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Copper-Catalyzed Oxidative Acetalization of Boronic Esters: An Umpolung Strategy for Cyclic Acetal Synthesis

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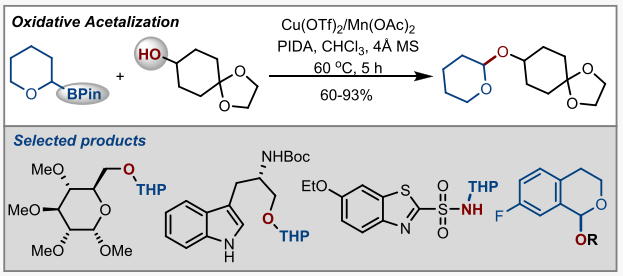
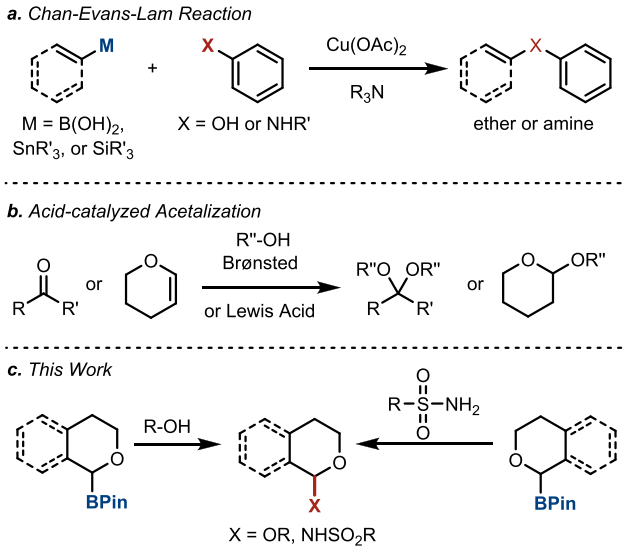
ABSTRACT: A protocol for the acetalization of boronic esters is described. The reaction is catalyzed by copper, and the conditions proved to be mild and were amenable to a variety of functional groups. We expanded the Chan−Lam coupling to include C(sp^3) nucleophiles and converted them into corresponding acetals. This method allows for the orthogonal acetalization of substrates with reactive, acid-sensitive functional groups.



Oxidative carbon−heteroatom bond formation reactions using transition-metal catalysis constitute one of the main methods for the synthesis of ethers, amines, and thioethers.[1−7] A number of copper mediated carbon−oxygen bond forming reactions have significantly progressed past the classical Ullmann ether synthesis.[8−14] The generality of this approach has been demonstrated in complex systems, and most reported examples focus on C(sp^2) nucleophiles. Organometals such as Sn,[8] Bi,[9] and B[10−13] are competent coupling partners with oxygen-based nucleophiles. Chan,[10] Evans,[11] and Lam[12] simultaneously reported the use of stoichiometric copper(II) acetate to cross-couple aryl boronic acids with phenols and aryl amines.[15] Following this discovery, numerous reports detailing the use of phenols,[16−26] carboxylic acids,[27] sulfonamides,[10,27,28] silanols,[29] oximes,[30] and *N*-hydroxyphthalimides[31] in cross-couplings with aryl[19−24,26,31,32] or vinyl[18,25,29] partners appeared. Batey reported aerobic oxidation using O_2 as a method to employ catalytic amounts of copper with trifluoroborate salts to expand the scope of the Chan−Evans−Lam reaction to include aliphatic alcohols.[13] This report of oxidative coupling represents a significant advance; however, it still suffers from long reaction times and included only C(sp^2) boronic acid nucleophiles.

Unlike reactions with aryl boronic acids, there are far fewer examples of oxidative couplings with C(sp^3) nucleophiles. Allylic and benzylic boronic acid derivatives are the sole examples of cross-coupling reactions with phenols[14] or large excess of aliphatic alcohols.[33] Despite these encouraging advances, oxidative reactions forming acetals using boronic ester or relative derivatives have not been reported to the best of our knowledge. Unlike other methods that require Brønsted or Lewis acids to convert the carbonyl group or a vinyl ether into an acetal (Scheme 1), an oxidative process may be prone to orthogonal control for the acetalization process. This proposal was further supported by recent investigations from our group on oxidative glycosylation of anomeric stannanes using iodine(III) reagents[34] where unique reactivity of anomeric nucleophiles was exploited in sequential glycosylations. These stereoconvergent reactions proceed with exclusive anomeric control and involve a transfer of hypervalent iodine

Scheme 1. Selected C−O Bond Forming Reactions



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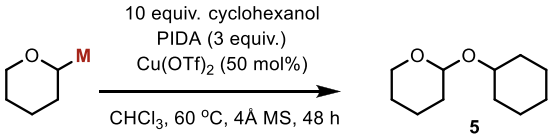
into the anomeric position. Capitalizing on these results, we wondered if α-heteroatom substituted C(sp^3) boronic esters and their derivatives could undergo similar C−O bond-forming processes, provided that a suitable oxidant compatible with alcohol nucleophiles could be identified. Herein, we report oxidative acetalization of α-alkoxy boronic esters catalyzed by copper and manganese salts. This method represents an orthogonal approach to acetal synthesis and has been demonstrated in a range of substrates.

First, we tested which nucleophiles were suitable for the oxidative acetalization using tetrahydropyran derivatives as the model substrates (Scheme 2). We examined reactions using

Scheme 2. Initial Condition Optimizations

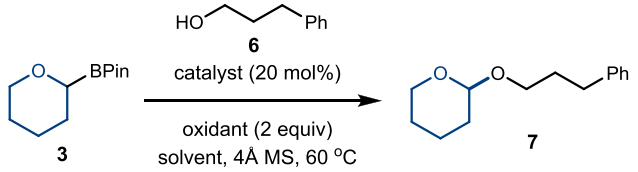


1, M = $SnBu_3$ — **5**, 38%
2, M = $SiMe_2OH$ — **5**, N.D.
3, M = BPin — **5**, 48%
4, M = BF_3K — **5**, 48%

copper(II) salts and iodobenzene diacetate (PIDA) as the oxidant in the presence of excess cyclohexanol as a competent alcohol. We found that α-stannane **1** was a viable substrate for this transformation (38%) whereas silanol **2** was resistant to the general conditions, resulting in the recovery of the substrate. Gratifyingly, boronic ester **3** and trifluoroborate **4** underwent the oxidative reaction in more satisfactory yields (48% for both). Although these modest yields were obtained over a long reaction time (2 days), we remained optimistic for the acetalization of α-alkoxy substrates. Boronic esters proved to be the most suitable nucleophile due to their favorable solubility and increased reactivity relative to the other nucleophiles tested. We were pleasantly surprised that, unlike reactions of anomeric stannanes that in the presence of copper catalyst and PIDA form anomeric esters, boronic esters form exclusively acetals.[34]

Encouraged by the results with boronic esters as our model substrates, we next wanted to develop useful conditions for acetalization in a wide variety of substrates. Initially, boronic ester **3** and 3-phenyl-1-propanol **6** were chosen to optimize the acetalization conditions (Table 1). Early attempts using stoichiometric copper(II) acetate with amine base (entry 1) yielded no detectable amounts of the product. Through additional experimentation, we established that the yield of the acetalization reaction could be increased if superstoichiometric amounts of manganese(III) salts (2 equiv) were added (entry 2). The beneficial effect of Mn(III) additives in copper-catalyzed oxidations is well-established.[35] Based on our prior work,[34] we hypothesized hypervalent iodide oxidants could allow for the use of catalytic amounts of copper and manganese (entry 3); however, the yields suffered. Other Mn(II) and Mn(III) catalysts were tested to increase the yield (entries 4 and 5), and $Mn(OAc)_2$ afforded the desired product **7** in 76% yield (entry 5). Manganese(III) salts can act as single-electron transfer (SET) oxidants that can generate radicals,[36] so we proceeded to test other SET metals even though the electron transfer processes for manganese, cobalt, and iron complexes are known to be ligand-centered.[37] Unfortunately, both iron and cobalt provided diminished yields (entries 6 and 7). With

