Oxidation of Alcohols and Oxidative Cyclization of Diols using NaBr and Selectfluor

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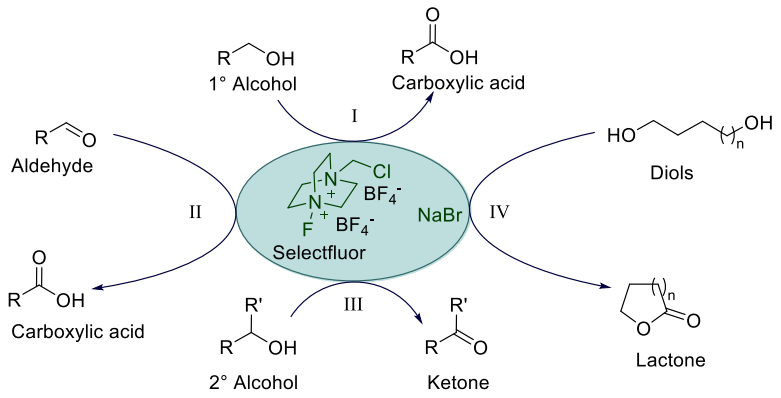
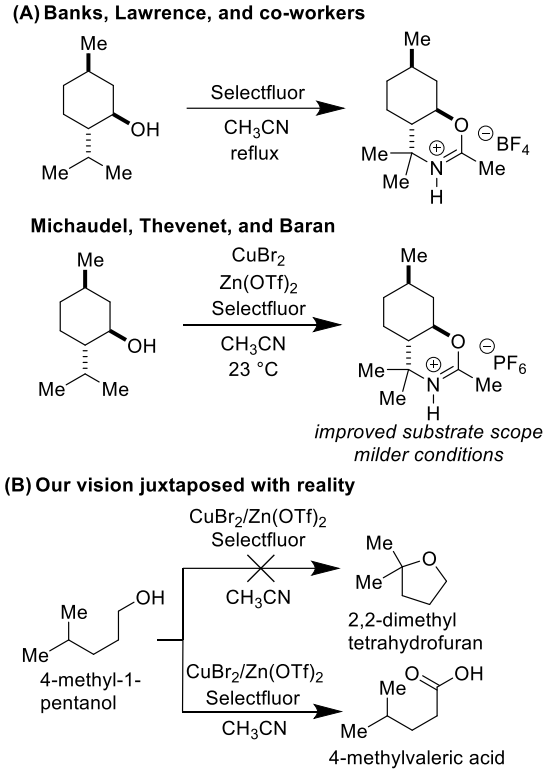


Abstract

We present protocols for the oxidation of alcohols and aldehydes and for the oxidative cyclization of diols which use a combination of Selectfluor and NaBr. For most substrates, the optimal solvent system is a 1:1 mixture of CH_3CN/H_2O, but, in select cases, biphasic 1:1 mixtures of $EtOAc/H_2O$ or CH_2Cl_2/H_2O are superior. This procedure is operationally simple, uses inexpensive and readily available reagents, and tolerates a variety of functional groups. Mechanistic studies suggest that the active oxidant is hypobromous acid, generated by the almost instantaneous oxidation of Br^- by Selectfluor in an aqueous milieu.

Introduction

Scheme 1. Our serendipitous discovery of a mild alcohol oxidation was inspired by C-H functionalization studies using Selectfluor.



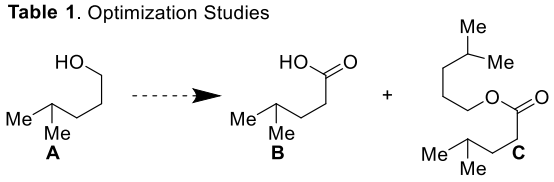
Selectfluor (1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)) was developed by Banks and Sharif at the University of Manchester Institute of Science and Technology as a crystalline, air-stable source of F^+, has been commercialized by Air Products, and is now inexpensive and widely available.[1, 2] Soon after its discovery, chemists came to appreciate that not only was Selectfluor a manageable source of electrophilic fluorine[3, 4] but also that it was a remarkable oxidant, at once strong enough to trigger a variety of interesting reactions but mild enough to be compatible with a range of functional groups.[5-8] One particularly interesting application of Selectfluor as an oxidant has been in its use for site-selective sp^3 C–H functionalization reactions,[9-30] an area of long-standing interest to us.[31-35] We were particularly attracted to the early work of Banks[36] and later improvement by Baran[37] on a Ritter-type C–H functionalization of menthol using a $CuBr_2$/Selectfluor manifold (**Scheme 1A**).

At the outset of this project, it was our intention to adapt Baran's protocol for an intramolecular C – H etherification, and we chose 4-methyl-1-pentanol as a convenient optimization substrate. When 4-methyl-1-pentanol was treated with $CuBr_2$, $Zn(OTf)_2$, and Selectfluor, none of the desired 2,2-dimethyltetrahydrofuran formed. A very polar spot was visualized by thin-layer chromatography, and the crude sample had the acrid odor of a carboxylic acid. ^{1}H NMR analysis confirmed that 4-methylvaleric acid was the predominant product, an interesting surprise. Mild protocols for the direct oxidation of alcohols to carboxylic acids are especially valuable[38-42]; generally two-pot reactions are employed, with aldehydes

serving as intermediates.[43-47] Furthermore, while Selectfluor is a known oxidant, its use in the oxidation of alcohols remains limited.[46] Thus, we wondered if we could develop these conditions into a general platform for the oxidation of primary alcohols and aldehydes into carboxylic acids and of secondary alcohols into ketones.[48, 49] We were also interested in exploring these conditions for a one-pot oxidative cyclization of diols into lactones.[50] Such technology would complement recent protocols for these transformations[51-71] and would increase the versatility of Selectfluor as an oxidant. What follows is an account of our efforts in these directions.

Results and Discussion

Table 1. Optimization Studies



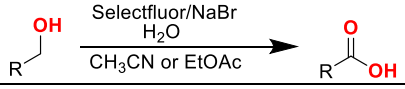
Entry	Conditions	Yield of B & C
1	$CuBr_2$ (0.25 equiv.) Selectfluor (2 equiv.) $Zn(OTf)_2$ (0.5 equiv.) CH_3CN, 23 °C	30% and 20%
2	$CuBr_2$ (0.25 equiv.) Selectfluor (2 equiv.) $Zn(OTf)_2$ (0.5 equiv.) 9:1 CH_3CN/H_2O, 23 °C	60% and 8%
3	$CuBr_2$ (0.25 equiv.) Selectfluor (2 equiv.) 9:1 CH_3CN/H_2O, 23 °C	70% and 8%
4	$CuBr_2$ (0.25 equiv.) Selectfluor (2 equiv.) 1:1 CH_3CN/H_2O, 23 °C	64% and 3%
5	$Cu(OAc)_2$ (0.25 equiv.) Selectfluor (2 equiv.) 1:1 CH_3CN/H_2O, 23 °C	0% (B and C) 100% A
6	$CuCl_2$ (0.25 equiv.) Selectfluor (2 equiv.) 1:1 CH_3CN/H_2O, 23 °C	0% (B and C) 100% A
7	NaBr (1 equiv.) Selectfluor (2 equiv.) 1:1 CH_3CN/H_2O, 23 °C	65% and 3%

