JOC The Journal of Organic Chemistry

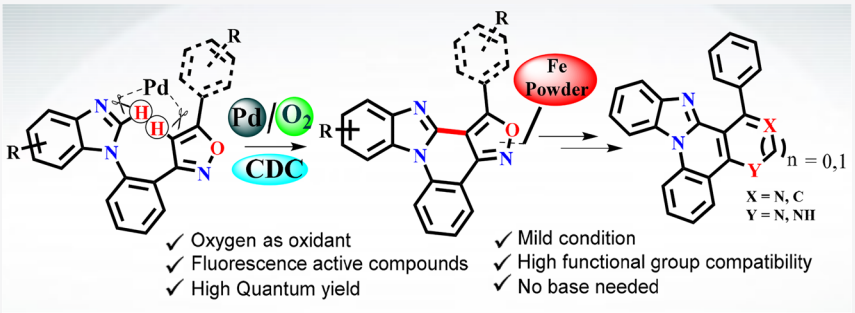
pubs.acs.org/joc Article

Rapid Access to Benzimidazo[1,2-*a*]quinoline-Fused Isoxazoles via Pd(II)-Catalyzed Intramolecular Cross Dehydrogenative Coupling: Synthetic Versatility and Photophysical Studies

Subrata Sahoo and Shantanu Pal*

Cite This: *J. Org. Chem.* 2021, 86, 4081−4097 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: An efficient and atom-economical palladium-catalyzed intramolecular cross dehydrogenative coupling (CDC) reaction has been developed for the construction of highly π-conjugated benzimidazo[1,2-*a*]quinoline-fused isoxazole scaffolds using molecular oxygen as sole oxidant. The approach portrayed wide substrate scope with good functional group tolerance and depicted a useful tool for the generation of fluorescence active compounds with high quantum yield. Synthetic versatility of the method via Fe-catalyzed reductive isoxazole ring cleavage toward pyridine, pyrimidine, pyrazole fused heteropolycyclic compounds has been showcase.

INTRODUCTION

Fused heteropolycyclic aromatic compounds are an important class of π-conjugated molecules, which have been extensively used in the field of pharmaceuticals, organic electronics, and materials sciences.[1] In particular, benzimidazo[1,2-*a*]-quinolines are reported to have a variety of biological activities, such as antiviral, antifungal, antibacterial, etc.[2] (Figure 1). In addition, 1,2-disubstituted (hetero) aryl-fused imidazole or benzimidazole scaffolds and their metal complexes have been significantly explored as organic light-emitting diodes (OLEDs), organic solar cells, organic field-effect transistors (OFETs), etc.[3] On the other hand, isoxazoles are pervasive scaffolds that are found in a variety of life-saving drugs and pharmaceuticals as well as biologically active natural products.[4] The design and synthesis of new molecules by combining different pharmacophores are fascinating topics in drug discovery. Benzoimidazo[1,2-*a*]isoxazolo[4,3-*c*]quinoline with a fused cyclic ring system comprises benzimidazole, quinoline, and isoxazole components, which belong to a captivating family of structurally unique heterocycles having an interesting biological profile[5] (Figure 1). Consequently, there have been significant interests in developing novel methodologies for the construction of such kinds of fused polycyclic skeletons as represented in Scheme 1. In 2012, Chen and co-workers conveyed the rhodium(III)-catalyzed benzimidazole-fused quinoline synthesis,[6] while Peng's research group in 2019 reported π-conjugated benzimidazole-fused quinoline via palladium-catalyzed sequential Heck and oxidative amination reactions.[7] Most recently, Li and co-workers disclosed a C−H activation cascade reaction from imidamides and anthranils toward benzimidazo[1,2-*a*]quinolines using a rhodium(III) catalyst.[8] However, those methods for the synthesis of the benzimidazole-fused quinoline skeleton mostly involved prefunctionalization of the starting materials, and its synthetic application is limited because of the required overall multistep transformations. Although few approaches have been documented in the literature for benzimidazole-fused quinoline, no such reports are available for the synthesis of benzimidazole-quinoline-fused isoxazole to the best of our knowledge. Notably, the synthesis of fused polycyclic compounds containing benzimidazole, quinoline, and isoxazole has not been explored, thus limiting the biological evaluation of such

Received: December 12, 2020
Published: February 24, 2021

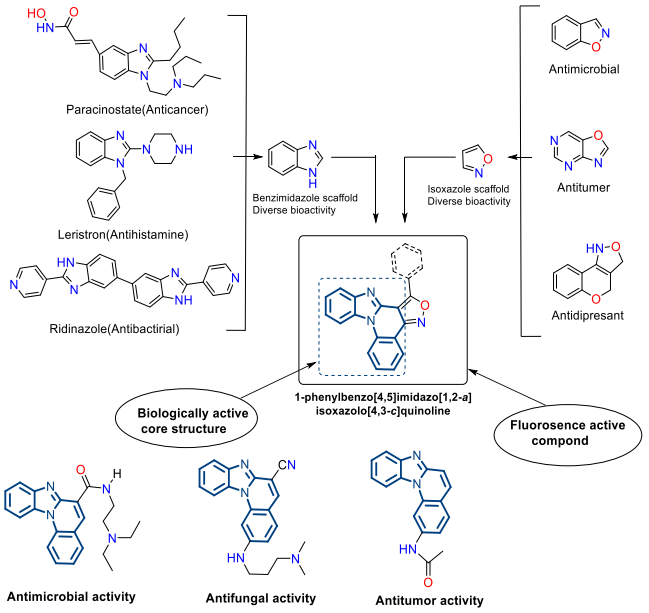
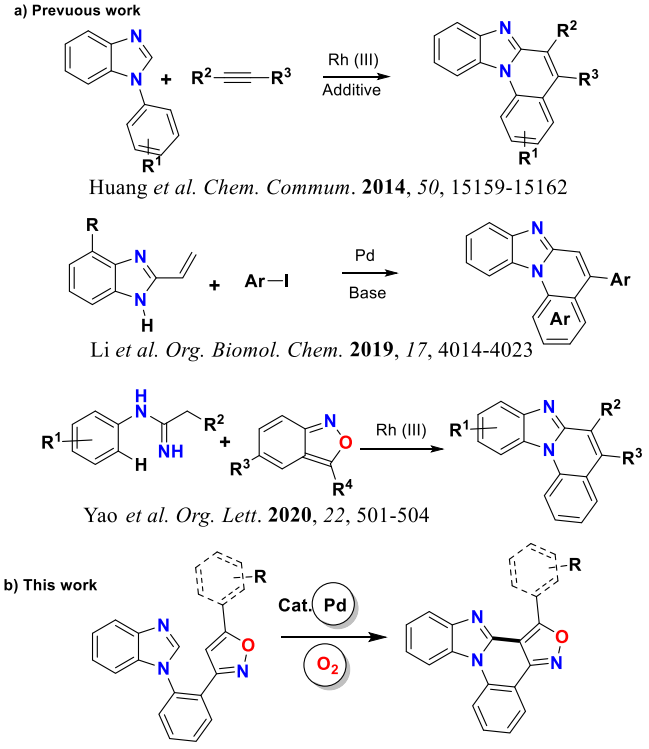


Figure 1. Designing of novel 1-henylbenzo[4,5]imidazo[1,2-*a*]-isoxazolo[4,3-*c*]quinoline and an example of biologically active benzimidazo-quinoline derivatives.

Scheme 1. Previously Reported Approaches and Present Approach



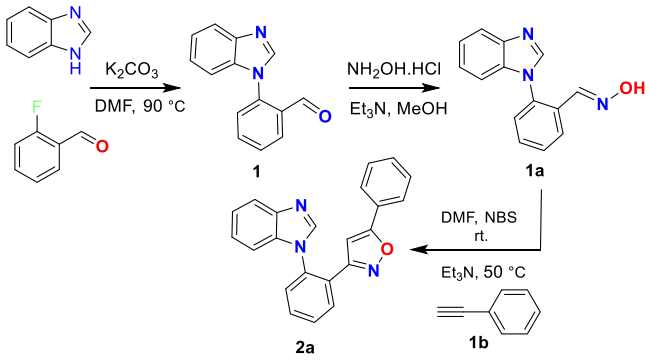
compounds. Therefore, an atom-economical and step-economical method is highly desirable.

From the past few years, transition-metal-catalyzed cross-dehydrogenative coupling (CDC) reactions,[9] forming carbon−carbon bonds by directly connecting two C−H bonds. This method is favorable in terms of the atom and step economy since prefunctionalization of the starting materials is not required. Although impressive attention has been given toward intermolecular[10] and intramolecular[11] cross-dehydrogenative coupling reactions, methods for developing the intramolecular CDC reaction to construct heteropolycyclic skeletons are still rare[12] and stimulating the ongoing research. Herein, we disclosed the first synthesis of benzimidazoquinoline-fused isoxazole compounds via the palladium-catalyzed intramolecular cross-dehydrogenative coupling reaction under base-free, Co-catalyst-free, and metallic oxidant-free conditions,[13a−c] using molecular oxygen as the sole oxidant. Substrate scope, functional group diversity, and photophysical studies of the products are unveiled. Moreover, the synthesized product was diversified to pyridine-, pyrimidine-, pyrazole-fused heteropolycyclic compounds, among others, via Fe-catalyzed reductive isoxazole ring cleavage. In addition, the isoxazole-cleaved product was converted to the derivatives of pharmacologically potent benzo[4,5]imidazo[1,2-*a*]quinoline. Notably, in this developed synthetic avenue, the C4 functionalization of isoxazole has been accomplished, which is otherwise difficult to achieve without a cocatalyst such as Ag(I).[13c]

RESULTS AND DISCUSSION

Our expedition commenced with the preparation of biheterocyclic scaffolds **2** through 1,3-dipolar cycloaddition between oxime **1a** and phenyl acetylene **1b** highlighted in Scheme 2.

Scheme 2. Synthesis of the Biheterocyclic Scaffold

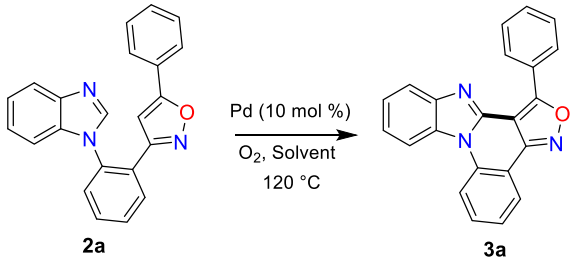


First, oxime **1a** was subjected to the dipolar cycloaddition reaction as per reported literature[13d] precedent, which was found to be not suitable for this substrate because of the very low yield. Therefore, we started screening the reaction conditions using a different solvent, reagent, base, and temperature to get scaffold **2a** in the best yield. *N*-Bromosuccinimide along with triethyl ammine in DMF as a solvent at 50 °C was found to be the best condition for this reaction.

With the desired starting precursor, **2a**, we started optimization of the reaction conditions. At the beginning, the reaction was performed with $PdCl_2$ (10 mol %) as a catalyst and $Cu(OAc)_2$ (1.2 equiv) as an oxidant in xylene as a solvent at 120 °C (Table 1, entry 1). However, no desired product was formed with the recovery of starting material **2a**. Upon changing the catalyst from $PdCl_2$ to $Pd(OAc)_2$, the desired coupling product **3a** was formed in 44% yield (Table 1, entry 2). The product yield was improved to 65% upon the addition of Piv−OH as an additive (Table 1, entry 3), indicating the crucial role of Piv−OH. No improvement in the yield was observed upon the addition of a base (Table 1, entry 4) and changing the palladium sources, such as $Pd(PPh_3)_4$, $PdCl_2(MeCN)_2$, and $Pd(PPh_3)_2Cl_2$ (Table 1, entries 5−7).

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (10 mol %)	oxidant (1.2 equiv)	solvent 6	::	additives 1	yield[b] (%)
1	$PdCl_2$	$Cu(OAc)_2$	xylene	:		nd
2	$Pd(OAc)_2$	$Cu(OAc)_2$	xylene	:		44
3	$Pd(OAc)_2$	$Cu(OAc)_2$	xylene	:	Piv−OH	65
4	$Pd(OAc)_2$	$Cu(OAc)_2$	xylene	:	K_2CO_3	42
5	$Pd(PPh_3)_4$	$Cu(OAc)_2$	xylene	:	Piv−OH	nd
6	$PdCl_2(MeCN)_2$	$Cu(OAc)_2$	xylene	:	Piv−OH	nd
7	$Pd(PPh_3)_2Cl_2$	$Cu(OAc)_2$	xylene	:	Piv−OH	nd
8	$PdCl_2$	$Cu(OAc)_2$	xylene	:	Piv−OH	trace
9		$Cu(OAc)_2$	xylene	:	Piv−OH	nd
10	$Pd(OAc)_2$	CuI	xylene	:	Piv−OH	nd
11	$Pd(OAc)_2$	O_2	xylene	:	Piv−OH	84
12	$Pd(OAc)_2$	O_2	xylene	:		67
13	$Pd(OAc)_2$	air	xylene	:	Piv−OH	50
14	$Pd(OAc)_2$	O_2	acetonitrile	:	Piv−OH	trace
15	$Pd(OAc)_2$	O_2	DMF	:	Piv−OH	35
16	$Pd(OAc)_2$	O_2	THF	:	Piv−OH	<30
17	$Pd(OAc)_2$	O_2	1,4-dioxane	:	Piv−OH	trace
18	$Pd(OAc)_2$	O_2	DCE	:	Piv−OH	trace
19	$Pd(OAc)_2$	Ag_2CO_3	xylene	:	Piv−OH	40
20	$Pd(OAc)_2$	AgOAc	xylene	:	Piv−OH	trace
21	$Pd(OAc)_2$	$AgNO_3$	xylene	:	Piv−OH	trace
22	$Pd(OAc)_2$	$K_2S_2O_8$	xylene	:	Piv−OH	nd
23	$Pd(OAc)_2$	BQ	xylene	:	Piv−OH	nd
24	$Pd(OAc)_2$	O_2	xylene	:	CH_3CO_2H	nd
25	$Pd(OAc)_2$	O_2	xylene	:	CF_3CO_2H	31

[a]General conditions: **2a** (1.0 mmol), $Pd(OAc)_2$ (0.1 equiv), solvent/PivOH 6:1 v/v, O_2 balloon, 12 h. [b]Isolated yield.

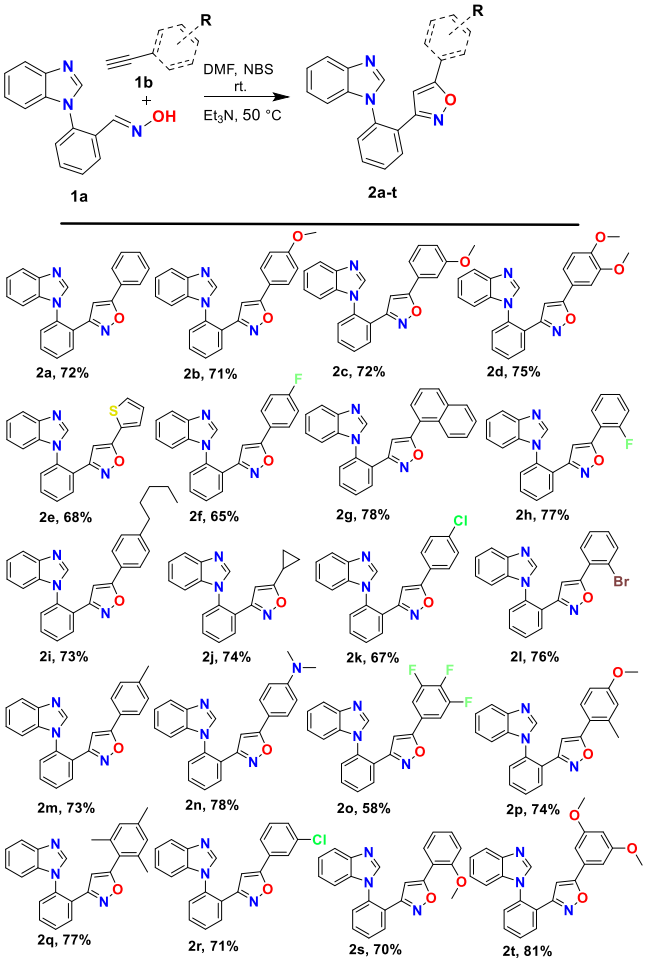
The reaction did not work in the absence of a palladium catalyst (Table 1, entry 9), indicating the essential role of palladium. In addition, lowering the temperature from 120 to 100 °C led to an increase in reaction time and a decrease in the yield of the reaction. Fortunately, product **3a** was formed in a maximum yield of 84% when the reaction was performed under an oxygen atmosphere using an oxygen balloon (Table 1, entry 11), without an external oxidant. In the absence of pivalic acid, the yield of the reaction was decreased to 67% (Table 1, entry 12). In open air, product **3a** was formed in 50% yield (Table 1, entry 13), and the reaction took a longer time for completion. When $Cu(OAc)_2$ was used as an oxidant, the yield of the reaction was low. However, when the same reaction was performed in the presence of CuI (Table 1, entry 10), no desired coupling product was observed, and the starting material was consumed. This may be due to the formation of some copper complexes that led to the decrease in the yield of the reaction. Furthermore, the screening of different solvents (such as toluene, acetonitrile, DMF, THF, 1,4-dioxane, *N*,*N*-dimethylacetamide, and DCE), oxidants (such as Ag_2CO_3, AgOAc, $AgNO_3$, $K_2S_2O_8$, and BQ), and different additives did not give improved results (Table 1, entries 14−25).