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant	solvent	time	yield (%)[b]
1	$Cu(OAc)_2$	none	$CHCl_3$	2 d	0[c]
2	$Cu(OTf)_2$/$Mn(OAc)_3$	none	$CHCl_3$	5 h	71[d]
3	$Cu(OTf)_2$/$Mn(OAc)_3$	PIDA	$CHCl_3$	5 h	53
4	$Cu(OTf)_2$/$Mn(acac)_3$	PIDA	$CHCl_3$	5 h	62
5	$Cu(OTf)_2$/$Mn(OAc)_2$	PIDA	$CHCl_3$	5 h	76
6	$Cu(OTf)_2$/$Co(OAc)_2$	PIDA	$CHCl_3$	5 h	73
7	$Cu(OTf)_2$/$Fe(acac)_3$	PIDA	$CHCl_3$	5 h	57
8	$Cu(OTf)_2$/$Mn(OAc)_2$	PIDA	$CHCl_3$	5 h	11
9	$Cu(OTf)_2$/$Mn(OAc)_2$	PhIO	$CHCl_3$	5 h	62
10	$Cu(OTf)_2$/$Mn(OAc)_2$	PhI(OH)OTs	$CHCl_3$	5 h	0
11	$Cu(OTf)_2$/$Mn(OAc)_2$	PIDA	MeCN	5 h	69
12	$Cu(OTf)_2$/$Mn(OAc)_2$	PIDA	dioxane	5 h	58
13	$Cu(OTf)_2$/$Mn(OAc)_2$	PIDA	$CHCl_2$	5 h	75

[a]Reactions were performed using 0.1 mmol of **3**, 0.3 mmol of **6**, 10 mol % of each catalyst, and 1 mL of solvent. [b]Yield was determined by NMR using 1,3,5-trimethoxybenzene as a calibrated internal standard. [c]Reaction was performed using 2 equiv of Et_3N as a base. [d]Reaction was performed with 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and 10 mol % $Cu(OTf)_2$ at 80 °C.

a catalytic system in hand, we attempted to compare various hypervalent iodine oxidants. [Bis(trifluoroacetoxy)iodo]-benzene (PIFA, entry 8) led to a significantly lower yield, likely due to overoxidizing the reaction mixture. Changing the oxidant to iodosobenzene (PhIO) provided a lower yield, possibly due to the poor solubility of the oxidant, and Koser's reagent[38] resulted in undetectable amounts of the acetal product (entries 9 and 10). Solvent screening revealed that acetonitrile and 1,4-dioxane (entries 11 and 12) both furnished the product in acceptable, albeit lower yields. Dichloromethane (entry 13) allowed for indistinguishable product formation; however, due to the temperature of the reaction, chloroform proved to be the solvent of choice.

With a set of general conditions, investigation into the scope of this transformation proceeded (Scheme 3). We established that the general conditions could be applied to acetalization reactions with benzylic alcohols to give products **9a** and **9b** in 81 and 80% yield, respectively. Alcohols bearing aromatic halides were tolerated to give **9b**−**9d** in yields ranging from 80 to 87%. Sterically congested alcohol such as (1*R*,2*S*,5*R*)-(−)-menthol was cleanly acetalized to provide **9e** in 84% yield. Conjugated alkynes endured the oxidative conditions to deliver **9f** in a modest yield of 68%. As a demonstration of the mildness of the oxidative conditions, we were able to convert an acetal derived from cyclohexanone into the corresponding product **9g** in 60% yield without cleavage of the sensitive acetal

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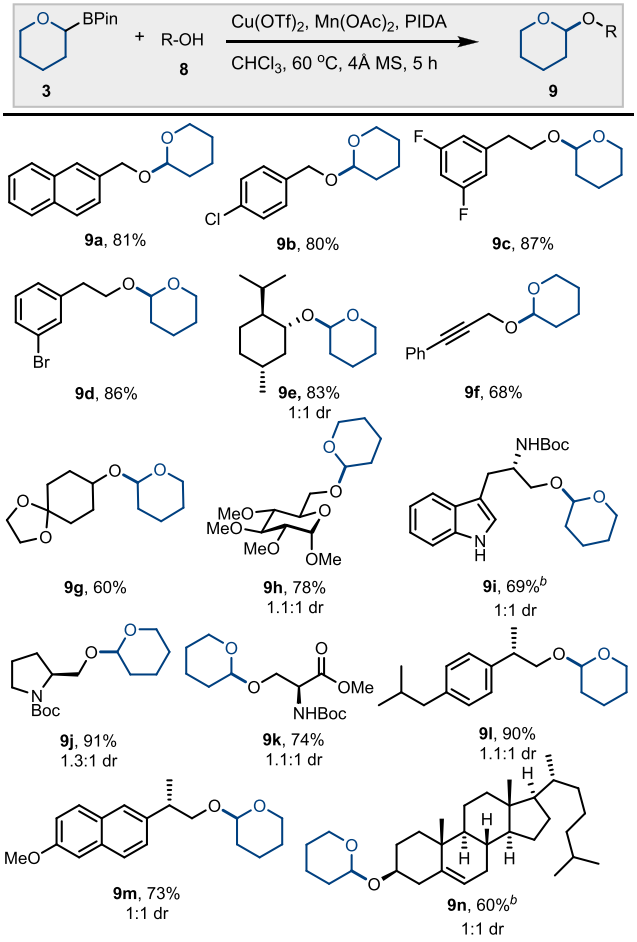
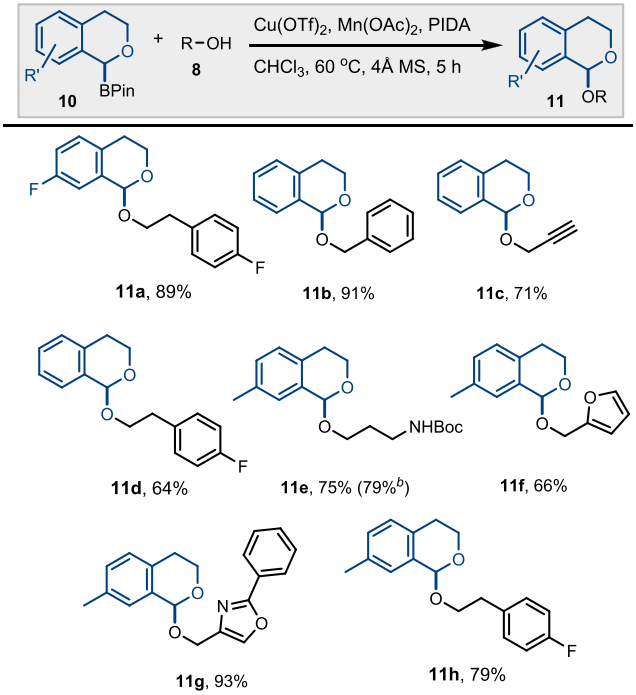
Scheme 3. Scope of Various Alcohols[a]



[a]Reactions were performed using 0.2 mmol of **3**, 0.6 mmol of **8**, $Cu(OTf)_2$ (10 mol %), $Mn(OAc)_2$ (10 mol %), 0.4 mmol of PIDA, and 2 mL of $CHCl_3$. [b]Reaction were performed using 0.2 mmol of **6**, 0.6 mmol of **2a**, 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$, and 10 mol % $Cu(OTf)_2$ in PhMe at 80 °C for 6 h.

Scheme 4. Scope of Various Boron Derivatives[a]



[a]Reaction was performed using 0.2 mmol of **10**, 0.6 mmol of **8**, $Cu(OTf)_2$ (10 mol %), $Mn(OAc)_2$ (10 mol %), 0.4 mmol of PIDA, and 2 mL of $CHCl_3$. [b]Reaction was performed using 1 mmol of **10**.

groups. The acetalization of methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranoside proceeded smoothly to furnish acetalized **9h** with a yield of 78%. Boc-protected amines proceeded to give **9i**, **9j**, and **9k** with no appreciable deprotection of the amine. Alcohol derivatives of therapeutics naproxen and ibuprofen were also effective in delivering the corresponding acetal products (**9l** and **9m**). Remarkably, electron-rich aromatic substrate **9m** was compatible with the hypervalent iodine oxidant, even though overoxidation of the aromatic ring has been shown to occur.[39] Finally, cholesterol was acetalized to give product **9n** in 60% yield. Primary and secondary alcohols were easily protected; however, tertiary alcohol 1-adamantol was unable to yield any product (results not shown).

Having established conditions compatible with a variety of functional groups, we set to expand the scope of α-alkoxy boronic esters (Scheme 4). Isochromans have been shown to produce acetals using DDQ as an oxidant in the presence of alcohol nucleophiles.[40] We found that alkyl and benzyl alcohol nucleophiles were cleanly acetalized to furnish products **11a**, **11b**, **11d**, and **11h**. It is noteworthy that unsubstituted alkynes were unreactive in producing off-target products. Propargyl alcohol produced product **11c** in 71% yield. This example provides evidence for a very fast secondary oxidation given that, if a potential radical is formed, it is quickly oxidized to a carbocation before reacting with a radical acceptor. Boc-protected amino alcohol gave product **11e** in 75% yield. To show the scalability of the conditions, we tested this reaction on a 1 mmol scale to produce **11e** in comparable yields. Aromatic heterocycles gave the acetal product **11f** and **11g** in 66 and 93%, respectively.