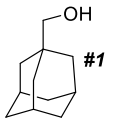
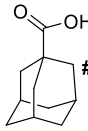
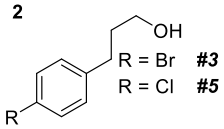
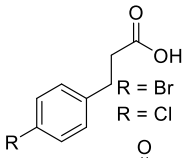
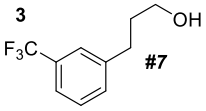
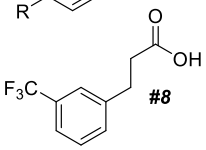
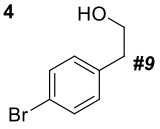
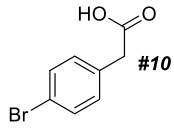
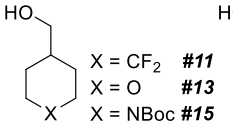
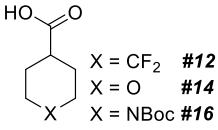
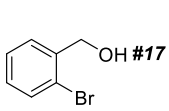
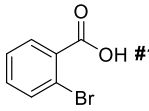
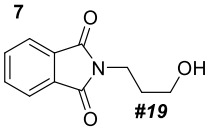
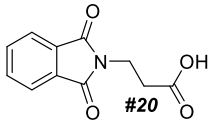
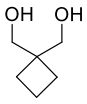
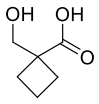
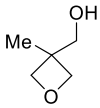
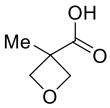
Careful analysis of our initial crude mixture (**Table 1**, **Entry 1**) by ^1H NMR revealed the presence of 4-methylvaleric acid (**B**) and ester **C**, the product of oxidative dimerization of 4-methyl-1-pentanol (**A**). We hypothesized that carboxylic acid formation would increase in the presence of water. Indeed, with a 9:1 mixture of CH_3CN/H_2O, the yield of acid **B** dramatically increased with a concomitant reduction in the formation of ester **C** (**Table 1**, **Entry 2**). Eliminating $Zn(OTf)_2$ slightly improved the yield of **B** (**Table 1**, **Entry 3**). With a 1:1 mixture of CH_3CN/H_2O, only a trace amount of ester **C** was detected (**Table 1**, **Entry 4**). When $CuBr_2$ was replaced with either $Cu(OAc)_2$ (**Table 1**, **Entry 5**) or $CuCl_2$ (**Table 1**, **Entry 6**), the oxidation reaction completely shut down. We thus suspected that bromide was essential for this reaction and was likely becoming oxidized to Br^+ in the reaction milieu.[72-82] We sought

to replace Cu^{2+} with a redox-innocent counter cation with the reasoning that a spectator cation was less likely to interfere with sensitive functional groups. We were pleased that replacing $CuBr_2$ with NaBr did not affect the yield or selectivity for desired acid **B** (**Table 1**, **Entry 7**).

We sought to test the substrate scope for the oxidation of primary alcohols into carboxylic acids using our optimized protocol of NaBr/Selectfluor in a 1:1 mixture of CH_3CN/H_2O. For most substrates, a 1:1 mixture of CH_3CN/H_2O was the optimal solvent system; however, a biphasic mixture of 1:1 $EtOAc/H_2O$ was optimal for substrate **15** (**Scheme 2**, **Entry 5**). With substrate **17**, switching solvents from a 1:1 mixture of CH_3CN/H_2O to 1:1 $EtOAc/H_2O$ changed product selectivity from the carboxylic acid to the aldehyde (**Scheme 2**, **Entry 6** and **Supporting Information, Section I**). The functional group compatibility of this transformation was quite good. Substituted aromatic rings, cyclic ethers, Boc-protected amines, and phthalimide-protected amines were all found to be compatible. With diol substrate **21**, mono-carboxylic acid **22** was the sole product along with a small amount of unreacted starting material (**Scheme 2**, **Entry 8**). In many cases, the mass balance of the reaction could be mainly attributed to product and unreacted starting material; an example is the oxidation of

Scheme 2. Oxidation of primary alcohols into carboxylic acids.

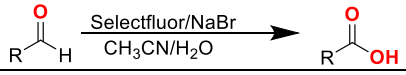


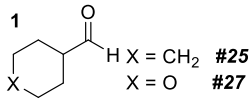
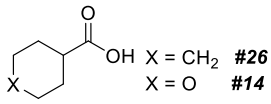
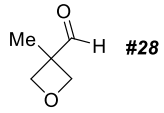
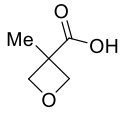
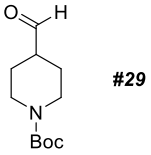
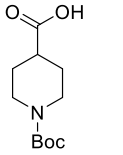
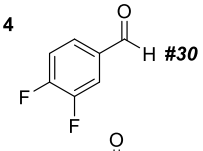
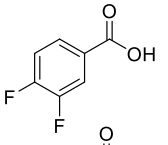
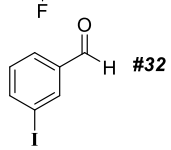
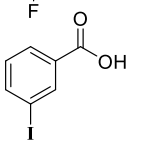
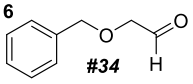
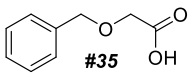
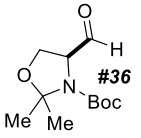
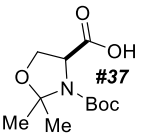
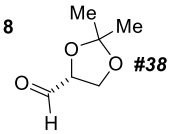
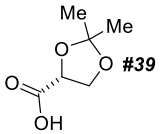
entry	substrate	product	isolated yield (%)
1			93%
2			64% (R = Br), 82% (R = Cl)
3			75%
4			93%
5			69% (X = CF_2), 61% (X = O), 46% (X = NBoc)
6			56%[a]
7			54% (34%[b])
8			60%
9			21%

[a]Reaction in a 1:1 mixture of CH_3CN/H_2O. In a 1:1 mixture of $EtOAc/H_2O$, aldehyde (~70%) is the major product.
[b]Recovered starting material.

substrate **19** (**Scheme 2**, **Entry 7**). However, this was not always the case; with substrate **23** (**Scheme 2**, **Entry 9**), only 21% of desired carboxylic acid **24** was isolated without any recovered starting material.

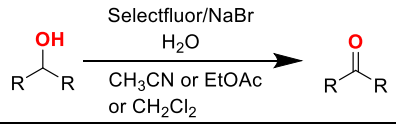
Scheme 3. Oxidation of aldehydes into carboxylic acids.

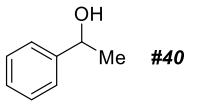
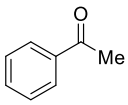
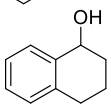
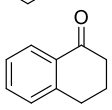
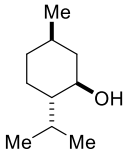
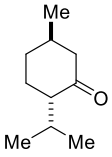
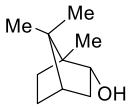
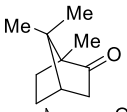
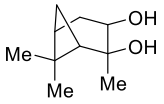
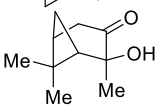
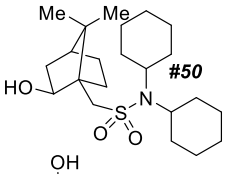
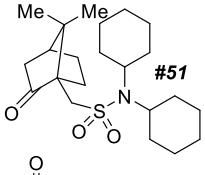
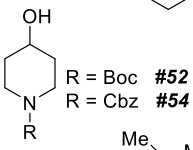
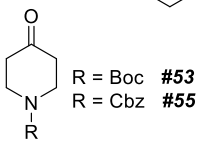
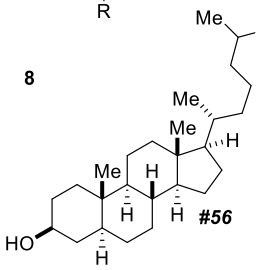
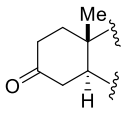
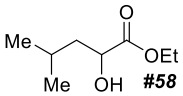
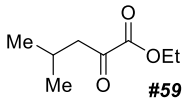


entry	substrate	product	isolated yield (%)
1	 X = CH_2 ***#25*** X = O ***#27***	 X = CH_2 ***#26*** X = O ***#14***	>95% 68%
2	 ***#28***	 ***#24***	84%
3	 ***#29***	 ***#16***	94%
4	 ***#30***	 ***#31***	68%
5	 ***#32***	 ***#33***	48% (36%[a])
6	 ***#34***	 ***#35***	79%
7	 ***#36***	 ***#37***	78%
8	 ***#38***	 ***#39***	42%

[a]recovered starting material

Scheme 4. Oxidation of secondary alcohols into ketones.

