7.26−7.24 (m, 2H), 7.20−7.16 (m, 1H), 7.03−6.97 (m, 2H), 6.66 (s, 1H), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 157.1, 154.6, 150.2, 135.1, 132.1, 131.4, 129.3, 126.8, 125.3, 122.8, 121.3, 120.8, 117.9, 116.6, 111.3, 80.7, 55.7; HRMS (APCI) m/z: calcd for $C_{21}H_{18}BrN_2O_3$ $[M + H]^+$, 425.0501; found, 425.0470.

*4-(4-Bromophenyl)-3-(2,4-dichlorophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3m**).* The product was obtained in a 88% yield (195 mg). White solid; mp 109−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.51 (m, 1H), 7.46−7.40 (m, 5H), 7.37−7.33 (m, 3H), 7.24−7.19 (m, 3H), 6.64 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.2, 149.0, 137.0, 134.2, 134.0, 132.5, 131.1, 130.4, 129.6, 129.0, 128.6, 126.3, 121.5, 118.9, 117.6, 81.5; HRMS (APCI) m/z: calcd for $C_{20}H_{14}BrCl_2N_2O_2$ $[M + H]^+$, 462.9616; found, 462.9622.

*3-(2-Bromo-4-chlorophenyl)-4-(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3n**).* The product was obtained in a 94% yield (229 mg). White solid; mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 1.6 Hz, 1H), 7.48−7.37 (m, 8H), 7.27−7.23 (m, 1H), 7.21−7.19 (m, 2H), 6.64 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.2, 148.7, 137.0, 134.1, 133.4, 132.5, 132.4, 129.5, 129.2, 129.1, 126.4, 123.6, 121.7, 118.9, 117.9, 83.5; HRMS (APCI) m/z: calcd for $C_{20}H_{14}Br_2ClN_2O_2$ $[M + H]^+$, 506.9105; found, 506.9122.

*3-(Benzo[d][1,3]dioxol-5-yl)-4-(4-bromophenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3o**).* The product was obtained in a 93% yield (203 mg). White solid; mp 141−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.36 (m, 4H), 7.23−7.18 (m, 5H), 7.00 (s, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.01−6.005 (m, 2H), 5.99 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.8, 149.3, 148.8, 134.6, 132.3, 129.4, 128.9, 126.0, 122.9, 121.7, 119.0, 117.6, 108.6, 107.2, 101.7, 86.3, 29.7; HRMS (APCI) m/z: calcd for $C_{21}H_{16}BrN_2O_4$ $[M + H]^+$, 439.0293; found, 439.0297.

*4-(4-Bromophenyl)-3-(2-((4-methoxyphenyl)ethynyl)-4-methylphenyl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3p**).* The product was obtained in a 72% yield (193 mg). White solid; mp 168−169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.43−7.41 (m, 5H), 7.38−7.35 (m, 2H), 7.33−7.29 (m, 4H), 7.20−7.14 (m, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.82 (s, 1H), 3.85 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 160.2, 154.2, 149.6, 140.2, 134.8, 133.5, 133.1, 133.06, 132.2, 130.3, 129.3, 126.3, 125.6, 122.9, 121.3, 118.2, 117.3, 114.2, 96.0, 85.2, 83.3, 55.4, 21.1; HRMS (APCI) m/z: calcd for $C_{30}H_{24}BrN_2O_3$ $[M + H]^+$, 539.0965; found, 539.0973.

*4-(4-Bromophenyl)-3-phenyl-2-(m-tolyl)-1,2,4-oxadiazolidin-5-one (**3q**).* The product was obtained in a 85% yield (173 mg). White solid; mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.43 (m, 5H), 7.38 (d, J = 8.8 Hz, 2H), 7.29−7.25 (m, 1H), 7.21 (d, J = 8.8 Hz, 2H), 7.07 (s, 1H), 7.03−7.01 (m, 2H), 6.11 (s, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.1, 149.3, 139.6, 135.3, 134.8, 132.2, 130.2, 129.3, 129.26, 127.1, 126.7, 122.3, 118.7, 117.9, 114.3, 86.3, 21.6; HRMS (APCI) m/z: calcd for $C_{21}H_{18}BrN_2O_2$ $[M + H]^+$, 409.0552; found, 409.0563.