To expand the scope of nucleophiles with the α-alkoxy boronic esters, we continued to test biomedically relevant nucleophiles such as sulfonamides, a structural element frequently found in medicinal chemistry.[41,42] Previously, the Chan–Evans–Lam coupling was studied in the context of *N*-arylations[43−45] and resulted in the development of a cationic Cu catalyst operational under ambient conditions.[28] Sulfonamides have been also shown to couple with cyclic ethers and isochroman through C(sp^3)–H functionalization[46,47] or using metal–organic frameworks.[48] These studies demonstrated that hypervalent iodine can oxidize sulfonamides to nitrenes, leading us to replace PIDA with another oxidant.[46] We tested the feasibility of conditions already established in the optimization work (entry 2, Table 1) that could be compatible with sulfonamides. Gratifyingly, benzenesulfonamide gave the amination product **13a** in 75% yield (Scheme 5). Halogenated sulfonamides observed coupling to give **13b** and **13c** in 78 and 76%, respectively. Alkyl sulfonamide gave the corresponding product **13d** in 92% yield. Para-substituted electron-withdrawing groups had minimal effect on yield, as para-trifluoromethylbenzenesulfonamide produced **13e** in 73% yield. In contrast, para-methyl furnished the corresponding amidated product **13f** in a higher yield of 82%, and 3-methoxybenzenesulfonamide gave **13g** in 81%. To further examine the compatibility of the oxidative conditions with diverse sulfonamides, we looked toward commercially available

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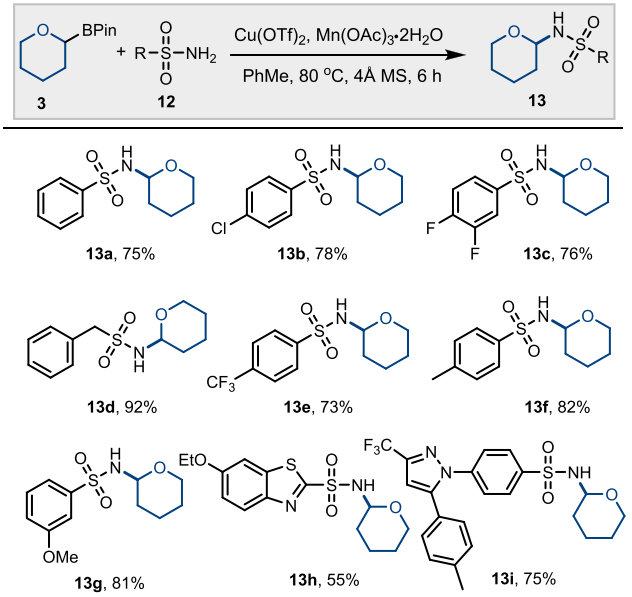
Scheme 5. Scope of Sulfonamide Substrates[a]



[a]Reaction was performed using 0.2 mmol of **3**, 0.6 mmol of **2a**, 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$, and 10 mol % $Cu(OTf)_2$ in PhMe at 80 °C for 6 h.

therapeutics. Ethoxzolamide, a carbonic anhydrase inhibitor for the potential treatment of tuberculosis,[49] yielded **13h** in 55% yield. Celecoxib, a COX-selective nonsteroidal anti-inflammatory drug that relieves pain and swelling used in the treatment of rheumatoid arthritis,[50] proceeded to give **13i** in 76%.

Kinetic isotope effect (KIE) and radical trapping experiments were performed to assess the mechanism of the oxidative coupling (Supporting Information). The KIE observed is consistent with a normal secondary effect which suggests a change in hybridization from sp^3 to sp^2 as the reaction proceeds and is consistent with the formation of oxocarbenium. We posited the initial generation of a radical with manganese(III) from the boronic ester.[51−54] To substantiate our hypothesis, our model substrate **3** was reacted with both TEMPO and 1,1-diphenylethylene. However, there was no formation of any radical adducts, which could indicate the radical is oxidized faster than the formation of an adduct. Following this result, we determined the role of copper and manganese in the reaction. Removing copper from standard conditions gave acetal **7** in just 13% yield, highlighting the importance of copper to rapidly oxidize the radical to an oxocarbenium.[49] Replacing manganese(III) with manganese(II) produced no product, confirming manganese(III) is needed to oxidize boronic esters. Combined, the KIE studies and mechanistic studies are consistent with the generation of oxocarbenium intermediate that undergoes quenching with a competent nucleophile.

In conclusion, we developed a copper-catalyzed oxidative acetalization of α-alkoxy boronic esters with a variety of nucleophiles. The mild chemistry tolerates diverse functional groups, including acid-sensitive protecting groups. KIE and mechanistic testing helped elucidate the potential reaction mechanism. This protocol can allow for orthogonal acetalization or stereospecific coupling of alcohols and C(sp^3) boronic esters.

EXPERIMENTAL SECTION

General Information. All chemicals were purchased as reagent grade and used without further purification unless otherwise noted. Solvents were filtered through a column of activated alumina prior to use. Molecular sieves (4 Å) were purchased from Acros Organic, Inc. Visualizations were performed with UV light and/or Hanessian's stain. Column chromatography was performed on silica gel (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on Bruker/Varian 300/400/500 MHz instruments and are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz), and integration. The residual solvent peaks were used from published literature. IR measurements were performed on Agilent Cary 630 FT/IR instrument, and optical rotations were measured on JASCO P-1030 and are reported as averages of five data points. High-resolution mass spectra (HR-MS) were recorded on a Waters Synapt G2 HDMS q-TOF hybrid mass spectrometer. Nucleophiles **8** and **12** were commercially available with few exceptions. 3-Phenylprop-2-yn-1-ol,[55] Methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranose,[56] (*S*)-2-(4-isobutylphenyl)propan-1-ol,[57] (*S*)-2-(6-methoxynaphthalen-2-yl)-propan-1-ol,[57] 4-methylbenzenesulfonamide,[58] and 4-methoxybenzenesulfonamide[58] were prepared according to previously reported procedures

General Procedure for Oxidative Coupling Reactions Using PIDA. To a solution of α-alkoxy boronic ester (0.200 mmol, 1.0 equiv) and nucleophile (0.600 mmol, 3.0 equiv) in anh. chloroform (0.100 M) were added $CuOTf_2$ (10 mol %), $Mn(OAc)_2$ (10 mol %), and 4 Å molecular sieves. The mixture was allowed to stir for 5 min before (diacetoxyiodo)benzene (0.400 mmol, 2.0 equiv) was added. The reaction mixture was heated in an oil bath (60 °C) for 5 h, cooled to rt, filtered through a pad of silica, and concentrated. The crude material was purified by column chromatography on SiO_2.

*2-(3-Phenylpropoxy)tetrahydro-2H-pyran (**7**).* Colorless oil (33.5 mg, 76%), purified on silica gel (Hexanes:EtOAc, 20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.25 (m, 2H), 7.24−7.14 (m, 3H), 4.59 (dd, *J* = 4.4, 2.7 Hz, 1H), 3.89 (tt, *J* = 8.1, 3.3 Hz, 1H), 3.79 (dt, *J* = 9.7, 6.6 Hz, 1H), 3.51 (dddd, *J* = 11.0, 5.4, 3.8, 1.3 Hz, 1H), 3.42 (dt, *J* = 9.7, 6.5 Hz, 1H), 2.72 (td, *J* = 7.5, 2.8 Hz, 2H), 2.01−1.67 (m, 4H), 1.67−1.47 (m, 4H). Characterization data matched the literature report.[59]

*2-(Naphthalen-2-ylmethoxy)tetrahydro-2H-pyran (**9a**).* Colorless oil (39.0 mg, 81%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3056, 2944, 2869, 1458, 1343, 1205, 1123, 1030, 817, 754 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.77 (m, 4H), 7.57−7.42 (m, 3H), 4.96 (d, *J* = 12.3 Hz, 1H), 4.77 (dd, *J* = 4.0, 3.1 Hz, 1H), 4.69 (d, *J* = 12.3 Hz, 1H). 4.05−3.90 (m, 1H), 3.65−3.51 (m, 1H), 1.98−1.51 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 133.5, 133.1, 128.2, 128.0, 127.8, 126.7, 126.2, 126.1, 125.9, 97.9, 69.1, 62.4, 30.8, 25.7, 19.6; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{16}H_{18}O_2Na$ 265.1204; found 265.1235.