After having optimized the reaction conditions (10 mol % $Pd(OAc)_2$, 6:1 xylene/pivalic acid, oxygen atmosphere) to check the substrate diversity of the present CDC reaction, a wide range of benzimidazole-based biheterocyclic scaffolds **2a−t** have been synthesized by the cycloaddition reaction between oxime **1a** and substituted phenyl acetylene **1b** as represented in Scheme 3.

The substrates with electron-donating groups reacted slightly faster compared to those with electron-withdrawing groups in the CDC reaction (Scheme 4). Substrates, having para-substitution of the aryl ring with methoxy **2b**, pentyl **2i**, chloro **2k**, methyl **2m**, and *N*,*N*-dimethyl **2n** underwent the CDC reaction smoothly to give the corresponding heteropolycycles in 61−84% yields. 2-Bromo compound **2l** did not give the desired coupling product with complex TLC; however, the starting material was consumed completely. In the case of meta-substituted compound **2c** and 3,4-disubstituted compound **2d**, the CDC reaction proceeded smoothly to yield the corresponding coupling products **3c** and **3d** in 72% and 68% yields, respectively. Conversely, substrate **2p**, having 2,4-disubstitution, was converted to the coupling product in 72% yield. Sterically hindered 1,3,5-trisubstituted compound **2q** was converted to the corresponding coupling product **3q** in 68% yield. 2-Chloro compound **2r**, 2-methoxy compound **2s**, and

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

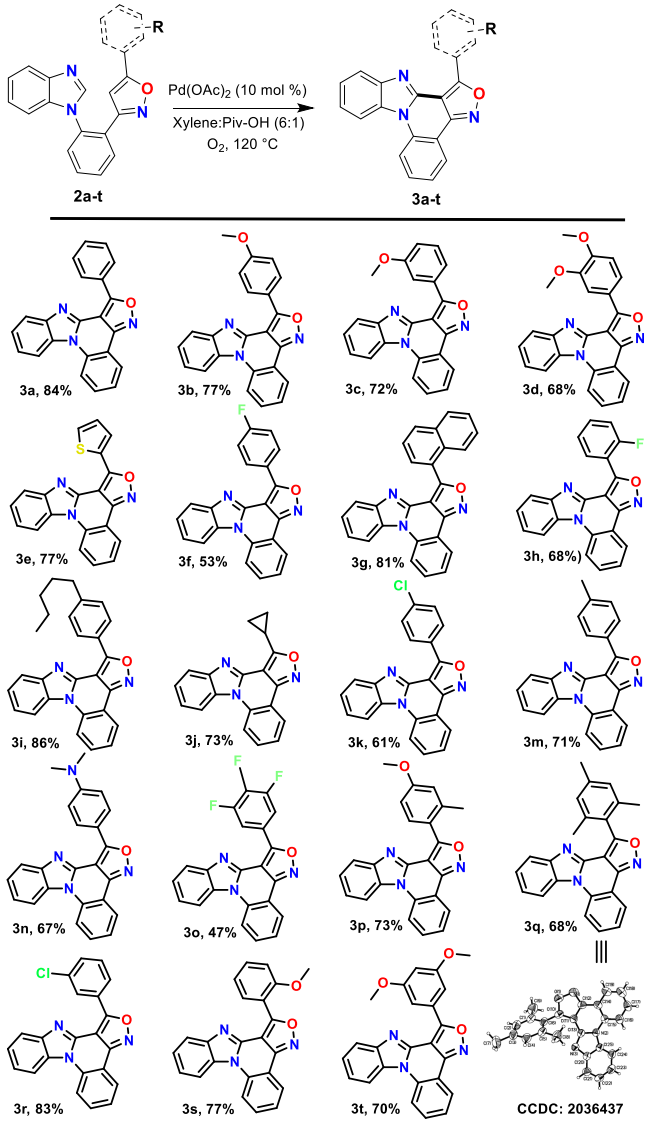
Scheme 3. Cycloaddition Reaction for the Synthesis of Biheterocyclic Scaffolds



3,5-dimethoxy compound **2t** underwent the CDC reaction smoothly to give the corresponding coupling products in 83%, 77%, and 70% yields, respectively.

To see the substituent effect in the benzimidazole ring, compounds **2u**−**2zc** were prepared by using the same procedure describe in Scheme 2. The symmetrically substituted benzimidazole ring containing starting material **2u** proceeded with the smooth CDC reaction to give the corresponding coupling product **3u** in a good yield. However, during the synthesis of aldehyde type **1**, unsymmetrical substituted benzimidazole yielded an inseparable mixture of two regio isomers; e.g., 5-methyl, 5-methoxy, 5- carboxylate, and 5-nitro benzimidazole provided a mixture of both 5- and 6-substituted aldehydes. With this inseparable mixture of aldehyde type **1**, biheterocyclic scaffolds of type **2** were prepared, which was also found to be an inseparable mixture. In order to check the feasibility of the reaction, with this inseparable mixture of starting material, the CDC reaction was performed and found that both electron-donating and electron-withdrawing group substitution on the benzimidazole ring underwent the smooth CDC reaction to give the corresponding coupling product in a good yield (Scheme 5). Substrates containing a nitro group in the benzimidazole ring (**2zb** and **2zc**) were futile to give the corresponding coupling product.

Scheme 4. Substrate Scope of the CDC Reaction

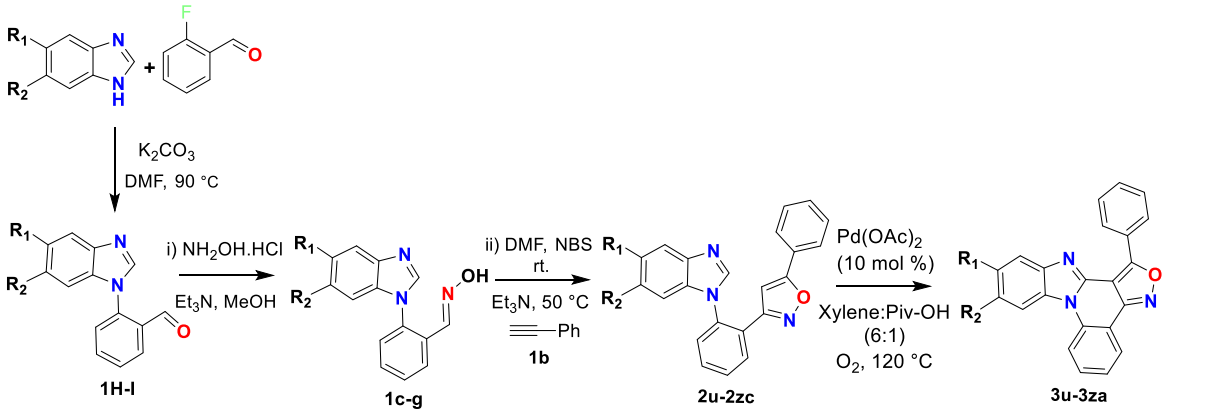


In order to know which C−H bond between C2 of benzimidazole and C4 of isoxazole is being activated first, the compound **2a** was treated with highly reactive coupling partners such as stilbene, diphenyl acetylene, iodobenzene, etc. in an intermolecular fashion (Scheme 6). Unfortunately, all of the reactions were futile to give the intermolecular CDC product; rather, the intramolecular coupling product was isolated. This is probably because of the steric environment, which did not allow coupling partners to come closer to either C2 of benzimidazole or C4 of isoxazole.

Toward the kinetic isotopic experiment, compound **2a** was treated with ^{n}BuLi and D_2O to get deuterated compound **2a-C_2D**. Initially, the hydrogen present at the C2 position of benzimidazole was replaced by deuterium within 1.5 h. Further rotation of the reaction mixture for 3 h resulted in the replacement of C4 hydrogen of isoxazole also. After 12 h, complete conversion to the product **2a-C_2D-C_4D** was observed. This observation indicated that the benzimidazole C_2−H bond is more acidic than the isoxazole C_4−H bond. The reported pK_a values for the hydrogen at the C2 position of the benzimidazole are 32.5 and 34.0 for the C4 position of isoxazole.[14a] From this, it can be stated that palladium was

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

Scheme 5. Substituent Effect in the Benzimidazole Ring for the CDC Reaction



1A :$R_1 = R_2$ = Me
1B : R_1 = Me, R_2 = H
1C : R_1 = H, R_2 = Me
1D : R_1 = OMe, R_2 = H
1E : R_1 = H, R_2 = OMe
1F : R_1 = COOMe, R_2 = H
1G : R_1 = H, R_2 = COOMe
1H : R_1 = NO_2, R_2 = H
1I : R_1 = H, R_2 = NO_2

1c :$R_1 = R_2$ = Me
1d : R_1 = Me, R_2 = H
1e : R_1 = H, R_2 = Me
1f : R_1 = OMe, R_2 = H
1g : R_1 = H, R_2 = OMe
1h : R_1 = COOMe, R_2 = H
1i : R_1 = H, R_2 = COOMe
1j : R_1 = NO_2, R_2 = H
1k : R_1 = H, R_2 = NO_2

2u :$R_1 = R_2$ = Me
2v : R_1 = Me, R_2 = H
2w : R_1 = H, R_2 = Me
2x : R_1 = OMe, R_2 = H
2y : R_1 = H, R_2 = OMe
2z : R_1 = COOMe, R_2 = H
2za : R_1 = H, R_2 = COOMe
2zb : R_1 = NO_2, R_2 = H
2zc : R_1 = H, R_2 = NO_2

2u :$R_1 = R_2$ = Me
3v : R_1 = Me, R_2 = H
3w : R_1 = H, R_2 = Me
3x : R_1 = OMe, R_2 = H
3y : R_1 = H, R_2 = OMe
3z : R_1 = COOMe, R_2 = H
3za : R_1 = H, R_2 = COOMe

incorporated at the C2 position of benzimidazole prior to C4 of isoxazole. Compound **2a-C_4D** was prepared via the cycloaddition reaction between **2a** and deuterated phenyl acetylene in DMF.

Furthermore, the KIE was determined to be 1.01 for the parallel reaction using **2a** and **2a-C_2D** and 1.17 for the reaction using **2a** and **2a-C_4D**. These values indicated that the C−H activation step is not involved in the rate-limiting step. As the C−H activation step is not the rate-limiting step for both the transformations, therefore, it is quite possible that the carbometalation could be the rate-limiting step in this reaction. Based on control experiments, H/D exchange, kinetic studies, and previous literature reports, a possible catalytic cycle for the palladium-catalyzed CDC reaction has been represented in Scheme 7.

First, palladium was coordinated to the nitrogen atom of benzimidazole, and then, it was shifted to the C-2 position of the benzimidazole ring via metallotropism-triggered[14b] activation to form intermediate **I**. Subsequently, an intramolecular C−H bond cleavage happened via a concerted metalation deprotonation (CMD) pathway to generate intermediate **II**. Finally, reductive elimination provided product **3a** and regenerated palladium(0), which was oxidized in the presence of oxygen to its active form palladium(II).

Synthetic Versatility. To further explore the potential of synthesized compounds, 1-phenylbenzo[4,5]imidazo[1,2-*a*]-isoxazolo[4,3-*c*]quinoline was subjected to different isoxazole ring cleavage reaction conditions to generate potential intermediate *β*-amino *α*,*β*-unsaturated ketone. Fortunately, treatment of **3a** with Fe-powder in acetic acid under reflux conditions provided *β*-amino *α*, *β*-unsaturated ketone intermediate **4**, which is a versatile intermediate and converted to pyridine-, pyrimidine-, and pyrazole-fused heteropolycyclic compounds as well as functionalized benzimidazoquinoline-fused compounds in good yields (Scheme 8).

The *β*-amino *α*,*β*-unsaturated ketone **4**, under basic conditions in the presence of acetone, delivered substituted pyridine-fused heteropolycyclic compound **5a** in 82% yield (Scheme 8).[15a] The corresponding purine-fused compound **5b** was obtained (93% yield) from compound **4** in the presence of urea under heating conditions (Scheme 8).[15b] Moreover, the thermal cycloaddition of compound **4** with ethyl propiolate afforded **5c** in 91% yield (Scheme 8). The hydrazine cyclization of **4** with hydrazine hydrate furnished corresponding pyrazole-fused product **5d** in 78% yield (Scheme 8).[15c] Furthermore, the $-NH_2$ group in compound **4** was substituted by chloride under treatment with $NaNO_2$ in HCl and afforded compound **5e** in 85% yield, which underwent Pd-catalyzed hydrodehalogenation to furnish **5f** in 73% yield and $NaBH_4$ reduction to give alcohol **5g** in 95% yield (Scheme 8).

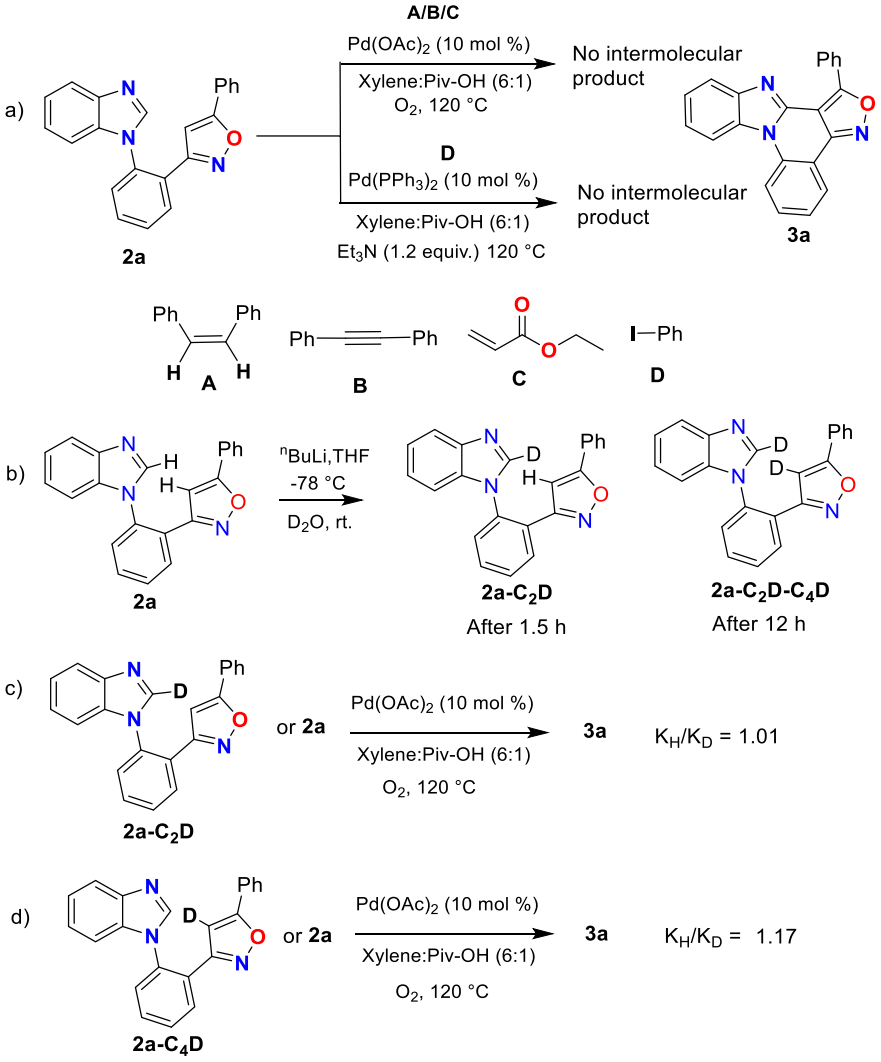
Photophysical Studies. Photophysical properties of the synthesized compounds have been shown in Table 2. The fluorescence emission spectra of benzoimidazo[1,2-*a*]-isoxazolo[4,3-*c*]quinolines were measured in $CHCl_3$ as shown in Figure 2.

UV−vis studies displayed that the absorption band of compounds **3a−q** covers from 275 to 425 nm, involving two to three absorption peaks, which are attributed to $\pi-\pi^*$ and $n-\pi^*$ charge transfer transition, respectively. The nature of substituents in aryl ring plays a crucial role in absorption wavelength and fluorescent quantum yield. The compounds **3a−q** showed blue fluorescent emission with a moderate to high quantum yield (Φ_F), 0.24−0.86. The products **3b** and **3g** bearing *p*-methoxy aryl ring and extended *π*-conjugated ring, respectively, have displayed a longer absorption wavelength and comparatively high Φ_F with respect to **3a**. Compound **3j**, having cyclopropyl ring substitution, showed the lowest absorption wavelength as compared to the rest with a quantum yield of 0.24.

Notably, compound **3n** exhibited maximum absorption wavelength and maximum quantum yield (Φ_F 0.86) in this

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

Scheme 6. Control Experiments, H/D Exchange, and Kinetic Studies



archive. The compound **3p** having methoxy- and methyl-substituted aryl rings has shown strong UV absorption (log ε = 5.77) with a quantum yield of 0.68.

