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Arene Amination Instead of Fluorination: Substitution Pattern Governs the Reactivity of Dialkoxybenzenes with Selectfluor

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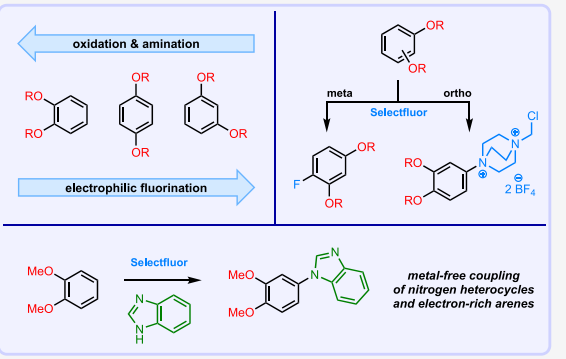
ABSTRACT: Arene substitution patterns are well-known to affect the regioselectivity of a given transformation but not necessarily the type of reactivity. Herein, we report that the substitution pattern of alkoxyarenes dictates whether a putative one-electron or two-electron reaction predominates in reactions with Selectfluor. A series of amination products is presented, resulting from the single-electron oxidation of electron-rich arenes followed by direct C−H to C−N bond formation. We demonstrate the ability of this transformation to synthesize medicinally and biologically relevant nitrogen heterocycles. Lastly, this unusual "mechanistic switch" is probed with computational chemistry and competition experiments.



1. INTRODUCTION

Electron-rich aromatic compounds are typically best-known for their ability to engage in electrophilic aromatic substitution (EAS) reactions with strong electrophiles.[1] This classic reaction paradigm and the complementary topic of directing group effects are fundamental concepts taught to every student of organic chemistry. Less appreciated is the dual ability of these electron-rich arenes to undergo single-electron oxidation to the corresponding radical cations.[2] Several groups have recently demonstrated the synthetic utility of this approach en route to compounds of biological or pharmaceutical interest.[3] Our laboratory has found a class of electron-rich arenes that can be predictably tuned to favor either an apparent two-electron or a sequential one-electron reactivity (i.e., EAS vs oxidation to the radical cation, respectively) under the same conditions.

Using Selectfluor as the key reagent in our studies, we found that dialkoxyarenes react based on their substitution patterns. At the onset, we reasoned that Selectfluor would be ideal for this study as it possesses the necessary dual reactivity; it is widely employed as both an electrophilic fluorination reagent and an oxidant.[4] Surprisingly, upon the reaction with Selectfluor, *meta*-dialkoxyarenes give exclusively the EAS fluoride product whereas *ortho*- and *para*-dialkoxyarenes predominantly form amination products, resulting from the putative single-electron oxidation of the electron-rich arene. We quickly recognized the potential of this divergent reactivity to be useful as a synthetic method as well as a tool to better understand these archetypal reactions.

C−N bond-forming reactions are well-studied and widely employed throughout synthetic chemistry.[5] Methods that functionalize an unactivated carbon atom, as opposed to substitution chemistry involving amines and alkyl, acyl, or aryl halides, are particularly useful; however, they may suffer from a lack of regioselectivity.[6] Thus, the site-selective amination of electron-rich arenes is of practical utility, especially given the ubiquity of nitrogen-containing pharmaceuticals.[7] Typically, these valuable products are synthesized in a roundabout fashion from the electron-rich arene via either a halogenation−cross-coupling sequence or a nitration−reduction−substitution sequence.[8] Direct C−H to C−N bond formation between arenes and nitrogen heterocycles is more rare, although a few recent methods have been reported.[9] In this article, we disclose a remarkably simple and effective solution to this problem using only the coupling partners (the nitrogen heterocycle and electron-rich arene) and commercially available Selectfluor. Moreover, we reveal a mechanistic switch that occurs based on the substitution pattern of the electron-rich arene, allowing a user to toggle between the amination and fluorination products.