*2-((4-Chlorobenzyl)oxy)tetrahydro-2H-pyran (**9b**).* Colorless oil (36.0 mg, 80%), purified on silica gel (Hexanes:EtOAc, 20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 4H), 4.75 (d, *J* = 12.2 Hz, 1H), 4.69 (dd, *J* = 4.0, 3.0 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 3.94−3.85 (m, 1H), 3.54 (dddd, *J* = 11.2, 5.0, 4.2, 1.8 Hz, 1H), 1.93−1.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.0, 133.4, 129.2, 128.6, 98.0, 68.2, 62.3, 30.7, 25.6, 19.5. Characterization data matched the literature report.[60]

*2-(3,5-Difluorophenethoxy)tetrahydro-2H-pyran (**9c**).* Yellow oil (39.0 mg, 87%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3089, 2944, 1599, 1462, 1119, 1037, 981, 855 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82−6.73 (m, 2H), 6.65 (tt, *J* = 9.1, 2.3 Hz, 1H), 4.58 (dd, *J* = 4.0, 2.8 Hz, 1H), 3.94 (dt, *J* = 9.8, 6.8 Hz, 1H), 3.81−3.66 (m, 1H), 3.60 (dt, *J* = 9.8, 6.7 Hz, 1H), 3.54−3.40 (m, 1H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.92−1.41 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7 (d, *J* = 12.9 Hz), 161.4 (d, *J* = 12.9 Hz), 143.5 (t, *J* = 9.2 Hz), 112.0 (d, *J* = 7.4 Hz), 111.8 (d, *J* = 7.4 Hz), 101.7 (t, *J* = 25.3 Hz), 98.9, 67.5, 62.4, 36.2 (t, *J* = 2.0 Hz), 30.7, 25.6, 19.6; ^{19}F

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NMR (282 MHz, $CDCl_3$) δ −110.92; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{16}F_2O_2Na$ 265.1016; found 265.1021.

*2-(3-Bromophenethoxy)tetrahydro-2H-pyran (**9d**).* Colorless oil (49.0 mg, 86%), purified on silica gel (Hexanes:EtOAc, 20:1): ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.40 (m, 1H), 7.36−7.31 (m, 1H), 7.19−7.11 (m, 2H), 4.58 (dd, J = 4.1, 2.8 Hz, 1H), 3.93 (dt, J = 9.7, 7.0 Hz, 1H), 3.77−3.66 (m, 1H), 3.60 (dt, J = 9.7, 6.9 Hz, 1H), 3.51−3.39 (m, 1H), 2.88 (t, J = 7.0 Hz, 2H), 1.89−1.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 132.3, 130.0, 129.4, 127.8, 122.4, 98.8, 67.9, 62.3, 36.13, 30.8, 25.6, 19.6. Characterization data matched the literature report.[61]

*2-(((1R,2S,5R)-2-iso-Propyl-5-methylcyclohexyl)oxy)tetrahydro-2H-pyran (**9e**).* Colorless oil (40.0 mg, 83%), purified on silica gel (Hexanes:EtOAc, 20:1): ^1H NMR (300 MHz, $CDCl_3$) major diastereomer δ 4.79 (t, J = 3.6 Hz, 1H), 4.03−3.82 (m, 1H), 3.55−3.42 (m, 2H), 2.35 (pd, J = 7.0, 2.6 Hz, 1H), 2.21−2.00 (m, 1H), 1.90−1.46 (m, 8H), 1.44−1.14 (m, 2H), 1.14−0.66 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 101.5, 94.5, 80.1, 74.3, 63.2, 62.6, 49.1, 48.3, 43.7, 40.3, 34.7, 34.6, 32.0, 31.6, 31.5, 31.4, 25.8 (2), 25.7, 25.4, 23.4, 23.2, 22.5, 22.4, 21.4, 21.3, 20.4, 19.9, 16.4, 15.8. Characterization data matched the literature report.[62]

*2-((3-Phenylprop-2-yn-1-yl)oxy)tetrahydro-2H-pyran (**9f**).* Yellow oil (29.0 mg, 68%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3059, 2944, 2854, 1495, 1346, 1123, 1026, 907, 762, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.34−7.27 (m, 3H), 4.95−4.83 (m, 1H), 4.53 (d, J = 15.7 Hz, 1H), 4.46 (d, J = 15.7 Hz, 1H), 3.97−3.82 (m, 1H), 3.67−3.48 (m, 1H), 1.97−1.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.0, 128.5, 128.4, 122.9, 97.0, 85.9, 85.3, 62.2, 54.9, 30.5, 25.5, 19.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{16}O_2Na$ 239.1048; found 239.1065.

*8-((Tetrahydro-2H-pyran-2-yl)oxy)-1,4-dioxaspiro[4.5]decane (**9g**).* Colorless oil (29.0 mg, 60%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 2933, 2873, 1447, 1372, 1104, 1026, 929 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (dd, J = 4.6, 2.8 Hz, 1H), 3.99−3.84 (m, 5H), 3.76 (td, J = 7.2, 3.5 Hz, 1H), 3.53−3.42 (m, 1H), 1.92−1.42 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 108.6, 96.9, 71.7, 64.4 (2), 62.8, 31.8, 31.5, 31.4, 30.3, 28.1, 25.7, 20.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{13}H_{22}O_4Na$ 265.1416; found 265.1413.

*Methyl 2,3,4-Tri-O-methyl-6-O-(tetrahydro-2H-pyran-2-yl)-α-D-glucopyranose (**9h**).* Colorless oil (50.0 mg, 78%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 2936, 2840, 1447, 1164, 1104, 1030, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major diastereomer δ 4.81 (d, J = 3.6 Hz, 1H), 4.64 (ddd, J = 12.7, 4.3, 3.1 Hz, 1H), 4.01−3.81 (m, 2H), 3.67−3.45 (m, 13H), 3.39 (d, J = 0.9 Hz, 3H), 3.25−3.05 (m, 2H), 1.99−1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.5, 98.9, 97.5, 97.4, 83.9, 83.8, 82.0, 79.9, 79.6, 70.2, 70.0, 66.5, 65.9, 62.5, 62.2, 61.0 (2), 60.6, 60.5, 59.1, 55.2, 55.1, 30.7, 30.7, 25.6, 25.5, 19.7, 19.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{28}O_7Na$ 343.1733; found 343.1725.

*(2S)-tert-Butyl 2-(((Tetrahydro-2H-pyran-2-yl)oxy)methyl)-pyrrolidine-1-carboxylate (**9j**).* Colorless oil (59.0 mg, 91%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 2944, 2877, 1696, 1391, 1171, 1037, 873, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major diastereomer 4.81 (d, J = 3.6 Hz, 1H), 4.64 (ddd, J = 12.7, 4.3, 3.1 Hz, 1H), 4.01−3.81 (m, 2H), 3.67−3.45 (m, 13H), 3.39 (d, J = 0.9 Hz, 3H), 3.25−3.05 (m, 2H), 1.99−1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 154.6, 99.5, 99.0, 98.3, 79.3, 68.9, 68.4, 68.0, 67.7, 62.2, 62.0, 56.9, 56.5, 46.6, 30.8 (2), 29.0, 28.7, 28.7, 28.3, 25.6 (2), 23.2, 19.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{27}NO_4Na$ 308.1838; found 308.1848.

*(2R)-Methyl-((tert-butoxycarbonyl)amino)-3-((tetrahydro-2H-pyran-2-yl)oxy)propanoate (**9k**).* White solid (45.0 mg, 74%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3447, 2948, 2877, 1756, 1719, 1506, 1391, 1167, 1041 cm^{-1}; ^1H NMR (300 MHz, Methanol-d_4) major diastereomer δ 4.62 (dd, J = 3.8, 2.8 Hz, 1H), 4.36 (dt, J = 10.1, 4.6 Hz, 1H), 4.02 (dd, J = 10.1, 4.9 Hz, 1H), 3.95−3.76 (m, 2H), 3.75 (s, 3H), 3.64 (dd, J = 10.0, 3.9 Hz, 1H), 3.57−3.45 (m, 1H), 1.90−1.48 (m, 6H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, Methanol-d_4) δ 171.3, 156.5, 99.5, 98.5, 79.4, 67.3, 66.7, 62.2, 61.6, 54.2, 53.8, 51.4, 30.2, 29.9, 27.2, 25.1, 25.0, 19.1, 18.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{25}NNaO_6$ 326.1580; found 326.1567.