*2,4-Bis(4-bromophenyl)-3-phenyl-1,2,4-oxadiazolidin-5-one (**3r**).* The product was obtained in a 89% yield (209 mg). White solid; mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.49 (m, 2H), 7.47−7.43 (m, 5H), 7.40−7.38 (m, 2H), 7.17 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.8 Hz, 2H), 6.05 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.6, 148.0, 134.7, 134.4, 132.5, 132.3, 130.5, 129.4, 127.2, 122.7, 119.1, 119.0, 86.3; HRMS (APCI) m/z: calcd for $C_{20}H_{15}Br_2N_2O_2$ $[M + H]^+$, 472.9500; found, 472.9513.

*4-(4-Bromophenyl)-3-phenyl-2-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazolidin-5-one (**3s**).* The product was obtained in a 77% yield (178 mg). White solid; mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.4 Hz, 2H), 7.51−7.46 (m, 5H), 7.40 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 6.15 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.2, 151.8, 134.7, 134.2, 132.4, 130.6, 129.5, 127.2, 126.8, 126.7, 122.9, 119.4, 116.6, 86.1; HRMS (APCI) m/z: calcd for $C_{21}H_{15}BrF_3N_2O_2$ $[M + H]^+$, 463.0269; found, 463.0271.

*4-(4-Bromophenyl)-3-(furan-2-yl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3t**).* The product was obtained in a 86% yield (165 mg), yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.44−7.39 (m, 4H), 7.28−7.20 (m, 5H), 6.54−6.53 (m, 1H), 6.42−6.41 (m, 1H), 6.21 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.7, 149.0, 147.9, 144.3, 134.6, 132.3, 129.5, 125.9, 121.9, 118.9, 117.1, 111.0, 110.6, 79.9; HRMS (APCI) m/z: calcd for $C_{18}H_{14}BrN_2O_3$ $[M + H]^+$, 385.0188; found, 385.0197.

*4-(4-Bromophenyl)-2-phenyl-3-(thiophen-2-yl)-1,2,4-oxadiazolidin-5-one (**3u**).* The product was obtained in a 81% yield (162 mg). Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.38 (m, 5H), 7.25−7.21 (m, 5H), 7.15−7.14 (m, 1H), 7.01−6.99 (m, 1H), 6.38 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.4, 148.5, 138.6, 134.3, 132.4, 129.5, 128.3, 127.9, 127.1, 126.1, 123.2, 119.4, 117.5, 82.4; HRMS (APCI) m/z: calcd for $C_{18}H_{14}BrN_2O_2S$ $[M + H]^+$, 400.9959; found, 400.9967.

*4-(4-Bromophenyl)-3-(naphthalen-1-yl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3v**).* The product was obtained in a 90% yield (200 mg). White solid; mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J = 8.4 Hz, 1H), 7.97−7.93 (m, 2H), 7.65−7.55 (m, 3H), 7.49−7.45 (m, 1H), 7.42−7.38 (m, 2H), 7.34−7.24 (m, 5H), 7.20−7.16 (m, 2H), 6.88 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.5, 148.7, 134.8, 134.3, 132.2, 131.1, 130.6, 129.6, 129.5, 129.2, 127.3, 126.7, 126.3, 126.2, 125.3, 122.2, 122.1, 119.0, 118.7, 82.9; HRMS (APCI) m/z: calcd for $C_{24}H_{18}BrN_2O_2$ $[M + H]^+$, 445.0546; found, 445.0558.

*4-(4-Bromophenyl)-3-cyclohexyl-2-phenyl-1,2,4-oxadiazolidin-5-one (**3w**).* The product was obtained in a 62% yield (124 mg). White solid; mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H), 7.40−7.36 (m, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.19−7.15 (m, 3H), 5.16 (d, J = 3.2 Hz, 1H), 1.85−1.82 (m, 4H), 1.76−1.70 (m, 2H), 1.54−1.39 (m, 2H), 1.33−1.22 (m, 2H), 1.19−1.16 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.3, 151.0, 135.0, 132.5, 129.4, 125.2, 122.3, 118.5, 116.3, 88.9, 40.6, 28.9, 26.0, 25.5; HRMS (APCI) m/z: calcd for $C_{20}H_{22}BrN_2O_2$ $[M + H]^+$, 401.0859; found, 401.0866.

*4-(4-Bromophenyl)-3-(cyclohex-3-en-1-yl)-2-phenyl-1,2,4-oxadiazolidin-5-one (**3x**).* The product was obtained in a 71% yield (141 mg). White solid; mp 162−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.46 (m, 2H), 7.41−7.37 (m, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.21−7.17 (m, 3H), 5.70−5.69 (m, 2H), 5.28−5.25 (m, 1H), 2.37−1.93 (m, 6H), 1.81−1.62 (m, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.3, 150.8, 134.9, 132.5, 129.5, 127.4, 126.5, 125.3,

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125.1, 122.6, 116.4, 88.6, 37.1, 27.3, 24.7, 22.0; HRMS (APCI) *m/z*: calcd for $C_{20}H_{20}BrN_2O_2$ [M + H]$^+$, 399.0703; found, 399.0709.

2,3,4-Triphenyl-1,2,4-oxadiazolidin-5-one (**3y**). The product was obtained in a 90% yield (142 mg). White solid; mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70−7.08 (m, 15H), 6.21 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.3, 149.5, 135.8, 135.7, 130.1, 129.5, 129.31, 129.3, 127.2, 125.8, 125.7, 121.1, 117.3, 86.5; HRMS (APCI) *m/z*: calcd for $C_{20}H_{17}N_2O_2$ [M + H]$^+$, 317.1285; found, 317.1293.

2,3-Diphenyl-4-(m-tolyl)-1,2,4-oxadiazolidin-5-one (**3z**). The product was obtained in a 87% yield (143 mg). White solid; mp 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.50 (m, 2H), 7.45−7.37 (m, 5H), 7.27−7.25 (m, 2H), 7.22−7.18 (m, 2H), 7.16−7.12 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.14 (s, 1H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.3, 149.5, 139.3, 135.9, 135.5, 130.0, 129.4, 129.2, 129.0, 127.1, 126.5, 125.7, 121.7, 118.0, 117.2, 86.5, 21.4; HRMS (APCI) *m/z*: calcd for $C_{21}H_{19}N_2O_2$ [M + H]$^+$, 331.1441; found, 331.1449.

4-(4-Chlorophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3aa**). The product was obtained in a 83% yield (145 mg). White solid; mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.47 (m, 2H), 7.46−7.43 (m, 3H), 7.42−7.38 (m, 2H), 7.25−7.23 (m, 5H), 7.22−7.20 (m, 2H), 6.11 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.0, 149.2, 135.2, 134.1, 131.1, 130.3, 129.5, 129.4, 129.3, 127.2, 125.9, 122.3, 117.4, 86.4; HRMS (APCI) *m/z*: calcd for $C_{20}H_{16}ClN_2O_2$ [M + H]$^+$, 351.0895; found, 351.0899.

2,3-Diphenyl-4-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazolidin-5-one (**3ab**). The product was obtained in a 89% yield (171 mg). White solid; mp 111−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.44 (m, 9H), 7.43−7.38 (m, 2H), 7.27−7.26 (m, 1H), 7.25−7.20 (m, 2H), 6.20 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.0, 149.1, 138.84, 138.8, 134.9, 130.3, 129.53, 129.5, 127.0, 126.4, 126.36, 126.1, 119.8, 117.4, 86.0; HRMS (APCI) *m/z*: calcd for $C_{21}H_{16}F_3N_2O_2$ [M + H]$^+$, 385.1158; found, 385.1161.

2,3-Diphenyl-4-(4-(trifluoromethoxy)phenyl)-1,2,4-oxadiazolidin-5-one (**3ac**). The product was obtained in a 92% yield (186 mg). White solid; mp 93−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.48 (m, 2H), 7.47−7.44 (m, 3H), 7.42−7.38 (m, 2H), 7.35−7.33 (m, 2H), 7.25−7.20 (m, 3H), 7.13−7.11 (m, 2H), 6.13 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.1, 149.1, 146.3, 146.2, 135.2, 134.2, 130.3, 129.5, 129.4, 127.1, 125.9, 122.1, 121.8, 117.3, 86.5; HRMS (APCI) *m/z*: calcd for $C_{21}H_{16}F_3N_2O_3$ [M + H]$^+$, 401.1108; found, 401.1112.

4-(2-Nitrophenyl)-2,3-diphenyl-1,2,4-oxadiazolidin-5-one (**3ad**). The product was obtained in a 72% yield (129 mg). Yellow solid; mp 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03−7.97 (m, 1H), 7.57−7.51 (m, 2H), 7.48−7.29 (m, 7H), 7.23−7.12 (m, 3H), 7.91−6.86 (m, 1H), 6.09 (s, 1H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 153.6, 147.5, 145.9, 134.4, 133.8, 130.7, 130.4, 129.18, 129.17, 129.1, 128.8, 128.1, 126.2, 125.9, 118.6, 87.4; HRMS (APCI) *m/z*: calcd for $C_{20}H_{16}N_3O_4$ [M + H]$^+$, 362.1135; found, 362.1139.

N′-(4-Bromophenyl)-N-phenylbenzimidamide (**4a**). The product was obtained in a 84% yield (147 mg). White solid; mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2SO_4): δ 7.40−7.33 (m, 1H), 7.26−7.18 (m, 3H), 7.14 (d, *J* = 8.7 Hz, 1H), 7.09−7.03 (m, 4H), 6.98−6.89 (m, 3H), 6.87−6.77 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + D_2SO_4): δ 135.56, 134.96, 132.44, 132.08, 130.47, 129.20, 129.03, 127.10, 126.81, 125.29, 120.60; HRMS (ESI-TOF) *m/z*: calcd for $C_{19}H_{16}BrN_2$ [M + H]$^+$, 351.0491; found, 351.0507.

N′-(4-Chlorophenyl)-N-phenylbenzimidamide (**4b**). The product was obtained in a 92% yield (140 mg). White solid; mp 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2SO_4): δ 14.16 (br s, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.13−7.01 (m, 5H), 6.90 (d, *J* = 6.8 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + D_2SO_4): δ 162.02, 136.41, 135.32, 132.17, 131.83, 130.11, 129.27, 128.92, 128.83, 126.42, 126.32, 126.03, 124.95; HRMS (ESI-TOF) *m/z*: calcd for $C_{19}H_{16}ClN_2$ [M + H]$^+$, 307.0997; found, 307.1003.

N-Phenyl-N′-(4-(trifluoromethyl)phenyl)benzimidamide (**4c**). The product was obtained in a 87% yield (147 mg). White solid; mp 110−111 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2SO_4): δ 14.28 (br s, 1H), 7.52−7.45 (m, 1H), 7.40−7.30 (m, 5H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.18−7.09 (m, 3H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.98−6.92 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + D_2SO_4): δ 162.24, 139.94, 136.24, 132.50, 130.12, 129.45, 128.93, 128.08, 127.76, 126.68, 126.14, 126.00, 125.97, 125.00, 124.59, 122.36; HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{16}F_3N_2$ [M + H]$^+$, 341.1260; found, 341.1277.

N-Phenyl-N′-(4-(trifluoromethoxy)phenyl)benzimidamide (**4d**). The product was obtained in a 88% yield (157 mg). White solid; mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2SO_4): δ 7.45 (t, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.20 (d, *J* = 7.6 Hz, 2H), 7.16−7.03 (m, 3H), 7.01−6.85 (m, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + D_2SO_4): δ 162.05, 146.90, 136.44, 135.39, 132.26, 130.08, 129.32, 128.86, 126.44, 126.33, 126.04, 124.92, 121.56, 121.31, 119.00; HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{16}F_3N_2O$ [M + H]$^+$, 357.1209; found, 357.1217.

N′-(4-Bromophenyl)-4-methyl-N-phenylbenzimidamide (**4e**). The product was obtained in a 90% yield (163 mg). White solid; mp 121−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + D_2SO_4): δ 7.27 (d, *J* = 8.6 Hz, 1H), 7.23−7.14 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.05−6.94 (m, 2H), 6.87 (d, *J* = 8.6 Hz, 1H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$ + D_2SO_4): δ 163.51, 144.00, 132.34, 130.60, 130.11, 129.27, 127.41, 126.67, 126.63, 125.16, 125.12, 121.58, 120.98, 21.73; HRMS (ESI-TOF) *m/z*: calcd for $C_{20}H_{18}BrN_2$ [M + H]$^+$, 365.0648; found, 365.0657.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03279.

NMR spectra of compounds **3** and **4** (PDF)
X-ray crystallographic data for **3a** (CIF)
X-ray crystallographic data for **4e** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

Markus D. Kärkäs − *Department of Chemistry, KTH Royal Institute of Technology, Stockholm SE-100 44, Sweden;* orcid.org/0000-0002-6089-5454; Email: karkas@kth.se

Jian-Quan Liu − *School of Chemistry and Materials Science, Jiangsu Key Laboratory of Green Synthesis for Functional Materials, Jiangsu Normal University, Xuzhou, Jiangsu 221116, China; Department of Chemistry, KTH Royal Institute of Technology, Stockholm SE-100 44, Sweden;* orcid.org/0000-0002-5533-2075; Email: liujq316@jsnu.edu.cn

Authors

Xuanyu Shen − *School of Chemistry and Materials Science, Jiangsu Key Laboratory of Green Synthesis for Functional Materials, Jiangsu Normal University, Xuzhou, Jiangsu 221116, China*

Andrey Shatskiy − *Department of Chemistry, KTH Royal Institute of Technology, Stockholm SE-100 44, Sweden*

Yan Chen − *School of Chemistry and Materials Science, Jiangsu Key Laboratory of Green Synthesis for Functional Materials, Jiangsu Normal University, Xuzhou, Jiangsu 221116, China*

Xiang-Shan Wang − *School of Chemistry and Materials Science, Jiangsu Key Laboratory of Green Synthesis for Functional Materials, Jiangsu Normal University, Xuzhou, Jiangsu 221116, China;* orcid.org/0000-0002-0077-7819

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.9b03279

Notes

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■ REFERENCES

(1) Feuer, H.; Torssell, K. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*, 2nd ed.; Wiley Interscience: Hoboken, NJ, 2008.

(2) (a) Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. Isocyanoacetate Derivatives: Synthesis, Reactivity, and Application. *Chem. Rev.* **2010**, *110*, 5235−5331. (b) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. Metal-Mediated and Metal-Catalyzed Reactions of Isocyanides. *Chem. Rev.* **2015**, *115*, 2698−2779. (c) Zhang, B.; Studer, A. Recent Advances in the Synthesis of Nitrogen Heterocycles via Radical Cascade Reactions using Isonitriles as Radical Acceptors. *Chem. Soc. Rev.* **2015**, *44*, 3505−3521. (d) Song, B.; Xu, B. Metal-Catalyzed C−H Functionalization Involving Isocyanides. *Chem. Soc. Rev.* **2017**, *46*, 1103−1123.

(3) Nenajdenko, V. G. *Isocyanide Chemistry: Applications in Synthesis and Material Science*, 1st ed.; Wiley-VCH, 2012.

(4) Shi, W.-M.; Ma, X.-P.; Su, G.-F.; Mo, D.-L. New Developments of Ketonitrones in Organic Synthesis. *Org. Chem. Front.* **2016**, *3*, 116−130.

(5) For a review on base-induced synthesis of heterocycles involving isocyanides, see: Schöllkopf, U. Recent Applications of α-Metalated Isocyanides in Organic Synthesis. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 339−348.

(6) (a) Zeeh, B. Reactions between Isocyanides and Nitrones1. *Synthesis* **2002**, *1969*, 37. (b) Moderhack, D.; Lorke, M. Stable 4-Imino-1,2-oxazetidines from *N*-Neopentylidene-*tert*-butylamine *N*-Oxide and Isocyanides. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 45−46. (c) Grassot, J.-M.; Masson, G.; Zhu, J. Synthesis of α-Ketoamides by a Molecular-Sieves-Promoted Formal Oxidative Coupling of Aliphatic Aldehydes with Isocyanides. *Angew. Chem., Int. Ed.* **2008**, *47*, 947−950.

(7) Tian, Z.; Xu, J.; Liu, B.; Tan, Q.; Xu, B. Copper-Catalyzed Synthesis of Polysubstituted Pyrroles through [3+1+1] Cycloaddition Reaction of Nitrones and Isocyanides. *Org. Lett.* **2018**, *20*, 2603−2606.

(8) For a recent example, see: Martínez-Pardo, P.; Blay, G.; Escrivá-Palomo, A.; Sanz-Marco, A.; Vila, C.; Pedro, J. R. Catalytic Diastereo- and Enantioselective Synthesis of 2-Imidazolinones. *Org. Lett.* **2019**, *21*, 4063−4066.

(9) Luzyanin, K. V.; Tskhovrebov, A. G.; Guedes da Silva, M. F. C.; Haukka, M.; Pombeiro, A. J. L.; Kukushkin, V. Y. Metal-Mediated [2+3] Cycloaddition of Nitrones to Palladium-Bound Isonitriles. *Chem.—Eur. J.* **2009**, *15*, 5969−5978.

(10) (a) Safir, S. R.; Lopresti, R. J. The Synthesis of Some 1,2,4-Oxadiazolidinones. *J. Am. Chem. Soc.* **1958**, *80*, 4921−4923. (b) Ashburn, S. P.; Coates, R. M. Preparation of Oxazoline *N*-Oxides and Imidate *N*-Oxides by Amide Acetal Condensation and Their [3+2] Cycloaddition Reactions. *J. Org. Chem.* **1985**, *50*, 3076−3081. (c) Ritter, T.; Carreira, E. M. 1,2,4-Oxadiazolidinones as Configurationally Stable Chiral Building Blocks. *Angew. Chem., Int. Ed.* **2005**, *44*, 936−938. (d) Mo, D.-L.; Pecak, W. H.; Zhao, M.; Wink, D. J.; Anderson, L. L. Synthesis of *N*-Styrenyl Amidines from α,β-Unsaturated Nitrones and Isocyanates through CO_2 Elimination and Styrenyl Migration. *Org. Lett.* **2014**, *16*, 3696−3699.

(11) For a review, see: (a) Wang, Y.; Kumar, R. K.; Bi, X. Silver-Catalyzed Organic Reactions of Isocyanides. *Tetrahedron Lett.* **2016**, *57*, 5730−5741. . For selected examples, see: (b) Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. Tuning the Reactivity of Isocyano Group: Synthesis of Imidazoles and Imidazoliums from Propargylamines and Isonitriles in the Presence of Multiple Catalysts. *Angew. Chem., Int. Ed.* **2015**, *54*, 1293−1297. (c) Hu, Z.; Yuan, H.; Men, Y.; Liu, Q.; Zhang, J.; Xu, X. Cross-Cycloaddition of Two Different Isocyanides: Chemoselective Heterodimerization and [3+2]-Cyclization of 1,4-Diazabutatriene. *Angew. Chem., Int. Ed.* **2016**, *55*, 7077−7080. (d) Hu, Z.; Dong, J.; Men, Y.; Lin, Z.; Cai, J.; Xu, X. Silver-Catalyzed Chemoselective [4+2] Annulation of Two Isocyanides: A General Route to Pyridone-Fused Carbo-and Heterocycles. *Angew. Chem., Int. Ed.* **2017**, *56*, 1805−1809. (e) Hu, Z.; Dong, J.; Xu, X. Silver-Catalyzed [3+2] Cycloaddition of Azomethine Ylides with Isocyanides for Imidazole Synthesis. *Adv. Synth. Catal.* **2017**, *359*, 3585−3591. (f) Gao, Y.; Hu, Z.; Dong, J.; Liu, J.; Xu, X. Chemoselective Double Annulation of Two Different Isocyanides: Rapid Access to Trifluoromethylated Indole-Fused Heterocycles. *Org. Lett.* **2017**, *19*, 5292−5295. (g) Zhang, X.; Wang, X.; Gao, Y.; Xu, X. Silver-Catalyzed Formal [3+2]-Cycloaddition of α-Trifluoromethylated Methyl Isocyanides: A Facile Stereoselective Synthesis of CF_3-substituted Heterocycles. *Chem. Commun.* **2017**, *53*, 2427−2430.

(12) For our previous reports on isocyanides, see: (a) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. Silver-Catalyzed Isocyanide-Alkyne Cycloaddition: A General and Practical Method to Oligosubstituted Pyrroles. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953−6957. (b) Liu, J.; Liu, Z.; Liao, P.; Bi, X. Modular Synthesis of Sulfonyl Benzoheteroles by Silver-Catalyzed Heteroaromatization of Propargylic Alcohols with *p*-Toluenesulfonylmethyl Isocyanide (TosMIC): Dual Roles of TosMIC. *Org. Lett.* **2014**, *16*, 6204−6207. (c) Meng, X.; Liao, P.; Liu, J.; Bi, X. Silver-Catalyzed Cyclization of 2-Pyridyl Alkynyl Carbinols with Isocyanides: Divergent Synthesis of Indolizines and Pyrroles. *Chem. Commun.* **2014**, *50*, 11837−11839. (d) Fang, G.; Liu, J.; Fu, J.; Liu, Q.; Bi, X. Silver-Catalyzed Cascade Reaction of β-Enaminones and Isocyanoacetates To Construct Functionalized Pyrroles. *Org. Lett.* **2017**, *19*, 1346−1349. (e) Liu, J.-Q.; Shen, X.; Liu, Z.; Wang, X.-S. Copper-Catalyzed Synthesis of Arylcarboxamides from Aldehydes and Isocyanides: The Isocyano Group as an N1 Synthon. *Org. Biomol. Chem.* **2017**, *15*, 6314−6317. (f) Liu, J.-Q.; Shen, X.; Wang, Y.; Wang, X.-S.; Bi, X. [3 + 2] Cycloaddition of Isocyanides with Aryl Diazonium Salts: Catalyst-Dependent Regioselective Synthesis of 1,3- and 1,5-Disubstituted 1,2,4-Triazoles. *Org. Lett.* **2018**, *20*, 6930−6933. (g) Liu, J. Q.; Chen, X.; Shen, X.; Wang, Y.; Wang, X. S.; Bi, X. Silver-Catalyzed Sequential Cascade Reaction of Isocyanides with 1-(2-Ethynyl-phenyl)-prop-2-yn-1-ol: Access to Benzo[*b*]fluorenes and Benzofuran-Pyrroles. *Adv. Synth. Catal.* **2019**, *361*, 1543−1548. (h) Liu, J.-Q.; Chen, X.; Shatskiy, A.; Kärkäs, M. D.; Wang, X.-S. Silver-Mediated Synthesis of Substituted Benzofuran- and Indole-Pyrroles via Sequential Reaction of *ortho*-Alkynylaromatics with Methylene Isocyanides. *J. Org. Chem.* **2019**, *84*, 8998−9006. (i) Liu, J. Q.; Shen, X.; Shatskiy, A.; Zhou, E.; Kärkäs, M. D.; Wang, X. S. Silver-Induced [3+2] Cycloaddition of Isocyanides with Acyl Chlorides: Regioselective Synthesis of 2,5-Disubstituted Oxazoles. *ChemCatChem* **2019**, *11*, 4272−4275.

(13) For an overview, see: Barbachyn, M. R.; Ford, C. W. Oxazolidinone Structure−Activity Relationships Leading to Linezolid. *Angew. Chem., Int. Ed.* **2003**, *42*, 2010−2023.

(14) González-Cruz, D.; Tejedor, D.; de Armas, P.; Morales, E. Q.; García-Tellado, F. Organocatalysis "on Water". Regioselective [3 + 2]-Cycloaddition of Nitrones and Allenolates. *Chem. Commun.* **2006**, 2798−2800.

(15) (a) Lang, S. Unravelling the Labyrinth of Palladium-Catalysed Reactions Involving Isocyanides. *Chem. Soc. Rev.* **2013**, *42*, 4867−4880. (b) Qiu, G.; Ding, Q.; Wu, J. Recent Advances in Isocyanide Insertion Chemistry. *Chem. Soc. Rev.* **2013**, *42*, 5257−5269.

(16) (a) Liu, J.; Liu, Z.; Liao, P.; Zhang, L.; Tu, T.; Bi, X. Silver-Catalyzed Cross-Coupling of Isocyanides and Active Methylene Compounds by a Radical Process. *Angew. Chem., Int. Ed.* **2015**, *54*, 10618−10622. (b) Huang, X.; Cong, X.; Mi, P.; Bi, X. Azomethine-Isocyanide [3+2] Cycloaddition to Imidazoles Promoted by Silver and DBU. *Chem. Commun.* **2017**, *53*, 3858−3861.

(17) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. Synthesis of Imidazoles through the Copper-Catalyzed Cross-Cycloaddition

https://dx.doi.org/10.1021/acs.joc.9b03279
J. Org. Chem. 2020, 85, 3560−3567

between Two Different Isocyanides. *J. Am. Chem. Soc.* **2006**, *128*, 10662−10663.
(18) (a) Piera, J.; Bäckvall, J.-E. Catalytic Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer—A Biomimetic Approach. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506−3523. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. Recent Advances in Transition-Metal Catalyzed Reactions Using Molecular Oxygen as the Oxidant. *Chem. Soc. Rev.* **2012**, *41*, 3381−3430.

https://dx.doi.org/10.1021/acs.joc.9b03279
J. Org. Chem. 2020, 85, 3560−3567