2. RESULTS AND DISCUSSION

2.1. The Substitution Pattern Determines Amination vs Fluorination. Our attention was drawn to this reactivity upon treating Selectfluor with veratrole (1,2-dimethoxyben-

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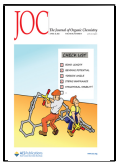

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zene) in acetonitrile at room temperature. Instead of the expected EAS product 1-fluoro-3,4-dimethoxybenzene, we isolated an amination product, an adduct of veratrole and the Selectfluor-derived amine, in a nearly quantitative yield (Figure 1, compound 7). This came as a surprise given our

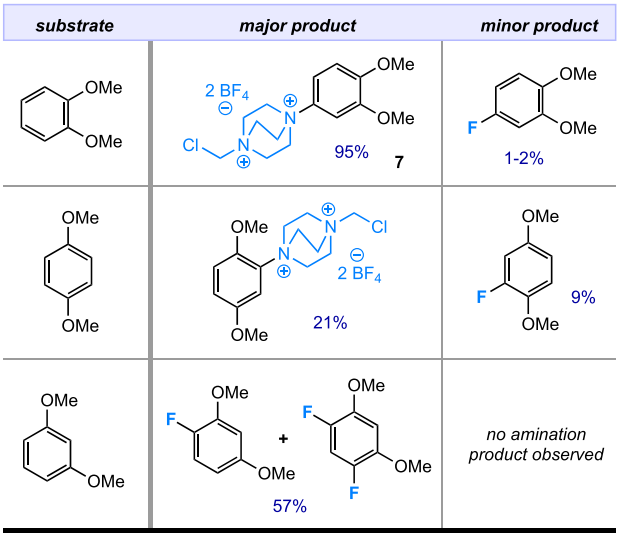
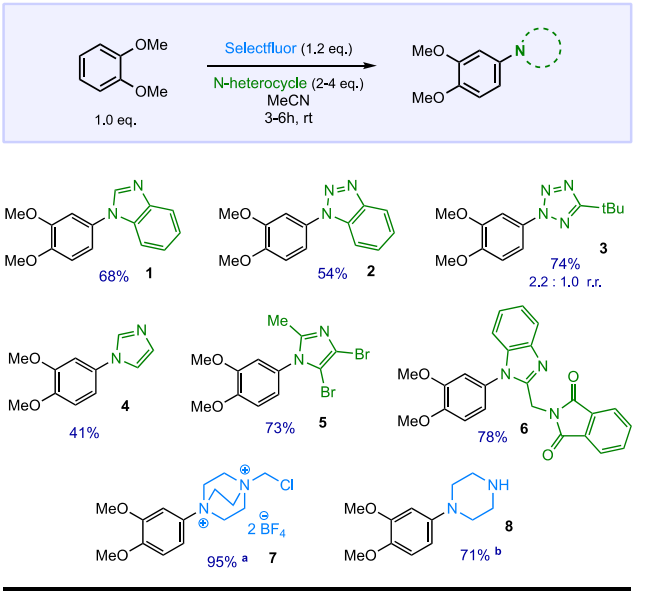


Figure 1. Divergent reactivity of dialkoxybenzenes with Selectfluor.

knowledge of similar products being prepared using a dual-catalyst system, since no examples have been reported using Selectfluor alone.[10] Accordingly, several analogous arenes were tested to determine the generality of the reaction. Anisole afforded only the EAS fluorination product upon a reaction with Selectfluor,[11] suggesting the need for an increased electron-rich character to accomplish the amination. That idea, however, was contravened by the reaction of 1,3-dimethoxybenzene with Selectfluor, which exclusively formed the EAS aryl fluoride.[12] Further complicating the situation, 1,4-dimethoxybenzene predominately gave the amination product, although in lower yield than veratrole. Given the trend presented in Figure 1, it was not immediately obvious what might be causing the reactivity switch between the fluorination and amination reactions. From both a steric and an electronic viewpoint, one would not predict a large difference between the three isomers of dimethoxybenzene in regard to fluorination versus amination.

2.2. Synthetic Utility and Product Examples. While the aryl−Selectfluor adducts are not high-demand compounds themselves, they can be easily transformed to medicinally relevant aryl piperazines using a one-pot process developed by the Ritter group (Figure 2, compounds 7 and 8).[10] We found that other types of adducts can be formed in a high yield by performing the reaction in the presence of a variety of nitrogen heterocycles, thereby greatly increasing the synthetic utility of the reaction. As some veratrole−nitrogen heterocycle adducts are known to be medicinally active, such as the drug Domipizone,[13] these products demonstrate the simple and direct synthesis of pharmaceutically relevant veratrole adducts. Screening was performed using veratrole as a model electron-rich arene; many nitrogen heterocycles were found to be competent in the reaction, although the use of Selectfluor could be problematic with certain highly reactive heterocycles. Nevertheless, benzimidazole, benzotriazole, 5-*t*Bu-tetrazole, and imidazole were found to work well in the reaction,



[a] no N-heterocycle was added; [b] $Na_2S_2O_3$ was added after formation of 7

Figure 2. Scope of nitrogen heterocycles.