*2-((S)-2-(4-iso-Butylphenyl)propoxy)tetrahydro-2H-pyran (**9l**).* Colorless oil (50.0 mg, 90%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3052, 3015, 2955, 2873, 1518, 1469, 1127, 1033, 803 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major diastereomer δ 7.15 (dd, J = 8.1, 2.2 Hz, 2H), 7.10−7.05 (m, 2H), 4.59 (dd, J = 3.7, 2.7 Hz, 1H), 3.88−3.70 (m, 1H), 3.66−3.55 (m, 1H), 3.55−3.34 (m, 2H), 3.01 (h, 1H), 2.44 (d, J = 7.1 Hz, 2H), 1.92−1.38 (m, 7H), 1.33 (d, J = 4.9 Hz, 6H), 0.89 (d, J = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 141.8, 139.7, 139.6, 129.1 (2), 127.2 (2), 98.9, 98.6, 62.1, 62.0, 45.2, 39.8, 39.7, 30.8 (2), 30.4 (2), 25.7 (2), 22.5 (2), 19.6, 19.5, 18.5, 18.4; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{28}O_2Na$ 299.1987; found 299.1978.

*2-((S)-2-(6-Methoxynaphthalen-2-yl)propoxy)tetrahydro-2H-pyran (**9m**).* Colorless oil (44.0 mg, 73%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3059, 2940, 2873, 1611, 1488, 1268, 1127, 1033, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major diastereomer δ 7.72−7.65 (m, 2H), 7.64−7.58 (m, 1H), 7.41−7.34 (m, 1H), 7.16−7.09 (m, 2H), 4.62 (dd, J = 4.0, 2.8 Hz, 1H), 4.02−3.76 (m, 1H), 3.95 (dd, J = 9.6, 6.0 Hz, 1H), 3.91 (s, 3H), 3.71−3.64 (m, 1H), 3.54−3.36 (m, 1H), 3.18 (h, J = 7.0 Hz, 1H), 1.91−1.43 (m, 6H), 1.40 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 139.9 (2), 133.4, 129.2 (2), 126.9 (2), 126.8, 126.7, 125.6 (2), 118.8, 118.7, 105.7, 99.0, 98.7, 62.2, 62.1, 55.4, 40.1, 30.8, 25.7, 25.6, 19.6, 19.5, 18.7, 18.6; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{19}H_{24}O_3Na$ 323.1623; found 323.1621.

*7-Fluoro-1-(4-fluorophenethoxy)isochroman (**11a**).* Pale yellow oil (52.0 mg, 89%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3044, 2936, 2880, 1503, 1223, 1082, 1041, 825 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.16 (m, 2H), 7.13−6.90 (m, 4H), 6.82 (dd, J = 9.0, 2.7 Hz, 1H), 5.47 (s, 1H), 4.18−3.94 (m, 2H), 3.91−3.74 (m, 2H), 3.02−2.83 (m, 3H), 2.58 (ddd, J = 16.4, 3.4, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1 (d, J = 32.3 Hz), 159.9 (d, J = 33.1 Hz), 135.8 (d, J = 6.8 Hz), 134.8 (d, J = 3.3 Hz), 130.5 (d, J = 7.9 Hz), 130.1 (d, J = 7.5 Hz), 129.8 (d, J = 3.0 Hz), 115.6 (d, J = 21.5 Hz), 115.2 (d, J = 21.1 Hz), 114.1 (d, J = 21.7 Hz), 96.6 (d, J = 2.1 Hz), 69.1 (d, J = 1.3 Hz), 58.2, 35.7, 27.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −116.13, −117.10; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{16}F_2O_2Na$ 313.1016; found 313.1028.

*1-(Benzyloxy)isochroman (**11b**).* Pale yellow oil (44.0 mg, 91%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3067, 3033, 2970, 2936, 2880, 1499, 1458, 1026, 1000, 750, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.41−7.27 (m, 3H), 7.26−7.20 (m, 3H), 7.16−7.10 (m, 1H), 5.63 (s, 1H), 4.90 (d, J = 12.0 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.22 (dddd, J = 12.0, 11.2, 3.4, 0.6 Hz, 1H), 3.94 (ddd, J = 11.2, 6.1, 1.6 Hz, 1H), 3.05 (dddd, J = 16.5, 12.1, 6.0, 1.0 Hz, 1H), 2.64 (dddd, J = 16.5, 3.4, 1.6, 0.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 134.3, 134.2, 128.6, 128.3 (2), 127.8, 127.7, 126.4, 95.8, 69.5, 58.1, 28.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{16}O_2Na$ 263.1048; found 263.1062.

*1-(Prop-2-yn-1-yloxy)isochroman (**11c**).* Pale yellow oil (27.0 mg, 71%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3294, 3070, 3033, 2925, 1391, 1097, 1074, 1030, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.20 (m, 3H), 7.17−7.09 (m, 1H), 5.78 (s, 1H), 4.46 (dd, J = 15.8, 2.4 Hz, 1H), 4.37 (dd, J = 15.8, 2.4 Hz, 1H), 4.13 (dddd, J = 12.1, 11.2, 3.3, 0.7 Hz, 1H), 3.93 (ddd, J = 11.2, 6.1, 1.5 Hz, 1H), 3.05 (dddd, J = 16.5, 12.1, 6.0, 1.0 Hz, 1H), 2.64 (dddd, J = 16.5, 3.4, 1.6, 0.7 Hz, 1H), 2.49 (t, J = 2.4 Hz, 1H; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 133.6, 128.5, 128.4, 127.8, 126.5, 95.0, 79.9, 74.6, 58.3, 54.5, 28.1; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{12}O_2Na$ 211.0735; found 211.0726.

*1-(4-Fluorophenethoxy)isochroman (**11d**).* White solid (35.0 mg, 64%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3070, 3033, 2936, 2880, 1514, 1223, 1078, 1033, 829, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−7.21 (m, 4H), 7.19−7.11 (m, 2H), 7.08−6.96 (m, 2H), 5.56 (s, 1H), 4.18−4.02 (m, 2H), 3.96−3.81 (m, 2H), 3.15−2.90 (m, 3H), 2.64 (ddd, J = 16.5, 3.6, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 160.1, 134.9 (d, J = 3.1 Hz), 134.2,

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130.5 (d, J = 7.9 Hz), 128.4 (d, J = 25.2 Hz), 127.6, 126.4, 115.2 (d, J = 21.1 Hz), 97.1, 69.0, 68.9, 58.1, 35.7, 28.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.24; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{17}H_{17}FO_2Na$ 295.1110; found 295.1115.

*tert-Butyl (3-((7-Methylisochroman-1-yl)oxy)propyl)carbamate (**11e**).* Colorless oil (48.0 mg, 75%), purified on silica gel (Hexanes:EtOAc, 4:1): IR (ATR) ν = 3361, 2974, 2933, 2880, 1700, 1510, 1369, 1164, 1048, 1019, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10−6.96 (m, 3H), 5.50 (s, 1H), 4.78 (s, 1H), 4.09 (td, J = 11.5, 3.4 Hz, 1H), 3.99−3.82 (m, 2H), 3.68 (dt, J = 9.9, 6.0 Hz, 1H), 3.28 (ddq, J = 19.2, 12.6, 6.3 Hz, 2H), 2.97 (ddd, J = 17.3, 11.8, 5.9 Hz, 1H), 2.58 (ddd, J = 16.5, 3.4, 1.6 Hz, 1H), 2.32 (s, 3H), 1.85 (p, J = 6.4 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 133.9, 131.1, 129.2, 128.5, 127.9, 97.1, 66.1, 58.3, 38.6, 30.0, 28.6, 28.5, 27.8, 21.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{27}NO_4Na$ 344.1838; found 344.1865.

Procedure for 1 mmol Oxidative Acetalization. 4,4,5,5-Tetramethyl-2-(7-methylisochroman-1-yl)-1,3,2-dioxaborolane (272 mg, 1.00 mmol), 3-(Boc-amino)-1-propanol (525 mg, 3.00 mmol), $Cu(OTf)_2$ (36.1 mg, 0.100 mmol), $Mn(OAc)_2$ (17.3 mg, 0.100 mmol), and 4 Å molecular sieves were added in chloroform (10.00 mL). The mixture was allowed to stir for 5 min before (diacetoxyiodo)benzene (644 mg, 2.00 mmol) was added. The reaction mixture was heated at 60 °C for 5 h, cooled to rt, filtered through a pad of silica, and concentrated. The crude mixture was purified via flash chromatography on SiO_2 (Hexanes:EtOAc, 4:1) to afford **11e** (255 mg, 79%) as a colorless oil.

*1-(Furan-2-ylmethoxy)-7-methylisochroman (**11f**).* Yellow oil (32.0 mg, 66%), purified on silica gel (Hexanes:EtOAc, 20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (dd, J = 1.9, 0.9 Hz, 1H), 7.11−6.93 (m, 3H), 6.49−6.28 (m, 2H), 5.60 (s, 1H), 4.79 (d, J = 12.9 Hz, 1H), 4.72 (d, J = 12.9 Hz, 1H), 4.17 (dddd, J = 12.0, 11.2, 3.4, 0.7 Hz, 1H), 3.93 (ddd, J = 11.2, 6.0, 1.5 Hz, 1H), 3.00 (ddd, J = 17.5, 12.1, 6.0 Hz, 1H), 2.58 (ddd, J = 16.5, 3.5, 1.4 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 143.0, 136.0, 133.7, 131.1, 129.2, 128.4, 128.0, 110.4, 109.7, 95.6, 61.2, 58.3, 27.8, 21.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{16}O_3Na$ 267.0997; found 267.1025.