CONCLUSIONS

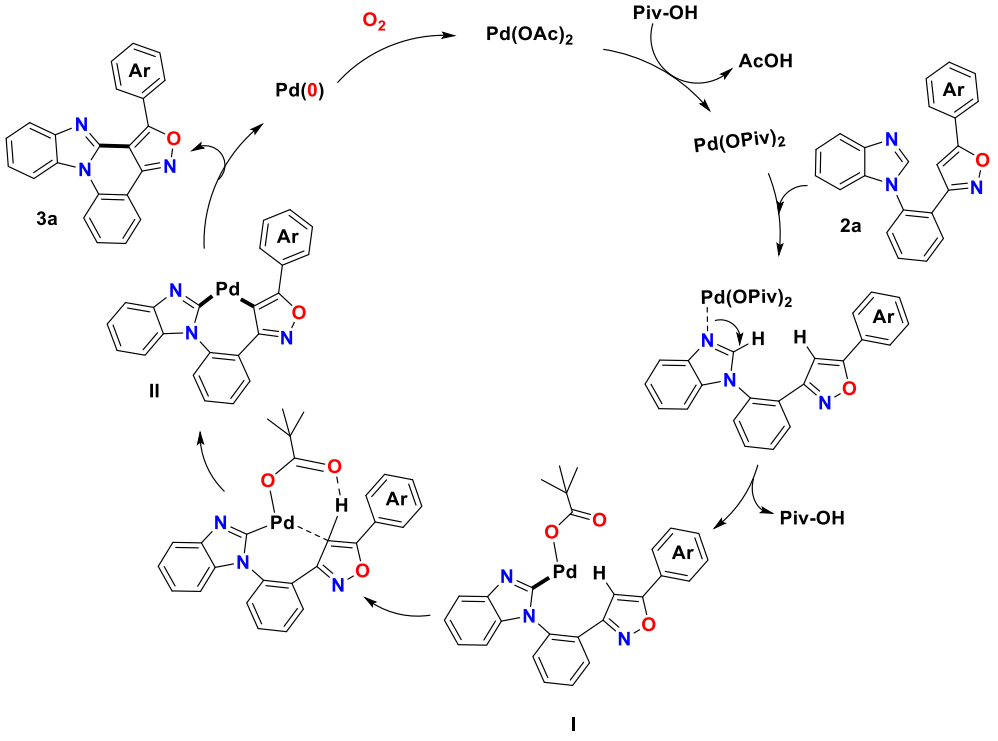
To conclude, we have reported the first synthesis of benzoimidazo[1,2-*a*]isoxazolo[4,3-*c*]quinoline compounds using a palladium-catalyzed intramolecular cross-dehydrogenative coupling reaction. Diverse heteropolycyclic compounds have been synthesized with a good yield and functional group tolerance. The kinetic isotope experiments suggested that the C−H activation step was not involved in the rate-determining step. The synthetic utility of the product toward other fused *N*-heteropolycyclic compounds (pyridine, pyrimidine, and pyrazole) has also been explored via Fe-catalyzed isoxazole ring cleavage. Moreover, the isoxazole-cleaved product was converted to the derivatives of pharmacologically potent benzo[4,5]imidazo[1,2-*a*]quinoline. The photophysical studies displayed a strong blue fluorescence emission of the compounds with a high quantum yield. The results presented here may have considerable interest in medicinal and materials sciences.

EXPERIMENTAL SECTION

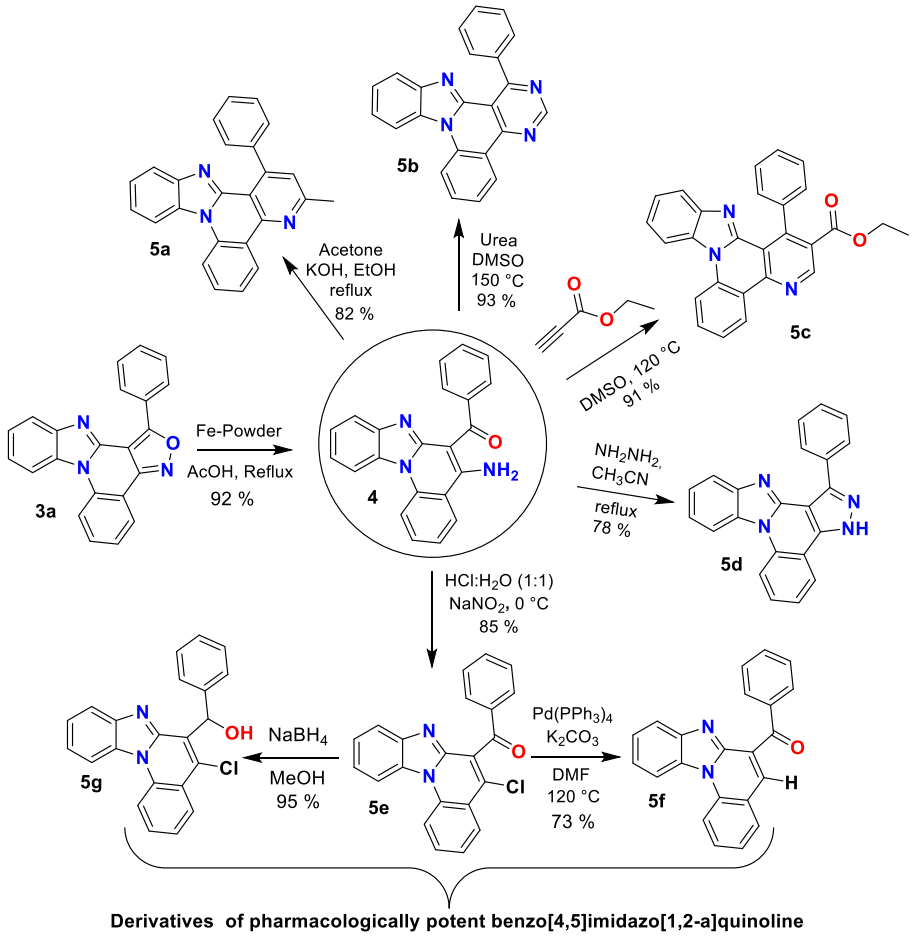
General Information. Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. Column chromatography purifications were performed using 100−200 mesh silica gel. Commercial grade solvents and reagents were used without further purification. Experiments involving moisture-senstive and/or air-sensitive components were performed in oven-dried glassware under a positive pressure of nitrogen/argon using freshly distilled solvents. Analytical thin-layer chromatography (TLC) was performed using Merck 60 F_{254} precoated silica gel plates (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Flash chromatography was performed using 100−200 mesh silica gel with the indicated solvent system. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. High-resolution mass spectral analysis (HRMS) was performed on a Bruker Daltonics MicroTOF-Q-II mass spectrometer and Thermoscintific Exactive Plus ORBITRAP mass spectrometer using MeOH as a solvent with an electrospray ionization (ESI) positive method. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 NMR spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) relative to the signal of chloroform-*d* (δ 7.28, singlet). Multiplicities were given as s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); dt (doublets of triplet); or m (multiplet). The number of protons (*n*) for a given

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

Scheme 7. Proposed Mechanism



Scheme 8. Synthetic Versatility



https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

Table 2. Photophysical Properties of the Products

compounds	$\lambda_{abs,max}$ [a] (nm)	$\lambda_{em,max}$ [b] (nm)	log ε	Φ_F [c]
3a	314	451	5.25	0.52
3b	343	450	5.23	0.74
3g	324	451	5.25	0.76
3i	346	451	5.70	0.24
3j	290	450	5.00	0.41
3k	341	451	5.14	0.52
3m	342	451	5.15	0.56
3n	395	450	5.53	0.86
3p	305	451	5.77	0.68
3q	341	451	5.77	0.56

[a]Absorption maxima in $CHCl_3$ (1×10^{-6} mol/L). [b]Emission maxima in $CHCl_3$ (1×10^{-6} mol/L). [c]Fluorescence quantum yield, determined by quinine sulfate ($\Phi_F = 0.546$ in H_2SO_4).

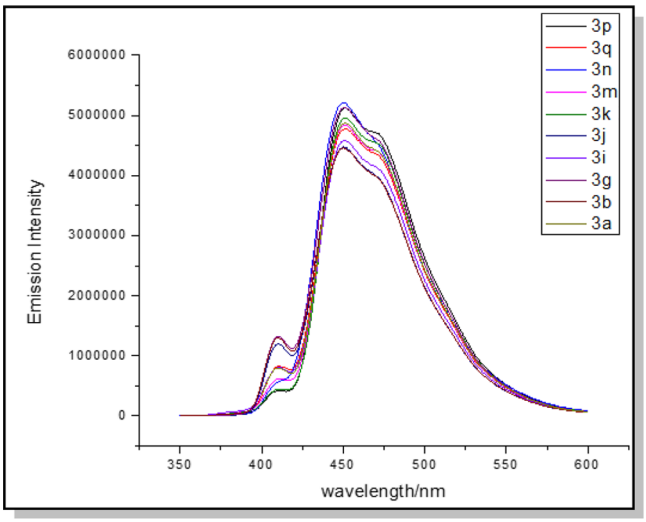


Figure 2. Emission spectra of **3a**, **3b**, **3g**, **3i**, **3j**, **3k**, **3m**, **3n**, **3p**, and **3q** in $CHCl_3$ (1×10^{-6} mol/L).

resonance is indicated by *n*H. Coupling constants are reported as a *J* value in hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.0, triplet).

Procedure for the Synthesis of Aldehyde (1).[16] To a 25 mL round-bottom flask, 2-fluorobenzaldehydes (2.0 equiv, 13.6 mmol), benzo[*d*]imidazoles (1.0 equiv, 6.8 mmol), and K_2CO_3 (2.0 equiv, 13.6 mmol) in DMF (5.0 mL) were added, and the reaction was stirred at 90 °C for 10 h. Upon the completion of the reaction (confirm by TLC), the solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with H_2O (3 × 40 mL), dried over anhydrous Na_2SO_4, and removed under the reduced pressure. The crude was purified with silica gel column chromatography to afford the target compound **1**.

Procedure for the Synthesis of Oxime (1a). Et_3N (1.2 equiv) was added to the stirring solution of **1** (1.0 equiv, 10 mmol) and $NH_2OH{\cdot}HCl$ (1.2 equiv) in 20 mL of methanol. The resulting solution was allowed to stir at room temperature, and the progress of the reaction was monitored by TLC until completion. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure by removing the solvent. The residue was extracted with DCM (25 mL) and water (25 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 25 mL). The organic extract was washed with brine 25 mL and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel 100−200 to get desired product **1a**.

*2-(1H-Benzo[d]imidazol-1-yl)benzaldehyde Oxime (**1a**).* The compound **1a** was synthesized by the procedure as described above and obtained as a white solid: 87% yield (2.06 g); R_f = 0.4 (40% EtOAc + pet ether); ^1H NMR (400 MHz, DMSO-d_6) δ 11.55 (1H, s), 8.44 (1H, s), 8.08−7.96 (1H, m), 7.88−7.74 (1H, m), 7.70−7.60 (2H, m), 7.60−7.52 (1H, m), 7.51 (1H, s), 7.37−7.24 (2H, m), 7.17−7.10 (1H, m); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 144.8, 143.8, 143.4, 135.4, 134.1, 131.1, 130.1, 130.0, 128.8, 127.1, 124.0, 122.8, 120.3, 110.7; HRMS (ESI-ORBITRAP) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{12}N_3O$ 238.0975, found 238.0976.

General Procedure for the Synthesis of Isoxazoles (2a−t). To an oven-dried round-bottom flask were added aldoxime of type **1a** (1 mmol), *N*-bromosuccinimide (1.2 mmol), 5 mL of DMF, and allowed to rotate 1 h at rt. Then triethyl ammine (1.2 mmol) was added dropwise, followed by the dropwise addition of substituted acetylene (1.1 mmol). The reaction mixture was allowed to rotate at 50 °C (using an oil bath) until the completion of the reaction (confirmed by TLC). After completion of the reaction, DMF was evaporated under a high vacuum and extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using 100−200 silica gel to get the desired product **2**.

Characterization Data for the Products (2a−t). *3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-phenylisoxazole (**2a**).* The compound **2a** was synthesized by the procedure as described above and obtained as a yellow liquid: 72% yield (239 mg); R_f = 0.5 (40% EtOAc + pet ether); ^1H NMR (400 MHz, DMSO-d_6) δ 8.36 (1H, s), 8.05−7.98 (1H, m), 7.83−7.76 (2H, m), 7.76−7.70 (2H, m), 7.67−7.63 (2H, m), 7.48 (3H, dd, *J* = 5.1, 1.9 Hz), 7.26−7.16 (2H, m), 7.09 (1H, dd, *J* = 7.0, 1.6 Hz), 6.66 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 169.6, 160.9, 144.6, 143.4, 134.9, 134.1, 132.0, 131.1, 130.2, 129.7, 129.3, 126.9, 126.7, 125.8, 123.7, 122.6, 120.1, 110.6, 100.2, 39.9; HRMS (ESI-ORBITRAP) *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{16}N_3O$ 338.1288, found 338.1296.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(4-methoxyphenyl)-isoxazole (**2b**).* The compound **2b** was synthesized by the procedure as described above and obtained as a yellow liquid: 71% yield (260 mg); R_f = 0.5 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13−8.09 (1H, m), 7.96 (1H, s), 7.90 (1H, d, *J* = 8.0 Hz), 7.72−7.66 (2H, m), 7.59−7.55 (1H, m), 7.44−7.40 (2H, d, *J* = 8.0 Hz), 7.37−7.29 (2H, m), 7.25 (1H, m), 6.91−6.85 (2H, d, *J* = 8.0 Hz), 5.38 (1H, s), 3.83 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 161.1, 160.0, 143.2, 143.0, 134.7, 133.9, 131.0, 130.7, 129.6, 128.1, 127.4, 127.4, 123.9, 122.9, 120.4, 119.6, 114.2, 110.3, 96.8, 55.3; HRMS (ESI-ORBITRAP) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{18}N_3O_2$ 368.1394, found 368.1406.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(3-methoxyphenyl)-isoxazole (**2c**).* The compound **2c** was synthesized by the procedure as described above and obtained as a yellow liquid: 72% yield (264 mg); R_f = 0.6 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.14−8.08 (1H, m), 7.96 (1H, s), 7.93−7.87 (1H, m), 7.72−7.68 (2H, m), 7.60−7.56 (1H, m), 7.37−7.30 (2H, m), 7.28−7.22 (2H, m), 7.06−7.02 (2H, m), 6.92 (1H, ddd, *J* = 8.3, 2.5, 0.9 Hz), 5.50 (1H, s), 3.81 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 160.1, 159.8, 143.2, 143.0, 134.7, 133.9, 131.1, 130.7, 130.0, 129.7, 128.2, 127.9, 127.3, 124.0, 122.9, 120.4, 118.3, 116.4, 110.7, 110.3, 98.4, 55.3; HRMS (ESI-ORBITRAP) *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{18}N_3O_2$ 368.1394, found 368.1404.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(3,4-dimethoxyphenyl)isoxazole (**2d**).* The compound **2d** was synthesized by the procedure as described above and obtained as a yellow liquid: 75% yield (296 mg); R_f = 0.6 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13−8.08 (1H, m), 7.96 (1H, s), 7.89 (1H, m), 7.71−7.66 (2H, m), 7.60−7.55 (1H, m), 7.36−7.28 (2H, m), 7.25 (1H, m), 7.06−6.97 (2H, m), 6.82 (1H, d, *J* = 8.3 Hz), 5.38 (1H, s), 3.89 (3H, s), 3.88 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 160.0, 150.7, 149.1, 143.2, 143.1, 134.7, 133.9, 131.1, 130.7,