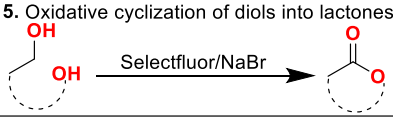


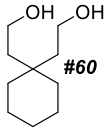
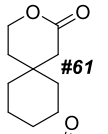
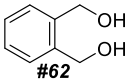
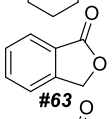
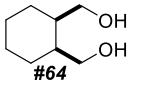
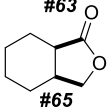
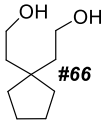
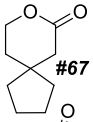
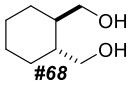
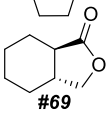
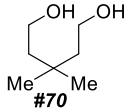
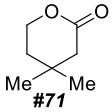
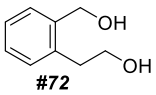
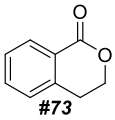
entry	substrate	product	isolated yield (%)
1	 ***#40***	 ***#41***	72%
2	 ***#42***	 ***#43***	90%
3	 ***#44***	 ***#45***	66%
4	 ***#46***	 ***#47***	87%
5	 ***#48***	 ***#49***	87%
6	 ***#50***	 ***#51***	66% (27%[a])
7	 R = Boc ***#52*** R = Cbz ***#54***	 R = Boc ***#53*** R = Cbz ***#55***	69% 85%
8	 ***#56***	 ***#57***	94%
9	 ***#58***	 ***#59***	58%[b]

[a]recovered starting material
[b]estimated by ^{1}H NMR integration due to product volatility

We next explored the oxidation of aldehydes into carboxylic acids using NaBr and Selectfluor (**Scheme 3**). With this oxidation, across a range of substrates, 1:1 CH_3CN/H_2O was the optimal solvent system. The functional group compatibility was good, and aldehyde substrates bearing oxetanes (**Scheme 3**, **Entry 2**), Boc-protected amines (**Scheme 3**, **Entry 3**), iodoarenes (**Scheme 3**, **Entry 5**), benzyl ethers (**Scheme 3**, **Entry 6**), *N*,*O*-ketals (**Scheme 3**, **Entry 7**), and ketals (**Scheme 3**, **Entry 8**) were all compatible. The substrate scope for oxidations of secondary alcohols into ketones (**Scheme 4**) was similarly robust. With this oxidation reaction, several natural product substrates (**Scheme 4**, **Entries 3–5 and 8**) reacted smoothly. We were particularly pleased that (1S,2S,3R,5S)-(+)-Pinanediol converted into (1S,2S,5S)-(−)-2-Hydroxy-3-pinanone (**Scheme 4**, **Entry 5**) without forming any detectable products of C–C bond cleavage.[83, 84]

Scheme 5. Oxidative cyclization of diols into lactones.

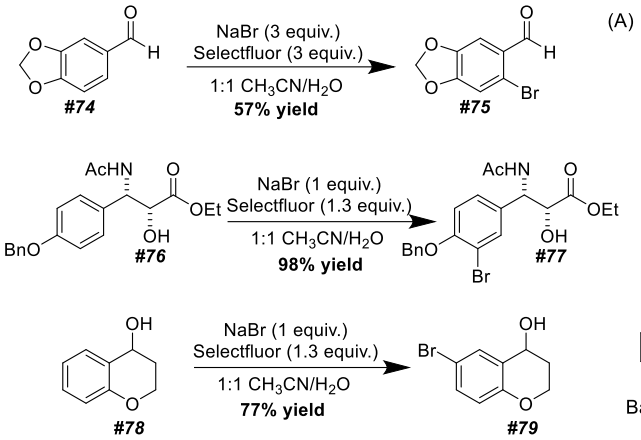


entry	substrate	product	isolated yield (%)
1	 #60	 #61	90%
2	 #62	 #63	79%
3	 #64	 #65	78%
4	 #66	 #67	90%
5	 #68	 #69	62%
6	 #70	 #71	69%
7	 #72	 #73	82%

Finally, we examined the oxidative cyclization of diols to give lactone products (**Scheme 5**). When treated with NaBr and Selectfluor, a variety of diols converted into the corresponding lactone products; we hypothesize that a two electron oxidation occurs to give a transient lactol, which is then rapidly oxidized into the lactone.[85] With unsymmetrical diol **72**, cyclization occurred to give 1-isochromanone exclusively (**Scheme 5**, **Entry 7**); there was no trace of the isomeric 3-isochromanone. Thus, the primary benzylic alcohol oxidized preferentially to the primary aliphatic one.

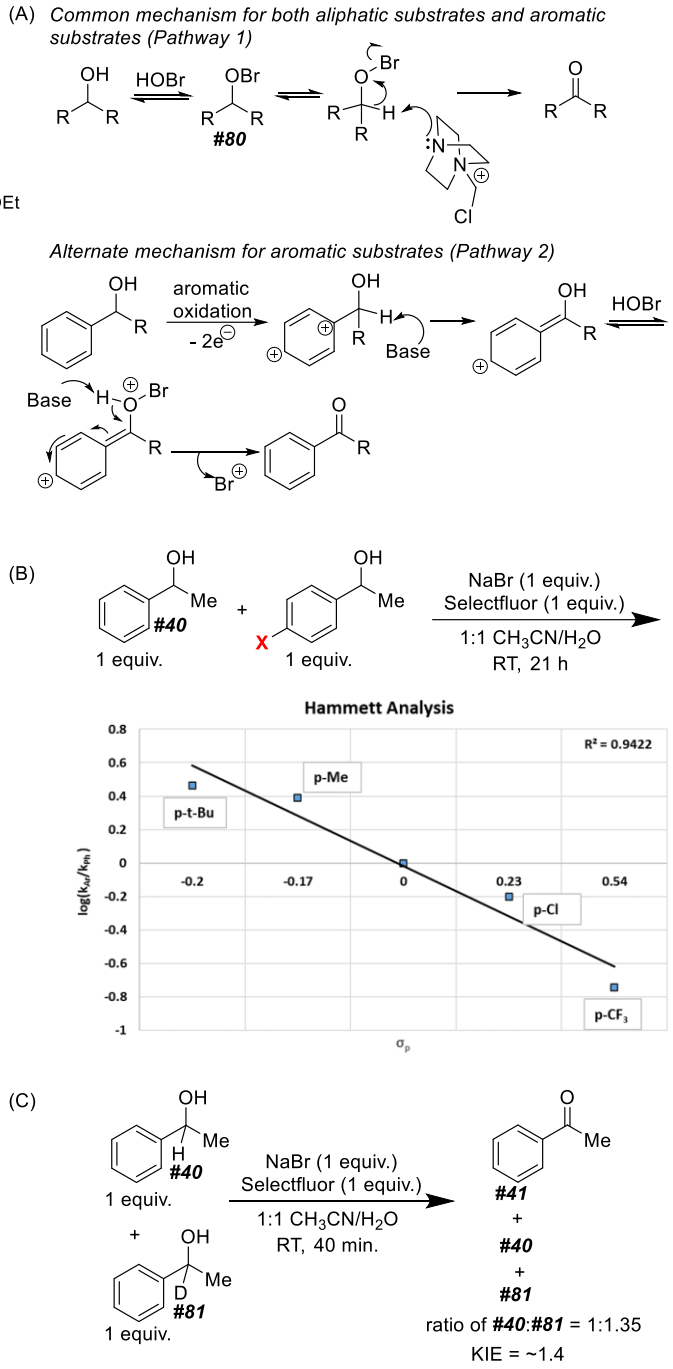
With substrates containing electron-rich aromatic rings, only products of aromatic bromination were isolated (**Scheme 6**). Even with complex, functionally group laden substrates, this process was

Scheme 6. Aromatic bromination predominates with substrates containing electron-rich aryl rings.