*4-(((7-Methylisochroman-1-yl)oxy)methyl)-2-phenyloxazole (**11g**).* Colorless oil (60.0 mg, 93%), purified on silica gel (Hexanes:EtOAc, 10:1): IR (ATR) ν = 3134, 3052, 3015, 2925, 2880, 1559, 1488, 1030, 989, 717 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13−7.98 (m, 2H), 7.75−7.67 (m, 1H), 7.49−7.42 (m, 3H), 7.15−6.93 (m, 4H), 5.71 (s, 1H), 4.88 (dd, J = 12.7, 1.0 Hz, 1H), 4.76 (dd, J = 12.7, 1.0 Hz, 1H), 4.20 (dddd, J = 12.0, 11.2, 3.4, 0.6 Hz, 1H), 3.95 (ddd, J = 11.1, 6.0, 1.6 Hz, 1H), 3.01 (ddd, J = 17.5, 12.1, 6.0 Hz, 1H), 2.60 (ddd, J = 16.5, 3.6, 1.5 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 139.5, 136.5, 136.0, 133.7, 131.2, 130.5, 129.3, 128.9, 128.4, 128.2, 127.7, 126.6, 96.4, 61.6, 58.4, 27.8, 21.2; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{20}H_{19}NO_3Na$ 344.1263; found 344.1258.

*1-(4-Fluorophenethoxy)-7-methylisochroman (**11h**).* Pale yellow oil (45.0 mg, 79%), purified on silica gel (Hexanes:EtOAc, 20:1): IR (ATR) ν = 3018, 2925, 2880, 1514, 1223, 1078, 1041, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.20 (m, 2H), 7.09−6.95 (m, 4H), 6.94−6.89 (m, 1H), 5.49 (s, 1H), 4.15−3.96 (m, 2H), 3.93−3.77 (m, 2H), 3.06−2.84 (m, 3H), 2.56 (ddd, J = 16.5, 3.6, 1.7 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 160.1, 136.0, 134.9 (d, J = 3.2 Hz), 133.9, 131.1, 130.5 (d, J = 7.8 Hz), 129.2, 128.2 (d, J = 34.4 Hz), 115.2 (d, J = 21.2 Hz),, 97.2, 69.0 (2), 58.2, 35.7, 27.8, 21.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.29; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{18}H_{19}FO_2Na$ 309.1267; found 309.1291.

General Procedure for Oxidative Coupling Reactions Using $Mn(OAc)_3{\cdot}2H_2O$. To a solution of α-alkoxy boronic ester (1.0 equiv) and nucleophile (3.0 equiv) in anh. toluene (0.100 M) were added $CuOTf_2$ (10 mol %), $Mn(OAc)_3{\cdot}H_2O$ (2.0 equiv), and 4 Å molecular sieves. The reaction mixture was heated in an oil bath (80 °C) for 6 h, cooled to rt, filtered through a pad of silica, and concentrated. The crude material was purified by column chromatography on SiO_2.

*tert-Butyl ((2S)-1-(1H-Indol-3-yl)-3-((tetrahydro-2H-pyran-2-yl)oxy)propan-2-yl)carbamate (**9i**).* Yellow solid (26.0 mg, 69%) was obtained from 0.100 mmol of α-alkoxy boronic ester and purified on silica gel (Hexanes:EtOAc, 50:1): IR (ATR) ν = 3413, 3335, 3011, 2933, 2873, 1693, 1503, 1167, 1033, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) major diastereomer δ 8.14 (s, 1H), 7.70 (t, J = 7.0 Hz, 1H), 7.35 (s, 1H), 7.23−7.07 (m, 2H), 7.03 (t, J = 2.9 Hz, 1H), 5.08 (s, 1H), 4.59 (t, J = 3.5 Hz, 1H), 4.21−3.96 (m, 1H), 3.93−3.78 (m, 1H), 3.71 (td, J = 9.9, 9.5, 4.3 Hz, 1H), 3.56−3.33 (m, 2H), 3.04 (dd, J = 7.7, 3.7 Hz, 2H), 1.94−1.50 (m, 6H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 136.3, 128.1, 122.8, 122.1, 119.5, 119.2, 112.6, 112.4, 111.1, 99.9, 99.0, 79.3, 77.4, 68.5, 68.4, 63.0, 62.2, 51.3, 50.7, 30.9, 30.7, 29.8, 28.6, 27.7, 27.3, 25.6, 25.5, 20.0, 19.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{21}H_{30}N_2O_4Na$ 397.2103; found 397.2130.

*2-(((3S,8S,9S,10R,13R,14S,17R)-10,13-Dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)tetrahydro-2H-pyran (**9n**).* White solid (28.0 mg, 60%), purified on silica gel (Hexanes:EtOAc, 50:1): ^{1}H NMR (300 MHz, $CDCl_3$) major diastereomer δ 5.46−5.23 (m, 1H), 4.71 (dd, J = 4.8, 2.8 Hz, 1H), 4.03−3.77 (m, 1H), 3.68−3.28 (m, 2H), 2.42−2.13 (m, 2H), 2.09−0.75 (m, 44H), 0.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 141.1, 121.7 (2), 97.1, 97.0, 76.2 (2), 63.1, 63.0, 56.9, 56.3, 50.4, 50.3, 42.5, 40.4, 39.9, 39.7, 38.9, 37.6, 37.4, 37.0, 36.9, 36.3, 35.9, 32.1 (2), 31.5, 31.4, 29.9, 28.4, 28.2, 28.1, 25.7, 24.5, 24.0, 23.0, 22.7, 21.2, 20.3, 20.2, 19.5, 18.9, 12.0. Characterization data matched the literature report.[60]

*N-(Tetrahydro-2H-pyran-2-yl)benzenesulfonamide (**13a**).* White solid (36.0 mg, 75%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3279, 3067, 2948, 2858, 1451, 1328, 1171, 1082, 728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99−7.84 (m, 2H), 7.62−7.40 (m, 3H), 5.41 (d, J = 9.5 Hz, 1H), 4.77 (td, J = 9.3, 2.5 Hz, 1H), 3.69 (dtd, J = 11.7, 3.7, 1.6 Hz, 1H), 3.45−3.28 (m, 1H), 1.81 (dddd, J = 11.2, 7.9, 4.3, 1.7 Hz, 2H), 1.68−1.31 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 132.6, 128.9, 127.2, 82.1, 66.3, 31.9, 24.8, 22.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{15}NO_3SNa$ 264.0670; found 264.0703.

*4-Chloro-N-(tetrahydro-2H-pyran-2-yl)benzenesulfonamide (**13b**).* White solid (43.0 mg, 78%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3256, 3071, 2942, 2842, 1455, 1301, 1165, 1079, 728 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92−7.79 (m, 2H), 7.49−7.38 (m, 2H), 5.40 (d, J = 9.5 Hz, 1H), 4.76 (td, J = 9.4, 2.4 Hz, 1H), 3.70 (dtd, J = 11.8, 3.9, 1.6 Hz, 1H), 3.50−3.26 (m, 1H), 1.90−1.76 (m, 2H), 1.65−1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 139.1, 129.1, 128.8, 82.2, 66.4, 31.9, 24.7, 22.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{14}ClNO_3SNa$ 298.0281; found 298.0301.

*3,4-Difluoro-N-(tetrahydro-2H-pyran-2-yl)benzenesulfonamide (**13c**).* Colorless oil (42.0 mg, 76%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3283, 3126, 3063, 2948, 2858, 1514, 1283, 1149, 683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.62 (m, 2H), 7.37−7.18 (m, 1H), 5.38 (d, J = 9.6 Hz, 1H), 4.77 (td, J = 9.5, 2.4 Hz, 1H), 3.83−3.62 (m, 1H), 3.50−3.31 (m, 1H), 1.92−1.78 (m, 2H), 1.70−1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8 (d, J = 12.5 Hz), 151.5, 151.3, 148.3 (d, J = 13.4 Hz), 138.7 (dd, J = 4.8, 4.1 Hz), 124.5, 124.4 (dd, J = 7.4, 4.0 Hz), 118.0, 117.7, 117.4 (dd, J = 20.1, 1.7 Hz), 82.3, 66.5, 31.9, 24.7, 22.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −130.05, −134.34; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{13}F_2NO_3SNa$ 300.0482; found 300.0515.