providing compounds **1**−**4** in good yields. A dibrominated imidazole and 2-methylphthalimidobenzimidazole provided the desired aryl adducts in a higher yield than unsubstituted imidazole and benzimidazole (compounds **5** and **6**, respectively), a notable result given the prevalence of imidazole- and benzimidazole-containing pharmaceuticals that are substituted at the 2-position.[14]

Having established some representative examples for the substrate scope of the nitrogen heterocycles, we next shifted our focus to examining the substrate scope of the electron-rich arenes. Beyond 1,2-dialkoxybenzenes, we also demonstrate that their 1,4-substituted analogues can undergo the amination, albeit in slightly lower yields than their *ortho*-counterparts (Figure 3, compound **9**). Importantly, in this case we found that the amination reaction with benzimidazole was higher yielding than the amination without benzimidazole (to form the aryl−Selectfluor adduct). Replacing one of the methoxy groups in veratrole with either a thiomethyl or a dimethylamino group proved to be detrimental to the desired amination. On the other hand, adding a third alkoxy group at the 3-position resulted in a productive reaction; the amination with benzimidazole had a slightly higher yield than that of veratrole (compound **10**). This allowed for the expeditious derivitization of 1,2,3-trialkoxybenzene compounds that are common in biology and medicine.[15] Along those lines, an alkyl substituent was also tolerated at the 3-position, as an *N*-benzylacetamide derivative underwent amination in a good yield (compound **11**). The phase-transfer catalyst dibenzo-18-crown-6 was found to be similarly successful in the amination (compound **12**), allowing one-step access to new catalysts that could be useful in specialty applications. As illustrated in Figure 3, each of these examples gives a small amount of an aryl fluoride byproduct due to the use of Selectfluor; however, the desired amination product is easily separated from the fluoride impurity by column chromatography, as the aromatic amines are significantly more polar than the fluorides.

The aptitude of other electron-rich arenes to participate in the reaction proved difficult to predict, although we did find that other species beyond the examples presented in Figure 3

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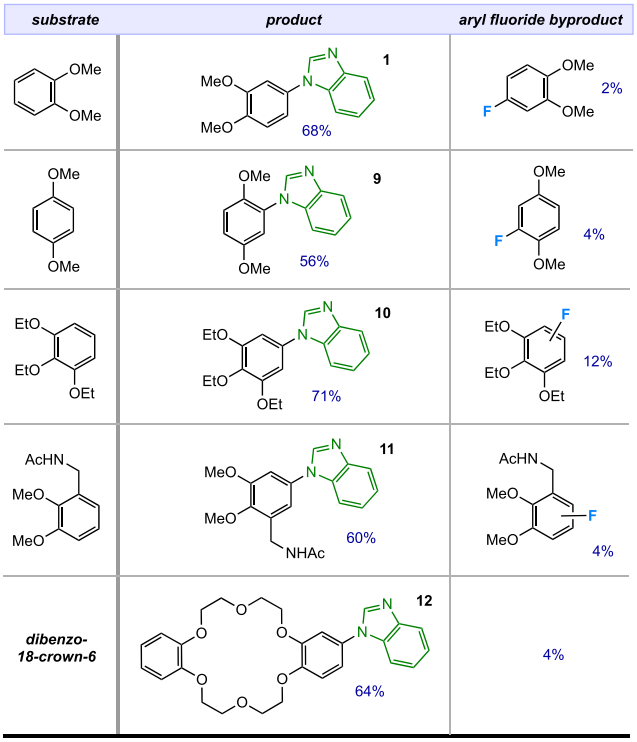

Figure 3. Substrate examples of alkoxyarenes.

can undergo the amination reaction. Carbazole, for instance, can engage in the amination with Selectfluor, albeit in a moderately low yield. This finding came as a surprise to us given the large structural difference between carbazole and the alkoxybenzenes; however, to further complicate the analysis, the oxygen analogue of carbazole (dibenzofuran) was unsuccessful in the reaction. This is consistent with our earlier observation that the dimethylamino and thiomethyl analogues of veratrole did not undergo the amination. Together, these results demonstrate the discriminate nature of the reaction, as certain electron-rich arenes are not competent in the amination and instead undergo either fluorination or no reaction.