exceptionally chemoselective (**Scheme 6**, Substrate **76** and Product **77**). These results suggest that Br^+, likely in the form of hypobromous acid (HOBr), is playing a key role in the oxidation. We suggest two possible mechanisms for this reaction (**Scheme 7A**); for simplicity, we focus on the oxidation of secondary alcohols into ketones, and we posit that other oxidations behave analogously. For both mechanisms, Selectfluor serves to rapidly oxidize Br^- into Br^+, which likely exists as hypobromous acid in an aqueous medium. There is visual evidence for this, as in all reactions examined, the color immediately became bright yellow upon addition of Selectfluor. In pathway 1, the reaction of HOBr with a secondary alcohol forms hypobromite intermediate **80**; base promoted elimination gives ketone product. With aromatic substrates, a second mechanism is also possible, as Selectfluor is a known oxidant of aromatic rings.[86-88] In this second pathway, aromatic oxidation occurs followed by sequential deprotonation reactions to form ketone product. Evidence

Scheme 7. (A) Mechanistic Proposal (B) Hammett Analysis (C) Kinetic Isotope Effect Analysis



for aromatic oxidation comes from a Hammett analysis (**Scheme 7B**). A series of competition experiments between 1-phenylethanol and *para*-substituted phenylethanols shows that there is a marked preference for oxidation of electron-rich aromatic substrates. A plot of $\log(k_{Ar}/k_{Ph})$ against the Hammett-Brown substituent constant σ_p[89] gives a linear relationship with a ρ value of -0.3 and an R^2 value of 0.94; this implies that oxidation of aromatic rings proceeds *via* a transition state with significant partial positive charge in the rate determining step. An intermolecular competition experiment between protio substrate **40** and deutero substrate **81** gives a kinetic isotope effect (KIE) of 1.4, implying that C–H cleavage is at least product-determining for this reaction (**Scheme 7C**).[90]

Conclusion

In summary, we have developed a protocol for the oxidation of alcohols and for the oxidative cyclization of diols using a combination of Selectfluor and NaBr. For most substrates, the optimal solvent system is a 1:1 mixture of CH_3CN/H_2O, but in select cases, biphasic 1:1 mixtures of $EtOAc/H_2O$ or CH_2Cl_2/H_2O are superior. This procedure is operationally simple, uses inexpensive and readily available reagents, and tolerates a variety of functional groups. Mechanistic studies suggest that the active oxidant is hypobromous acid, generated by the almost instantaneous oxidation of Br^- by Selectfluor in an aqueous milieu. Given that the oxidation of alcohols is a cornerstone transformation of synthetic organic chemistry, we expect this protocol to be a welcome addition to the existing armory.

Experimental Section

I. **General Considerations:** All reagents were obtained commercially unless otherwise noted. Solvents were purified by passage under 10 psi N_2 through activated alumina columns. Infrared (IR) spectra were recorded on a Thermo Scientific™ Nicolet™ iS™5 FT-IR Spectrometer; data are reported in frequency of absorption (cm^{-1}). ^1H NMR spectra were recorded at 400, 500, or 600 MHz. Data are recorded as: chemical shift in ppm referenced internally using residual solvent peaks, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of nonequivalent resonances), integration, coupling constant (Hz). ^{13}C NMR spectra were recorded at 101 or 126 MHz. Exact mass spectra were recorded using

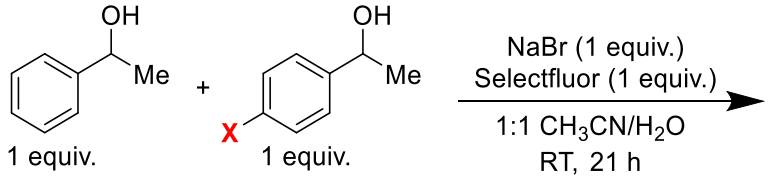
an electrospray ion source (ESI) either in positive mode or negative mode and with a time-of-flight (TOF) analyzer on a Waters LCT PremierTM mass spectrometer and are given in m/z. Thin Layer Chromatography (TLC) was performed on pre-coated glass plates (Merck) and visualized either with a UV lamp (254 nm) or by dipping into a solution of $KMnO_4$–K_2CO_3 or of ceric ammonium molybdate in water followed by heating. Flash chromatography was performed on silica gel (230-400 mesh) or Florisil (60-100 mesh).

II. General Procedure for Oxidations of Alcohols, Oxidative Cyclization of Diols, and Aryl Bromination (Schemes 2-6)

Note: Reactions were generally performed on a 0.5 mmol scale, and the general procedure reflects this. For reactions on other scales, the reagent quantities were changed appropriately.

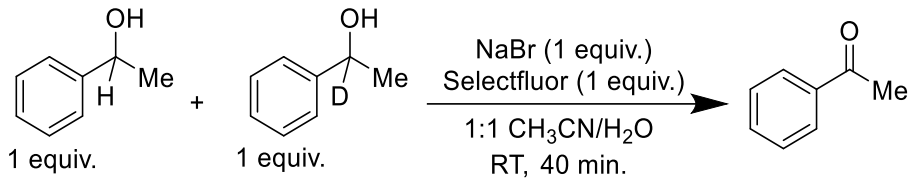
A 5 mL microwave vial was charged with a stir bar and alcohol substrate (0.5 mmol). 2.5 mL of organic solvent and 2.5 mL of H_2O were added followed by NaBr. Selectfluor was added in one portion (reaction color immediately became bright yellow), and the vial was capped and then wrapped in aluminum foil. The reaction was stirred in a dark fume hood for the appropriate time at ambient temperature. Following this period, the reaction vial was uncapped, and the contents were transferred to a separatory funnel with ethyl acetate. The organic layer was washed with one portion of saturated, aqueous $Na_2S_2O_3$ solution (yellow color disappeared), collected, dried with $MgSO_4$, and concentrated under reduced pressure. When necessary, the resulting residue was purified by chromatography on silica gel. Specific details including amounts of NaBr and Selectfluor, solvent conditions, and chromatography conditions are given with each product's characterization data.

III. Procedure for Competition Experiments for the Hammett Analysis (Scheme 7B)



A 5 mL microwave vial was charged with a stir-bar, 1-phenylethanol (0.031 g, 0.25 mmol, 1 equiv.), *p*-substituted competition substrate (0.25 mmol, 1 equiv.), 2.5 mL of CH_3CN, and 2.5 mL of H_2O. NaBr (0.026 g, 0.25 mmol, 1 equiv.) and Selectfluor (0.089 g, 0.25 mmol, 1 equiv.) were sequentially added. The vial was capped and then wrapped in aluminum foil. The reaction was stirred in a dark fume hood for 21 hours at ambient temperature. Following this period, the reaction vial was uncapped, and the contents were transferred to a separatory funnel with ethyl acetate. The organic layer was washed with one portion of saturated, aqueous $Na_2S_2O_3$ solution (yellow color disappeared), collected, dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was fully dissolved in $CDCl_3$ and analyzed by ^1H NMR. Product ratios were determined by integrating relevant signals.

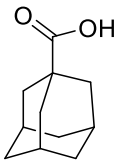
IV. Procedure for KIE Analysis (Scheme 7C)



A 5 mL microwave vial was charged with a stir-bar, 1-phenylethanol (0.031 g, 0.25 mmol, 1 equiv.), 1-phenylethan-1-d1-ol (0.031 g, 0.25 mmol, 1 equiv.), 2.5 mL of CH_3CN, and 2.5 mL of H_2O. NaBr (0.026 g, 0.25 mmol, 1 equiv.) and Selectfluor (0.089 g, 0.25 mmol, 1 equiv.) were sequentially added. The vial was capped and then wrapped in aluminum foil. The reaction was stirred in a dark fume hood for 40 minutes at ambient temperature. Following this period, the reaction vial was uncapped, and the contents were transferred to a separatory funnel with ethyl acetate. The organic layer was washed with one portion of saturated, aqueous $Na_2S_2O_3$ solution (yellow color disappeared), collected, dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was fully dissolved in $CDCl_3$ and analyzed by ^1H NMR and ^{13}C NMR. Product ratios were determined by integrating relevant signals in the ^{13}C NMR (spectral parameters are given in the Supporting Information).

V. Characterization of Products

Note: Starting materials are commercially available or previously characterized in the literature. For the reader's benefit, we have tabulated the characterization data of the products and have included copies of the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra in the supporting information.