*1-Phenyl-N-(tetrahydro-2H-pyran-2-yl)methanesulfonamide (**13d**).* Colorless oil (47.0 mg, 92%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3257, 3067, 3037, 2948, 2858, 2363, 1458, 1328, 1082, 1041, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.45 (m, 2H), 7.42−7.34 (m, 3H), 4.92 (d, J = 9.9 Hz, 1H), 4.68 (td, J = 10.0, 2.2 Hz, 1H), 4.41 (d, J = 13.6 Hz, 1H), 4.35 (d, J = 13.6 Hz, 1H), 4.10−3.96 (m, 1H), 3.64−3.49 (m, 1H), 1.95−1.77 (m, 2H), 1.67−1.49 (m, 3H), 1.41−1.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.3, 129.5, 128.8, 128.7, 82.7, 67.2, 61.1, 31.8, 25.0, 23.0; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}NO_3SNa$ 278.0827; found 278.0862.

*N-(Tetrahydro-2H-pyran-2-yl)-4-(trifluoromethyl)-benzenesulfonamide (**13e**).* Colorless oil (45.0 mg, 73%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3283, 3054, 2929,

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2880, 1559, 1454, 1328, 1171, 1067, 1041, 717 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13−7.99 (m, 2H), 7.82−7.66 (m, 2H), 5.41 (d, J = 9.5 Hz, 1H), 4.79 (td, J = 9.5, 2.4 Hz, 1H), 3.69 (dtd, J = 11.7, 3.8, 1.8 Hz, 1H), 3.49−3.27 (m, 1H), 1.95−1.75 (m, 2H), 1.71−1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 134.5, 134.1, 127.8, 126.0 (q, J = 3.8 Hz),125.22, 82.3, 66.6, 31.9, 24.7, 22.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.11; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{14}F_3NO_3SNa$ 332.0544; found 332.0578.

*4-Methyl-N-(tetrahydro-2H-pyran-2-yl)benzenesulfonamide (**13f**).* Colorless oil (21.0 mg, 82%) was obtained from 0.100 mmol of α-alkoxy boronic ester and purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3282, 3054, 2948, 2858, 1415, 1326, 1171, 1072, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00−7.66 (m, 2H), 7.40−7.00 (m, 2H), 5.26 (d, J = 9.6 Hz, 1H), 4.75 (td, J = 9.4, 2.4 Hz, 1H), 3.71 (dtd, J = 11.8, 3.8, 1.7 Hz, 1H), 3.47−3.31 (m, 1H), 2.41 (s, 3H), 1.93−1.74 (m, 2H), 1.70−1.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 138.9, 129.5, 127.3, 82.2, 66.4, 32.0, 24.8, 22.6, 21.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}NO_3SNa$ 278.0827; found 278.0854.

*3-Methoxy-N-(tetrahydro-2H-pyran-2-yl)benzenesulfonamide (**13g**).* Colorless oil (42.0 mg, 81%), purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3275, 3054, 2944, 2854, 1599, 1436, 1320, 1246, 1149, 1037, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (ddd, J = 7.7, 1.7, 1.0 Hz, 1H), 7.45 (dd, J = 2.6, 1.6 Hz, 1H), 7.37 (ddd, J = 8.1, 7.7, 0.4 Hz, 1H), 7.07 (ddd, J = 8.3, 2.6, 1.0 Hz, 1H), 5.31 (d, J = 9.5 Hz, 1H), 4.77 (td, J = 9.3, 2.4 Hz, 1H), 3.84 (s, 3H), 3.73 (dtd, J = 11.7, 3.8, 1.7 Hz, 1H), 3.48−3.33 (m, 1H), 1.82 (dddd, J = 11.1, 7.8, 4.1, 1.6 Hz, 2H), 1.67−1.49 (m, 2H), 1.48−1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 143.0, 129.9, 119.4, 119.3, 111.8, 82.2, 66.4, 55.7, 32.0, 24.8, 22.5; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{12}H_{17}NO_4SNa$ 294.0776; found 294.0775.

*6-Ethoxy-N-(tetrahydro-2H-pyran-2-yl)benzo[d]thiazole-2-sulfonamide (**13h**).* Colorless oil (19.0 mg, 55%) was obtained from 0.100 mmol of α-alkoxy boronic ester and 0.200 mmol of sulfonamide. Purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3275, 3057, 2934, 2852, 1599, 1430, 1242, 1149, 1037, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 9.0 Hz, 1H), 7.33 (d, J = 2.5 Hz, 1H), 7.17 (dd, J = 9.1, 2.5 Hz, 1H), 5.85 (d, J = 9.7 Hz, 1H), 4.86 (td, J = 9.3, 2.6 Hz, 1H), 4.12 (q, J = 7.0 Hz, 2H), 3.72−3.61 (m, 1H), 3.50−3.27 (m, 1H), 1.96−1.75 (m, 2H), 1.65−1.36 (m, 4H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 146.8, 138.6, 126.0, 118.1, 104.2, 82.5, 66.5, 64.4, 31.6, 29.9, 24.6, 22.3, 14.9; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{14}H_{18}N_2O_4S_2Na$ 365.0606; found 365.0641.

*N-(Tetrahydro-2H-pyran-2-yl)-4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (**13i**).* Colorless oil (23.0 mg, 75%) was obtained from 0.066 mmol of α-alkoxy boronic ester and 0.131 mmol of sulfonamide. Purified on silica gel (Hexanes:EtOAc, 3:1): IR (ATR) ν = 3283, 3022, 2929, 2858, 1603, 1477, 1238, 1164, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98−7.84 (m, 2H), 7.50−7.36 (m, 2H), 7.22−7.04 (m, 4H), 6.73 (d, J = 0.6 Hz, 1H), 5.16 (d, J = 9.6 Hz, 1H), 4.75 (td, J = 9.4, 2.5 Hz, 1H), 3.73−3.59 (m, 1H), 3.41−3.18 (m, 1H), 2.37 (s, 3H), 1.90−1.75 (m, 2H), 1.64−1.29 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 143.9, 142.5, 141.4, 139.8, 129.8, 128.9, 128.4, 125.9, 125.3, 106.4, 82.2, 66.5, 32.0, 29.9, 24.8, 22.5, 21.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.43; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{22}H_{22}F_3N_3O_3SNa$ 488.1232; found 488.1263.

*Procedure for Borylation of 3,4-Dihydropyran 4,4,5,5-Tetramethyl-2-(tetrahydro-2H-pyran-2-yl)-1,3,2-dioxaborolane (**3**).* A flame-dried round-bottom flask was charged with 3,4-dihydropyran (1.30 mL, 15.0 mmol, 1.00 equiv), purged 3× with N_2, and dissolved in dry THF (15 mL). The reaction was cooled to −78 °C, and *tert*-butyllithium (8.80 mL, 1.70 M, 15.0 mmol, 1.00 equiv) was added dropwise and stirred for 30 min at 0 °C. Trimethyl borate (1.84 mL, 16.5 mmol, 1.10 equiv) was added; the ice bath was removed, and the reaction mixture was stirred for 1 h at ambient temperature. Pinacol (2.20 g, 18.8 mmol, 1.25 equiv) dissolved in anh. THF (15.0 mL) was added, and the reaction mixture was allowed to stir for another hour. Acetic acid (1.70 mL, 30.0 mmol, 2.00 equiv) was added, and the reaction mixture was stirred for 12 h. The mixture was quenched with H_2O; the aqueous layer was washed twice with EtOAc, and the organic layers were collected, dried with Na_2SO_4, filtered, and concentrated. The crude material was charged with Pd/C (200 mg, 10 w/w%) and backfilled with H_2. To the crude mixture was added a 1:1 EtOAc/MeOH (75.0 mL) solution, and the reaction mixture was allowed to stir for 12 h. After completion, it was filtered through Celite and concentrated. The crude material was purified via flash chromatography on SiO_2 (Hexanes:Et_2O, 10:1) to afford **3** (1.20 g, 38%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.11−3.88 (m, 1H), 3.57−3.08 (m, 2H), 1.91−1.74 (m, 1H), 1.74−1.37 (m, 4H), 1.27 (s, 12H). Characterization data matched the literature report.[63]

General Procedure for Borylation of Isochromans. A flame-dried round-bottom flask was charged with isochroman (1.00 equiv), purged 3× with N_2, and dissolved in dry THF (0.50 M). The reaction was cooled to −78 °C, and TMEDA (1.20 equiv) was added followed by *tert*-butyllithium (1.10 equiv) dropwise and stirred for 30 min at −78 °C. Trimethyl borate (1.20 equiv) was added, and the reaction mixture was stirred for 1 h, warming to ambient temperature. Pinacol (1.20 equiv) dissolved in anh. THF (1.00 M) was added, and the reaction mixture was allowed to stir for another hour. Acetic acid (2.00 equiv) was added, and the reaction stirred for 12 h. The mixture was quenched with H_2O; the aqueous layer was washed twice with EtOAc, and the organic layers were collected, dried with Na_2SO_4, filtered, and concentrated. The crude material was purified via flash chromatography on deactivated SiO_2.