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

129.7, 128.2, 127.4, 124.0, 122.9, 120.3, 119.7, 119.1, 111.1, 110.4, 108.5, 97.1, 55.9; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_3$ 398.1499, found 398.1499.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(thiophen-2-yl)-isoxazole (**2e**).* The compound **2e** was synthesized by the procedure as described above and obtained as a yellow liquid: 68% yield (233 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (1H, m), 7.94 (1H, s), 7.89 (1H, dd, J = 4.8, 3.7 Hz), 7.71−7.67 (2H, m), 7.59−7.54 (2H, m), 7.39−7.29 (3H, m), 7.28−7.22 (1H, m), 7.10 (1H, dd, J = 5.1, 1.2 Hz), 5.37 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.7, 159.9, 143.2, 143.0, 134.7, 133.9, 131.1, 130.8, 129.6, 128.2, 127.2, 126.9, 125.2, 124.6, 124.0, 122.9, 120.4, 110.3, 97.9, 77.3; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{20}H_{14}N_3OS$ 344.0852, found 344.0862.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(4-fluorophenyl)-isoxazole) (**2f**).* The compound **2f** was synthesized by the procedure as described above and obtained as a yellow liquid: 65% yield (231 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (1H, m), 7.98 (1H, s), 7.94−7.89 (1H, m), 7.72−7.68 (2H, m), 7.59−7.55 (1H, m) 7.50−7.44 (2H, m), 7.38−7.29 (2H, m), 7.28−7.22 (1H, m), 7.09−7.03 (2H, m), 5.44 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 160.1, 143.0, 135.54 (d, J = 176 Hz), 133.9, 131.2, 130.7, 129.7, 129.2, 128.2, 127.0, 125.2, 124.0, 123.0, 120.4, 110.3, 98.5; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{22}H_{15}FN_3O$ 356.1194, found 356.1204.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(naphthalen-1-yl)-isoxazole (**2g**).* The compound **2g** was synthesized by the procedure as described above and obtained as a yellow liquid: 78% yield (302 mg); R_f = 0.7 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.19 (1H, m), 8.06 (1H, s), 7.99 (1H, d, J = 8.1 Hz), 7.89 (1H, d, J = 8.2 Hz), 7.87−7.82 (1H, m), 7.76−7.70 (2H, m), 7.63−7.58 (1H, m), 7.57 (1H, dd, J = 7.2, 1.2 Hz), 7.53−7.43 (3H, m), 7.42−7.35 (2H, m), 7.33−7.24 (2H, m), 5.50 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.1, 159.8, 143.3, 142.9, 134.6, 134.0, 133.5, 131.2, 130.9, 130.7, 130.0, 129.8, 128.4, 128.2, 127.4, 127.3, 126.3, 124.9, 124.4, 124.1, 123.0, 120.5, 110.5, 102.5; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{26}H_{18}N_3O$ 388.1444, found 388.1439.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(2-fluorophenyl)-isoxazole (**2h**).* The compound **2h** was synthesized by the procedure as described above and obtained as a yellow liquid: 77% yield (273 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.04 (1H, m), 7.95 (1H, s), 7.89 (1H, d, J = 7.8), 7.82 (1H, td, J = 7.6, 1.6 Hz), 7.75−7.66 (2H, m), 7.62−7.55 (1H, m), 7.42−7.30 (3H, m), 7.27−7.18 (2H, m), 7.12−7.03 (1H, m), 5.82 (1H, d, J = 3.4 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.4, 160.4, 158.9 (d, J = 253 Hz), 143.0, 134.7, 131.8, 131.7, 131.1, 130.8, 129.6, 128.3, 127.5, 127.3, 124.5, 124.5, 123.9, 122.8, 120.5, 116.3, 116.1, 110.2, 102.5, 102.4; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{22}H_{15}FN_3O$ 356.1194, found 356.1198.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(4-pentylphenyl)-isoxazole (**2i**).* The compound **2i** was synthesized by the procedure as described above and obtained as a yellow liquid: 73% yield (297 mg); R_f = 0.7 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.08 (1H, m), 7.96 (1H, s), 7.90 (1H, dd, J = 4.8, 3.7 Hz), 7.73−7.63 (2H, m), 7.58−7.53 (1H, m), 7.43−7.36 (2H, m), 7.36−7.29 (1H, m), 7.29−7.21 (2H, m), 7.17 (2H, d, J = 8.3), 5.46 (1H, s), 2.86−2.44 (2H, m), 1.60 (2H, dt, J = 15.0, 7.6 Hz), 1.45−1.20 (4H, m), 0.89 (3H, t, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 160.0, 145.6, 143.2, 143.0, 134.7, 133.9, 131.0, 130.7, 129.6, 128.9, 128.1, 127.4, 125.7, 124.3, 123.9, 122.9, 120.4, 110.3, 97.6, 35.7, 31.3, 30.8, 22.4, 13.9; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{27}H_{26}N_3O$ 408.2070, found 408.2066.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-cyclopropylisoxazole (**2j**).* The compound **2j** was synthesized by the procedure as described above and obtained as a redish solid: 74% yield (222 mg); R_f = 0.6 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−7.99 (1H, m), 7.93−7.86 (2H, m), 7.71−7.60 (2H, m), 7.56−7.50 (1H, m), 7.38−7.25 (2H, m), 7.23−7.17 (1H, m), 4.88 (1H, s), 1.97−1.49 (1H, m), 1.13−0.82 (2H, m), 0.82−0.60 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.5, 159.6, 143.1, 134.6, 133.8, 130.8, 129.5, 128.0, 127.5, 123.8, 122.8, 120.4, 110.4, 97.6, 8.4, 7.9; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{19}H_{16}N_3O$ 302.1288, found 302.1285.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(4-chlorophenyl)-isoxazole (**2k**).* The compound **2k** was synthesized by the procedure as described above and obtained as a yellow liquid: 67% yield (249 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.08 (1H, m), 7.96 (1H, s), 7.90 (1H, d, J = 7.9 Hz), 7.76−7.65 (2H, m), 7.62−7.53 (1H, m), 7.44−7.37 (2H, m), 7.37−7.30 (3H, m), 7.26 (2H, m), 5.48 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.6, 160.1, 143.0, 133.9, 132.1, 131.1, 130.7, 130.3, 129.7, 128.8, 128.2, 127.3, 127.2, 126.8, 125.7, 124.0, 122.9, 120.5, 110.3, 98.2; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{22}H_{15}ClN_3O$ 372.0898, found 372.0896.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(2-bromophenyl)-isoxazole (**2l**).* The compound **2l** was synthesized by the procedure as described above and obtained as a yellow liquid: 76% yield (316 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21−8.13 (1H, m), 7.99 (1H, s), 7.88 (1H, d, J = 7.8 Hz), 7.70 (3H, m), 7.60−7.54 (2H, m), 7.41−7.29 (3H, m), 7.27−7.16 (2H, m), 5.93 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 159.6, 142.8, 134.8, 134.0, 133.9, 131.2, 131.0, 130.6, 129.8, 129.8, 128.8, 128.5, 127.7, 127.5, 127.4, 124.0, 122.9, 121.2, 120.5, 110.4, 103.2; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{22}H_{15}BrN_3O$ 416.0393, found 416.0394.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(p-tolyl)isoxazole (**2m**).* The compound **2m** was synthesized by the procedure as described above and obtained as a yellow liquid: 73% yield (256 mg); R_f = 0.6 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.08 (1H, m), 7.96 (1H, s), 7.90 (1H, d, J = 7.8 Hz), 7.72−7.64 (2H, m), 7.58−7.54 (1H, m), 7.37 (2H, d, J = 8.2 Hz), 7.36−7.29 (1H, m), 7.28−7.22 (2H, m), 7.16 (2H, d, J = 8.0 Hz), 5.46 (1H, s), 2.35 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.8, 160.0, 143.2, 143.0, 140.6, 134.7, 133.9, 131.9, 130.7, 129.6, 129.5, 128.1, 127.4, 125.7, 124.1, 123.9, 122.9, 120.4, 110.3, 97.6, 21.4; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{23}H_{18}N_3O$ 352.1444, found 352.1442.

*4-(3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)isoxazol-5-yl)-N,N-dimethylaniline (**2n**).* The compound **2n** was synthesized by the procedure as described above and obtained as a yellow liquid: 78% yield (296 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.07 (1H, m), 7.99 (1H, s), 7.90 (1H, d, J = 7.7 Hz), 7.72−7.63 (2H, m), 7.62−7.51 (1H, m), 7.36−7.29 (3H, m), 7.28−7.21 (2H, m), 6.63 (2H, d, J = 9.0 Hz), 5.32 (1H, s), 2.98 (6H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 177.1, 171.4, 159.8, 151.4, 143.1, 134.7, 133.8, 130.8, 130.7, 129.5, 128.1, 127.7, 127.0, 123.9, 122.8, 120.4, 114.7, 111.6, 110.4, 95.3, 40.1; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{24}H_{21}N_4O$ 381.1710, found 381.1707.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(3,4,5-trifluorophenyl)isoxazole (**2o**).* The compound **2o** was synthesized by the procedure as described above and obtained as a yellow liquid: 58% yield (226 mg); R_f = 0.5 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.05 (1H, m), 7.94 (1H, s), 7.91 (1H, d, J = 7.9 Hz), 7.72 (2H, m), 7.62−7.56 (1H, m), 7.39−7.29 (2H, m), 7.23 (1H, d, J = 7.7 Hz), 7.11 (2H, dd, J = 7.7, 6.4 Hz), 5.44 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.3 (d, J = 2.5 Hz), 160.4 (s), 152.7 (dd, J = 10.4, 4.0 Hz), 150.2 (dd, J = 10.4, 4.1 Hz), 143.2 (s), 142.9 (s), 142.2 (t, J = 15.3 Hz), 139.6 (t, J = 15.2 Hz), 134.6 (s), 133.9 (s), 131.5 (s), 130.7 (s), 129.8 (s), 128.2 (s), 126.7 (s), 124.1 (s), 123.1 (s), 120.6 (s), 110.5−110.0 (m), 99.4 (s); HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{22}H_{13}F_3N_3O$ 392.1005, found 392.1000.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(4-methoxy-2-methylphenyl)isoxazole (**2p**).* The compound **2p** was synthesized by the procedure as described above and obtained as a yellow liquid: 74% yield (282 mg); R_f = 0.6 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.13 (1H, m), 7.97 (1H, s), 7.91−7.86 (1H, m), 7.73−7.67 (2H, m), 7.60−7.54 (1H, m), 7.44 (1H, d, J =

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

8.6 Hz), 7.36−7.20 (3H, m), 6.74 (1H, dd, J = 8.6, 2.6 Hz), 6.68 (1H, d, J = 2.6 Hz), 5.18 (1H, s), 3.80 (3H, s), 1.93 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.3, 160.7, 159.6, 143.2, 142.9, 138.0, 134.8, 133.8, 131.0, 130.5, 129.8, 129.7, 128.3, 127.7, 124.0, 122.9, 120.4, 119.2, 116.5, 111.5, 110.4, 100.3, 55.2, 21.1; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_2$ 382.1550, found 382.1544.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-mesitylisoxazole (**2q**).* The compound **2q** was synthesized by the procedure as described above and obtained as a yellow liquid: 77% yield (292 mg); R_f = 0.6 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20−8.13 (1H, m), 8.02 (1H, s), 7.84 (1H, d, J = 7.9 Hz), 7.73−7.67 (2H, m), 7.58−7.52 (1H, m), 7.32−7.16 (3H, m), 6.82 (2H, s), 5.16 (1H, s), 2.26 (3H, s), 1.79 (6H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.5, 159.5, 143.2, 142.5, 139.9, 137.8, 134.5, 134.0, 131.1, 130.7, 129.7, 128.3, 128.1, 127.5, 124.0, 123.9, 122.9, 120.5, 110.4, 103.0, 21.1, 19.7; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{25}H_{22}N_3O$ 380.1757, found 380.1754.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(3-chlorophenyl)-isoxazole (**2r**).* The compound **2r** was synthesized by the procedure as described above and obtained as a yellow liquid: 71% yield (263 mg); R_f = 0.5 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13−8.08 (1H, m), 7.95 (1H, s), 7.93−7.88 (1H, m), 7.75−7.66 (2H, m), 7.60−7.56 (1H, m), 7.49 (1H, t, J = 1.6 Hz), 7.38−7.29 (5H, m), 7.24 (1H, m), 5.52 (1H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.1, 160.2, 143.2, 142.9, 134.9, 134.6, 133.9, 131.3, 130.8, 130.3, 130.2, 129.7, 128.3, 128.2, 127.0, 125.7, 124.0, 123.9, 123.0, 120.5, 110.3, 99.0; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{22}H_{15}ClN_3O$ 372.0898, found 372.0894.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(2-methoxyphenyl)-isoxazole (**2s**).* The compound **2s** was synthesized by the procedure as described above and obtained as a yellow liquid: 70% yield (257 mg); R_f = 0.6 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.24−8.17 (1H, m), 7.94 (1H, s), 7.91 (1H, d, J = 7.8 Hz), 7.86 (1H, d, J = 7.8 Hz), 7.74−7.65 (2H, m), 7.60−7.52 (1H, m), 7.41−7.23 (4H, m), 7.01 (1H, t, J = 7.6 Hz), 6.86 (1H, d, J = 8.4 Hz), 5.70 (1H, s), 3.60 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.6, 159.9, 156.1, 143.3, 143.1, 135.0, 133.8, 131.2, 130.8, 130.5, 129.8, 128.5, 128.0, 127.3, 123.8, 122.7, 120.6, 120.3, 115.9, 111.1, 110.4, 102.2, 55.0; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{23}H_{18}N_3O_2$ 368.1394, found 368.1397.

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-(3,5-dimethoxyphenyl)isoxazole (**2t**).* The compound **2t** was synthesized by the procedure as described above and obtained as a yellow liquid: 81% yield (321 mg); R_f = 0.6 (40% EtOAc + pet ether); ^1H NMR (400 MHz, $CDCl_3$) δ 8.13−8.06 (1H, m), 7.95 (1H, s), 7.89 (1H, d, J = 7.9 Hz), 7.70 (2H, d, J = 7.8 Hz), 7.61−7.56 (1H, m), 7.38−7.20 (3H, m), 6.62 (2H, d, J = 2.0 Hz), 6.48 (1H, s), 5.48 (1H, s), 3.79 (6H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.4, 161.0, 160.0, 143.2, 143.0, 134.7, 133.9, 131.1, 130.7, 129.6, 128.4, 128.2, 127.3, 124.0, 122.9, 120.4, 110.3, 103.8, 102.7, 98.6, 55.4; HRMS (ESI-ORBITRAP) m/z $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_3$ 398.1499, found 398.1497.

General Procedure for the Palladium-Catalyzed Cross-Dehydrogenative Coupling Reaction. To an oven-dried 50 mL Schlenk tube fitted with an oxygen balloon were added 1 mmol cycloaddition product **2**, 10 mol % $Pd(OAc)_2$, 1.2 mL of xylene, and 0.2 mL of pivalic acid, and the mixture was allowed to rotate at 120 °C in an oil bath for 12−24 h. After completion (confirmed by TLC), the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **3**.

Characterization Data of the Compounds (3a−zc). *1-Phenylbenzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3a**).* The compound **3a** was synthesized by the general procedure described above and obtained as an off-white solid: 84% yield (281 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 183−185 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.11−9.03 (2H, m), 8.57−8.47 (2H, m), 8.30−8.21 (1H, m), 8.08−7.97 (1H, m), 7.84−7.77 (1H, m), 7.73−7.59 (3H, m), 7.55−7.47 (3H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.9, 155.8, 144.3, 142.5, 136.1, 131.9, 131.6, 131.5, 128.9, 128.6, 126.9, 125.6, 125.0, 123.9, 123.9, 120.8, 116.0, 114.3, 113.2, 103.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{14}N_3O$ 336.1131, found 336.1131.

*1-(4-Methoxyphenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3b**).* The compound **3b** was synthesized by the general procedure described above and obtained as an off-white solid: 77% yield (281 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 178−180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.12−9.09 (1H, m), 8.42 (1H, dd, J = 7.8 Hz, 1.5), 8.33 (1H, d, J = 8.5 Hz), 8.31−8.25 (1H, m), 8.14−8.07 (1H, m), 7.84−7.76 (1H, m), 7.74−7.68 (1H, m), 7.54−7.35 (4H, m), 7.14−7.10 (1H, m), 4.05 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.7, 159.8, 155.6, 144.0, 142.4, 135.9, 131.7, 131.4, 129.7, 127.9, 125.5, 124.9, 123.8, 120.5, 120.2, 118.7, 115.9, 114.2, 113.2, 103.1, 55.7; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{16}N_3O_2$ 336.1237, found 336.1237.

*1-(3-Methoxyphenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3c**).* The compound **3c** was synthesized by the general procedure described above and obtained as an off-white solid: 72% yield (263 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 175−180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (1H, dd, J = 7.8, 1.5 Hz), 8.53 (1H, d, J = 8.4 Hz), 8.31−8.25 (1H, m), 8.19 (1H, dd, J = 7.7, 1.7 Hz), 7.94−7.89 (1H, m), 7.84−7.78 (1H, m), 7.65−7.59 (1H, m), 7.57−7.42 (3H, m), 7.24 (1H, td, J = 7.5, 0.9 Hz), 7.18 (1H, d, J = 8.4 Hz), 4.10 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.8, 158.1, 155.1, 144.8, 142.5, 136.3, 133.1, 131.7, 131.7, 131.5, 125.9, 125.7, 124.9, 123.7, 123.6, 120.8, 120.5, 116.1, 114.6, 113.1, 111.9, 105.0, 55.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{16}N_3O_2$ 336.1237, found 336.1237.

*1-(3,4-Dimethoxyphenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3d**).* The compound **3d** was synthesized by the general procedure described above and obtained as an off-white solid: 68% yield (268 mg); R_f = 0.7 (10% EtOAc + pet ether); mp 238−241 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, d, J = 2.0 Hz), 8.55−8.49 (2H, m), 8.44 (1H, dd, J = 8.5 Hz, 2.1 Hz), 8.29−8.24 (1H, m), 7.93−7.87 (1H, m), 7.84−7.78 (1H, m), 7.56−7.46 (3H, m), 7.13 (1H, d, J = 8.6 Hz), 4.23 (3H, s), 4.04 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 168.2, 155.7, 151.6, 149.0, 144.2, 143.0, 136.1, 131.8, 131.6, 125.6, 125.0, 123.8, 121.7, 120.4, 119.8, 116.0, 114.5, 113.3, 112.4, 111.0, 102.0, 56.4, 56.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{18}N_3O_3$ 396.1343, found 396.1343.

*1-(Thiophen-3-yl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3e**).* The compound **3e** was synthesized by the general procedure described above and obtained as an off-white solid: 77% yield (262 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 177−180 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H, dd, J = 3.0 Hz, 1.2 Hz), 8.64−8.43 (2H, m), 8.31−8.25 (2H, m), 8.11−7.94 (1H, m), 7.85−7.79 (1H, m), 7.64−7.44 (4H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1, 155.5, 144.5, 142.7, 136.2, 135.0, 131.9, 131.6, 131.4, 128.2, 126.6, 126.6, 125.7, 125.0, 123.9, 123.8, 120.7, 116.1, 114.4, 113.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{12}N_3OS$ 342.0696, found 342.0696.

*1-(4-Fluorophenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3f**).* The compound **3f** was synthesized by the general procedure described above and obtained as an off-white solid: 53% yield (187 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 208−210 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.17−9.10 (2H, m), 8.57−8.49 (2H, m), 8.31−8.25 (1H, m), 8.05−7.99 (1H, m), 7.85−7.79 (1H, m), 7.58−7.47 (3H, m), 7.43−7.31 (2H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.9, 164.6 (d, J = 252 Hz), 155.8, 144.2, 142.5, 136.1, 132.0, 131.6, 131.1, 131.0, 125.7, 125.1, 124.0, 123.3, 120.8, 116.2, 116.1, 114.3, 113.3, 103.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{13}FN_3O$ 354.1037, found 354.1037.

*1-(Naphthalen-1-yl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3g**).* The compound **3g** was synthesized by the general procedure described above and obtained as an off-white solid: 81%

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

yield (312 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 255−258 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65−8.58 (2H, m), 8.55 (1H, d, J = 8.5 Hz), 8.36−8.25 (2H, m), 8.16 (1H, d, J = 8.2 Hz), 8.05−7.97 (1H, m), 7.90−7.82 (2H, m), 7.78 (1H, dd, J = 8.0 Hz, 7.4 Hz), 7.63−7.54 (3H, m), 7.52−7.41 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.9, 155.5, 144.5, 142.3, 136.3, 133.9, 132.4, 132.0, 131.6, 130.9, 130.5, 128.6, 127.5, 126.5, 125.7, 125.1, 123.9, 123.8, 123.7, 121.0, 116.2, 114.4, 113.2, 105.3; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{16}N_3O$ 386.1288, found 386.1288.

*1-(2-Fluorophenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3h**).* The compound **3h** was synthesized by the general procedure described above and obtained as an off-white solid: 68% yield (240 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (1H, td, J = 7.6 Hz, 1.8 Hz), 8.58 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.54 (1H, d, J = 8.5 Hz), 8.32−8.25 (1H, m), 8.01−7.94 (1H, m), 7.86−7.80 (1H, m), 7.68−7.60 (1H, m), 7.58−7.45 (4H, m), 7.40−7.32 (1H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 160.1 (d, J = 256 Hz), 155.2, 144.5, 142.0, 136.2, 133.4, 132.0, 131.9, 131.6, 125.7, 125.1, 124.4, 123.9, 121.0, 116.8, 116.5, 116.1, 115.3, 114.3, 113.2, 105.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{13}FN_3O$ 354.1037, found 354.1036.

*1-(4-Pentylphenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3i**).* The compound **3i** was synthesized by the general procedure described above and obtained as an off-white solid: 86% yield (348 mg); R_f = 0.7 (10% EtOAc + pet ether). M.p.: 178−181 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (2H, d, J = 8.2 Hz), 8.53 (2H, t, J = 8.5 Hz), 8.30−8.23 (1H, m), 8.07−7.98 (1H, m), 7.80 (1H, t, J = 7.9 Hz), 7.55−7.45 (5H, m), 2.76 (2H, t, J = 7.6 Hz), 1.86−1.68 (2H, m), 1.45−1.45 (4H, m), 0.95 (3H, t, J = 6.8 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.3, 155.8, 147.1, 144.4, 142.8, 136.2, 131.8, 131.6, 129.0, 128.6, 125.6, 124.9, 124.4, 123.9, 123.8, 120.8, 116.0, 114.5, 113.2, 102.7, 36.1, 31.5, 30.8, 22.5, 14.0; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{27}H_{24}N_3O$ 406.1914, found 406.1914.

*1-Cyclopropylbenzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3j**).* The compound **3j** was synthesized by the general procedure described above and obtained as a reddish solid: 73% yield (218 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 177−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, d, J = 8.5 Hz), 8.43 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.28−8.21 (1H, m), 8.00−7.93 (1H, m), 7.82−7.75 (1H, m), 7.53−7.42 (3H, m), 3.24−3.13 (1H, m), 1.61−1.55 (2H, m), 1.47−1.40 (2H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 174.1, 154.9, 144.8, 143.2, 136.4, 131.8, 131.4, 125.7, 124.9, 123.9, 123.4, 120.2, 116.2, 114.4, 113.1, 104.0, 10.7, 9.8; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{14}N_3O$ 300.1131, found 300.1131.

*1-(4-Chlorophenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3k**).* The compound **3k** was synthesized by the general procedure described above and obtained as an off-white solid: 61% yield (225 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 258−260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10−9.03 (2H, m), 8.55−8.49 (2H, m), 8.30−8.24 (1H, m), 8.04−7.98 (1H, m), 7.85−7.78 (1H, m), 7.67−7.63 (2H, m), 7.56−7.48 (3H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 155.9, 144.3, 142.3, 137.6, 136.1, 132.0, 131.6, 129.9, 129.2, 125.7, 125.4, 125.1, 124.0, 120.8, 116.1, 114.3, 113.3, 103.5; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{13}ClN_3O$ 370.0742, found 370.0742.

*1-(p-Tolyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3m**).* The compound **3m** was synthesized by the general procedure described above and obtained as an off-white solid: 71% yield (248 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 212−215 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (2H, d, J = 8.3 Hz), 8.57−8.45 (2H, m), 8.29−8.23 (1H, m), 8.06−7.96 (1H, m), 7.83−7.77 (1H, m), 7.57−7.43 (5H, m), 2.52 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.2, 155.7, 144.4, 142.8, 142.1, 136.1, 131.8, 131.6, 129.6, 128.6, 125.6, 124.9, 124.3, 123.9, 123.8, 120.8, 116.0, 114.5, 113.2, 102.8, 21.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{16}N_3O$ 350.1288, found 350.1288.

*4-(Benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinolin-1-yl)-N,N-dimethylaniline (**3n**).* The compound **3n** was synthesized by the general procedure described above and obtained as an off-white solid: 67% yield (253 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 180−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.10−8.93 (2H, m), 8.60−8.44 (2H, m), 8.35−8.18 (1H, m), 8.14−7.95 (1H, m), 7.82−7.76 (1H, m), 7.55−7.43 (3H, m), 7.00−6.87 (2H, m), 3.16 (6H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.0, 155.7, 152.3, 144.5, 143.6, 136.2, 131.7, 131.5, 130.2, 125.6, 124.7, 123.6, 123.3, 120.5, 115.9, 114.8, 114.6, 113.1, 111.5, 100.7, 40.1; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{19}N_4O$ 379.1553, found 379.1552.

*1-(3,4,5-Trifluorophenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3o**).* The compound **3o** was synthesized by the general procedure described above and obtained as an off-white solid: 47% yield (182 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 251−255 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99−8.88 (2H, m), 8.50−8.42 (2H, m), 8.28−8.17 (1H, m), 8.04−7.93 (1H, m), 7.80 (1H, m), 7.57−7.45 (3H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.53, 156.05, 152.83−152.61 (m), 150.22 (dd, J = 10.1, 4.0 Hz). 144.07, 141.68, 136.12, 132.27, 131.57, 125.75, 125.26, 124.43, 124.31, 122.71, 121.06, 116.16, 114.02, 113.35, 113.27, 113.10, 104.20; HRMS (APCI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{11}F_3N_3O$ 390.0849, found 390.0847.

*1-(4-Methoxy-2-methylphenyl)benzo[4,5]imidazo[1,2-a]-isoxazolo[4,3-c]quinoline (**3p**).* The compound **3p** was synthesized by the general procedure described above and obtained as a white solid: 73% yield (273 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (1H, s), 8.58−8.53 (2H, m), 8.44 (1H, dd, J = 8.5 Hz, 2.1 Hz), 8.27 (1H, m), 7.90 (1H, m), 7.85−7.76 (1H, m), 7.56−7.45 (3H, m), 7.13 (1H, d, J = 8.6 Hz), 4.23 (3H, s), 4.04 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 155.7, 151.6, 149.0, 144.2, 143.0, 136.1, 131.8, 131.6, 125.6, 125.0, 123.8, 123.8, 121.7, 120.4, 119.8, 116.0, 114.5, 113.3, 112.4, 111.0, 56.4, 56.0; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{18}N_3O_2$ 380.1394, found 380.1395.

*1-Mesitylbenzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3q**).* The compound **3q** was synthesized by the general procedure described above and obtained as an off-white solid: 68% yield (256 mg); R_f = 0.6 (10% EtOAc + pet ether); R_f = 0.6 (10% EtOAc + pet ether); mp 222−225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62−8.52 (2H, m), 8.28 (1H, dd, J = 7.5 Hz, 1.0 Hz), 7.94−7.78 (1H, m), 7.87−7.81 (1H, m), 7.61−7.52 (1H, m), 7.51−7.40 (2H, m), 7.10 (2H, s), 2.44 (3H, s), 2.28 (6H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.9, 155.0, 145.0, 142.1, 140.9, 138.6, 136.4, 131.9, 131.5, 128.8, 125.7, 125.0, 123.7, 123.3, 121.1, 116.2, 114.5, 113.1, 106.3, 21.4, 20.0; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{25}H_{20}N_3O$ 378.1601, found 378.1603.

*1-(3-Chlorophenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3r**).* The compound **3r** was synthesized by the general procedure described above and obtained as an off-white solid: 83% yield (360 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 206−208 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (1H, s), 8.89 (1H, dd, J = 4.6 Hz, 1.5 Hz), 8.33 (2H, dd, J = 26.5 Hz, 8.1 Hz), 8.06 (1H, m), 7.91−7.79 (1H, m), 7.69 (1H, t, J = 7.9 Hz), 7.54 (2H, m), 7.46−7.34 (3H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.9, 155.6, 144.0, 141.8, 135.8, 134.9, 131.8, 131.3, 131.2, 130.0, 128.3, 128.3, 126.4, 125.4, 124.9, 124.0, 123.9, 120.8, 115.8, 114.0, 113.1, 103.6; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{13}ClN_3O$ [M + H]$^+$ 370.0742, found 370.0738.

*1-(2-Methoxyphenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline (**3s**).* The compound **3s** was synthesized by the general procedure described above and obtained as an off-white solid: 77% yield (281 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 185−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (1H, s), 8.94−8.84 (1H, m), 8.33 (2H, dd, J = 26.5 Hz, 8.1 Hz), 8.10−8.02 (1H, m), 7.89−7.82 (1H, m), 7.69 (1H, t, J = 7.9), 7.58−7.49 (2H, m), 7.46−7.34 (3H, m), 3.93 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 158.1, 155.1, 144.8, 142.5, 136.3, 133.1, 131.7, 131.7, 131.5, 125.9, 125.7, 124.9, 123.7, 123.6, 120.8, 120.5, 116.1, 114.6, 113.1, 111.9, 105.0, 55.8; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{23}H_{16}N_3O_2$ 336.1237, found 336.1239.

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

*1-(3,5-Dimethoxyphenyl)benzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3t**).* The compound **3t** was synthesized by the general procedure described above and obtained as an off-white solid: 70% yield (276 mg); R_f = 0.7 (10% EtOAc + pet ether); mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.51 (1H, d, J = 8.5 Hz), 8.46 (2H, d, J = 2.3 Hz), 8.30−8.24 (1H, m), 7.92−7.87 (1H, m), 7.81 (1H, ddd, J = 8.7 Hz, 7.4 Hz, 1.6 Hz), 7.56−7.46 (3H, m), 6.72 (1H, t, J = 2.3 Hz), 4.05 (6H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.8, 161.0, 155.8, 144.2, 142.6, 136.1, 131.8, 131.5, 128.3, 125.6, 125.0, 124.0, 123.9, 120.6, 116.0, 114.4, 113.3, 106.1, 105.1, 103.4, 55.8; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{18}N_3O_3$ 396.1343, found 396.1346.

*10,11-Dimethyl-1-phenylbenzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3u**).* The compound **3u** was synthesized by the general procedure described above and obtained as an off-white solid: 78% yield (283 mg); R_f = 0.6 (10% EtOAc + pet ether); mp 261−263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06−9.01 (2H, m), 8.49 (1H, dd, J = 7.8, 1.4 Hz), 8.43 (1H, d, J = 8.5 Hz), 7.94 (1H, s), 7.80−7.74 (1H, m), 7.71 (1H, s), 7.69−7.62 (2H, m), 7.59 (1H, dt, J = 9.5, 4.3 Hz), 7.47 (1H, t, J = 7.5 Hz), 2.49 (3H, s), 2.43 (3H, s); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 155.8, 142.9, 141.7, 136.2, 133.0, 132.9, 131.7, 131.3, 130.1, 128.8, 128.5, 127.1, 125.5, 124.6, 120.8, 115.9, 114.2, 113.5, 103.5, 21.0, 20.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{18}N_3O$ 364.1444, found 364.1451.

*11(12)-Methyl-1-phenylbenzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]quinoline (**3v,w**).* The compound **3v,w** were synthesized by the general procedure described above and obtained as an inseparable mixture: white solid, 82% yield (286 mg); R_f = 0.6 (10% EtOAc + pet ether); R_f = 0.6 (10% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01−8.94 (2H, m), 8.37 (1H, dt, J = 7.8, 1.9 Hz), 8.30−8.21 (1H, m), 7.91−7.79 (1H, m), 7.75−7.53 (5H, m), 7.38 (1H, t, J = 7.6 Hz), 7.21−7.10 (1H, m), 2.51 (3H, s, major + minor); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.4, 167.3, 155.6, 144.5, 142.2, 141.8, 136.0, 135.9, 133.8, 133.6, 131.6, 131.6, 131.3, 129.4, 128.8, 128.8, 128.5, 128.4, 127.0, 125.3, 125.3, 125.1, 124.6, 124.6, 120.5, 120.1, 115.8, 115.7, 114.2, 114.1, 113.2, 112.5, 103.2, 22.2, 21.3; HRMS (ESI-ORBITRAPE) m/z [M + H]$^+$ calcd for $C_{23}H_{16}N_3O$ 350.1288, found 350.1289.

*11(12)-Methoxy-1-phenylbenzo[4,5]imidazo[1,2-a]isoxazolo-[4,3-c]quinoline (**3xy**).* The compound **3x,y** were synthesized by the general procedure described above and obtained as an inseparable mixture: yellowish white solid, 73% yield (266 mg); R_f = 0.5 (10% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (2H, dd, J = 8.2, 1.4 Hz), 8.46 (1H, dd, J = 7.8, 1.5 Hz), 8.22 (1H, d, J = 8.5 Hz), 8.1 (1H, s), 7.80−7.72 (1H, m), 7.69−7.54 (5H, m), 7.49 (1H, t, J = 7.3 Hz,), 4.06 (3H, s, major isomer); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 155.4, 152.9, 142.3, 139.2, 135.6, 131.8, 131.5, 131.1, 128.8, 128.4, 126.8, 125.7, 125.2, 124.6, 115.4, 114.5, 108.8, 103.0, 96.9, 57.1; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{23}H_{16}N_3O_2$ 366.1237; Found:366.1242.

*Methyl 1-Phenylbenzo[4,5]imidazo[1,2-a]isoxazolo[4,3-c]-quinoline-11(12)-carboxylate (**3z,za**).* The compound **3z,za** was synthesized by the general procedure described above and obtained as an inseparable mixture: yellowish white solid, 71% yield (279 mg); R_f = 0.5 (10% EtOAc + pet ether); R_f = 0.6 (10% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08−8.96 (2H, m), 8.60−8.50 (2H, m), 8.48−8.22 (1H, m), 8.21−8.12 (1H, m), 7.99 (1H, d, J = 8.5 Hz), 7.88−7.78 (1H, m), 7.64 (3H, m), 7.59−7.51 (1H, m), 4.02 (3H, s, major + minor); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.7, 167.3, 167.0, 155.7, 147.7, 145.1, 144.1, 135.7, 132.2, 132.0, 131.8, 131.7, 131.3, 128.9, 128.7, 128.6, 126.7, 125.8, 125.7, 125.5, 125.3, 125.1, 122.7, 120.2, 116.3, 116.1, 115.4, 114.4, 112.9, 102.9, 52.4, 52.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{16}N_3O_3$ 394.1186, found 394.1190.

Deuteration of Compound 2a.

(a) Deuteration at the C2 position of benzimidazole ring[17]

A 50 mL Schlenk flask equipped with a stir bar was charged with **2a** (0.337 g, 1 mmol) in dry THF (5 mL) under nitrogen. The solution was cooled to −78 °C, and *n*-butyllithium (1.2 mmol) was added dropwise. After the addition of the *n*-butyllithium, the reaction mixture was allowed to rotate at room temperature for 20 min. After that, again the temperature of the reaction bath was lowered to −78 °C, and D_2O (1 mL) was added dropwise. The solution was then slowly warmed to room temperature and allowed to rotate for 1.5 h. The solvent was removed under reduced pressure. The residue was purified by flash column using ethyl acetate and pet ether as an eluent: R_f = 0.5 (40% EtOAc + pet ether). The weight of the product is 252 mg (75% yield).

*3-(2-(1H-Benzo[d]imidazol-1-yl-2-d)phenyl)-5-phenylisoxazole (**2a-C$_2$D**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.08 (1H, m), 7.90 (1H, d, J = 7.9 Hz), 7.74−7.65 (2H, m), 7.59−7.54 (1H, m), 7.48 (2H, dt, J = 5.3, 2.1 Hz), 7.41−7.29 (5H, m), 7.30−7.26 (1H, m), 5.52 (1H, s).

(b) Deuteration at the C2 and C4 position of the benzimidazole ring

*3-(2-(1H-Benzo[d]imidazol-1-yl-2-d)phenyl)-5-phenylisoxazole-4-d (**2a-C$_2$D-C$_4$D**).* A 50 mL Schlenk flask equipped with a stir bar was charged with **2a** (0.337 g, 1 mmol) in dry THF (5 mL) under nitrogen. The solution was cooled to −78 °C, and *n*-butyllithium (1.2 mmol) was added dropwise. After the addition of *n*-butyllithium, the reaction mixture was allowed to rotate at room temperature for 20 min. After that, again the temperature of the reaction bath was lowered to −78 °C, and D_2O (1 mL) was added dropwise. The solution was then slowly warmed to room temperature and allowed to rotate for 12 h. The solvent was removed under reduced pressure. The residue was purified by flash column using ethyl acetate and pet ether as an eluent: R_f = 0.5 (40% EtOAc + pet ether). The weight of the product is 240 mg (71% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.09 (1H, m), 7.91 (1H, d, J = 7.7 Hz,), 7.75−7.66 (2H, m), 7.61−7.55 (1H, m), 7.52−7.46 (2H, m), 7.40−7.28 (5H, m), 7.25 (1H, d, J = 7.6 Hz).

(c) Deuteration at the C4 position of the isoxazole ring

To an oven-dried round-bottom flask were added aldoxime of type **2a** (1 mmol), *N*-bromosuccinimide (1.2 mmol), and 5 mL of DMF, and the mixture was allowed to rotate 1 h at rt. Then, triethyl ammine (1.2 mmol) was added dropwise, followed by the dropwise addition of deutereated phenyl acetylene[18] (1.1 mmol). The reaction mixture was allowed to rotate at 50 °C until the completion of the reaction (confirmed by TLC). After completion of the reaction, DMF was evaporated under a high vacuum and extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using 100−200 silica gel to get the desired products **2a-C$_4$D**: R_f = 0.5 (40% EtOAc + pet ether). The weight of the product was 230 mg (68% yield).

*3-(2-(1H-Benzo[d]imidazol-1-yl)phenyl)-5-phenylisoxazole-4-d (**2a-C$_4$D**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.08 (1H, m), 7.97 (1H, s), 7.90 (1H, d, J = 7.8 Hz), 7.74−7.65 (2H, m), 7.61−7.54 (1H, m), 7.51−7.45 2H, m), 7.40−7.30 (4H, m), 7.30−7.27 (1H, m), 7.24 (1H, d, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 160.0, 143.2, 143.0, 134.7, 133.9, 131.1, 130.7, 130.3, 129.7, 128.8, 128.2, 127.3, 126.8, 125.7, 124.0, 122.9, 120.5, 110.3, 98.1.

General Procedure for the Synthesis of *β*-Amino *α,β*-Unsaturated Ketone 4. To an oven-dried 25 mL round-bottom flask were added compound **3a** (1 mmol), Fe-power (10 mmol), and 3 mL of glacial AcOH, and the mixture was allowed to rotate 1 h under reflux conditions. After completion of the reaction (confirmed by TLC), the reaction mixture was diluted with ethyl acetate (10 mL) and neutralized with dilute NaOH solution. The reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product.

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

(5-Aminobenzo[4,5]imidazo[1,2-a]quinolin-6-yl)(phenyl)-methanone (4). The compound **4** was synthesized by the procedure as described above and obtained as a yellow liquid: 92% yield (347 mg); R_f = 0.6 (40% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (1H, d, J = 8.4), 8.18 (1H, dd, J = 7.0, 1.9), 7.97 (1H, d, J = 8.1), 7.87−7.74 (3H, m), 7.63 (1H, dd, J = 6.8, 2.1), 7.48 (2H, dt, J = 12.6, 7.5), 7.3−7.30 (4H, m), 7.24 (2H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.9, 149.1, 149.1, 144.6, 140.3, 136.5, 132.0, 131.9, 130.4, 129.5, 127.8, 123.9, 123.8, 123.6, 121.3, 119.4, 117.0, 116.1, 112.8, 100.6; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{16}N_3O$ 338.1288, found 338.1282.

3-Methyl-1-phenylbenzo[h]benzo[4,5]imidazo[2,1-f][1,6]-naphthyridine (5a).[19] To an oven-dried 25 mL round-bottom flask were added compound **4** (1 mmol), acetone (0.5 mL), and 5 mL of 20% KOH ethanol solution, and the mixture was allowed to rotate overnight under reflux conditions. After completion of the reaction (confirmed by TLC), the reaction mixture was quench with 1 N hydrochloric acid solution and extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **5a** as an off-white solid: 82% yield (294 mg); R_f = 0.7 (20% EtOAc + pet ether); mp 169−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (400 MHz, $CDCl_3$) 9.30 (1H, d, J = 8.0), 8.57 (1H, d, J = 8.4), 8.35 (1H, d, J = 8.1), 7.82 (1H, t, J = 7.8), 7.70 (1H, d, J = 8.0), 7.61 (1H, t, J = 7.6), 7.57−7.49 (5H, m), 7.42 (2H, dt, J = 14.9, 7.2), 7.34 (1H, s), 2.84 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.6, 150.0, 147.3, 146.1, 144.3, 140.5, 135.8, 130.9, 130.6, 129.0, 127.9, 127.8, 127.1, 126.2, 124.4, 123.6, 123.1, 123.0, 121.0, 115.1, 114.7, 113.4, 25.0; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{25}H_{18}N_3$ 360.1495, found 360.1493.

1-Phenylbenzo[4,5]imidazo[1,2-a]pyrimido[5,4-c]quinilone (5b). To an oven-dried 25 mL sealed tube were added compound **4** (0.25 mmol), thiourea (0.25 mmol), and 2 mL of DMSO, and the mixture was allowed to rotate at 150 °C in an oil bath. After completion of the reaction (confirmed by TLC), the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **5b** as a white solid: 93% yield (80 mg); R_f = 0.7 (20% EtOAc + pet ether); mp 222−225 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.47 (1H, s), 9.20 (1H, dd, J = 8.0, 1.2), 8.56 (1H, d, J = 8.4), 8.34 (1H, d, J = 8.1), 7.96−7.85 (3H, m), 7.80 (1H, d, J = 7.6), 7.62 (2H, dd, J = 15.1, 7.3), 7.58−7.44 (4H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.7, 157.0, 153.8, 144.0, 139.0, 137.2, 133.1, 131.0, 130.0, 129.8, 127.8, 127.3, 124.9, 124.2, 123.9, 121.4, 121.2, 115.4, 114.3, 113.4; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{23}H_{15}N_4$ 347.1291, found 347.1297.

Ethyl-1-phenylbenzo[h]benzo[4,5]imidazo[2,1-f][1,6]-naphthyridine-2-carboxylate (5c). To an oven-dried 25 mL sealed tube were added compound **4** (1 mmol), ethyl propiolet (1 mmol), and 2 mL of DMSO, and the mixture was allowed to rotate at 150 °C using an oil bath. After completion of the reaction (confirmed by TLC), the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **5c** as a white solid: 91% yield (379 mg); R_f = 0.7 (10% EtOAc + pet ether); mp 181−183 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 9.28 (1H, s), 9.25 (1H, d, J = 8.1), 8.55 (1H, d, J = 8.4), 8.33 (1H, d, J = 8.3), 7.91−7.80 (1H, m), 7.66−7.57 (2H, m), 7.58−7.49 (3H, m), 7.46 (1H, t, J = 7.7), 7.43−7.35 (3H, m), 4.12 (2H, q, J = 7.1), 1.03 (3H, t, J = 7.1); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 150.3, 149.3, 148.9, 145.3, 144.2, 138.3, 136.2, 131.7, 130.7, 128.7, 128.4, 127.8, 127.7, 127.6, 124.6, 123.8, 123.7, 122.4, 121.4, 117.4, 115.1, 113.5, 61.5, 13.6; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{27}H_{20}N_3O_2$ 418.1550, found 418.1542.

Procedure for the Synthesis of 5d.[20] To an oven-dried 25 mL round-bottom flask were added compound **4** (1 mmol), hydrazine hydrate (1.2 mmol), triethy ammine (1.2 mmol), and 5 mL of acetonitrile, and the mixture was allowed to rotate overnight under reflux conditions using an oil bath. After completion of the reaction (confirmed by TLC), the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product.

1-Phenyl-3H-benzo[4,5]imidazo[1,2-a]pyrazolo[4,3-c]quinoline (5d). The compound **5d** was synthesized by the general procedure described above and obtained as a yellow liquid: 78% yield (268 mg); R_f = 0.4 (40% EtOAc + pet ether); ^{1}H NMR δ (400 MHz, DMSO) 14.52 (1H, d, J = 58.0), 8.96−8.53 (4H, m), 8.50 (1H, d, J = 7.6), 7.89 (2H, s), 7.54 (6 H, d, J = 41.8); ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 145.2, 144.2, 134.3, 131.3, 130.5, 128.9, 128.8, 125.1, 124.1, 123.8, 123.1, 119.9, 116.9, 114.4, 105.3; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{15}N_4$ 335.1291, found 335.1291.

(5-Chlorobenzo[4,5]imidazo[1,2-a]quinolin-6-yl)(phenyl)-methanone (5e). To a mixture of **4** (1 mmol) in concentrated hydrochloric acid (1 mL) and water (1 mL) was added $NaNO_2$ (2 mmol) in one portion at 0 °C. After that, the reaction mixture was allowed to rotate at room temperature for 30 min. After completion of the reaction (confirmed by TLC), the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **5e** as a reddish yellow solid: 85% yield (302 mg); R_f = 0.5 (20% EtOAc + pet ether); mp 250−252 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.72 (1H, d, J = 8.5), 8.43 (2H, dd, J = 14.2, 6.1), 8.08−8.00 (3H, m), 7.95 (1H, t, J = 7.9), 7.66 (2H, dd, J = 14.2, 7.1), 7.59−7.54 (2H, m), 7.50 (2H, t, J = 7.7); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 191.0, 145.3, 145.0, 135.5, 135.4, 134.4, 131.5, 131.4, 130.5, 130.0, 128.9, 127.5, 127.1, 124.9, 124.9, 123.6, 121.3, 120.7, 115.3, 113.8; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{14}ClN_2O$ 357.0789, found 357.0785.

Benzo[4,5]imidazo[1,2-a]quinolin-6-yl(phenyl)methanone (5f). To an oven-dried 50 mL Schlenk tube fitted with a nitrogen balloon were added compound **5e** (178 mg 0.5 mmol), 10 mol % $Pd(PPh_3)_2$, K_2CO_3 (69 mg, 2 mmol), and 2 mL of dry DMF, and the mixture was allowed to rotate at 120 °C in an oil bath for 12 h. After completion (confirmed by TLC), the reaction mixture was extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **5f** as a yellow solid: 73% yield (235 mg); R_f = 0.5 (20% EtOAc + pet ether); mp 226−228 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.70 (1H, d, J = 8.5), 8.51−8.44 (1H, m), 8.10−8.01 (3H, m), 7.97−7.85 (3H, m), 7.65 (1H, t, J = 7.4), 7.61−7.54 (3H, m), 7.50 (2H, t, J = 7.7); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.9, 145.8, 144.8, 136.7, 136.2, 133.7, 132.0, 131.2, 130.6, 130.4, 128.5, 128.4, 124.7, 124.6, 123.2, 122.1, 121.4, 115.3, 113.8; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{15}N_2O$ 323.1179, found 323.1178.

(5-Chlorobenzo[4,5]imidazo[1,2-a]quinolin-6-yl)(phenyl)-methanol (5g). To a mixture of **5e** (100 mg, 0.28 mmol) in ethanol (1 mL) and chloroform (1 mL) was added $NaBH_4$ (21 mg, 2 mmol) in one portion at 0 °C. After that, the reaction mixture was allowed to rotate at room temperature for 1 h. After completion of the reaction

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

(confirmed by TLC), the solvent was evaporated under a vacuum and extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using silica gel 100−200 to give the desired product **5g** as a white solid: 95% yield (95 mg); R_f = 0.5 (10% EtOAc + pet ether); mp 227−230 °C; ^{1}H NMR δ (400 MHz, $CDCl_3$) 8.58 (1H, d, J = 8.4), 8.38 (2H, dd, J = 21.1, 8.2), 7.99 (1H, d, J = 8.1), 7.82 (1H, t, J = 7.8), 7.74 (2H, d, J = 7.6), 7.67−7.47 (4H, m), 7.33 (2H, t, J = 7.4), 7.25 (1H, d, J = 7.3), 6.64 (1H, d, J = 11.0); ^{13}C{^{1}H} NMR δ (10 MHz, $CDCl_3$) 146.3, 143.5, 142.5, 134.6, 131.9, 130.5, 129.9, 128.3, 128.2, 127.6, 127.3, 126.3, 125.0, 124.9, 123.4, 121.4, 120.6, 115.1, 114.0, 73.6; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{16}ClN_2O$ [M + H]$^+$ 359.0946, found 359.0938.

Experimental Procedure for Compounds 1A−E, 1c−k, 2u−2zc: General Procedure for the Synthesis of Aldehydes 1A−E. To a 25 mL round-bottom flask, were added 2-fluorobenzaldehydes (2.0 equiv, 13.6 mmol), benzo[d]imidazoles (1.0 equiv, 6.8 mmol), and K_2CO_3 (2.0 equiv, 13.6 mmol) in DMF (5.0 mL), and the reaction was stirred at 90 °C for 10 h. Upon the completion of the reaction (confirm by TLC), the solvent was removed under reduced pressure, and the residue was dissolved in AcOEt (150 mL). The organic layer was washed with H_2O (3 × 40 mL), dried over anhydrous Na_2SO_4, and removed under the reduced pressure. The crude was purified with silica gel column chromatography to afford the target compound **1**.

*2-(5,6-Dimethyl-1H-benzo[d]imidazol-1-yl)benzaldehyde (**1A**).* The compound **1A** was synthesized by the procedure as described above and obtained as a white solid: 44% yield (748 mg); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, s), 8.11 (1H, dd, J = 7.8, 1.5 Hz), 7.94 (1H, s), 7.79 (1H, td, J = 7.7, 1.6 Hz), 7.70−7.58 (2H, m), 7.47 (1H, dd, J = 7.9, 0.8 Hz), 6.98 (1H, s), 2.37 (3H, s), 2.30 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.5, 142.5, 141.9, 138.3, 135.4, 134.4, 133.8, 132.3, 131.6, 129.4, 129.3, 127.8, 120.6, 110.0, 20.5, 20.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{16}H_{15}N_2O$ 251.1179, found 251.1181.

*2-(5(6)-Methyl-1H-benzo[d]imidazol-1-yl)benzaldehyde (**1B,C**).* The compound **1B,C** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow liquid, 67% yield (1.076 g); R_f = 0.5 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (1H, s), 8.16−8.11 (1H, m), 8.01 (1H, d, J = 8.3 Hz), 7.84−7.78 (1H, m), 7.78−7.63 (2H, m), 7.49 (1H, d, J = 7.8 Hz), 7.21−6.99 (2H, m), 2.46 (3H, s, major + minor); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 188.4, 188.4, 143.7, 143.2, 142.8, 141.4, 138.1, 136.0, 135.4, 135.4, 134.6, 133.9, 133.1, 131.7, 131.6, 129.5, 129.4, 129.4, 129.4, 127.9, 127.8, 125.9, 124.9, 120.4, 120.2, 109.7, 109.4, 77.4, 77.0, 76.7, 21.7, 21.5; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{15}H_{13}N_2O$ 237.1022, found 237.1028.

*2-(5(6)-Methoxy-1H-benzo[d]imidazol-1-yl)benzaldehyde (**1D,E**).* The compound **1D,E** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow liquid, 68% yield (1.16 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78−9.69 (1H, s), 8.13 (1H, ddd, J = 7.9, 6.6, 1.5 Hz), 7.99 (1H, d, J = 21.6 Hz), 7.81 (1H, qd, J = 7.6, 1.6 Hz), 7.76, 7.11 (1H, d, major + minor), 7.67 (1H, q, J = 7.4 Hz), 7.50 (1H, d, J = 7.9 Hz), 7.35, 6.64 (1H, d, major + minor), 6.96 (1H, td, J = 9.1, 2.4 Hz), 3.82 (3H, s, major + minor); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.4, 188.8, 157.8, 156.8, 144.3, 143.5, 142.4, 138.0, 137.7, 136.4, 135.5, 135.4, 131.6, 131.5, 130.4, 129.6, 129.5, 127.8, 127.7, 121.2, 114.5, 112.7, 110.4, 102.6, 93.1, 55.8; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{15}H_{13}N_2O_2$ 253.0972, found 253.0976.

*Methyl 1-(2-Formylphenyl)-1H-benzo[d]imidazole-5(6)-carboxylate (**1F,G**).* The compound **1F,G** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow liquid, 72% yield (1.15 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, s, major + minor), 8.57, 7.21 (1H, d, major minor), 8.15 (1H, d, J = 13.7 Hz), 8.13−8.08 (1H, m), 8.2−7.77 (1H, m), 7.89 (1H, dd, J = 10.5, 4.8 Hz), 7.86−7.79 (1H, m), 7.71 (1H, d, J = 7.1 Hz,), 7.50 (1H, ddd, J = 7.8, 3.3, 0.7 Hz), 3.89 (3H, s, major + minor); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.0, 167.1, 166.9, 146.6, 145.8, 144.9, 143.0, 138.6, 136.9, 136.7, 135.5, 135.4, 131.7, 131.5, 130.5, 130.3, 130.1, 130.0, 128.2, 128.0, 126.3, 125.8, 125.5, 124.5, 123.1, 120.4, 112.3, 109.8, 52.3, 52.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{16}H_{13}N_2O_3$ 281.0921, found 281.0923.

*2-(5(6)-Nitro-1H-benzo[d]imidazol-1-yl)benzaldehyde (**1H,I**).* The compound **1H,I** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow solid, 63% yield (1.14 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, s, major + minor), 8.77 (1H, d, J = 2.1 Hz), 8.29−8.19 (2H, m), 8.18−8.09 (1H, m), 7.93−7.85 (1H, m), 7.80 (1H, td, J = 8.4, 0.6 Hz,), 7.57−7.52 (1H, m, J = 7.8, 4.8, 0.9 Hz), 7.29−7.22 (1H, m); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.0, 188.0, 147.7, 147.6, 146.5, 144.7, 144.3, 142.8, 139.3, 135.6, 135.3, 134.8, 132.0, 131.6, 131.5, 130.7, 130.6, 128.4, 128.3, 121.0, 119.9, 118.8, 117.4, 110.2, 107.1; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{14}H_{10}N_3O_3$ 268.0717, found 268.0719.

General Procedure for the Synthesis of Aldehyde 1c−k. Et_3N (1.2 equiv) was added to the stirring solution of **1** (1.0 equiv, 10 mmol) and $NH_2OH{\cdot}HCl$ (1.2 equiv) in 20 mL of methanol. The resulting solution was allowed to stir at room temperature, and the progress of the reaction was monitored by TLC until completion. Upon completion of the reaction, the reaction mixture was concentrated under reduced pressure by removing the solvent. The residue was extracted with DCM (25 mL) and water (25 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 25 mL). The organic extract was washed with brine (25 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel 100−200 to get the desired product.

*2-(5,6-Dimethyl-1H-benzo[d]imidazol-1-yl)benzaldehyde Oxime (**1c**).* The compound **1c** was synthesized by the procedure as described above and obtained as a yellow solid: 82% yield (2.17 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.66 (1H, s), 8.36 (1H, s), 8.15−8.05 (1H, m), 7.75−7.69 (2H, m), 7.66 (1H, s), 7.62−7.57 (1H, m), 7.56 (1H, s), 7.00 (1H, s), 2.42 (3H, s), 2.36 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 143.9, 143.8, 141.8, 134.3, 134.1, 132.9, 131.4, 131.1, 130.1, 129.9, 128.7, 126.9, 120.2, 110.6, 40.5, 40.3, 40.1, 39.9, 39.7, 39.5, 39.3, 20.4, 20.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{16}H_{16}N_3O$ 266.1288, found 266.1292.

*2-(5(6)-Methyl-1H-benzo[d]imidazol-1-yl)benzaldehyde Oxime (**1d,e**).* The compound **1d,e** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow solid, 83% yield (1.50 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO) δ 11.58 (1H, s, major + minor), 8.33 (1H, d, J = 10.3 Hz), 8.03−7.96 (1H, m), 7.69−7.53 (3H, m), 7.53−7.44 (2H, m), 7.13−7.06 (1H, m), 7.02−6.87 (1H, m), 2.38 (3H, s, major + minor); ^{13}C{^{1}H} NMR (101 MHz, DMSO) δ 144.7, 144.3, 143.8, 143.8, 143.7, 141.4, 135.7, 134.2, 134.2, 133.6, 132.0, 131.1, 130.2, 130.0, 129.9, 129.9, 128.8, 128.6, 127.0, 125.4, 124.4, 120.0, 119.8, 110.3, 110.3, 21.7, 21.5; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_3O$ 252.1131, found 252.1133.

*2-(5(6)-Methoxy-1H-benzo[d]imidazol-1-yl)benzaldehyde Oxime (**1f,g**).* The compound **1f,g** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow solid, 78% yield (2.08 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO) δ 11.60 (1H, s), 8.45 (1H, d, J = 46.3 Hz), 8.10−7.86 (1H, m), 7.75−7.45 (4H, m), 7.36−7.00 (1H, m), 6.99−6.88 (1H, m), 6.59 (1H, d, J = 2.3 Hz), 3.70 (3H, s, major + minor); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 157.4, 156.7, 144.7, 144.1, 143.9, 143.7, 142.9, 136.6, 135.9, 133.8, 133.8, 131.1, 131.0, 130.0, 130.0, 129.8, 128.7, 127.3, 127.2, 120.5, 114.1, 112.8, 111.4, 102.1, 93.9, 56.0, 56.0; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_2$ 268.1081, found 268.1084.

*Methyl-1-(2-((hydroxyimino)methyl)phenyl)-1H-benzo[d]-imidazole-5(6)-carboxylate (**1h,i**).* The compound **1h,i** was synthe-

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

sized by the procedure as described above and obtained as an inseparable mixture: yellow solid, 85% yield (2.51 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO) δ 11.74−11.59 (1H, m), 8.79−8.65 (1H, m), 8.05−8.13 (1H, m), 8.05−7.92 (2H, m), 7.79−7.71 (3H, m), 7.65−7.70 (1H, dd, J = 5.9, 3.2 Hz), 7.62 (1H, s), 3.90 (3H, s, major + minor); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 166.7, 147.8, 146.8, 143.9, 135.2, 133.3, 131.2, 130.4, 130.2, 129.0, 127.6, 125.2, 123.8, 120.4, 112.2, 52.6; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_3O_3$ 296.1030, found 296.1031.

*2-(5-Nitro-1H-benzo[d]imidazol-1-yl)benzaldehyde Oxime (**1j,k**).* The compound **1j,k** was synthesized as an inseparable mixture by the procedure as described above and obtained as a yellow solid: 78% yield (2.20 g); R_f = 0.4 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, DMSO) δ 11.55 (1H, s, major + minor), 8.73 (2H, dd, J = 50.0, 16.2 Hz), 8.14−8.22 (1H, m), 8.08−7.91 (2H, m), 7.75−7.57 (4H, m), 7.34 (1H, s, major + minor); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.0, 148.8, 147.9, 144.2, 144.1, 144.0, 143.7, 142.8, 139.5, 134.8, 132.8, 132.6, 131.1, 130.6, 130.6, 130.2, 130.1, 129.7, 128.9, 128.1, 128.0, 120.8, 119.6, 118.4, 116.5, 111.5, 107.4; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{14}H_{11}N_4O_3$ 283.0826, found 283.0832.

General Procedure for the Synthesis of Isoxazoles (2u−zc). To an oven-dried round-bottom flask were added aldoxime of type **1c** (1 mmol), *N*-bromosuccinimide (1.2 mmol), and 5 mL of DMF, and the mixture was allowed to rotate 1 h at rt. Then triethyl ammine (1.2 mmol) was added dropwise, followed by the dropwise addition of substituted acetylene (1.1 mmol). The reaction mixture was allowed to rotate at 50 °C (using an oil bath) until the completion of the reaction (confirmed by TLC). After completion of the reaction, DMF was evaporated under a high vacuum and extracted with ethyl acetate (10 mL) and water (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with 10 mL of brine solution, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography using 100−200 silica gel to get the desired product **2**.

*3-(2-(5,6-Dimethyl-1H-benzo[d]imidazol-1-yl)phenyl)-5-phenylisoxazole (**2u**).* The compound **2u** was synthesized by the procedure as described above and obtained as a reddish yellow liquid: 67% yield (244 mg); R_f = 0.5 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.09 (1H, m), 7.82 (1H, s), 7.73−7.66 (2H, m), 7.65 (1H, s), 7.57−7.48 (3H, m), 7.41−7.34 (3H, m), 7.02 (1H, s), 2.40 (3H, s), 2.32 (3H, s); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.5, 160.1, 142.2, 141.7, 134.2, 133.3, 133.2, 131.9, 131.1, 130.6, 130.2, 129.5, 128.8, 128.2, 127.2, 126.9, 125.8, 120.3, 110.3, 98.2, 20.5, 20.2; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{20}N_3O$ 366.1601, found 366.1610.

*3-(2-(5(6)-Methyl-1H-benzo[d]imidazol-1-yl)phenyl)-5-phenylisoxazole (**2v,w**).* The compound ***xx*** was synthesized by the procedure as described above and obtained as a yellow liquid: 77% yield (270 mg); R_f = 0.5 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.06 (1H, m), 7.87 (1H, d, J = 14.3 Hz), 7.78−7.61 (3H, m), 7.56−7.51 (1H, m, J = 5.2, 4.3, 2.0 Hz,), 7.51−7.45 (2H, m), 7.39−7.31 (3H, m), 7.18−7.00 (2H, m), 5.49 (1H, d, J = 13.3 Hz), 2.45 (3H, s, major minor); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.6, 170.5, 160.1, 160.1, 143.5, 142.9, 142.5, 141.2, 134.9, 134.1, 134.0, 134.0, 132.7, 132.7, 131.1, 130.7, 130.7, 130.3, 129.6, 129.5, 128.8, 128.2, 128.1, 127.3, 127.2, 126.8, 125.8, 125.8, 125.5, 124.6, 120.1, 119.9, 110.1, 109.8, 98.2, 98.2, 21.7, 21.5; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{23}H_{18}N_3O$ 352.1444, found 352.1445.

*3-(2-(5(6)-Methoxy-1H-benzo[d]imidazol-1-yl)phenyl)-5-phenylisoxazole (**2xy**).* The compound **2xy** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow liquid, 71% yield (260 mg); R_f = 0.5 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−7.99 (2H, m), 7.92−7.84 (1H, m), 7.72−7.65 (2H, m), 7.55−7.46 (3H, m), 7.40−7.30 (3H, m), 7.00 (1H, dd, J = 55.9, 8.8 Hz), 6.57 (1H, d, J = 41.3 Hz), 5.60 (1H, s, major + minor), 3.85 (3H, m, major + minor); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.79, 160.07, 160.00, 152.84, 144.19, 142.66, 133.59, 131.38, 131.25, 130.97, 130.92, 130.48, 130.44, 129.98, 129.94, 129.02, 128.95, 128.93, 128.17, 128.08, 127.25, 126.72, 125.85, 125.83, 125.58, 124.57, 110.69, 109.44, 98.17, 98.10, 93.11, 56.71; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{23}H_{18}N_3O_2$ 368.1394, found 368.1400.

*Methyl 1-(2-(5-Phenylisoxazol-3-yl)phenyl)-1H-benzo[d]imidazole-5(6)-carboxylate (**2z,za**).* The compound **2z,za** was synthesized by the procedure as described above and obtained as an inseparable mixture: reddish yellow liquid, 71% yield (280 mg); R_f = 0.5 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (1H, s), 8.12−7.87 (3H, m), 7.77−7.66 (2H, m), 7.62−7.53 (1H, m), 7.53−7.45 (2H, m), 7.41−7.32 (3H, m), 7.30−7.21 (1H, m), 5.59 (1H, d, J = 9.1 Hz), 3.92 (3H, s, major + minor); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.8, 167.3, 167.1, 159.9, 145.8, 144.7, 142.9, 137.7, 133.4, 133.2, 131.2, 130.9, 130.4, 130.0, 128.9, 128.3, 128.2, 127.5, 127.3, 126.6, 125.9, 125.7, 125.5, 125.2, 124.3, 122.9, 120.2, 112.6, 110.1, 98.0, 98.0, 52.2, 52.1; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{24}H_{18}N_3O_3$ 396.1343, found 396.1345.

*3-(2-(5(6)-Nitro-1H-benzo[d]imidazol-1-yl)phenyl)-5-phenylisoxazole (**2zb,zc**).* The compound **2zb,zc** was synthesized by the procedure as described above and obtained as an inseparable mixture: yellow liquid, 67% yield (256 mg); R_f = 0.5 (60% EtOAc + pet ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (1H, d, J = 2.1 Hz), 8.19 (1H, dd, J = 9.0, 2.1 Hz), 8.15 (1H, s), 8.07−8.01 (1H, m), 7.77−7.71 (2H, m), 7.59−7.50 (3H, m), 7.42−7.36 (3H, m), 7.29−7.24 (1H, m), 5.82 (1H, s, major); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.9, 159.7, 146.5, 144.2, 142.7, 138.7, 132.8, 131.4, 131.1, 130.6, 130.5, 129.0, 128.2, 127.4, 126.5, 125.7, 119.7, 117.3, 110.48, 97.9; HRMS (ESI-ORBITRAP) m/z [M + H]$^+$ calcd for $C_{22}H_{15}N_4O_3$ 383.1139, found 383.1143.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02926.

Mechanistic studies, NMR spectra, UV, fluorescence spectra, and X-ray data (PDF)

Accession Codes

CCDC 2036437 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/ data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Shantanu Pal − *Organic Chemistry Laboratory, School of Basic Sciences, Indian Institute of Technology Bhubaneswar, Argul, Odisha 752050, India;* orcid.org/0000-0001-5120-1679; Email: spal@iitbbs.ac.in

Author

Subrata Sahoo − *Organic Chemistry Laboratory, School of Basic Sciences, Indian Institute of Technology Bhubaneswar, Argul, Odisha 752050, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02926

Notes

The authors declare no competing financial interest.

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

REFERENCES

(1) (a) Forrest, S. R.; Thompson, M. E. Introduction: Organic Electronics and Optoelectronics. *Chem. Rev.* **2007**, *107*, 923−925. (b) Mishra, A.; Bauerle, P. Small Molecule Organic Semiconductors on the Move: Promises for Future Solar Energy Technology. *Angew. Chem., Int. Ed.* **2012**, *51*, 2020. (c) Itoh, T. Fluorescence and Phosphorescence from Higher Excited States of Organic Molecules. *Chem. Rev.* **2012**, *112*, 4541. (d) Dong, Y.; Yang, J.; Zhang, H.; Zhan, X. Y.; He, S.; Shi, Z. C.; Zhang, X. M.; Wang, J. Y. Cobalt-Catalyzed Cycloamination: Synthesis and Photophysical Properties of Polycyclic N-Heterocycles. *Org. Lett.* **2020**, *22*, 5151−5156. (e) Singh, K.; Vellakkaran, M.; Banerjee, D. A nitrogen-ligated nickel-catalyst enables selective intermolecular cyclisation of β- and γ-amino alcohols with ketones: access to five and sixmembered N-heterocycles. *Green Chem.* **2018**, *20*, 2250.

(2) (a) Hranjec, M.; Kralj, M.; Piantanida, I.; Sedic, M.; Suman, L.; Pavelic, K.; Karminski-Zamola, G. Novel Cyano- and Amidino-Substituted Derivatives of Styryl-2-Benzimidazoles and Benzimidazo-[1,2-a]quinolines. Synthesis, Photochemical Synthesis, DNA Binding, and Antitumor Evaluation, Part 3. *J. Med. Chem.* **2007**, *50*, 5696−5711. (b) Sedic, M.; Poznic, M.; Gehrig, P.; Scott, M.; Schlapbach, R.; Hranjec, M.; Karminski-Zamola, G.; Pavelic, K.; Pavelic, S. K. Differential antiproliferative mechanisms of novel derivative of benzimidazo[1,2-α]quinoline in colon cancer cells depending on their p53 status. *Mol. Cancer Ther.* **2008**, *7*, 2121−2132. (c) Perin, N.; Martin-Kleiner, I.; Nhili, R.; Laine, W.; David-Cordonnier, M. H.; Vugrek, O.; Karminski-Zamola, G.; Kralj, M.; Hranjec, M. Biological activity and DNA binding studies of 2- substituted benzimidazo[1,2-a]quinolines bearing different amino side chains. *MedChemComm* **2013**, *4*, 1537−1550.

(3) (a) Lai, M.-Y.; Chen, C.-H.; Huang, W.-S.; Lin, J. T.; Ke, T.-H.; Chen, L.-Y.; Tsai, M.-H.; Wu, C.-C. Benzimidazole/Amine-Based Compounds Capable of Ambipolar Transport for Application in Single-Layer Blue-Emitting OLEDs and as Hosts for Phosphorescent Emitters. *Angew. Chem., Int. Ed.* **2008**, *47*, 581. (b) Ge, Z.; Hayakawa, T.; Ando, S.; Ueda, M.; Akiike, T.; Miyamoto, H.; Kajita, T.; Kakimoto, M. Spin-Coated Highly Efficient Phosphorescent Organic Light-Emitting Diodes Based on Bipolar Triphenylamine-Benzimidazole Derivatives. *Adv. Funct. Mater.* **2008**, *18*, 584. (c) Benelhadj, K.; Massue, J.; Retailleau, P.; Ulrich, G.; Ziessel, R. 2-(20 -Hydroxyphenyl)benzimidazole and 9,10-Phenanthroimidazole Chelates and Borate Complexes: Solution- and Solid-State Emitters. *Org. Lett.* **2013**, *15*, 2918. (d) Zhuang, S.; Shangguan, R.; Huang, H.; Tu, G.; Wang, L.; Zhu, X. Synthesis, characterization, physical properties, and blue electroluminescent device applications of phenanthroimidazole derivatives containing anthracene or pyrene moiety. *Dyes Pigm.* **2014**, *101*, 93.

(4) For selected reviews, see: (a) Patil, N. T.; Yamamoto, Y. Coinage Metal-Assisted Synthesis of Heterocycles. *Chem. Rev.* **2008**, *108*, 3395. (b) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. Transition Metal-Mediated Synthesis of Monocyclic Aromatic Heterocycles. *Chem. Rev.* **2013**, *113*, 3084. (c) Hu, F.; Szostak, M. Recent Developments in the Synthesis and Reactivity of Isoxazoles: Metal Catalysis and Beyond. *Adv. Synth. Catal.* **2015**, *357*, 2583. (d) Li, L.; Tan, T.-D.; Zhang, Y.-Q.; Liu, X.; Ye, L.-W. Recent advances in transition-metal-catalyzed reactions of alkynes with isoxazoles. *Org. Biomol. Chem.* **2017**, *15*, 8483. (e) Agrawal, N.; Mishra, P. The synthetic and therapeutic expedition of isoxazole and its analogs. *Med. Chem. Res.* **2018**, *27*, 1309.

(5) (a) Akhtar, M. J.; Siddiqui, A. A.; Khan, A. A.; Ali, Z.; Dewangan, R. P.; Pasha, S.; Yar, M. S. Design, synthesis, docking and QSAR study of substituted benzimidazole linked oxadiazole as cytotoxic agents, EGFR and erbB2 receptor inhibitors. *Eur. J. Med. Chem.* **2017**, *126*, 853−869. (b) Rida, S. M.; El-Hawash, S. A. M.; Fahmy, H. T. Y.; Hazzaa, A. A.; El-Meligy, M. M. M. Synthesis of Novel Benzofuran and Related Benzimidazole Derivatives for Evaluation of In Vitro Anti-HIV-1, Anticancer and Antimicrobial Activities. *Arch. Pharmacal Res.* **2006**, *29*, 826. (c) Deady, L. W.; Rodemann, T.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. Synthesis and cytotoxic activity of carboxamide derivatives of benzimidazo[2,1-a]isoquinoline and pyrido[3′,2′:4,5]imidazo[2,1-a]isoquinoline. *Anti-Cancer Drug Des.* **2001**, *15*, 339.

(6) (a) Huang, J.; Dong, L.; Han, B.; Peng, C.; Chen, Y. Synthesis of Aza-Fused Polycyclic Quinolines via Double CH Bond Activation. *Chem. - Eur. J.* **2012**, *18*, 8896−8900. (b) Ghorai, D.; Choudhury, J. Exploring a unique reactivity of N-heterocyclic carbenes (NHC) in rhodium(III)-catalyzed intermolecular C−H activation/annulation. *Chem. Commun.* **2014**, *50*, 15159−15162. (c) Ge, Q.; Li, B.; Song, H.; Wang, B. Rhodium(III)-catalyzed cascade oxidative annulation reactions of aryl imidazolium salts with alkynes involving multiple C−H bond activation. *Org. Biomol. Chem.* **2015**, *13*, 7695−7710. (d) Wezeman, T.; Scopelliti, R.; Tirani, F. F.; Severin, K. Synthesis of Heteroaryl Triazenes via Rh(III)-catalyzed Annulation Reactions with Alkynyl Triazenes. *Adv. Synth. Catal.* **2019**, *361*, 1383−1388.

(7) Li, X.; Chen, X.; Wang, H.; Chen, C.; Sun, P.; Mo, B.; Peng, J. Palladium-catalyzed tandem one-pot synthesis of π-expanded imidazoles through a sequential Heck and oxidative amination reaction. *Org. Biomol. Chem.* **2019**, *17*, 4014−4023.

(8) Hu, Y.; Wang, T.; Liu, Y.; Nie, R.; Yang, N.; Wang, Q.; Li, G.-B.; Wu, Y. Practical Synthesis of Benzimidazo[1,2-a]quinolines via Rh(III)- Catalyzed C−H Activation Cascade Reaction from Imidamides and Anthranils. *Org. Lett.* **2020**, *22*, 501−504.

(9) For reviews, see: (a) Davies, H.; Morton, D. Recent Advances in C−H Functionalization. *J. Org. Chem.* **2016**, *81*, 343. (b) Yang, L.; Huang, H. Transition-Metal-Catalyzed Direct Addition of Unactivated C−H Bonds to Polar Unsaturated Bonds. *Chem. Rev.* **2015**, *115*, 3468. (c) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. Oxidative Coupling between Two Hydrocarbons: An Update of Recent C−H Functionalizations. *Chem. Rev.* **2015**, *115*, 12138. (d) Wu, Y.; Wang, J.; Mao, F.; Kwong, F. Y. Palladium-Catalyzed Cross-Dehydrogenative Functionalization of C(sp2)H Bonds. *Chem. - Asian J.* **2014**, *9*, 26. (e) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. CH Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Recent advances in the transition metal-catalyzed twofold oxidative C−H bond activation strategy for C−C and C−N bond formation. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Gutekunst, W. R.; Baran, P. S. C−H functionalization logic in total synthesis. *Chem. Soc. Rev.* **2011**, *40*, 1976. (h) Yeung, C. S.; Dong, V. M. Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds. *Chem. Rev.* **2011**, *111*, 1215.

(10) (a) Lerchen, A.; Knecht, T.; Koy, M.; Ernst, J. B.; Bergander, K.; Daniliuc, C. G.; Glorius, F. Non-Directed Cross-Dehydrogenative (Hetero)arylation of Allylic C(sp3)-H bonds enabled by C-H Activation. *Angew. Chem., Int. Ed.* **2018**, *57*, 15248. (b) Banjare, S. K.; Biswal, P.; Ravikumar, P. C. Cobalt-Catalyzed One-Step Access to Pyroquilon and C-7 Alkenylation of Indoline with Activated Alkenes Using Weakly Coordinating Functional Groups. *J. Org. Chem.* **2020**, *85*, 5330−5341. (c) Banjare, S. K.; Nanda, T.; Ravikumar, P. C. Cobalt Catalyzed Hydroarylation of Michael Acceptors with Indolines Directed by a Weakly Coordinating Functional Group. *Org. Lett.* **2019**, *21*, 8138−8143. (d) Qiu, Y.; Kong, W.-J.; Struwe, J.; Sauermann, N.; Rogge, T.; Scheremetjew, A.; Ackermann, L. Electrooxidative Rhodium-Catalyzed C-H/C-H Activation: Electricity as Oxidant for Cross-Dehydrogenative Alkenylation. *Angew. Chem., Int. Ed.* **2018**, *57*, 5828. (e) Gorsline, D. J.; Wang, L.; Ren, P.; Carrow, B. P. C−H Alkenylation of Heteroarenes: Mechanism, Rate, and Selectivity Changes Enabled by Thioether Ligands. *J. Am. Chem. Soc.* **2017**, *139*, 9605. (f) Xu, W.; Huang, Z.; Ji, X.; Lumb, J.-P. Catalytic Aerobic Cross-Dehydrogenative Coupling of Phenols and Catechols. *ACS Catal.* **2019**, *9*, 3800. (g) Yu, C.; Patureau, F. W. Cu-Catalyzed Cross-Dehydrogenative ortho-Aminomethylation of Phenols. *Angew. Chem., Int. Ed.* **2018**, *57*, 11807. (h) Zhu, C.; Zhu, R.; Zeng, H.; Chen, F.; Liu, C.; Wu, W.; Jiang, H. Copper-Catalyzed C(sp3)H/C(sp3)H Cross-Dehydrogenative Coupling with Internal Oxidants: Synthesis of 2-TrifluoromethylSubstituted Dihydropyrrol-2-ols. *Angew. Chem., Int. Ed.* **2017**, *56*, 13324. (i) Li, W.; Yuan, D.; Wang,

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097

G.; Zhao, Y.; Xie, J.; Li, S.; Zhu, C. Cooperative Au/Ag Dual-Catalyzed Cross-Dehydrogenative Biaryl Coupling: Reaction Development and Mechanistic Insight. *J. Am. Chem. Soc.* **2019**, *141*, 3187.

(11) (a) Li, Y.; Peng, J.; Chen, X.; Mo, B.; Li, X.; Sun, P.; Chen, C. Copper-Catalyzed Synthesis of Multisubstituted Indoles through Tandem Ullmann-Type C−N Formation and Cross-dehydrogenative Coupling Reactions. *J. Org. Chem.* **2018**, *83*, 5288. (b) Zhu, W.; Tong, S.; Zhu, J.; Wang, M.- X. Intramolecular Arylation of Tertiary Enamides through Pd(OAc)2-Catalyzed Dehydrogenative Cross-Coupling Reaction: Construction of Fused N-Heterocyclic Scaffolds and Synthesis of Isoindolobenzazepine Alkaloids. *J. Org. Chem.* **2019**, *84*, 2870. (c) Cheng, C.; Chen, W.-W.; Xu, B.; Xu, M.-H. Access to Indole-Fused Polyheterocycles via Pd-Catalyzed Base-Free Intramolecular Cross Dehydrogenative Coupling. *J. Org. Chem.* **2016**, *81*, 11501. (d) Reddy, B. N.; Ramana, C. V. Synthesis of Functionalized 6-Hydroxy-2-oxindole Derivatives by Phenoxide Cyclization. *Org. Lett.* **2016**, *18*, 6264. (e) Jiang, L.; Jin, W.; Hu, W. Double C−H Functionalization of Indoles via Three-Component Reactions/CuCl2-Catalyzed Aerobic Dehydrogenative Coupling for the Synthesis of Polyfunctional Cyclopenta[b]indoles. *ACS Catal.* **2016**, *6*, 6146. (f) Ray, D.; Manikandan, T.; Roy, A.; Tripathi, K. N.; Singh, R. P. Ligand-promoted intramolecular dehydrogenative cross-coupling using a Cu catalyst: direct access to polycyclic heteroarenes. *Chem. Commun.* **2015**, *51*, 7065. (g) Xu, J.; Shao, L.-D.; Li, D.; Deng, X.; Liu, Y.-C.; Zhao, Q.-S.; Xia, C. Construction of Tetracyclic 3-Spirooxindole through CrossDehydrogenation of Pyridinium: Applications in Facile Synthesis of (±)-Corynoxine and (±)-Corynoxine B. *J. Am. Chem. Soc.* **2014**, *136*, 17962. (h) Pintori, D. G.; Greaney, M. F. Intramolecular Oxidative C-H Coupling for Medium-Ring Synthesis. *J. Am. Chem. Soc.* **2011**, *133*, 1209.

(12) (a) Laha, J. K.; Kaur Hunjan, M.; Bhimpuria, R. A.; Kathuria, D.; Bharatam, P. V. Geometry Driven Intramolecular Oxidative Cyclization of Enamides: An Umpolung Annulation of Primary Benzamides with Acrylates for the Synthesis of 3-Methyleneisoindolin-1-ones. *J. Org. Chem.* **2017**, *82*, 7346. (b) Zhou, C.-J.; Gao, H.; Huang, S.-L.; Zhang, S.-S.; Wu, J.-Q.; Li, B.; Jiang, X.; Wang, H. Synthesis of Benzofused N-Heterocycles via Rh(III)-Catalyzed Direct Benzannulation with 1,3-Dienes. *ACS Catal.* **2019**, *9*, 556. (c) Youn, S. W.; Ko, T. Y.; Kim, Y. H.; Kim, Y. A. Pd(II)/Cu(II)-Catalyzed Regio- and Stereoselective Synthesis of (E)-3- Arylmethyleneisoindolin-1-ones Using Air as the Terminal Oxidant. *Org. Lett.* **2018**, *20*, 7869. (d) Sheykhan, M.; Shafiee-Pour, M.; Abbasnia, M. C−H Activation under the Guise of Diels−Alder Reaction: Annulation toward the Synthesis of Benzo[e]isoindole-1,3-diones. *Org. Lett.* **2017**, *19*, 1270. (e) An, Y.-L.; Yang, Z.-H.; Zhang, H.-H.; Zhao, S.-Y. Palladium-Catalyzed Tandem Regioselective Oxidative Coupling from Indoles and Maleimides: One-Pot Synthesis of Indolopyrrolocarbazoles and Related Indolylmaleimides. *Org. Lett.* **2016**, *18*, 152. (f) Laha, J. K.; Dayal, N. A Tandem Approach to Functionalized Carbazoles from Indoles via Two Successive Regioselective Oxidative Heck Reactions Followed by Thermal Electrocyclization. *Org. Lett.* **2015**, *17*, 4742. (g) Verma, A. K.; Danodia, A. K.; Saunthwal, R. K.; Patel, M.; Choudhary, D. Palladium-Catalyzed Triple Successive C−H Functionalization: Direct Synthesis of Functionalized Carbazoles from Indoles. *Org. Lett.* **2015**, *17*, 3658. (h) Saunthwal, R. K.; Patel, M.; Kumar, S.; Danodia, A. K.; Verma, A. K. Pd(II)-Catalyzed C¢H Activation of Styrylindoles: Short, Efficient, and Regioselective Synthesis of Functionalized Carbazoles. *Chem. - Eur. J.* **2015**, *21*, 18601.

(13) (a) Laha, J. K.; Jethava, K. P.; Dayal, N. Palladium-Catalyzed Intramolecular Oxidative Coupling Involving Double C(sp2)−H Bonds for the Synthesis of Annulated Biaryl Sultams. *J. Org. Chem.* **2014**, *79*, 8010−8019. (b) Laha, J. K.; Dayal, N.; Jethava, K. P.; Prajapati, D. V. Access to Biaryl Sulfonamides by Palladium-Catalyzed Intramolecular Oxidative Coupling and Subsequent Nucleophilic Ring Opening of Heterobiaryl Sultams with Amines. *Org. Lett.* **2015**, *17*, 1296−1299. (c) Kumar, P.; Kapur, M. Catalyst Control in Positional-Selective C−H Alkenylation of Isoxazoles and a Ruthenium-Mediated Assembly of Trisubstituted Pyrroles. *Org. Lett.* **2019**, *21*, 2134−2138. (d) Mohammed, S.; Vishwakarma, R. A.; Bharate, S. B. Metal-free DBU promoted regioselective synthesis of isoxazoles and isoxazolines. *RSC Adv.* **2015**, *5*, 3470−3473.

(14) (a) Shen, K.; Fu, Y.; Li, J. N.; Liu, L.; Guo, Q. X. What are the pKa values of C−H bonds in aromatic heterocyclic compounds in DMSO? *Tetrahedron* **2007**, *63*, 1568−1576. (b) Dutta, C.; Rana, S. S.; Choudhury, J. Rhodium(III)−N-Heterocyclic Carbene-Driven Cascade C−H Activation Catalysis. *ACS Catal.* **2019**, *9*, 10674−10679.

(15) (a) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. A Catalyst-Free Benzylic CH Bond Olefination of Azaarenes for Direct Mannich-like Reactions. *J. Org. Chem.* **2011**, *76*, 6849−6855. (b) Wang, Z. D.; Eilander, J.; Yoshida, M.; Wang, T. Mechanistic Study of a Complementary Reaction System that Easily Affords Quinazoline and Perimidine Derivatives. *Eur. J. Org. Chem.* **2014**, *2014*, 7664−7674. (c) Zhu, Z.; Tang, X.; Li, J.; Li, X.; Wu, W.; Deng, G.; Jiang, H. Synthesis of enaminones via copper-catalyzed decarboxylative coupling reaction under redox-neutral conditions. *Chem. Commun.* **2017**, *53*, 3228.

(16) Xu, H.; Xu, l.; Luo, X.; Wang, J.; Zhou, X.; Yang, B.; Li, D.; Luo, Z.; Liu, Y.; Liao, S. Transition-metal-free insertion of benzyl bromides into 2-(1*H*-benzo [*d*]imidazol-1-yl)benzaldehyde: One-pot switchable syntheses of benzo[4,5]imidazo[1,2-a]quinolin-5(7H)-ones and 3-arylquinolin-4- ones mediated by base. *Tetrahedron* **2019**, *75*, 2785−2796.

(17) Lee, W. C.; Wang, C. H.; Lin, Y. H.; Shih, W. C.; Ong, T. G. Tandem Isomerization and CH Activation: Regioselective Hydroheteroarylation of Allylarenes. *Org. Lett.* **2013**, *15* (20), 5358−5361.

(18) Dhara, K.; Kapat, A.; Ghosh, T.; Dash, J. Transition-Metal-Free Terminal Alkyne Addition to Isatins. *Synthesis* **2016**, *48*, 4260−4268.

(19) Yan, Y.; Xu, K.; Fang, Y.; Wang, Z. A Catalyst-Free Benzylic CH Bond Olefination of Azaarenes for Direct Mannich-like Reactions. *J. Org. Chem.* **2011**, *76*, 6849−6855.

(20) Zhu, Z.; Tang, X.; Li, J.; Li, X.; Wu, W.; Deng, G.; Jiang, H. Synthesis of enaminones via copper-catalyzed decarboxylative coupling reaction under redox-neutral conditions. *Chem. Commun.* **2017**, *53*, 3228−3231.

https://dx.doi.org/10.1021/acs.joc.0c02926
J. Org. Chem. 2021, 86, 4081−4097