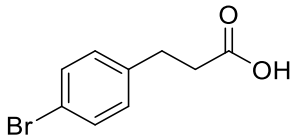
adamantane-1-carboxylic acid

Compound 2: Synthesized using the General Procedure on a 0.51 mmol scale using 3 equiv. of Selectfluor and 3 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours. Purified using a gradient of 0 to 50% EtOAc/hexanes on silica gel; (white solid, 0.085 g, 0.472 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 – 1.96 (m, 3H), 1.95 – 1.82 (m, 6H), 1.78 – 1.65 (m, 6H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 184.5, 40.6, 38.6, 36.5, 27.9.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



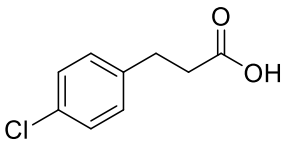
3-(4-bromophenyl)propanoic acid

Compound 4: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. Selectfluor and 3.5 equiv. NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours. Purified using a gradient of 10-100% EtOAc/hexanes on silica gel; (white solid, 0.073 g, 0.319 mmol, 64% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.35 (m, 2H), 7.16 – 6.98 (m, 2H), 2.91 (t, J = 7.6 Hz, 2H), 2.66 (t, J = 7.6 Hz, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 178.5, 141.0, 132.2, 128.8, 121.6, 38.3, 29.0.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



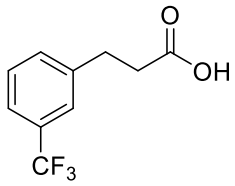
3-(4-chlorophenyl)propanoic acid

Compound 6: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. of Selectfluor and 3.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours. Purified using a gradient of 10 to 100% EtOAc/hexanes followed by a flush of 100% acetone on silica gel; (white solid, 0.076 g, 0.411 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 7.17 – 7.11 (m, 2H), 2.93 (t, J = 7.7 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 178.9, 138.6, 132.3, 129.8, 128.8, 35.5, 30.0.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



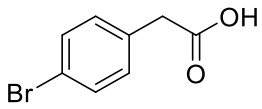
3-(3-(trifluoromethyl)phenyl)propanoic acid

Compound 8: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. of Selectfluor and 4 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 18 hours. Purified using a gradient of 0 to 100% EtOAc/hexanes on silica gel; (light yellow solid, 0.082 g, 0.375 mmol, 75% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 – 7.33 (m, 4H), 3.02 (t, J = 7.7 Hz, 2H), 2.71 (t, J = 7.7 Hz, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 177.7, 141.2, 131.8, 131.2 (q, J = 31 Hz), 129.1, 125.6 (q, J = 275 Hz), 125.36 – 125.10 (m), 123.61 – 123.42 (m), 35.2, 30.4.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



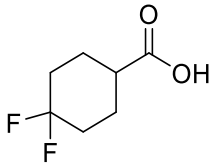
2-(4-bromophenyl)acetic acid

Compound 10: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. of Selectfluor and 4 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 48 hours. Purified using a gradient of 0 to 100% EtOAc/hexanes on silica gel; (white solid, 0.100 g, 0.465 mmol, 93% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.34 (m, 2H), 7.20 – 7.08 (m, 2H), 3.61 (s, 2H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 176.6, 132.2, 131.9, 131.2, 121.6, 40.3.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



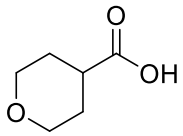
4,4-difluorocyclohexane-1-carboxylic acid

Compound 12: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. of Selectfluor and 4 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 18 hours. Purified using a gradient of 0 to 100% EtOAc/hexanes on silica gel; (white solid, 0.057 g, 0.347 mmol, 69% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (td, J = 8.5, 3.8 Hz, 1H), 2.11 (tdt, J = 12.8, 9.4, 3.6 Hz, 2H), 2.02 (dq, J = 14.1, 4.7 Hz, 2H), 1.96 – 1.72 (m, 4H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 180.8, 122.6 (t, *J* = 241.1 Hz), 40.3, 32.5 (t, *J* = 24.4 Hz), 27.8 – 21.7 (m).

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



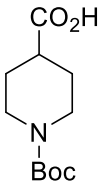
tetrahydro-2*H*-pyran-4-carboxylic acid

Compound 14: Alcohol to Carboxylic Acid: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. Selectfluor and 4 equiv. NaBr in a 1:1 mixture of CH_3CN/H_2O for 21 hours; Purified using a gradient of 0 to 100% EtOAc/hexanes on silica gel; (white solid, 0.040 g, 0.307 mmol, 61% yield). Aldehyde to Carboxylic Acid: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 20 hours.; Deemed pure after work-up and filtering through a plug of cotton; (off-white solid, 0.044 g, 0.338 mmol, 68% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.98 (dt, *J* = 11.7, 3.7 Hz, 2H), 3.45 (td, *J* = 11.4, 2.6 Hz, 2H), 2.57 (tt, *J* = 10.9, 4.2 Hz, 1H), 1.97 – 1.62 (m, 4H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 180.4, 67.0, 39.9, 28.4.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



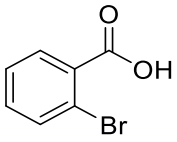
1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid

Compound 16: A. Aldehyde to Carboxylic Acid: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1.0 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 4 hours. Deemed pure after work up and filtering; (white solid, 0.108 g, 0.47 mmol, 94% yield). B. Alcohol to Carboxylic Acid: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. of Selectfluor and 3.5 equiv. of NaBr in a 1:1 mixture of $EtOAc/H_2O$ for 30 hours. Purified using a gradient of 0 to 4% Acetone/DCM on silica gel; (white solid, 0.053 g, 0.23 mmol, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (dt, *J* = 13.7, 4.0 Hz, 2H), 2.85 (ddd, *J* = 13.9, 11.4, 3.0 Hz, 2H), 2.48 (tt, *J* = 11.0, 3.9 Hz, 1H), 1.89 (dt, *J* = 12.8, 3.9 Hz, 2H), 1.63 (dtd, *J* = 13.4, 11.1, 4.2 Hz, 2H), 1.45 (s, 9H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 180.3, 154.9, 79.9, 43.1, 40.9, 28.5, 27.9.

Characterization data matches the literature.[91]



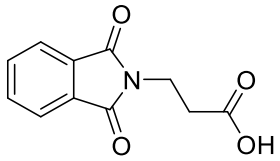
2-bromobenzoic acid

Compound 18: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. of Selectfluor and 4 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 60 hours; Purified using a gradient of 10 to 100% EtOAc/hexanes on silica gel; (white solid, 0.056 g, 0.279 mmol, 56% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.72 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.40 (qt, *J* = 7.3, 4.1 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.2, 135.0, 133.7, 132.6, 130.4, 127.4, 122.7.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



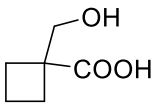
3-(1,3-dioxoisoindolin-2-yl)propanoic acid

Compound 20: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. of Selectfluor and 3.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours.; Purified using a gradient of 0 to 100% EtOAc/hexanes followed by a flush of 100% acetone on silica gel; (white solid, 0.059 g, 0.269 mmol, 54% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (dt, J = 7.7, 3.9 Hz, 2H), 7.71 (dq, J = 8.1, 4.6 Hz, 2H), 3.98 (t, J = 7.4 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H).

^{13}C{^{1}H}using NMR (101 MHz, $CDCl_3$) δ 176.4, 168.1, 134.2, 132.0, 123.5, 33.5, 32.6.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



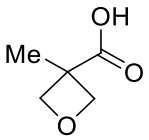
1-(hydroxymethyl)cyclobutane-1-carboxylic acid

Compound 22: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. of Selectfluor and 3.5 equiv. of NaBr in a 1:1 mixture of $EtOAc/H_2O$ for 48 hours. Purified using a gradient of 5 to 60% EtOAc/Hexane on silica gel; (White solid, 0.039 g, 0.3 mmol, 60% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 2H), 2.55 – 2.38 (m, 2H), 2.11 – 1.94 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 181.9, 66.5, 48.0, 26.9, 16.0.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



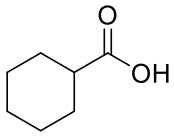
3-methyloxetane-3-carboxylic acid

Compound 24: A. Alcohol to Carboxylic Acid: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. of Selectfluor and 4 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours; deemed pure after workup and filtering through a plug of cotton; (white solid, 0.012 g, 0.103 mmol, 21% yield). B. Aldehyde to Carboxylic Acid: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 3 hours; deemed pure after workup and filtering through a plug of cotton; (white solid, 0.049 g, 0.42 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (d, J = 6.0 Hz, 2H), 4.45 (d, J = 6.1 Hz, 2H), 1.65 (s, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 180.1, 79.4, 44.3, 21.5.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



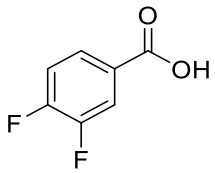
cyclohexanecarboxylic acid

Compound 26: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 20 hours.; Deemed pure after work up and filtering through a plug of cotton; (light yellow semi-solid, 0.065 g, 0.5 mmol, >95% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 11.54 (s, 1H), 2.32 (tt, *J* = 11.2, 3.6 Hz, 1H), 1.92 (dt, *J* = 12.2, 3.7 Hz, 2H), 1.75 (dq, *J* = 12.8, 3.8 Hz, 2H), 1.64 (ddd, *J* = 12.8, 6.0, 3.3 Hz, 1H), 1.45 (qd, *J* = 11.7, 3.4 Hz, 2H), 1.26 (ddtd, *J* = 24.4, 15.0, 11.9, 3.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 183.0, 43.0, 28.8, 25.8, 25.4.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



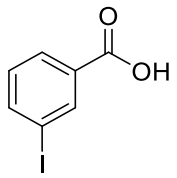
3,4-difluorobenzoic acid

Compound 31: Synthesized using the General Procedure on a 0.5 mmol scale using 2.5 equiv. of Selectfluor and 2.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 17 hours.; Purified using a gradient of 0 to 50% EtOAc/hexanes followed by a flush of 100% acetone on silica gel; (white solid, 0.054 g, 0.342 mmol, 68% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.60 (broad s, 1H), 7.93 (qt, *J* = 6.1, 2.0 Hz, 2H), 7.39 – 7.09 (m, 1H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.5, 154.4 (dd, *J* = 257.6, 12.7 Hz), 150.2 (dd, *J* =262.6, 10.1 Hz), 127.5 (d, *J* = 7.4 Hz), 126.4, 119.7 (d, *J* = 18.9 Hz), 117.7 (d, *J* = 17.9 Hz).

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



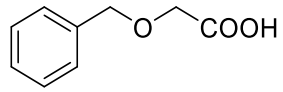
3-iodobenzoic acid

Compound 33: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. of Selectfluor and 3.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours; Purified using 10% EtOAc/hexanes followed by a flush of 100% EtOAc on silica gel; (white solid, 0.060 g, 0.242 mmol, 48% yield).

^{1}H NMR (400 MHz, Acetone-d_6) δ 8.36 (d, J = 1.8 Hz, 1H), 8.11 – 7.94 (m, 2H), 7.34 (t, J = 7.8 Hz, 1H).

^{13}C{^{1}H} NMR (101 MHz, Acetone-d6) δ 166.1, 142.5, 139.1, 133.5, 131.4, 129.7, 94.2.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



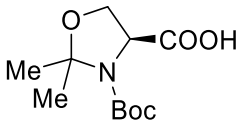
2-(benzyloxy)acetic acid

Compound 35: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1.0 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 5.5 hours. Purified using a gradient of 10 to 60% EtOAc/hexanes on silica gel; (light yellow oil, 0.066 g, 0.396 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 4.66 (s, 2H), 4.16 (s, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.4, 136.7, 128.7, 128.4, 128.3, 73.6, 66.7.

Characterization data matches the literature.[92]



(*S*)-3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidine-4-carboxylic acid

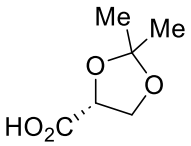
Compound 37: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1.0 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 6.5 hours. Purified using a gradient of 10 to 60% EtOAc/hexanes on silica gel; (light yellow oil, 0.096 g, 0.39 mmol, 78% yield).

Note: Compound exists as a mixture of rotamers, and characterization is provided for this mixture.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (ddd, J = 41.6, 7.0, 2.6 Hz, 1H), 4.29 – 4.01 (m, 2H), 1.64 (d, J = 20.4 Hz, 3H), 1.55 – 1.40 (m, 12H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.0, 175.1, 153.2, 151.3, 95.4, 94.8, 82.0, 80.9, 66.3, 65.7, 59.2, 28.5, 28.4, 26.3, 25.1, 24.9, 24.4.

Characterization data matches the literature.[93]



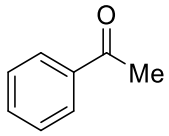
(*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid

Compound 39: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1.0 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 3 hours. Deemed pure after work up and filtering; (white solid, 0.031 g, 0.21 mmol, 42% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (dd, J = 7.5, 4.8 Hz, 1H), 4.30 (dd, J = 8.9, 7.5 Hz, 1H), 4.19 (dd, J = 8.8, 4.8 Hz, 1H), 1.53 (s, 3H), 1.42 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 175.2, 112.0, 73.7, 67.4, 26.1, 25.3.

Characterization data matches the literature.[45]



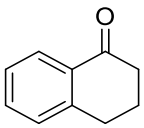
acetophenone

Compound 41: Synthesized using the General Procedure on a 0.5 mmol scale with 1.5 equiv. of Selectfluor and 1.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours; Purified using a gradient of 10 to 20% EtOAc/hexanes on silica gel; (light yellow oil, 0.043 g, 0.358 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.87 (m, 2H), 7.60 – 7.51 (m, 1H), 7.50 – 7.41 (m, 2H), 2.59 (s, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.2, 137.2, 133.1, 128.6, 128.3, 26.6.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



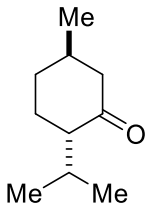
3,4-dihydronaphthalen-1(2*H*)-one

Compound 43: Synthesized using the General Procedure on a 0.5 mmol scale using 1.5 equiv. of Selectfluor and 1.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 20 hours.; Purified using a gradient of 0 to 15% EtOAc/hexanes on silica gel; (light yellow oil, 0.066 g, 0.451 mmol, 90% isolated).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.8, 1.5 Hz, 1H), 7.46 (td, J = 7.5, 1.5 Hz, 1H), 7.34 – 7.20 (m, 2H), 2.96 (t, J = 6.1 Hz, 2H), 2.65 (dd, J = 7.3, 5.8 Hz, 2H), 2.14 (p, J = 6.3 Hz, 2H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.3, 144.5, 133.4, 132.6, 128.8, 127.1, 126.6, 39.1, 29.7, 23.3.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



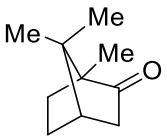
(2*S*,5*R*)-2-isopropyl-5-methylcyclohexan-1-one

Compound 45: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 5 hours; Purified using a gradient of 0 to 20% EtOAc/hexanes on silica gel; (light yellow oil, 0.051 g, 0.331 mmol, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (ddd, *J* = 12.9, 3.9, 2.2 Hz, 1H), 2.13 (ddd, *J* = 13.6, 6.6, 4.9 Hz, 1H), 2.08 – 1.97 (m, 2H), 1.95 (dd, *J* = 12.6, 1.2 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.45 – 1.24 (m, 2H), 0.99 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 212.5, 56.0, 50.9, 35.5, 34.0, 27.9, 26.0, 22.4, 21.3, 18.8.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



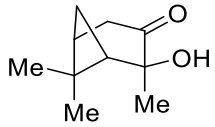
(1*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one

Compound 47: Synthesized using the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 20 hours; Deemed pure after work-up and purification; (light yellow solid, 0.066 g, 0.434 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 – 2.20 (m, 1H), 2.07 (t, *J* = 4.6 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.83 (d, *J* = 18.2 Hz, 1H), 1.67 (td, *J* = 12.1, 3.4 Hz, 1H), 1.46 – 1.26 (m, 2H), 0.94 (s, 3H), 0.89 (s, 3H), 0.82 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 219.8, 57.8, 46.9, 43.4, 43.1, 30.0, 27.1, 19.9, 19.2, 9.3.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



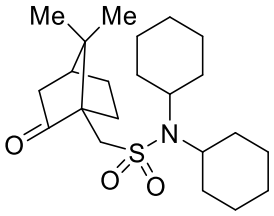
2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one

Compound 49: Synthesized using the General Procedure on a 0.5 mmol scale using 2 equiv. of Selectfluor and 2 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 20 hours; Purified using a gradient of 0 to 30% EtOAc/hexanes on silica gel; (light yellow oil, 0.074 g, 0.44 mmol, 87% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (t, *J* = 2.2 Hz, 2H), 2.43 (dddd, *J* = 12.6, 6.1, 4.6, 1.6 Hz, 1H), 2.36 (broad s, 1H), 2.15 – 2.00 (m, 2H), 1.68 (d, *J* = 10.9 Hz, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 0.88 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 214.2, 77.2, 49.7, 43.0, 39.3, 38.3, 28.5, 27.4, 25.3, 22.9.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



N,*N*-dicyclohexyl-1-((4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonamide

Compound 51: Synthesized using the General Procedure on a 0.5 mmol scale using 3 equiv. of Selectfluor and 3 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 20 hours; Purified using a gradient of 0 to 20% EtOAc/hexanes on silica gel; (white solid, 0.131 g, 0.331 mmol, 66% yield)

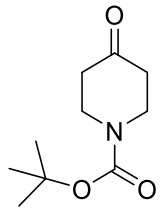
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 – 3.23 (m, 3H), 2.78 (d, *J* = 14.4 Hz, 1H), 2.59 (ddt, *J* = 12.3, 9.9, 4.4 Hz, 1H), 2.36 (ddd, *J* = 18.3, 5.0, 3.2 Hz, 1H), 2.09 – 1.96 (m, 2H), 1.91 (d, *J* = 18.4 Hz, 1H), 1.85 – 1.67

(m, 13H), 1.66 – 1.52 (m, 3H), 1.33 (dddt, J = 26.2, 13.8, 7.3, 2.9 Hz, 4H), 1.19 – 1.03 (m, 5H), 0.88 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 215.8, 59.1, 57.7, 52.3, 47.6, 43.1, 42.7, 33.0, 32.6, 26.9, 26.59, 26.58, 25.4, 25.3, 20.4, 20.0.

IR ν 2928, 1748, 1326, 1143, 981 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ calcd $C_{22}H_{37}NO_3SNa^+$ 418.2392, Found 418.2402 (2.4 ppm error).



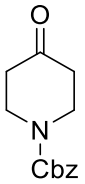
tert-butyl 4-oxopiperidine-1-carboxylate

Compound 53: Synthesized using the General Procedure on a 0.5 mmol scale using 1.5 equiv. of Selectfluor and 1.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours; Purified using a gradient of 0 to 40% EtOAc/hexanes on silica gel; (colorless semi-solid, 0.069 g, 0.346 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (t, J = 6.2 Hz, 4H), 2.42 (t, J = 6.2 Hz, 4H), 1.47 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 207.9, 154.5, 80.5, 43.1, 41.2, 28.4.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



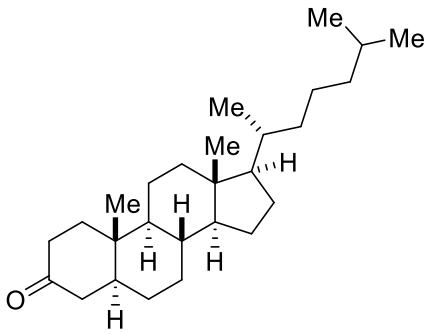
benzyl 4-oxopiperidine-1-carboxylate

Compound 55: Synthesized using the General Procedure on a 0.5 mmol scale using 1.5 equiv. of Selectfluor and 1.5 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours; Purified using a gradient of 10 to 100% EtOAc/hexanes on silica gel; (colorless oil, 0.099 g, 0.424 mmol, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 5H), 5.17 (s, 2H), 3.78 (t, J = 6.3 Hz, 4H), 2.44 (d, J = 8.8 Hz, 4H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 207.2, 155.1, 136.3, 128.6, 128.2, 128.0, 67.6, 43.1, 41.0.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



5-alpha-cholestan-3-one

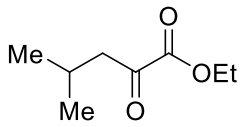
Compound 57: Synthesized with the General Procedure on a 0.5 mmol scale using 1.3 equiv. of Selectfluor and 1 equiv. of NaBr in a 1:1 mixture of $EtOAc/H_2O$ for 18 hours; Purified using a gradient of 0 to 10% EtOAc/hexanes on silica gel; (white solid, 0.181 g, 0.468 mmol, 94% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (td, J = 14.6, 6.6 Hz, 1H), 2.32 – 2.21 (m, 2H), 2.07 (ddd, J = 15.0, 4.0, 2.3 Hz, 1H), 1.99 (ddt, J = 16.5, 10.2, 2.8 Hz, 2H), 1.86 – 1.77 (m, 1H), 1.72 – 1.63 (m, 1H), 1.60 – 1.46

(m, 4H), 1.43 – 1.18 (m, 9H), 1.18 – 0.93 (m, 11H), 0.93 – 0.78 (m, 10H), 0.72 (ddd, J = 12.5, 10.5, 4.1 Hz, 1H), 0.67 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 212.2, 56.41, 56.39, 53.9, 46.8, 44.8, 42.7, 40.0, 39.6, 38.6, 38.3, 36.2, 35.9, 35.7, 35.5, 31.8, 29.1, 28.3, 28.1, 24.3, 23.9, 22.9, 22.6, 21.5, 18.8, 12.1, 11.5.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



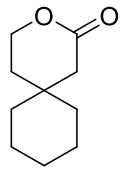
ethyl 4-methyl-2-oxopentanoate

Compound 59: Synthesized using the General Procedure on a 0.5 mmol scale using 4 equiv. of Selectfluor and 4 equiv. of NaBr in a 1:1 mixture of CH_2Cl_2/H_2O for 19 hours; Purified using a gradient of 0 to 30% EtOAc/hexanes on silica gel; (colorless oil, ~58% yield, estimated by ^{1}H NMR integration against an internal standard due to product volatility).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (q, J = 7.2 Hz, 2H), 2.70 (d, J = 6.9 Hz, 2H), 2.18 (dp, J = 13.4, 6.7 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H), 0.95 (d, J = 6.8 Hz, 6H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 194.5, 161.5, 62.4, 47.9, 24.3, 22.5, 14.1.

Characterization data matches the literature.[94]



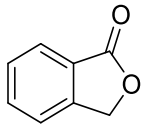
3-oxaspiro[5.5]undecan-2-one

Compound 61: Synthesized using the General Procedure on a 0.44 mmol scale using 3 equiv. of Selectfluor and 3 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 20 hours; Purified using a gradient of 0 to 50% EtOAc/hexanes on silica gel; (colorless oil, 0.067 g, 0.40 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 – 4.23 (m, 2H), 2.36 (s, 2H), 1.80 – 1.67 (m, 2H), 1.57 – 1.30 (m, 10H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.2, 66.0, 42.6, 37.7, 33.7, 32.8, 25.8, 21.7.

Characterization data matches the literature.[95]



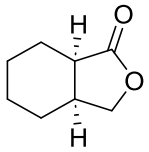
isobenzofuran-1(3*H*)-one

Compound 63: Synthesized using the General Procedure on a 0.5 mmol scale using 3.0 equiv. of Selectfluor and 3.0 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 22 hours. Purified using a gradient of 2 to 10% EtOAc/Hexane on silica gel; (white solid, 0.053 g, 0.395 mmol, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 1H), 7.68 (td, J = 7.5, 1.1 Hz, 1H), 7.59 – 7.44 (m, 2H), 5.32 (s, 2H).

$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 146.6, 134.1, 129.2, 125.88, 125.86, 122.2, 69.8.

Characterization data matches the literature.[96]



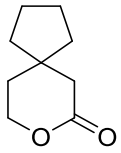
(3a*S*,7a*R*)-hexahydroisobenzofuran-1(3*H*)-one

Compound 65: Synthesized using the General Procedure on a 0.5 mmol scale using 3.5 equiv. of Selectfluor and 3.5 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 40 hours. Purified using a gradient of 5 to 15% EtOAc/Hexane on silica gel; (Colorless oil, 0.055 g, 0.39 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (dd, *J* = 8.8, 5.0 Hz, 1H), 3.95 (dd, *J* = 8.9, 1.5 Hz, 1H), 2.64 (td, *J* = 6.3, 2.8 Hz, 1H), 2.56 – 2.38 (m, 1H), 2.16 – 2.04 (m, 1H), 1.89 – 1.74 (m, 1H), 1.68 – 1.54 (m, 3H), 1.30 – 1.16 (m, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 178.6, 71.9, 39.6, 35.5, 27.3, 23.6, 23.1, 22.6.

Characterization data matches the literature.[97]



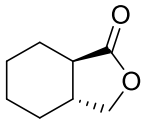
8-oxaspiro[4.5]decan-7-one

Compound 67: Synthesized using the General Procedure on a 0.5 mmol scale using 3.0 equiv. of Selectfluor and 3.0 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 22 hours. Purified using a gradient of 5 to 15% EtOAc/Hexane on silica gel; (Colorless oil, 0.069 g, 0.45 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 – 4.24 (m, 2H), 2.41 (s, 2H), 1.77 (t, *J* = 6.1 Hz, 2H), 1.75 – 1.63 (m, 4H), 1.62 – 1.40 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 67.5, 42.6, 40.9, 38.9, 34.5, 24.0.

Characterization data matches the literature.[95]



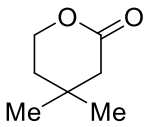
(3a*R*,7a*R*)-hexahydroisobenzofuran-1(3*H*)-one

Compound 69: Synthesized using the General Procedure on a 0.56 mmol scale using 3 equiv. of Selectfluor and 3 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 20 hours; Purified using a gradient of 0 to 50% EtOAc/hexanes on silica gel; (colorless oil, 0.049 g, 0.35 mmol, 62% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (dd, *J* = 8.4, 6.3 Hz, 1H), 3.86 (dd, *J* = 10.8, 8.4 Hz, 1H), 2.17 (dtd, *J* = 9.8, 6.4, 3.9 Hz, 1H), 2.09 – 1.79 (m, 5H), 1.38 – 1.18 (m, 4H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.6, 72.3, 45.3, 43.7, 28.2, 25.5, 24.98, 24.96.

Characterization data matches the literature.[98]



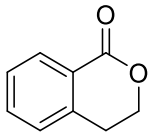
4,4-dimethyltetrahydro-2*H*-pyran-2-one

Compound 71: Synthesized using the General Procedure on a 0.52 mmol scale using 3 equiv. of Selectfluor and 3 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 20 hours; Purified using a gradient of 0 to 50% EtOAc/hexanes on silica gel; (colorless oil, 0.046 g, 0.36 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 – 4.28 (m, 2H), 2.30 (s, 2H), 1.67 (t, *J* = 6.1 Hz, 2H), 1.07 (s, 6H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.6, 66.7, 44.3, 36.0, 29.8, 28.9.

Characterization data matches the literature.[95]



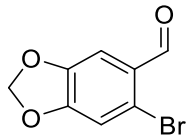
isochroman-1-one

Compound 73: Synthesized using the General Procedure on a 0.5 mmol scale using 3.0 equiv. of Selectfluor and 3.0 equiv. of NaBr in a 1:1 mixture of EtOAc/H_2O for 23 hours. Purified using a gradient of 5 to 15% EtOAc/Hexane on silica gel; (Colorless oil, 0.061 g, 0.41 mmol, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 7.8, 1.4 Hz, 1H), 7.52 (td, J = 7.6, 1.5 Hz, 1H), 7.37 (td, J = 7.6, 1.1 Hz, 1H), 7.27 – 7.23 (m, 1H), 4.54 – 4.49 (m, 2H), 3.05 (t, J = 6.0 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.2, 139.6, 133.7, 130.4, 127.7, 127.3, 125.4, 67.4, 27.9.

Characterization data matches the literature.[99]



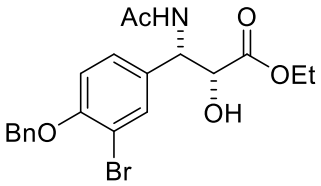
6-bromobenzo[*d*][1,3]dioxole-5-carbaldehyde

Compound 75: Synthesized using the General Procedure on a 0.5 mmol scale using 3 equiv. of Selectfluor and 3 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 19 hours; Purified using a gradient of 10 to 20% EtOAc/hexanes on silica gel; (white solid, 0.065 g, 0.284 mmol, 57% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.36 (s, 1H), 7.06 (s, 1H), 6.08 (s, 2H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 190.5, 153.5, 148.3, 128.2, 121.7, 113.4, 108.3, 102.9.

This compound is commercially available, and our synthetic sample matched in all respects with the authentic one.



ethyl (2*R*,3*S*)-3-acetamido-3-(4-(benzyloxy)-3-bromophenyl)-2-hydroxypropanoate

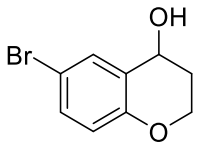
Compound 77: Synthesized using the General Procedure on a 0.47 mmol scale using 1 equiv. of Selectfluor and 1.3 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 7 hours; Purified using a gradient of 0 to 20% EtOAc/hexanes on silica gel; (white solid, 0.200 g, 0.46 mmol, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 2.2 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.42 – 7.35 (m, 2H), 7.35 – 7.30 (m, 1H), 7.29 – 7.25 (m, 1H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.23 (d, *J* = 9.2 Hz, 1H), 5.46 (dd, *J* = 9.3, 2.1 Hz, 1H), 5.15 (s, 2H), 4.44 (d, *J* = 2.0 Hz, 1H), 4.29 (qd, *J* = 7.1, 4.6 Hz, 2H), 2.00 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.8, 169.6, 154.6, 136.4, 133.0, 132.1, 128.7, 128.0, 127.3, 127.0, 113.7, 112.7, 73.1, 70.9, 62.7, 53.6, 23.2, 14.2.

IR ν 3353, 1733, 1651, 1371, 1052, 735 cm^{-1}.

HRMS (ESI) m/z: $[M + Na]^+$ calcd $C_{20}H_{22}BrNO_5Na^+$ 458.0579, found 458.0598 (4.1 ppm error).



6-bromochroman-4-ol

Compound 79: Synthesized using the General Procedure on a 0.50 mmol scale using 1 equiv. of Selectfluor and 1.3 equiv. of NaBr in a 1:1 mixture of CH_3CN/H_2O for 5 hours; Purified using a gradient of 0 to 30% EtOAc/hexanes on silica gel; (white solid, 0.088 g, 0.38 mmol, 77% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.5 Hz, 1H), 7.30 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 4.74 (t, *J* = 4.3 Hz, 1H), 4.26 (dd, *J* = 7.3, 3.7 Hz, 2H), 2.23 (s, 1H), 2.11 (dtd, *J* = 14.3, 7.2, 4.1 Hz, 1H), 2.01 (dq, *J* = 14.2, 4.1 Hz, 1H).

$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 153.7, 132.5, 132.1, 126.2, 118.9, 112.4, 62.9, 62.2, 30.6.

Characterization data matches the literature.[100]

Associated Content

Data Availability Statement: The data underlying this study are available in the published article and its Supporting Information.

Supporting Information: Additional experimental details including structural reasoning, mechanistic data, and NMR Spectra

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