2-(7-Fluoroisochroman-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Pale yellow oil (205.0 mg, 74%), purified on silica gel (Hexanes:EtOAc, 4:1): IR (ATR) ν = 3074, 2981, 2933, 2858, 1734, 1499, 1376, 1275, 1242, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.11−6.97 (m, 2H), 6.81 (tdd, J = 8.5, 2.7, 1.0 Hz, 1H), 4.69 (s, 1H), 4.25 (ddd, J = 11.1, 5.8, 2.4 Hz, 1H), 3.66 (td, J = 11.0, 3.5 Hz, 1H), 3.14−2.94 (m, 1H), 2.60 (dt, J = 16.0, 3.1 Hz, 1H), 1.29 (d, J = 3.9 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 159.5, 137.5, 137.4, 130.6, 130.5, 128.5, 128.4, 112.9, 112.6, 111.4, 111.1, 84.6, 65.9, 28.2, 25.0, 24.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{20}BFO_3Na$ 301.1387; found 301.1390.

2-(Isochroman-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Colorless oil (1.34 g, 74%), purified on silica gel (Hexanes:EtOAc, 4:1): IR (ATR) ν = 3067, 2981, 2923, 1730, 1376, 1343, 1145, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 1H), 7.20−7.04 (m, 3H), 4.75 (t, J = 1.5 Hz, 1H), 4.27 (ddd, J = 11.0, 5.8, 2.4 Hz, 1H), 3.71 (td, J = 11.0, 3.4 Hz, 1H), 3.24−2.97 (m, 1H), 2.73−2.54 (m, 1H), 1.29 (d, J = 4.8 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 133.0, 129.3, 125.9, 125.7, 124.6, 84.4, 65.8, 28.9, 25.0, 24.7; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{15}H_{21}BO_3Na$ 283.1481; found 283.1493.

4,4,5,5-Tetramethyl-2-(7-methylisochroman-1-yl)-1,3,2-dioxaborolane. Colorless oil (1.02 g, 91%), purified on silica gel (Hexanes:EtOAc, 4:1): IR (ATR) ν = 3065, 2981, 2925, 2858, 1730, 1376, 1343, 1145, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 1.8 Hz, 1H), 7.04−6.80 (m, 2H), 4.71 (s, 1H), 4.25 (ddd, J = 11.0, 5.8, 2.3 Hz, 1H), 3.67 (td, J = 11.0, 3.4 Hz, 1H), 3.07 (ddd, J = 16.5, 10.8, 5.9 Hz, 1H), 2.59 (d, J = 16.1 Hz, 1H), 2.29 (s, 3H), 1.30 (d, J = 3.7 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3 (2), 129.8, 129.1, 126.4, 124.9, 84.3, 65.9, 28.4, 25.0, 24.5, 21.3; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{23}BO_3Na$ 297.1638; found 297.1639.

Deuterium Kinetic Isotope Effect. *Synthesis of 4,4,5,5-Tetramethyl-2-(tetrahydro-2D-pyran-2-yl)-1,3,2-dioxaborolane (**14**).* A flame-dried round-bottom flask was charged with 3,4-dihydropyran (1.30 mL, 15.0 mmol, 1.00 equiv), purged 3× with N_2, and dissolved in dry THF (15 mL). The reaction was cooled to −78 °C, and *tert*-butyllithium (8.80 mL, 1.70 M, 15.0 mmol, 1.00 equiv) was added dropwise and stirred for 30 min at 0 °C. Trimethyl borate (1.84 mL, 16.5 mmol, 1.10 equiv) was added; the ice bath was removed, and the reaction mixture was stirred for 1 h at ambient temperature. Pinacol (2.20 g, 18.8 mmol, 1.25 equiv) dissolved in anh. THF (15.0 mL) was added, and the reaction mixture was allowed to stir for another hour. Acetic acid (1.70 mL, 30.0 mmol, 2.00 equiv)

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was added, and the reaction stirred for 12 h. The mixture was quenched with H_2O; the aqueous layer was washed twice with EtOAc, and the organic layers were collected, dried with Na_2SO_4, filtered, and concentrated. A portion (250 mg, 1.19 mmol, 1.00 equiv) of the crude material was charged with Pd/C (25 mg, 10 w/w%) and backfilled with D_2. To the crude mixture was added a 1:1 Acetone-d_6/D_2O (5.00 mL) solution, and the reaction mixture was allowed to stir for 12 h. After completion, it was filtered through Celite and concentrated. The crude material was purified via flash chromatography on SiO_2 (Hexanes:Et_2O, 10:1) to afford **14** (95.0 mg, 38%) as a colorless oil: IR (ATR) ν = 2981, 2923, 1720, 1379, 1343, 1141, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07−3.97 (m, 1H), 3.46−3.35 (m, 1H), 1.90−1.79 (m, 1H), 1.75−1.41 (m, 2H), 1.29 (d, J = 1.4 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.0, 77.4, 69.8, 26.4, 26.3, 24.9 (2); HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{19}D_2BO_3Na$ 237.1607; found 237.1618.

DKIE Experiment. 4,4,5,5-Tetramethyl-2-(tetrahydro-2*H*-pyran-2-yl)-1,3,2-dioxaborolane **3** (14.1 mg, 0.066 mmol), 4,4,5,5-tetramethyl-2-(tetrahydro-2*D*-pyran-2-yl)-1,3,2-dioxaborolane **14** (14.0 mg, 0.066 mmol), 3-phenyl-1-propanol **6** (27.0 mg, 0.198 mmol), $Cu(OTf)_2$ (2.5 mg, 0.007 mmol), $Mn(OAc)_2$ (1.2 mg, 0.007 mmol), and 4 Å molecular sieves were added in chloroform (700 μL). The mixture was allowed to stir for 5 min before (diacetoxyiodo)benzene (42.5 mg, 0.132 mmol) was added. The reaction mixture was heated at 60 °C for 30 min, cooled to rt, filtered through a pad of silica, and concentrated. The KIE value represents the average of four separate runs. Based on the ^1H NMR result a KIE of 1.50 was determined.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c00720.

Detailed experimental procedures and copies of NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Zhu, X.; Chiba, S. Copper-catalyzed oxidative carbon−heteroatom bond formation: a recent update. *Chem. Soc. Rev.* **2016**, *45*, 4504−4523.

(2) Zhang, C.; Tang, C.; Jiao, N. Recent advances in copper-catalyzed dehydrogenative functionalization via a single electron transfer (SET) process. *Chem. Soc. Rev.* **2012**, *41*, 3464−3484.

(3) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234−6458.

(4) Ley, S. V.; Thomas, A. W. Modern Synthetic Methods for Copper-Mediated C(aryl)-O, C(aryl)-N, and C(aryl)-S Bond Formation. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449.

(5) Kunz, K.; Scholz, U.; Ganzer, D. Renaissance of Ullmann and Goldberg Reactions - Progress in Copper Catalyzed C-N-, C-O- and C-S-Coupling. *Synlett* **2003**, *2003*, 2428−2439.

(6) Beletskaya, I. P.; Cheprakov, A. V. Copper in cross-coupling reactions: The post-Ullmann chemistry. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364.

(7) Qiao, J. X.; Lam, P. Y. S. Copper-Promoted Carbon-Heteroatom Bond Cross-Coupling with Boronic Acids and Derivatives. *Synthesis* **2011**, *2011*, 829−856.

(8) Blouin, M.; Frenette, R. A New Method for the Preparation of Aryl Vinyl Ethers. *J. Org. Chem.* **2001**, *66*, 9043−9045.

(9) Finet, J. P. Arylation reactions with organobismuth reagents. *Chem. Rev.* **1989**, *89*, 1487−1501.

(10) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. New N- and O-arylations with phenylboronic acids and cupric acetate. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.

(11) Evans, D. A.; Katz, J. L.; West, T. R. Synthesis of diaryl ethers through the copper-promoted arylation of phenols with arylboronic acids. An expedient synthesis of thyroxine. *Tetrahedron Lett.* **1998**, *39*, 2937−2940.

(12) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. New aryl/heteroaryl C-N bond cross-coupling reactions via arylboronic acid/cupric acetate arylation. *Tetrahedron Lett.* **1998**, *39*, 2941−2944.

(13) Quach, T. D.; