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Enhanced Reactivity for Aromatic Bromination via Halogen Bonding with Lactic Acid Derivatives

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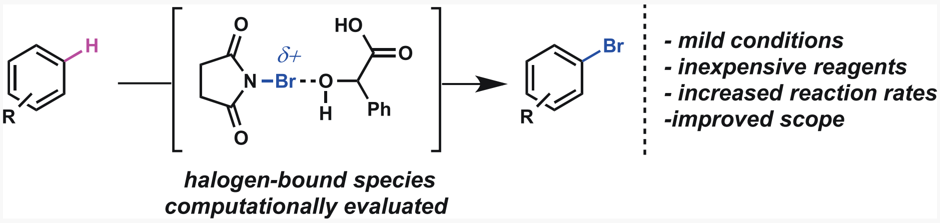

ABSTRACT: We report a new method for regioselective aromatic bromination using lactic acid derivatives as halogen bond acceptors with *N*-bromosuccinimide (NBS). Several structural analogues of lactic acid affect the efficiency of aromatic brominations, presumably via Lewis acid/base halogen-bonding interactions. Rate comparisons of aromatic brominations demonstrate the reactivity enhancement available via catalytic additives capable of halogen bonding. Computational results demonstrate that Lewis basic additives interact with NBS to increase the electropositive character of bromine prior to electrophilic transfer. An optimized procedure using catalytic mandelic acid under aqueous conditions at room temperature was developed to promote aromatic bromination on a variety of arene substrates with complete regioselectivity.

■ INTRODUCTION

Halogenated arenes are important components of metal-catalyzed cross-coupling reactions, pesticides, pharmaceuticals, and natural products.[1] Seminal reports of aromatic bromination involving molecular bromine provided access to these useful structures, although harsh reaction conditions limited the scope of substrates that could participate.[2] The development of *N*-bromosuccinimide (NBS) provided a bench-stable alternative to molecular bromine, although at the cost of diminished reactivity.[3] Because of this, standard bromination reactions using NBS have traditionally been limited to especially reactive electron-rich aromatics. Efforts to enhance the native reactivity of NBS have been of general interest to synthetic chemists, and several methods using catalytic activators or specialized reaction conditions have been developed.[4] A common strategy for activating *N*-halosuccinimides involves the coordination of a Lewis acidic additive to the imide carbonyl, rendering the halogen more electrophilic via induction.[5] Alternatively, Lewis basic additives may enhance reactivity via halogen bonding or by the formation of a new halogenating reagent via direct halogen displacement.[6] Several methods have been developed using sulfur-based additives that interact nucleophilically with the halogens of *N*-halosuccinimides. Thioureas and thioacetamides have been shown to doubly activate *N*-halosuccinimides via a combination of hydrogen and halogen bonding to functionalize electron-rich arenes.[7] Phosphine sulfide catalysts have shown promise for halogenating heteroarenes and electron-neutral aromatics, although air and moisture sensitivity diminishes their experimental utility.[8] Anionic sulfide catalysts promote regioselective halogenation at very low catalyst loadings, but require anhydrous conditions for efficacy.[9] Although simple alkyl sulfides and disulfides are effective catalysts for halogenation,[10,11] sterically hindered triptycenyl methyl sulfide successfully promoted aromatic halogenation that was previously unachievable without the use of Br_2 or Cl_2.[12] Although an improvement over previous methods, triptycenyl methyl sulfide catalysts also suffer from air and moisture sensitivity and must be custom synthesized. Alternative strategies, such as using hexafluoroisopropanol as a solvent, may also rely on halogen bonding to NBS for efficacy[13] but are impractical for routine or large-scale use.[14] To complement these existing methods, our group has developed an operationally simple protocol for aromatic bromination using lactic acid derivatives as halogen bond acceptors from NBS (Figure 1).

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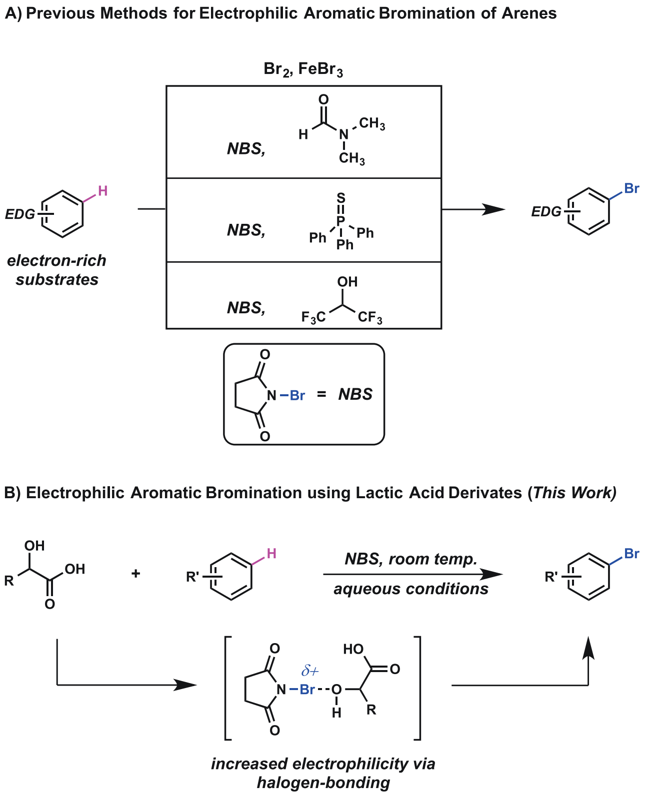
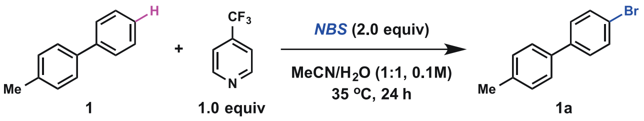


Figure 1. Methods for aromatic bromination.

Table 1. Development of Bromination Protocol[a]



entry	deviation from standard conditions	yield
1	none	78
2	room temperature	0
3	without 4-CF_3-pyridine	60
4	4-MeO-pyridine instead of 4-CF_3-pyridine	0
5	pyridine instead of 4-CF_3-pyridine	*trace*
6	acetone/H_2O solvent	30
7	methanol/H_2O solvent	62
8	ethyl lactate/H_2O solvent	91
9	ethyl lactate/H_2O solvent, no pyridine additive	77

[a] General reaction conditions: 4-methylbiphenyl (**1**, 0.2 mmol), 4-trifluoromethylpyridine (0.2 mmol), and NBS (0.40 mmol) in 2 mL of ACN/water (1:1, 0.1 M) stirred at 35 °C for 24 h. Yields refer to the chromatographically pure material.

■ RESULTS AND DISCUSSION

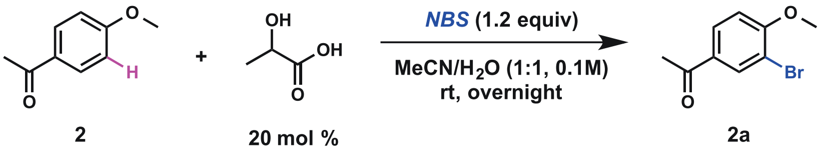
Previously, our laboratory reported radical C−H fluorination via nitrogen−fluorine halogen bonding between Selectfluor and pyridine additives.[15] Halogen bonding was found to be critical for successful fluorination, and the high yields of mono- and di-fluorination were observed. Computational and nuclear magnetic resonance (NMR) studies showed that the Lewis basicity of the pyridine additive must be optimum for halogen bonding but not strong enough to promote unwanted side reactions from direct fluorine transfer to the pyridine additive. We sought to expand this strategy to include C−H bromination using NBS as a standard bromine source.