2.3. Application to Medicinal Chemistry. To demonstrate the synthetic utility of this transformation, we propose an improved synthesis of a medicinally relevant compound (compound **13**, Figure 4). This commercially available benzodioxane derivative is employed as a precursor to dopamine D4 receptor ligands (via the *N*-benzylation of the piperazinyl secondary amine).[16] Additionally, **13** represents an analogue of eltoprazine, a drug useful for treating neurodegenerative disorders.[17] Two distinct methods have been utilized to synthesize **13** from 1,4-benzodioxane: (a) either a halogenation−cross-coupling sequence or (b) a nitration−reduction−substitution sequence, which provides the product in three steps.[18] On the other hand, using our method, **13** can be accessed in two steps, both of which are operationally simpler than the steps in the previous syntheses. Notably, our approach avoids undesirable reactions from the previous methods, such as the Buchwald−Hartwig cross coupling amination or the nitration using concentrated nitric acid. As demonstrated by this example, the direct C−H to C−N bond formation featured in this reaction represents a powerful strategy toward the expeditious synthesis of nitrogen heterocycles that are of medicinal interest.

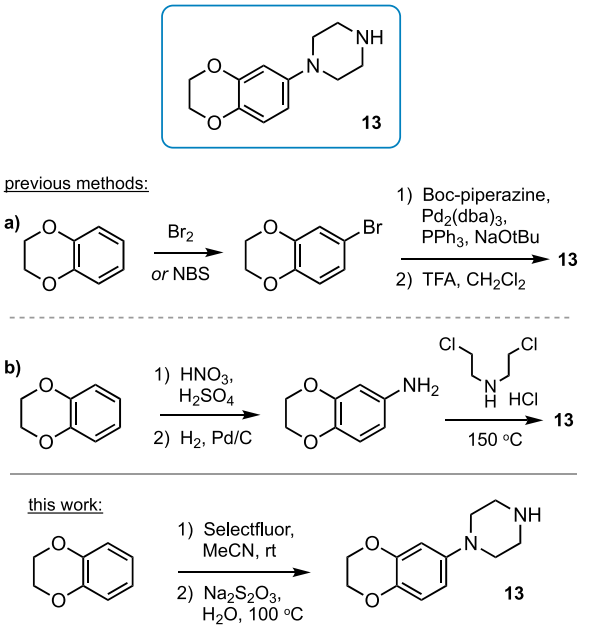

Figure 4. Application to medicinal chemistry.

2.4. Mechanistic Remarks. To understand the reaction mechanism, we first sought to shed light on the divergent reactivity of the dialkoxybenzene regioisomers. Why would the *ortho*- and *para*-isomers undergo amination while the *meta*-isomer undergoes fluorination instead? We turned to computational chemistry to address this question, calculating the energy difference for the oxidation of the three dimethoxybenzene isomers using DFT (B3LYP/6-311++G** (MeCN)). Consistent with experimental results, the oxidation of the *meta*-isomer was the most energetically uphill (7 kJ/mol higher than the *ortho*-isomer and 35 kJ/mol higher than the *para*-isomer (Figure 5)). This energy difference is significant and coincides

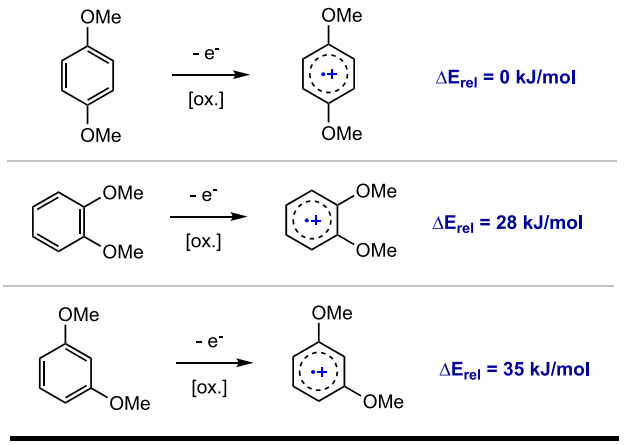

Figure 5. Energy of the arene oxidation calculated at B3LYP/6-311++G** (MeCN).

with the observation that in the present reaction the *meta* isomer may not undergo oxidation to its radical cation and the subsequent amination but could instead react with Selectfluor in a putative electrophilic aromatic halogenation. The oxidation of *para*-dialkoxy substrates is evidently more favorable than those of the *ortho*-substrates; however, the amination was higher-yielding for *ortho*-dialkoxyarenes. To

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rationalize this observation, we considered steric factors, which favor the *ortho*-substrates.

Next, we became interested in probing the relative reaction rates of the two competing reactions—amination vs fluorination. Thus, we subjected Selectfluor (1.0 equiv) to an intermolecular competition experiment with equimolar amounts of *ortho*- and *meta*-dimethoxybenzene (5.0 equiv each). A ratio of 1.0:3.5 was observed for the amination and fluoride products derived from the *ortho*- and *meta*-isomers, respectively (Figure 6). From this experiment, it is apparent

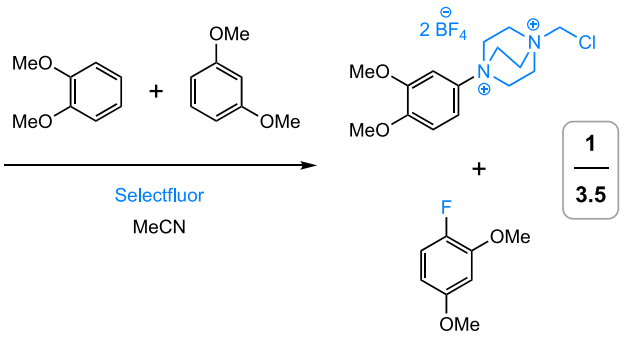

Figure 6. An intermolecular competition experiment.

that the aryl fluorination is much faster than the amination. This finding further demonstrates the unusual behavior of *ortho*-dialkoxybenzenes, which undergo amination in high yields despite the fact that fluorination is apparently faster.

Finally, we propose an initial mechanistic hypothesis for the amination reaction, relying on literature precedents and our own experience in working with Selectfluor. The reaction can begin with the oxidation of the electron-rich dialkoxyarene by Selectfluor to produce the corresponding arene radical cation, the Selectfluor-radical dication (SRD), and fluoride (Figure 7).

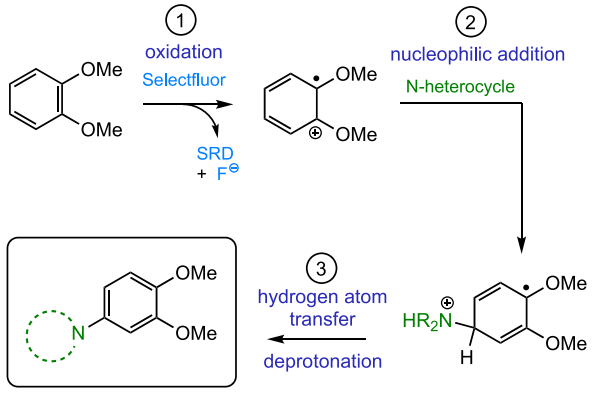

Figure 7. Proposed mechanism for arene amination.

The arene radical cation can be trapped by a nitrogen heterocycle via a nucleophilic addition to the allylic cation to form the 4-substituted adduct. This species could then undergo hydrogen atom transfer (HAT) to form the product. This HAT step is most likely accomplished with the SRD that was produced during the course of the reaction, as the Selectfluor-radical dication is known for its ability to abstract hydrogen atoms from a variety of substrates.[19] On the other hand, an alternate mechanism might involve a nucleophilic aromatic substitution of the Selectfluor−arene adduct with the nitrogen heterocycle. We ruled out this possibility by performing an experiment in which the Selectfluor−veratrole adduct was generated first and then benzimidazole was added after the Selectfluor was fully consumed. In this reaction, we observed no conversion of the Selectfluor−veratrole adduct to the benzimidazole−veratrole adduct, thereby disproving the nucleophilic aromatic substitution mechanism. An additional subtle mechanistic difference involves the oxidation of the radical produced from step two; in this case, the intermediate loses a proton to rearomatize instead of losing a hydrogen atom. Our group aims to investigate this distinction and elucidate further mechanistic details in a forthcoming study.

3. CONCLUSION

The arene substitution pattern of dialkoxybenzenes was shown to govern the divergent reactivity with Selectfluor. *Ortho*- and *para*-isomers predominately give amination products, whereas the *meta*-isomer exclusively gives fluoride products. The amination pathway allows direct access to pharmaceutically important nitrogen heterocycles using a simple yet efficient set of conditions. DFT calculations illuminated details regarding the mechanistic switch, as the *meta*-isomer was revealed to be more difficult to oxidize. Finally, an initial mechanism was proposed, involving oxidation, nucleophilic addition, hydrogen atom transfer, and rearomatization.

4. EXPERIMENTAL SECTION

4.1. General Methods. Unless otherwise stated, all reactions were carried out under strictly anhydrous conditions and a N_2 atmosphere. All solvents were dried and distilled by standard methods. Arene substrates and nitrogen heteocycles were purchased from Sigma-Aldrich and used directly in the reaction unless otherwise noted. All ^{1}H spectra were acquired on a 400 MHz NMR spectrometer in $CDCl_3$, ^{19}F spectra were acquired on a 300 MHz NMR spectrometer in either CD_3CN or $CDCl_3$, and ^{13}C NMR spectra were acquired on a 400 MHz NMR spectrometer in $CDCl_3$. The ^{1}H, ^{13}C, and ^{19}F NMR chemical shifts are given in parts per million (δ) with respect to an internal tetramethylsilane (TMS, δ 0.00 ppm) standard or 3-chlorobenzotrifluoride (δ −64.2 ppm relative to $CFCl_3$). NMR data are reported in the following format: chemical shift (integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz)).

4.2. General Amination Procedure. The arene substrate (1.0 mmol, 1.0 equiv) was added to an oven-dried round-bottom flask equipped with a stir bar and then dissolved in anhydrous acetonitrile (25 mL). The nitrogen heterocycle (2−4 equiv; yields reported with 3.5 equiv unless otherwise stated) was then added, and the solution was stirred at room temperature. Selectfluor (1.2 mmol, 1.2 equiv) was then added, and the reaction mixture was stirred for 3−6 h. The reaction was monitored by ^{1}H NMR (0.3 mL reaction aliquot + 0.2 mL of CD_3CN). Yields for the aryl-fluoride byproducts were determined by ^{19}F NMR spectroscopy of the crude reaction mixture via the integration of product signals relative to an internal standard. The reaction can be driven further to completion by adding an additional amount of Selectfluor relative to the amount of the unreacted arene substrate and stirring for an additional 2−5 h. After the reaction, most of the solvent was removed in vacuo, and the mixture was diluted with 1 M NaOH. The mixture was extracted with CH_2Cl_2 (×3); the combined organic layers were then washed with 2 M NaOH (to remove the excess nitrogen heterocycle), followed by brine. The organic solution was finally dried over Na_2SO_4 and concentrated to dryness. The residue was purified by gradient flash chromatography on silica gel.

4.3. Characterization of Amination Products. *4.3.1. 1-(3,4-Dimethoxyphenyl)-1H-benzo[d]imidazole (Compound **1**).* The amination was run according to the general procedure using 1,2-dimethoxybenzene as the arene substrate and benzimidazole as the

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nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (173 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (1H, s), 7.91−7.85 (1H, m), 7.50−7.45 (1H, m), 7.36−7.30 (2H, m), 7.07−6.99 (3H, m), 3.97 (3H, s), 3.93 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.9, 148.9, 142.6, 129.3, 123.6, 122.6, 120.5, 116.7, 111.7, 110.3, 108.2, 56.2, 56.1; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2^+$ 255.1128, found 255.1125.

*4.3.2. 1-(3,4-Dimethoxyphenyl)-1H-benzo[d][1,2,3]triazole (Compound **2**).* The amination was run according to the general procedure using 1,2-dimethoxybenzene as the arene substrate and benzotriazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (138 mg, 54%); spectral data match the previously reported characterization.[20]

*4.3.3. 5-(tert-Butyl)-2-(3,4-dimethoxyphenyl)-2H-tetrazole (Compound **3**, Major Isomer).* The amination was run according to the general procedure using 1,2-dimethoxybenzene as the arene substrate and 5-*t*Bu tetrazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (194 mg, 74% for both regioisomers); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65−7.58 (2H, m), 6.93 (1H, d, J = 8.6 Hz), 3.96 (3H, s), 3.92 (3H, s), 1.47 (9H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 149.7, 149.4, 130.6, 112.1, 111.0, 103.6, 56.2, 56.1, 31.6, 29.5; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{13}H_{19}N_4O_2^+$ 263.1503, found 263.1502.

*4.3.4. 1-(3,4-Dimethoxyphenyl)-1H-imidazole (Compound **4**).* The amination was run according to the general procedure using 1,2-dimethoxybenzene as the arene substrate and imidazole as the nitrogen heterocycle using the following modifications: 4.0 equiv of imidazole, 4.0 equiv $NaHCO_3$, and 3.5 equiv of Selectfluor. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (84 mg, 41%); spectral data match the previously reported characterization.[21]

*4.3.5. 4,5-Dibromo-1-(3,4-dimethoxyphenyl)-2-methyl-1H-imidazole (Compound **5**).* The amination was run according to the general procedure using 1,2-dimethoxybenzene as the arene substrate and 4,5-dibromo-2-methylimidazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (275 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (1H, d, J = 8.5 Hz), 6.82−6.77 (1H, m), 6.69 (1H, d, J = 2.4 Hz), 3.95 (3H, s), 3.89 (3H, s), 2.26 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.0, 149.5, 146.6, 128.4, 120.0, 115.7, 111.0, 110.7, 104.2, 56.2, 56.1, 14.5; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{12}H_{13}Br_2N_2O_2^+$ 374.9338, found 374.9338.

*4.3.6. 2-((1-(3,4-Dimethoxyphenyl)-1H-benzo[d]imidazol-2-yl)methyl)isoindoline-1,3-dione (Compound **6**).* The amination was run according to the general procedure using 1,2-dimethoxybenzene as the arene substrate and 2-methylphthalimidobenzimidazole[22] as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (322 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.81 (2H, m), 7.76−7.70 (3H, m), 7.28−7.19 (2H, m), 7.13−7.09 (1H, m), 7.06−7.02 (1H, m), 7.00−6.93 (2H, m), 5.04 (2H, s), 3.93 (3H, s), 3.87 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 167.5, 149.8, 149.6, 148.6, 137.1, 134.1, 132.1, 127.8, 123.5, 123.2, 122.6, 119.8, 119.7, 111.4, 110.6, 110.1, 56.1, 56.1, 34.9; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_4^+$ 414.1448, found 414.1440.

*4.3.7. 1-(Chloromethyl)-4-(3,4-dimethoxyphenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (Compound **7**).* The amination was run according to the general procedure with the following modification: no nitrogen heterocycle was added. The product was precipitated with the addition of 50% EtOAc in hexane, filtered, and washed with more EtOAc/hexane. The product was dissolved in acetone and concentrated to dryness: white hygroscopic solid (448.8 mg, 95%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.26 (2H, m), 7.13−7.09 (1H, m), 5.36 (2H, s), 4.42−4.36 (6H, t, J = 7.3 Hz), 4.16−4.10 (6H, t, J = 7.3 Hz), 3.92 (3H, s), 3.88 (3H, s); HRMS (ESI-Orbitrap) m/z $[M - BF_4]^+$ calcd for $C_{15}H_{23}N_2O_2ClBF_4^+$ 385.1472, found 385.1465. The product was inseparable from the Selectfluor byproducts, namely the DABCO monocation, as it was also a BF_4 salt and had similar properties. The ^{1}H NMR spectrum shows the product along with the Selectfluor-derived amine in a 1.0:1.1 ratio.

*4.3.8. 1-(3,4-Dimethoxyphenyl)piperazine (Compound **8**).* The amination was run according to the procedure for compound **7**. The DABCO adduct was reduced to a piperazine using a previously reported procedure.[10] After the amination had completed, a solution of saturated aq $Na_2S_2O_3$ (10.0 mL) was added to the mixture, followed by H_2O (10.0 mL). The mixture was stirred in the sealed flask or tube at 100 °C for 12−24 h using a heating mantle with sand. Upon cooling to room temperature, the reaction mixture was transferred to a separatory funnel and diluted with DCM (20 mL). Ethylene diamine (2 mL) was added, followed by 6 M NaOH (6 mL), and the mixture was shaken. The resulting emulsion was treated with brine (50 mL), and the organic layer was separated after shaking. The aqueous layer was re-extracted with DCM (2 × 20 mL), then the combined organic layers were extracted with 1 M HCl (2 × 20 mL). Ethylene diamine (6 mL) was added to the combined HCl extracts, followed by 6 M NaOH (10 mL). The basified aqueous mixture was then extracted with DCM (3 × 20 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and concentrated: yellow oil (157.8 mg, 71%); spectral data match the previously reported characterization.[23]

*4.3.9. 1-(2,5-Dimethoxyphenyl)-1H-benzo[d]imidazole (Compound **9**).* The amination was run according to the general procedure using 1,4-dimethoxybenzene as the arene substrate and benzimidazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (142 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (1H, s), 7.88−7.85 (1H, m), 7.37−7.29 (3H, m), 7.06 (1H, d, J = 8.9 Hz), 7.02−6.96 (2H, m), 3.82 (3H, s), 3.74 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.7, 148.0, 143.8, 143.3, 134.2, 125.3, 123.3, 122.4, 120.3, 114.2, 113.6, 113.1, 110.7, 56.3, 55.9; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{15}H_{15}N_2O_2^+$ 255.1128, found 255.1129.

*4.3.10. 1-(3,4,5-Triethoxyphenyl)-1H-benzo[d]imidazole (Compound **10**).* The amination was run according to the general procedure using 1,2,3-triethoxybenzene[24] as the arene substrate and benzimidazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (232 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (1H, s), 7.89−7.84 (1H, m), 7.55−7.50 (1H, m), 7.35−7.29 (2H, m), 6.67 (2H, s), 4.16−4.06 (6H, m), 1.46 (6H, t, J = 7.0 Hz), 1.41 (3H, t, J = 7.1 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 143.9, 142.4, 137.6, 133.9, 131.6, 123.6, 122.7, 120.6, 110.5, 103.1, 69.1, 65.0, 15.6, 14.8; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{19}H_{23}N_2O_3^+$ 327.1703, found 327.1703.

*4.3.11. N-(5-(1H-Benzo[d]imidazol-1-yl)-2,3-dimethoxybenzyl)acetamide (Compound **11**).* The amination was run according to the general procedure using *N*-(2,3-dimethoxybenzyl)acetamide as the arene substrate and benzimidazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (195 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (1H, s), 7.86−7.81 (1H, m), 7.50−7.46 (1H, m), 7.34−7.28 (2H, m), 7.03 (1H, d, J = 2.5 Hz), 6.95 (1H, d, J = 2.5 Hz), 6.37−6.20 (1H, m), 4.51 (2H, d, J = 6.1 Hz), 3.94 (3H, s), 3.90 (3H, s), 2.00 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 170.1, 153.4, 146.5, 143.7, 142.1, 133.7, 133.6, 131.9, 123.6, 122.7, 120.3, 116.5, 110.4, 107.8, 60.7, 56.0, 38.5, 23.1; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{18}H_{20}N_3O_3^+$ 326.1499, found 326.1499.

*4.3.12. 1-(6,7,9,10,17,18,20,21-Octahydrodibenzo[b,k][1,4,7,10,13,16]hexaoxacyclooctadecin-2-yl)-1H-benzo[d]imidazole (Compound **12**).* The amination was run according to the general procedure using dibenzo-18-crown-6 as the arene substrate and benzimidazole as the nitrogen heterocycle. The product was isolated via gradient column chromatography on silica gel with DCM/hexanes with 1.5% Et_3N: white solid (305 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (1H, s), 7.88−7.84 (1H, m), 7.47−7.42 (1H,

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m), 7.34−7.27 (2H, m), 7.02−6.98 (3H, m), 6.91−6.86 (4H, m), 4.26−4.22 (2H, m), 4.21−4.15 (6H, m), 4.08−4.01 (8H, m); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 149.6, 148.7, 148.7, 148.6, 143.8, 142.5, 134.1, 129.5, 123.5, 122.5, 121.3, 121.3, 120.4, 117.0, 113.9, 113.6, 113.6, 110.3, 110.1, 70.0, 69.7, 69.6, 69.2, 69.1, 68.7, 68.6; HRMS (ESI-Orbitrap) m/z $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_6^+$ 477.2020, found 477.2018.

4.4. Synthesis and Characterization of New Starting Materials. *4.4.1. N-(2,3-Dimethoxybenzyl)acetamide (Starting Material for Compound 11).* 2,3-Dimethoxybenzylamine (335 mg, 2.0 mmol, 1.0 equiv) was dissolved in 20 mL of CH_2Cl_2 in a round-bottom flask. Triethylamine (0.56 mL, 4.0 mmol, 2.0 equiv) and cat. DMAP (25 mg, 0.2 mmol, 0.1 equiv) were added. Acetic anhydride (0.2 mL, 2.1 mmol, 1.05 equiv) was added dropwise, and the solution was stirred at room temperature overnight (12 h). The reaction mixture was diluted with more CH_2Cl_2 and transferred to a separatory funnel. The solution was washed successively with aq 1 M HCl, saturated aq $NaHCO_3$, and finally brine. The organic layer was dried over anhydrous Na_2SO_4 and then concentrated to dryness. The product was isolated via gradient column chromatography on silica gel with EtOAc/hexanes: white solid (390 mg, 93%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.02 (1H, t, J = 7.9 Hz), 6.91−6.85 (2H, m), 5.92 (1H, br. s), 4.44 (2H, d, J = 5.7 Hz), 3.87 (3H, s), 3.86 (3H, s), 1.97 (3H, s); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 152.6, 147.2, 131.8, 124.2, 121.4, 111.9, 60.6, 55.7, 39.0, 23.2; HRMS (EI) m/z $[M]^{+\cdot}$ calcd for $C_{11}H_{15}NO_3^+$ 209.1052, found 209.1078.

COMPUTATIONAL METHODS

Density functional theory calculations were performed using the Gaussian 09, rev. E. 01 software package.[25] All geometry optimizations were performed applying the B3LYP functional with the 6-311++G(d,p) basis set.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00231.

NMR spectral data of amination products and new starting materials, computational data, and references (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **3**, **5**, **7**, **8**, **9**, **10**, **11**, and **12** (ZIP)

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Notes

The authors declare no competing financial interest.

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