Simply replicating the fluorination conditions with NBS in place of Selectfluor showed that aromatic bromination was favored over benzylic bromination. Although this may not be surprising considering the fluorination mechanism relies on a diazabicyclo radical cation for C−H abstraction, we sought to study the effect halogen bonding may have on simple electrophilic aromatic bromination. As shown in Table 1 (entry 1), 4-methylbiphenyl, **1**, could be brominated in a good yield in the presence of 4-trifluoromethylpyridine as a stoichiometric additive without the requirement of a silver catalyst. Heating to 35 °C was required, as no product was observed at room temperature (entry 2). The exclusion of the 4-trifluoromethylpyridine yielded product in reduced amounts, confirming a moderate additive effect for bromination (entry 3). Similar to the radical fluorination protocol, electron-rich pyridines led to poor conversion due to unproductive consumption of the halogenating agent, presumably via direct halogen displacement (entries 4 and 5). Although bromination was effective in multiple organic co-solvents, ethyl lactate appeared to be optimal (entries 6−8). Bromination in the absence of any pyridine additive is still efficient using aqueous ethyl lactate, demonstrating a clear solvent effect under these conditions (entry 9). Because ethyl lactate is known to hydrolyze into lactic acid and ethanol under aqueous conditions,[17] we were interested in studying how ethyl lactate or its constituents may be interacting with NBS to promote bromination.

As shown in Table 2, the bromination of 4′-methoxyacetophenone was explored to determine the effect lactic acid derivatives may have on the reaction efficacy. Entries 1−2 confirm that catalytic lactic acid enables aromatic bromination at room temperature, as no bromination is observed in the absence of lactic acid in aqueous acetonitrile (ACN). Stoichiometric lactic acid did not provide an increase in the yield (entry 3). Because NBS is capable of oxidizing secondary alcohols,[18] pyruvic acid (entry 4) was also explored as a potential additive and was found to be moderately superior to lactic acid. Alanine (entry 5) and phenylglycine (entry 6) were suitable alternatives to lactic acid, although we directly observed oxidative degradation of these amino acids on the timescale of a productive reaction (see the Supporting Information for degradation studies).[18] Phenylacetic acid (entry 7) and benzoic acid (entry 8) are ineffective, suggesting the α-substituted carboxylate structure of lactic acid is important. Mandelic acid (entry 9) was shown to be superior to lactic acid and was favored as an easily handled solid reagent. Benzoylformic acid (entry 10) was comparably effective to mandelic acid. Interestingly, all of the Brønsted acid additives that promote bromination have pK_a values below 4.00, suggesting that acid catalysis may play a role in NBS activation. Trifluoroacetic acid (pK_a 0.52, entry 11) enabled bromination, although with diminished conversion compared to other entries. Because no clear linear trend between pK_a and reaction conversion could be established, we computationally evaluated the possibility of in situ interactions with NBS to produce reactive brominating species.

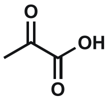
To explore the electronic structure details responsible for enhancing or depressing reactivity, we hypothesize the formation of halogen-bound complexes whose charge dipole impacts the electronic character of bromine. Initial geometry optimizations of the NBS-additive complex using the B3PW91/6-311G(d) model chemistry including implicit solvation were carried out using a local development version

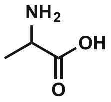
Table 2. Optimization of Bromination Protocol[a]

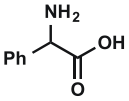


entry	deviation from standard condition	yield
1	none	**54**
2	without lactic acid	**0**
3	lactic acid (1.0 equiv)	**59**
4	pyruvic acid	**62**
5	alanine instead of lactic acid	**56**
6	2-phenylglycine instead of lactic acid	**71**
7	phenylacetic acid instead of lactic acid	**0**
8	benzoic acid instead of lactic acid	**0**
9	mandelic acid instead of lactic acid	**85**
10	benzoylformic acid instead of lactic acid	**86**
11	trifluoroacetic acid instead of lactic acid	**58**

structures for table entries above


(entry 4)


(entry 5)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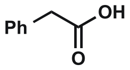
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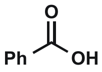
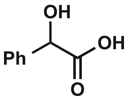
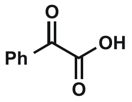

(entry 8)


(entry 9)


(entry 10)

[a] General reaction conditions: 4′-methyoxyacetophenone (**2**, 0.2 mmol), lactic acid (0.04 mmol), and NBS (0.24 mmol) in 2 mL of ACN/water (1:1, 0.1 M) stirred at room temperature for 24 h. Yields refer to the chromatographically pure material.

of Gaussian. The calculated optimized geometries presented elongated bromine additive bond lengths. To address this, we artificially introduced the basis set superposition error to counteract the lack of basis functions in the bond. Additional basis functions were added in a well-tempered manner to the bromine of NBS and the bonding atom of the additive. Many of the additives shown in Table 2 feature multiple Lewis basic sites for potential halogen bonding, and several halogen-bound intermediates were examined (see the Supporting Information for comprehensive data for NBS interactions with additives from entries 4−10). To compare the properties of halogen-bound species, we examined the optimized geometry, natural population analysis charges, and Δ*H* of formation for all the species. Of the species that exhibited favorable halogen-bonding interactions, all contain bromines with a partial positive charge character and negative Δ*H*'s of formation. Each complex structure features bond lengths longer than the ideal covalent bond length of 1.77 Å but within the sum of the van der Waals radii of 3.37 Å. For each of these complexes, we consider the NBS and the additive to be electrostatically bound to each other. An in-depth discussion of several possible complexes from mandelic and benzoylformic acid is provided below.

Multiple possible geometries for complexes between mandelic acid (**9**) and NBS were examined, but many structures relaxed to the three geometries shown in Figure 2a. Interestingly, although both the carboxylate and *α*-alcohol appear to be necessary for bromination, optimized structures could not be located for multiple-point or mixed halogen/hydrogen bonding. Simple protonation of NBS via mandelic acid yielded a slightly more electropositive bromine atom, but this process was found to be energetically unfavorable by >35 kcal/mol (Figure 2b). Starting geometries involving Brønsted acid/base interactions between the carboxylic acid and amide oxygen of NBS failed to optimize into energy-minimized structures (Figure 2c). The successfully computed **9**-NBS complexes shown in Figure 2a feature Br−O bond lengths between 2.69 and 2.90 Å and have comparable partial charges on bromine of approximately 0.30. The Δ*H*s of formation for each of these complexes are favorable and within 0.61 kcal/mol, with the most favorable being the complex bound at the sp^3 carboxylate oxygen (Figure 2, structure **9-NBS-a**). Alternative modes of attachment led to optimized structures with Br−O distances too great to be considered bound (>3.5 Å). Figure 3 shows the analogous structures for halogen bonding between benzoylformic acid (**10**) and NBS. These **10**-NBS complexes feature Br−O bond lengths between 2.72 and 2.94 Å and contain nearly identical partial charges for bromine of approximately 0.28. The Δ*H*s of formation for each of the **10**-NBS complexes are favorable and within 0.60 kcal/mol, with the most favorable being the complex bound at the *α*-keto carbonyl (Figure 3, structure **10-NBS-c**). Multiple-point or mixed halogen−hydrogen binding did not yield optimized structures, with complexes relaxing to structures containing a single Br−O bond.

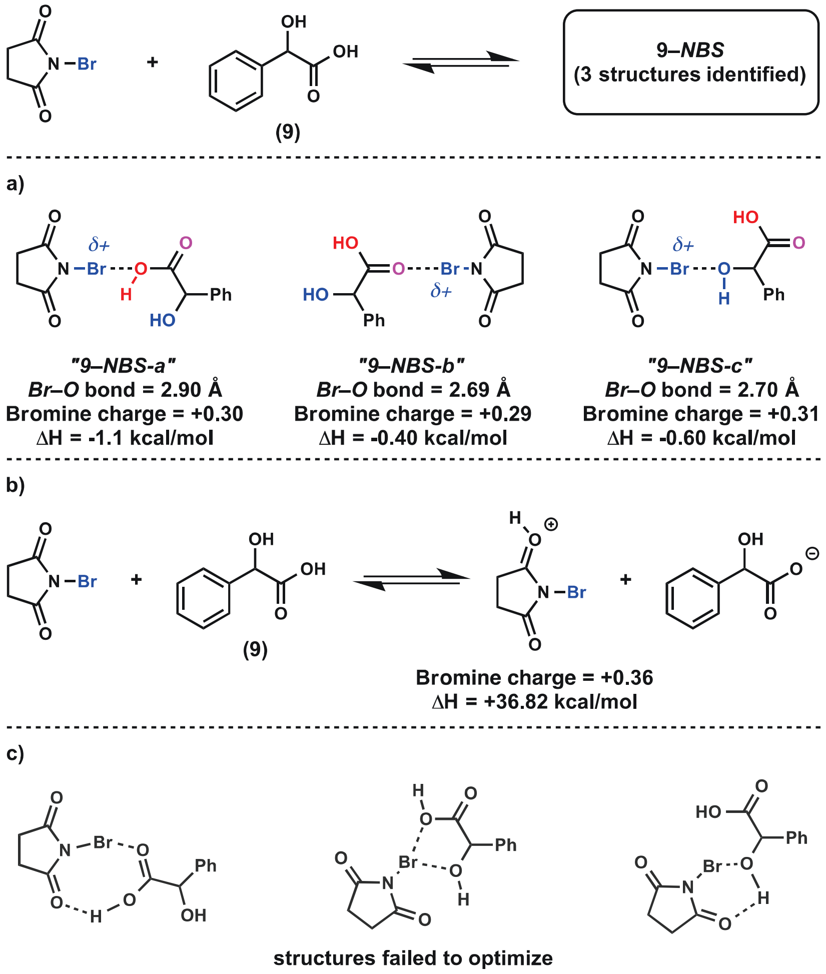


Figure 2. Computed values for halogen-bound structures of mandelic acid (**9**) and NBS. (a) Three energetically favored geometries. (b) Proton transfer without halogen bonding. (c) Structures containing multiple binding sites that failed to optimize.

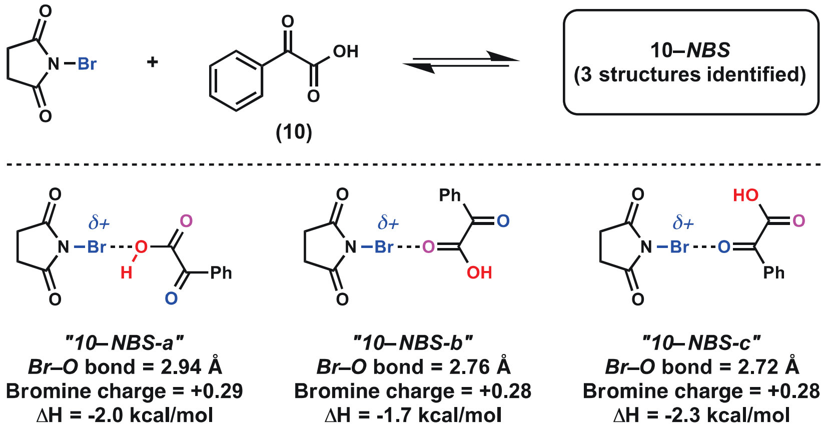


Figure 3. Computed values for halogen-bound structures of benzoylformic acid (**10**) and NBS.

Consistent with experimental results discussed in Table 2, computation suggests the thermodynamically favorable formation of halogen-bound species of NBS with either mandelic or benzoylformic acid. The electropositive character of the bromine atom is similar for all the halogen-bound species of mandelic and benzoylformic acid, suggesting similar electrophilic character for all the species. Because control reactions confirm that an α-oxygen is necessary for bromination (Table 2, entry 7), it is perhaps surprising that halogen bonding at that site is not heavily favored for mandelic acid based on Δ*H*. However, the Lewis acid/base interactions involved in halogen bonding are likely reversible under the optimized reaction conditions, and the observed reactivity may not depend exclusively on heats of formation. In situ ^{13}C NMR showed small chemical shifts for mandelic and benzoylformic acids when exposed to NBS under experimental conditions, with greater shifting noted near sites of proposed halogen bonding (see the Supporting Information for details). Regardless of the binding mode, computational results suggest halogen-bound species may enhance reactivity for aromatic bromination due to increased electropositivity at bromine. To further understand the role of Lewis basic additives in bromination, we experimentally explored the kinetic effect catalytic additives had on reaction efficiency. Initially, control reactions confirmed that the NBS-mediated oxidation of mandelic acid to benzoylformic acid is unlikely to occur on the timescale of a typical bromination reaction. This confirmed that any kinetic differences noted between reactions employing mandelic acid or benzoylformic acid are not complicated by the interconversion of the two species over time.

As shown in Figure 4, the rates of bromination for 4′-methoxyacetophenone were compared at room temperature using either mandelic (red data) or benzoylformic acid (blue data) as catalytic additives. Although both reactions are known to reach high overall conversion over the course of several hours (Table 2, entries 9−10), a significant (>2×) kinetic advantage is observed when using benzoylformic acid as the catalytic additive. This is perhaps surprising given the calculations suggest similar electropositive character for bromine when halogen bound to either mandelic or benzoylformic acid, although the observed rate of reaction is likely dependent both on the concentration of the halogen-bound species and the inherent kinetics of bromine transfer. Based on reactivity alone, benzoylformic acid appears to be the optimum catalytic additive to promote aromatic bromination under mild conditions. However, the high cost of benzoylformic acid compared to mandelic acid limits its use in large-scale applications ($460/mol vs $21/mol, respectively). Because both additives generally produced similar conversions overall, we selected mandelic acid as our additive of choice due to its lower cost.

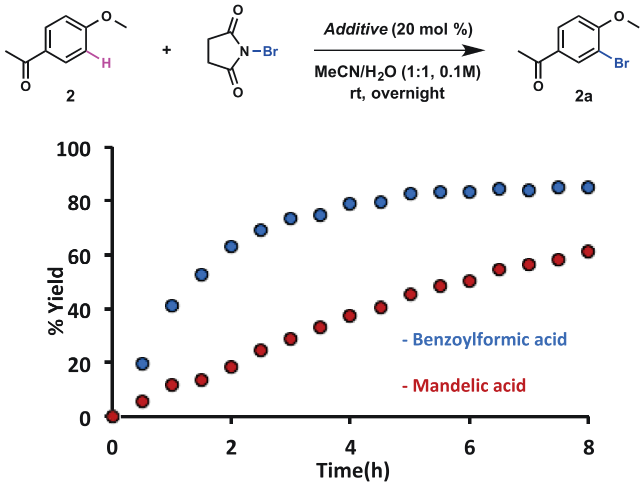
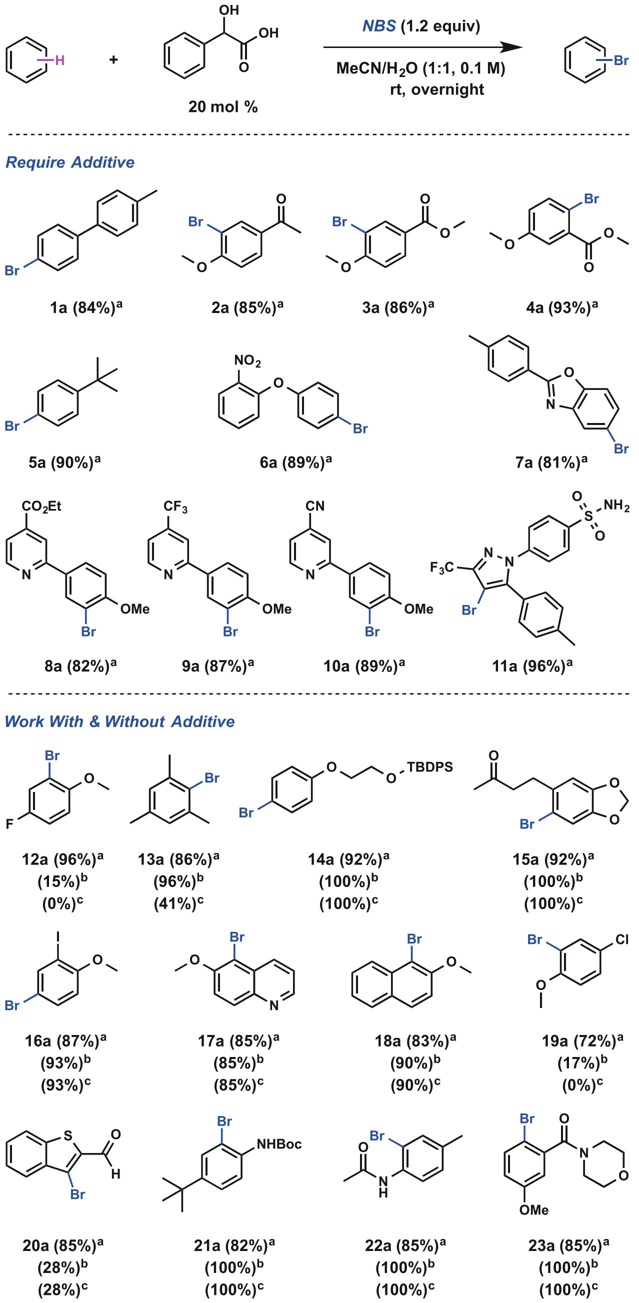


Figure 4. Rate comparison for the bromination of 4′-methoxyacetophenone (**2**) in the presence of catalytic benzoylformic acid (**10**, blue data points) and mandelic acid (**9**, red data points).

Scheme 1. Aromatic Bromination with Catalytic Mandelic Acid[a]



[a] General reaction conditions: (a) starting material (0.2 mmol), NBS (0.24 mmol), mandelic acid (0.04 mmol), and 2 mL of ACN/H$_2$O (1:1), rt for 24 h, yields reported as the chromatographically pure material. (b) Starting material (0.2 mmol), NBS (0.24 mmol), mandelic acid (0.04 mmol), and 2 mL of ACN/H$_2$O (1:1), rt for 30 min, yields reported as conversion via ^{1}H NMR. (c) Starting material (0.2 mmol), NBS (0.24 mmol), and 2 mL of ACN/H$_2$O (1:1), rt for 30 min, yields reported as conversion via ^{1}H NMR.

With general experimental conditions chosen, the scope of aromatic bromination was explored (Scheme 1). Substrates **1**−**11** require catalytic mandelic acid to yield any brominated products at room temperature, with no reactivity observed using NBS alone. Substrates **12**−**24** yield brominated products in the absence of mandelic acid, although increased reactivity is generally noted when catalytic mandelic acid is present. For these substrates, reaction conversion at 30 min under standard conditions is reported with and without mandelic acid for comparison. Anisole derivatives substituted with electron-withdrawing groups afforded the corresponding brominated compounds in high yields (**2a**−**4a**). Alkyl substitutions are well-tolerated (**5a**, **13a**), as are pre-installed halogens (**12a**, **16a**, **19a**). We were pleased to find that more substituted heterocyclic structures were tolerated (**7a**−**10a**, **20a**), although an interesting reaction feature was noted. Pyridines such as **8**–**10** that are substituted in the 4-position with electron-withdrawing groups were brominated in high yield, but electron-donating groups in the same position were not tolerated. These results mirror data discussed above, whereby more Lewis basic pyridines react with NBS unproductively, precluding aromatic bromination (Table 1, entries 4–5). Strongly Lewis basic substrates such as unprotected alcohols and amines were not tolerated, although protected primary alcohols (**14a**) and amides (**21a**–**23a**) participate in aromatic bromination in high yields. The bromination of celecoxib (**11**) in high yield impressively demonstrates how the modulation of Lewis basicity via electron delocalization may enable bromination in a more complex setting. No reactivity is observed for the bromination of celecoxib in the absence of catalytic mandelic acid, we believe the pyrazole and sulfonamide functional groups are well-tolerated because they do not interfere with the halogen bonding that occurs between NBS and mandelic acid to facilitate bromination.

Although half of the substrates examined in Scheme 1 produced brominated products by simply subjecting them to NBS at room temperature, we noted substrate-dependent variations in reaction efficiency when using catalytic amounts of mandelic acid. Specifically, only trace amounts of **12a** were observed via thin-layer chromatography (TLC) over the course of several hours when subjected to NBS alone, but a significant product was made in the same time period when using 20 mol % mandelic acid at room temperature. Time-course studies via NMR under synthetic conditions further quantified this effect (Figure 5). Whereas nearly complete conversion to **12a** was observed in 4 h when catalytic mandelic acid was present, only ~20% conversion was noted during the same timeframe with no additive present. An induction period is noted for each reaction in Figure 5, although this appears to be substrate dependent as no initiation period is observed for the bromination reaction to produce **2a** (Figure 4). The data compiled between Figures 4 and 5 supports our hypothesis that the presence of mandelic acid yields a more reactive brominating species regardless of the identity of the arene substrate.

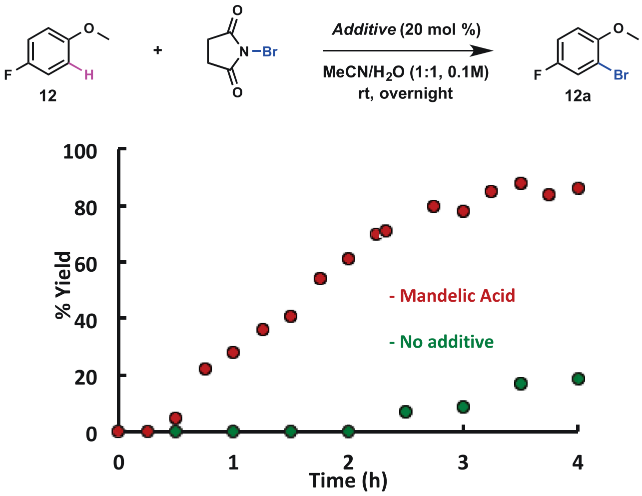


Figure 5. Rate comparison for the bromination of 4-fluoroanisole (**12**) in the presence of mandelic acid (red data points) and the absence of any additive (green data points).

■ CONCLUSIONS

In conclusion, we have identified a simple strategy for aromatic brominations under mild conditions using NBS. Catalytic amounts of lactic acid derivatives were shown to enable, or increase the efficacy of, bromination depending on the inherent reactivity of the aromatic substrate. Calculations showed that various modes of reversible halogen bonding to the lactic acid derivatives are reasonable, resulting in enhanced electrophilicity of the bromine source. Kinetic comparisons showed that catalytic additives promote bromination via enhanced reaction rates, with mandelic acid chosen as the additive of choice based on enhanced reactivity and cost-effectiveness when considering large-scale reactions.

■ EXPERIMENTAL SECTION

General Considerations. Reagents and solvents were purchased at the highest commercial quality and used without purification, unless otherwise specified. Yields refer to chromatographically and spectroscopically (^{1}H NMR and ^{13}C NMR) homogeneous materials, unless otherwise noted. The yields in the publication and the Supporting Information are the result of a single reaction. All the reactions were carried out at room temperature. Reactions were monitored by gas chromatography–mass spectroscopy (MS) (Agilent Technologies 5975 Series MSD GCMS) and TLC using 0.25 mm E. Merck silica gel plates (60F-254) using ultraviolet light. NMR spectra were recorded on a Varian-INOVA 400 MHz or 500 MHz spectrometer and calibrated using a residual undeuterated solvent as an internal reference ($CDCl_3$—^{1}H NMR: 7.26 ppm, ^{13}C NMR: 77.16 ppm; D_2O—^{1}H NMR: 4.79 ppm; CD_3CN—^{1}H NMR: 1.94 ppm, ^{13}C NMR: 1.32 ppm), whereas for ^{15}N spectra, a sealed capillary filled with nitromethane (0 ppm) was used as an internal standard. The following abbreviations were used to explain multiplicities (s—singlet, d—doublet, t—triplet, q—quartet, and m—multiplet). High-resolution MS (HRMS) data was collected on a Thermo Fisher Scientific Exactive Plus Orbitrap mass spectrometer. All the masses reported are in regard to bromine-79. All the synthesized substrates were prepared according to literature procedures, which are described below. The rate of the reaction when using the two additives was monitored over the course of 24 h. The study of how NBS interacted with the different additives was completed on CD_3CN/D_2O directly in the NMR tube. The degradation study of the amino acid phenylglycine with NBS was completed in CD_3CN/D_2O and the degradation of phenylglycine was almost immediate. The NMR rate comparison study for 4-fluoroanisole with and without the additives was completed over the course of 4 h. All the data calculations were performed using a local developed version of Gaussian.

General Reaction Procedures. *General Procedure.* The threads of a 4 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added NBS (43 mg, 0.24 mmol, 1.2 equiv), mandelic acid (6 mg, 0.04 mmol, 20 mol %), and an aromatic compound (0.2 mmol, 1.0 equiv). ACN (1 mL) and H_2O (1 mL) were then added. The reaction was capped with a Teflon screen cap and rubber septum (24/40). The reaction was then stirred at room temperature until completed, as judged by TLC.

Upon completion, the reaction was diluted with ethyl acetate (1 mL) and transferred to a test tube containing saturated $NaHCO_3$ (3 mL). The aqueous phase was extracted with ethyl acetate (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and carefully concentrated in vacuo. The crude material was purified by silica gel chromatography to yield the desired product.

HRMS Procedure. The purified product (~10 mg) was diluted with high-performance liquid chromatography grade CH_3CN/H_2O (1:1) to approximately 2 mL. The resulting solution was then filtered and injected onto HRMS. Data collection was performed using factory default parameters for positive ion electrospray ionization (ESI) MS.

Synthesis of 14, 21, and 23. *2-[[(tert-Butyl)diphenylsilyl]oxy]-ethoxy-benzene (**14**).* Using a modified literature procedure,[1] to a solution of 2-phenoxyethanol (7.2 mmol) in anhydrous dichloromethane (14.4 mL) cooled to 0 °C, imidazole (1.3 equiv) was added, followed by the dropwise addition of *tert*-butyl(chloro)diphenylsilane (1.1 equiv). The reaction mixture was allowed to warm to room temperature and stirred overnight, and then quenched by the addition of water and dichloromethane. The layers were separated, and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel using (9:1) hexanes/EtOAc as the eluent to get the compound **14**. The reaction afforded 2.654 g (98%) of isolated yield as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.77−7.74 (m, 4H), 7.49−7.39 (m, 6H), 7.30 (dd, J = 15.4, 7.6 Hz, 2H), 7.00−6.95 (m, 1H), 6.92 (d, J = 8.6 Hz, 2H), 4.12 (t, J = 5.2 Hz, 2H), 4.04 (t, J = 5.2 Hz, 2H), 1.11 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 159.2, 135.7, 133.6, 129.7, 129.4, 127.7, 120.7, 114.6, 68.9, 62.7, 26.8, 19.3. HRMS (ESI-TOF): calcd for $C_{24}H_{28}O_2Si$ $[M + H]^+$, 377.1931; found, 377.1933.

*1,1-Dimethylethyl N-[4-(1,1-Dimethylethyl)phenyl]carbamate (**21**).* Using a modified literature procedure,[2] to a round-bottom flask having dicarbonate (8 mmol) dissolved in glycerol (16 mL) at room temperature, 4-*tert*-butylaniline (1.0 equiv) was added. Let the reaction stir vigorously. The reaction mixture was allowed to stir for 3−4 h and then quenched by the addition of water, petroleum ether, and ethyl acetate (9:1). The layers were separated, and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a 1.774 g (89%) isolated yield of **21** as a khaki solid. ^{1}H NMR (500 MHz, $CDCl_3$): 7.33−7.25 (m, 4H), 1.51 (s, 9H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 152.9, 146.0, 135.6, 125.8, 118.5, 34.2, 31.4, 28.3. HRMS (ESI-TOF): calcd for $C_{15}H_{23}NO_2$ $[M + H]^+$, 250.1802; found, 250.1789.

*(3-Methoxyphenyl)-4-morpholinylmethanone (**23**).* Using a modified literature procedure,[3] to a solution of potassium carbonate (2 equiv) in anhydrous dichloromethane (12 mL) cooled to 0 °C, morpholine (2.5 equiv) was added, followed by the dropwise addition of 3-methoxybenzoyl chloride (6 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight, and then quenched by the addition of water and dichloromethane. The layers were separated, and the organic layer was dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a 1.167 g (88%) isolated yield of **23** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): 7.35−7.30 (m, 1H), 6.99−6.93 (m, 3H), 3.88−3.36 (m, 11H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 170.2, 159.7, 136.4, 129.7, 118.9, 115.6, 112.5, 66.9, 55.4. HRMS (ESI-TOF): calcd for $C_{12}H_{15}NO_3$ $[M + H]^+$, 222.1125; found, 222.1117.

Spectral Data of Products. *4-Bromo-4′-methylbiphenyl (**1a**).* General procedure **A** was modified using 4-methylbiphenyl **1** (33.6 mg, 0.2 mmol). The reaction afforded a 42 mg (84%) of isolated yield as a white solid separated by silica gel (in pentanes). The data matches those previously reported.[4] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 2H), 7.46−7.40 (m, 4H), 7.24 (d, J = S18 8.0 Hz, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.2, 137.6, 137.2, 131.9, 129.8, 128.6, 126.9, 121.3, 21.2.

*3-Bromo-4-methoxyacetophenone (**2a**).* General procedure **A** was employed using 4-methoxyacetophenone **2** (30 mg, 0.2 mmol). The reaction afforded a 39 mg (85%) isolated yield of **2a** as a white solid separated by silica gel (35% EtOAc in hexanes). A large-scale reaction using 4-methoxyacetophenone (150 mg, 1.0 mmol), NBS (213 mg, 1.2 mmol), and mandelic acid (30 mg, 0.2 mmol) in ACN (5 mL) and H_2O (5 mL) was carried out. The reaction afforded a 193.2 mg (84%) isolated yield of **2a**. The data matches those previously reported.[5] ^{1}H NMR (500 MHz, $CdCl_3$): δ 8.16, 8.15, 7.91, 7.91, 7.90, 7.89, 6.93, 6.92, 3.96, 2.54. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.6, 159.6, 133.8, 131.2, 129.5, 111.9, 111.1, 56.5, 26.3.

*Methyl 3-Bromo-4-methoxybenzoate (**3a**).* General procedure **A** was employed using methyl 4-methoxybenzoate **3** (33 mg, 0.2 mmol). The reaction afforded a 42.1 mg (86%) isolated yield of **3a** as a white solid separated by silica gel (15% EtOAc in hexanes). The data matches those previously reported.[5] ^{1}H NMR (500 MHz, $CDCl_3$): 8.24 (d, J = 2.1 Hz, 1H), 7.99 (dd, J = 8.6, 2.8 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 3.96 (s, 4H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): 165.7, 159.5, 134.8, 130.5, 123.8, 111.4, 111.0, 56.5, 56.5, 52.1, 52.1.

*Methyl 2-Bromo-5-methoxybenzoate (**4a**).* General procedure **A** was employed using methyl 3-methoxybenzoate **4** (29 μL, 0.2 mmol). The reaction afforded a 45.6 (93%) isolated yield of **4a** as a yellow oil separated by silica gel (15% EtOAc in hexanes). The data matches those previously reported.[6] ^{1}H NMR (500 MHz, $CDCl_3$): 7.53 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 3.1 Hz, 1H), 6.90 (dd, J = 8.8, 3.1 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): 166.5, 158.6, 135.0, 132.6, 119.0, 116.2, 111.9, 55.6, 52.5.

*1-Bromo-4-t-butylbenzene (**5a**).* General procedure **A** was employed using *t*-butylbenzene **5** (26.8 mg, 0.2 mmol). The reaction afforded a 38 mg (90%) isolated yield of **5a** colorless oil separated by silica gel (pentanes). The data matches those previously reported.[7] ^{1}H NMR (500 MHz, $CdCl_3$): δ 7.39 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 1.29 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 150.3, 131.2, 127.3, 119.3, 34.7, 31.4.

*1-(4-Bromophenoxy)-2-nitrobenzene (**6a**).* The general produce was used to procedure **6**.[8] General procedure **A** was employed using 1-nitro-2-phenoxybenzene **6** (43 mg, 0.2 mmol). The reaction afforded a 52 mg (89%) isolated yield of **6a** as yellow oils separated by silica gel (2 to 20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CdCl_3$): δ 8.00 (dd, J = 8.2, 1.4 Hz, 1H), 7.60−7.54 (m, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 8.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CdCl_3$): δ 155.3, 150.1, 141.7, 134.4, 133.2, 126.0, 123.9, 121.0, 120.7, 117.3. HRMS (ESI-TOF): calcd for $C_{12}H_8BrNO_3$ $[M + H]^+$, 293.9760; found, 293.9751.

*5-Bromo-2-(4-methylphenyl)benzoxazole (**7a**).* General procedure **A** was employed using 2-(4-methylphenyl)benzoxazole **7** (41.8 mg, 0.2 mmol). The reaction afforded a 46.5 mg (81%) isolated yield of **7a** as a pale white solid separated by silica gel (dichloromethane). ^{1}H NMR (500 MHz, $CdCl_3$): δ 8.08 (d, J = 8.0 Hz, 1H), 7.69 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 2.42 (s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CdCl_3$): δ 163.9, 151.2, 142.5, 141.5, 129.8, 127.9, 127.7, 123.9, 120.8, 117.7, 114.1, 21.8. HRMS (ESI-TOF): calcd for $C_{14}H_{10}BrNO$; $[M + H]^+$, 288.0019; found, 288.0011.

*2-(3-Bromo-4-methoxyphenyl)-, ethyl ester-4-Pyridinecarboxylic Acid (**8a**).* The general produce was used to procedure **8**.[9] A general procedure was employed using 2-(4-methoxyphenyl)-, ethyl ester-4-pyridinecarboxylic acid **8** (51.5 mg, 0.2 mmol). The reaction afforded a 55 mg (82%) isolated yield of **8a** as pale yellow oils separated by silica gel (20 to 25% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CdCl_3$): δ 8.77 (d, J = 5.0 Hz, 1H), 8.29 (d, J = 2.2 Hz, 1H), 8.19 (s, 1H), 7.98 (dd, J = 8.6, 2.2 Hz, 1H), 7.73 (dd, J = 5.0, 1.4 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CdCl_3$): δ 165.3, 157.0, 156.7, 150.4, 138.7, 132.5, 132.0, 127.3, 121.0, 119.1, 112.4, 111.9, 62.0, 56.5, 14.4. HRMS (ESI-TOF): calcd for $C_{15}H_{15}BrNO_3$ $[M + H]^+$, 336.0231; found, 336.0223.

*2-(3-Bromo-4-methoxyphenyl)-4-(trifluoromethyl)-pyridine (**9a**).* The general produce was used to procedure 9.[9] General procedure **A** was employed using 2-(4-methoxyphenyl)-4-(trifluoromethyl)- pyridine **9** (50.6 mg, 0.2 mmol). The reaction afforded a 57.4 mg (87%) isolated yield of **9a** as a yellow oil separated by silica gel (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CdCl_3$): δ 8.81 (d, J = 5.0 Hz, 1H), 8.27 (d, J = 2.2 Hz, 1H), 7.96 (dd, J = 8.6, 2.2 Hz, 1H), 7.83 (s, 1H), 7.40 (d, J = 5.0 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CdCl_3$) ^{13}C NMR (126 MHz, $CdCl_3$): δ 157.24, 156.90, 150.58, 139.16 (q, J = 33.8 Hz), 131.97, 131.75, 127.20, 122.89 (q, J = 273.2 Hz), 117.27 (q, J = 3.5 Hz), 115.20 (q, J = 3.6 Hz), 112.38, 111.85, 56.37. ^{19}F NMR (470 MHz, $CdCl_3$): δ −64.85. HRMS (ESI-TOF): calcd for $C_{13}H_9BrF_3NO$ $[M + H]^+$, 331.9892; found, 331.9883.

*2-(3-Bromo-4-methoxyphenyl)isonicotinonitrile (**10a**).* The general produce was used to procedure **10**.[9] General procedure **A** was employed using 2-(4-methoxyphenyl)-4-pyridinecarbonitrile **10** (42 mg, 0.2 mmol). The reaction afforded a 51.3 mg (89%) isolated yield of **10a** as an orange solid separated by silica gel (dichloromethane).

^{1}H NMR (500 MHz, CdCl$_3$): δ 8.80 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 2.2 Hz, 1H), 7.91 (dd, J = 8.6, 2.2 Hz, 1H), 7.84 (s, 1H), 7.39 (dd, J = 4.9, 1.3 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CdCl$_3$): δ 157.6, 156.9, 150.7, 132.1, 131.1, 127.3, 122.9, 121.4, 121.3, 116.8, 112.6, 112.0, 56.6. HRMS (ESI-TOF): calcd for $C_{13}H_9BrN_2O$ [M + H]$^+$, 288.9971; found, 288.9963.

*4-[4-Bromo-5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide (**11a**).* General procedure **A** was employed using Celebrex **11** (76 mg, 0.2 mmol). The reaction afforded a 88 mg (96%) isolated yield of **11a** as a pale yellow-green solid separated by silica gel (2% methanol in dichloromethane).[10] ^{1}H NMR (500 MHz, CdCl$_3$): δ 7.88 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.1 Hz, 2H), 4.82 (s, 3H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CdCl$_3$): δ 143.8, 142.6, 142.3, 142.2, 142.0, 141.74, 141.70, 140.6, 130.0, 129.9, 127.5, 125.2, 123.9, 123.8, 121.6, 119.5, 117.3, 94.5, 21.5.

*2-Bromo-4-fluoroanisole (**12a**).* General procedure **A** was employed using 4-fluoroanisole **12** (25 mg, 0.2 mmol). The reaction afforded a 96% isolated yield of **12a** as a yellow oil separated by acid/base extraction (1 M HCl in H_2O). The data matches those previously reported.[11] ^{1}H NMR (500 MHz, CdCl$_3$): δ 7.30 (dd, J = 7.8, 3.1 Hz, 1H), 6.99 (td, J = 9.0, 3.0 Hz, 1H), 6.84 (dd, J = 9.0, 4.6 Hz, 1H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CdCl$_3$): δ 156.7 (d, J = 242.5 Hz), 120.6 (d, J = 25.7 Hz), 114.8 (d, J = 22.6 Hz), 112.4 (d, J = 8.3 Hz), 111.8 (d, J = 10.0 Hz).

*1-Bromomesitylene (**13a**).* General procedure **A** was employed using mesitylene **13** (28 μL, 0.2 mmol). The reaction afforded a 22.3 mg (56%) isolated yield of **13a** as a colorless oil separated by silica gel (n-pentane). The data matches those previously reported.[12] ^{1}H NMR (500 MHz, CDCl$_3$): 6.89 (s, 2H), 2.37 (s, 6H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 138.0, 136.4, 129.2, 124.3, 23.9, 20.8.

*1-Bromo-4-[2-[[(tert-butyl)diphenylsilyl]oxy]ethoxy]-benzene (**14a**).* General procedure **A** was employed using 2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethoxy]-benzene **14** (75 mg, 0.2 mmol). The reaction afforded a 83.8 mg (92%) isolated yield of **14a** as a colorless oil separated by silica gel (only in hexanes). ^{1}H NMR (400 MHz, CDCl$_3$): 7.74–7.69 (m, 4H), 7.48–7.33 (m, 8H), 6.79–6.72 (m, 2H), 4.06–4.04 (m, 2H), 4.01–3.98 (m, 2H), 1.08 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$): 158.1, 135.6, 133.4, 132.2, 129.7, 127.7, 116.4, 112.8, 69.3, 62.6, 26.9, 19.3. HRMS (ESI-TOF): calcd for $C_{24}H_{27}BrO_2Si$ [M + H]$^+$, 455.1036; found, 455.1007.

*4-(6-Bromo-1,3-benzodioxol-5-yl)-2-butanone (**15a**).* General procedure **A** was employed using 4-(1,3-benzodioxol-5-yl)-2-butanone **15** (38 mg, 0.2 mmol). The reaction afforded a 47.2 (92%) isolated yield of **15a** as a yellow oil separated by silica gel (30% EtOAc in hexanes). ^{1}H NMR (500 MHz, CDCl$_3$): 6.98 (s, 1H), 6.74 (s, 1H), 5.94 (s, 2H), 2.91 (t, J = 7.6 Hz, 2H), 2.72 (t, J = 7.6 Hz, 2H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 207.6, 147.4, 146.9, 133.2, 114.2, 112.7, 110.2, 101.6, 43.6, 30.2, 30.0. HRMS (ESI-TOF): calcd for $C_{11}H_{11}BrO_3$ [M + H]$^+$, 270.9964; found, 270.9956.

*4-Bromo-2-iodoanisole (**16a**).* General procedure **A** was employed using 2-iodoanisole **16** (26 μL, 0.2 mmol). The reaction afforded a 54.5 (87%) isolated yield of **16a** separated by silica gel (20% EtOAc in hexanes). The data matches those previously reported.[13] ^{1}H NMR (500 MHz, CDCl$_3$): 7.89 (d, J = 2.4 Hz, 1H), 7.42 (dd, J = 8.7, 2.4 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 157.4, 140.9, 132.1, 113.5, 112.1, 86.7, 56.6.

*5-Bromo-6-methoxyquinoline (**17a**).* General procedure **A** was employed using 6-methoxyquinoline **17** (28 μL, 0.2 mmol). The reaction afforded a 40.5 mg (85%) isolated yield of **17a** as an off-white solid separated by silica gel (35% EtOAc in hexanes). The data matches those previously reported.[14] ^{1}H NMR (500 MHz, CDCl$_3$): 8.82 (d, J = 3.2 Hz, 1H), 8.58 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.51 (dd, J = 8.6, 4.1 Hz, 1H), 4.08 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 154.2, 148.3, 143.8, 135.2, 129.9, 128.7, 122.4, 116.8, 107.4, 57.1.

*1-Bromo-2-methoxynaphthalene (**18a**).* General procedure **A** was employed using 2-methoxynaphthalene **18** (31 mg, 0.2 mmol). The reaction afforded a 39.3 mg (83%) isolated yield of **18a** separated by silica gel (5% EtOAc in hexanes). The data matches those previously reported.[15] ^{1}H NMR (500 MHz, CDCl$_3$): 8.24 (d, J = 8.6 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 8.2 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 4.05 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 153.8, 133.0, 129.8, 128.9, 128.0, 127.7, 126.1, 124.3, 113.8, 108.7, 57.1.

*2-Bromo-4-chloroanisole (**19a**).* General procedure **A** was modified using 4-chloroanisole **19** (24 μL, 0.2 mmol). The reaction afforded a 31.9 mg (72%) isolated yield of **19a** as an orange-brown oil separated by silica gel (5% EtOAc in hexanes). ^{1}H NMR (500 MHz, CDCl$_3$): 7.54 (s, 1H), 7.25 (d, J = 8.7 Hz, 1H), 6.83 (d, J = 8.7 Hz, 1H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 154.8, 132.8, 128.3, 125.9, 112.5, 112.1, 56.4. HRMS (ESI-TOF): calcd for C_7H_6BrClO [M + H]$^+$, 220.9363; found, 220.9356.

*3-Bromobenzo[b]thiophene-2-carboxaldehyde (**20a**).* General procedure **A** was employed using benzo[b]thiophene-2-carboxaldehyde **20** (32.4 mg, 0.2 mmol). The reaction afforded a 41.0 mg (85%) isolated yield of **20a** as a yellow solid separated by silica gel (20% EtOAc in hexanes). The data matches those previously reported.[16] ^{1}H NMR (500 MHz, CDCl$_3$): 10.29 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.61–7.49 (m, 2H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 184.9, 140.5, 138.2, 136.4, 129.4, 125.9, 125.1, 123.4, 118.8.

*1,1-Dimethylethyl-N-[2-bromo-4-(1,1-dimethylethyl) Phenyl] Carbamate (**21a**).* General procedure **A** was employed using 1,1-dimethylethyl-N-[4-(1,1-dimethylethyl) phenyl] carbamate **21** (45 mg, 0.2 mmol). The reaction afforded a 53.9 mg (82%) isolated yield of **21a** as an orange oil separated by silica gel (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, CDCl$_3$): 8.02 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.31 (dd, J = 8.7, 2.1 Hz, 1H), 6.91 (s, 1H), 1.54 (s, 9H), 1.30 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 152.6, 147.3, 133.6, 129.1, 125.3, 119.9, 112.5, 80.9, 34.3, 31.2, 28.3. HRMS (ESI-TOF): calcd for $C_{15}H_{22}BrNO_2$ [M + H]$^+$, 328.0907; found, 328.0897.

*N-(2-Bromo-4-methylphenyl) Acetamide (**22a**).* General procedure **A** was employed using 4-methylacetanilide **22** (25 μL, 0.2 mmol). The reaction afforded a 38.6 mg (85%) isolated yield of **22a** as a pale yellow solid separated by silica gel (15% EtOAc in hexanes). The data matches those previously reported.[17] ^{1}H NMR (500 MHz, CdCl$_3$): δ 8.14 (d, J = 8.3 Hz, 1H), 7.53 (s, 1H), 7.34 (s, 1H), 7.09 (d, J = 8.2 Hz, 1H), 2.28 (s, 3H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, CdCl$_3$): δ 168.3, 135.4, 133.2, 132.5, 129.1, 122.1, 113.4, 24.9, 20.6.

*(2-Bromo-5-methoxyphenyl)-4-morpholinylmethanone (**23a**).* General procedure **A** was employed using (3-methoxyphenyl)-4-morpholinylmethanone **23** (42.4 mg, 0.2 mmol). The reaction afforded a 51.0 mg (85%) isolated yield of **23a** as a yellow oil separated by silica gel (30% acetone in hexanes).

^{1}H NMR (500 MHz, CDCl$_3$): 7.48–7.42 (m, 1H), 6.81 (m, 2H), 3.91–3.70 (m, 8H), 3.59 (m, 1H), 3.31 (m, 1H), 3.21 (m, 1H). ^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$): 167.51, 159.18, 138.17, 133.73, 116.64, 113.10, 109.27, 66.74, 66.62, 55.68, 47.12, 41.98. HRMS (ESI-TOF): calcd for $C_{12}H_{14}BrNO_3$ [M + H]$^+$, 300.0230; found, 300.0234.

General Procedure for NMR Studies. *Determining Rate of Reaction with Mandelic Acid.* In the absence of mandelic acid, 4-methoxyacetophenone (30 mg, 0.2 mmol, 1.0 equiv) and NBS (43 mg, 0.24 mmol, 1.2 equiv) in D_2O/CH_3CN (1:1, 0.2 M) were placed in an NMR tube. The first time point (t = 0 min) was then collected via NMR. After mandelic acid (6 mg, 0.04 mmol, 20 mol %) was added in one portion directly to the NMR tube, NMR time points were taken over the course of 24 h at rt.

Determining Rate of Reaction with Benzoylformic Acid. In the absence of benzoylformic acid, 4-methoxyacetophenone (30 mg, 0.2 mmol, 1.0 equiv) and NBS (43 mg, 0.24 mmol, 1.2 equiv) in D_2O/CH_3CN (1:1, 0.2 M) were placed in an NMR tube. The first time point (t = 0 min) was then collected via NMR. After benzoylformic acid (6 mg, 0.04 mmol, 20 mol %) was added in one portion directly to the NMR tube, NMR time points were taken over the course of 24 h at rt.

Kinetic NMR Study of 4-Methoxyacetophenone. *General Procedure Using Mandelic Acid.* In each ^1H NMR experiment, 0.2 mmol 4-methoxyacetophenone (30 mg) was mixed with NBS (43 mg, 0.24 mmol, 1.2 equiv). 1000 μL of CH_3CN and 1000 μL of D_2O were added to the sample. The sample was then transferred to an NMR tube. The initial time point $t = 0$ was then taken via NMR. After $t = 0$, mandelic acid (6 mg, 0.04 mmol, 20 mol %) was added directly to the NMR tube and inverted several times to ensure the mandelic acid was fully dissolved. NMR was taken every 15 min over the course of 8 h. The final time point was taken at 24 h. D_2O was used as the lock solvent (4.79 ppm). The chemical shift for the methoxy peak of the starting material (4.39 ppm) versus the product (4.46 ppm) for each time point was tabulated in excel (Table S3). The NMR conversion was calculated by setting the integration of the methoxy peak of the starting material to 1 and integrating the product. The integration of the product methoxy peak was then divided by the total of the starting material and product integration combined, and multiplied by 100. To eliminate any discrepancy between whether the reaction must stir, the same experiment was completed where 400 μL of the reaction was pipetted into an NMR tube and NMR was taken. The sample was then carefully poured back into the reaction vial to continue stirring. This was performed every 30 min to compare the reaction when it was completed in NMR versus stirring in a reaction vial (Figure S1C).

General Procedure Using Benzoylformic Acid. In each ^1H NMR experiment, 0.2 mmol of 4-methoxyacetophenone (30 mg) was mixed with NBS (43 mg, 0.24 mmol, 1.2 equiv). 1000 μL of CH_3CN and 1000 μL of D_2O were added to the sample. The sample was then transferred to an NMR tube. The initial time point $t = 0$ was then taken via NMR. After $t = 0$, benzoylformic acid (6 mg, 0.04 mmol, 20 mol %) was added directly to the NMR tube and inverted several times to ensure the mandelic acid was fully dissolved. NMR was taken every 15 min over the course of 8 h. The final time point was taken at 24 h. D_2O was used as the lock solvent (4.79 ppm). The chemical shift for the methoxy peak of the starting material (4.39 ppm) versus the product (4.46 ppm) for each time point was tabulated in excel (Table S4). The NMR conversion was calculated by setting the integration of the methoxy peak of the starting material to 1 and integrating the product. The integration of the product methoxy peak was then divided by the total of the starting material and product integration combined, and multiplied by 100. To eliminate any discrepancy between whether the reaction must stir, the same experiment was completed where 400 μL of the reaction was pipetted into an NMR tube and an NMR was taken. The sample was then carefully poured back into the reaction vial to continue stirring. This was performed every 30 min to compare the reaction when it was completed in an NMR versus stirring in a reaction vial (Figure S2C).

General Procedure Using Phenylglycine. In each ^1H NMR experiment, 0.2 mmol of 4-methoxyacetophenone (30 mg) was mixed with NBS (43 mg, 0.24 mmol, 1.2 equiv). 1000 μL of CH_3CN and 1000 μL of D_2O were added to the sample. The sample was then transferred to an NMR tube. The initial time point $t = 0$ was then taken via NMR. After $t = 0$, phenylglycine (6 mg, 0.04 mmol, 20 mol %) was added directly to the NMR tube and inverted several times to ensure the phenylglycine was fully dissolved. NMR was taken every 30 min over the course of 8 h. The final time point was taken at 24 h. D_2O was used as the lock solvent (4.79 ppm). The chemical shift for the methoxy peak of the starting material (4.39 ppm) versus the product (4.46 ppm) for each time point was tabulated in excel (Table S3). The NMR conversion was calculated by setting the integration of the methoxy peak of the starting material to 1 and integrating the product. The integration of the product methoxy peak was then divided by the total of the starting material and product integration combined, and multiplied by 100.

Kinetic NMR Benzoylformic Acid Formation. *General Procedure.* In each ^1H NMR experiment, 0.2 mmol of 4-methoxyacetophenone (30 mg) was mixed with NBS (43 mg, 0.24 mmol, 1.2 equiv). 1000 μL of CH_3CN and 1000 μL of D_2O were added to the sample. The sample was then transferred to an NMR tube. The initial time point $t = 0$ was then taken via NMR. After $t = 0$, mandelic acid (6 mg, 0.04 mmol, 20 mol %) was added directly to the NMR tube and inverted several times to ensure the mandelic acid was fully dissolved. NMR was taken every 15 min over the course of 8 h. The final time point was taken at 24 h. D_2O was used as the lock solvent (4.79 ppm). The chemical shift for mandelic acid ranged from 7.87 to 7.97 ppm and the chemical shift for benzoylformic acid ranged from 8.10 to 8.25 ppm. The conversion of mandelic acid to benzoylformic acid was monitored over the course of 24 h.

NMR Study of Additives with NBS. *General Procedure.* In each ^1H NMR experiment, 0.4 mmol of additive and 0.4 mmol of NBS (when applicable) were used. To a test tube, the compound(s) under investigation was added and diluted using a mixture of 300 CD_3CN/D_2O, 300 μL of each solvent was used, vigorously stirred, and transferred to an NMR tube.

NMR Study of the Degradation of Phenylglycine. *General Procedure.* In each ^1H NMR experiment, 0.04 mmol of phenylglycine and 0.24 mmol of NBS (when applicable) were used. To a test tube, the compound(s) under investigation was added and diluted using a mixture of 600 μL CD_3CN/D_2O, 300 μL of each solvent was used, vigorously stirred, and transferred to an NMR tube. CD_3CN was used as the lock solvent (^1H: 1.94, ^{13}C: 118.26 ppm). The chemical shift for phenylglycine was 7.36 ppm for the aromatic and 4.60 ppm for the benzlic singlet. To confirm the degradation of phenylglycine into benzyladehyde, the mixture of phenylglycine and NBS was spiked with benzaldehyde (8 μL, 0.04 mmol, 20 mol %), causing the peaks for benzaldehyde to grow (δ 9.18 (s, 1H), 7.14 (d, J = 8.3 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 6.82 (t, J = 7.7 Hz, 2H)), confirming the degradation of phenylglycine into benzaldehyde.

NMR Rate Comparison Study for 4-Fluoroanisole. *General Procedure without Additive.* The threads of a 4 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added NBS (43 mg, 0.24 mmol, 1.2 equiv) and 4-fluoroanisole (22.6 μL, 0.2 mmol, 1.0 equiv). ACN (1 mL) and H_2O (1 mL) were then added. The reaction was capped with a Teflon screen cap and rubber septum (24/40). The reaction was then stirred at room temperature. Every 30 min, 100 μL of the reaction solution was pipetted into an NMR and diluted with 400 μL of CD_3CN. This continued over the course of 4 h to determine the rate of reaction.

General Procedure Using Additive. The threads of a 4 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added NBS (43 mg, 0.24 mmol, 1.2 equiv), mandelic acid (6 mg, 0.04 mmol, 20 mol %), or benzoylformic acid (6 mg, 0.04 mmol, 20 mol %) and 4-fluoroanisole (22.6 μL, 0.2 mmol, 1.0 equiv). ACN (1 mL) and H_2O (1 mL) were then added. The reaction was capped with a Teflon screen cap and rubber septum (24/40). The reaction was then stirred at room temperature. Every 15 min, 100 μL of the reaction solution was pipetted into NMR and diluted with 400 μL of CD_3CN (1.94 ppm). This continued over the course of 4 h to determine the rate of reaction. The NMR conversion was calculated by setting the integration of the methoxy peak of the starting material (3.71 ppm) to 1 and integrating the methoxy peak of the product (3.80 ppm). The integration of the product methoxy peak was then divided by the total of the starting material and product integration combined, and multiplied by 100.

NMR 30 min Rate Comparison of Product Conversion. *General Procedure with Mandelic Acid.* The threads of a 4 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar was added NBS (43 mg, 0.24 mmol, 1.2 equiv), mandelic acid (6 mg, 0.04 mmol, 20 mol %), and an aromatic compound (0.2 mmol, 1.0 equiv). ACN (1 mL) and H_2O (1 mL) were then added. The reaction was capped with a Teflon screen cap and rubber septum (24/40). The reaction was then stirred at room temperature for 30 min.

After 30 min, the reaction was diluted with ethyl acetate (1 mL) and transferred to a test tube containing saturated $NaHCO_3$ (3 mL). The aqueous phase was extracted with ethyl acetate (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and carefully concentrated in vacuo. NMR of the crude reaction mixture was taken using $CDCl_3$ as the solvent lock. The product conversion was then calculated based on NMR.

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General Procedure without Mandelic Acid. The threads of a 4 mL borosilicate scintillation vial were thoroughly taped with Teflon tape. To this vial containing a stir bar, was added NBS (43 mg, 0.24 mmol, 1.2 equiv) and an aromatic compound (0.2 mmol, 1.0 equiv). ACN (1 mL) and H_2O (1 mL) were then added. The reaction was capped with a Teflon screen cap and rubber septum (24/40). The reaction was then stirred at room temperature for 30 min.

After 30 min, the reaction was diluted with ethyl acetate (1 mL) and transferred to a test tube containing saturated $NaHCO_3$ (3 mL). The aqueous phase was extracted with ethyl acetate (3 × 3 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and carefully concentrated in vacuo. NMR of the crude reaction mixture was taken using $CDCl_3$ as the solvent lock. The product conversion was then calculated based on NMR.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00611.

> Detailed development of the bromination protocol including optimization of the solvent, temperature, concentration, and additives, raw data regarding reaction progressions and kinetic analysis is also provided, additional computational details regarding methods and interpretation of results are also provided, including data for halogen-bound structures from multiple additives displayed in Table 2, and spectroscopic data for all the relevant materials are also provided in the Supporting Information (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

NBS, *N*-bromosuccinimide; TLC, thin-layer chromatography

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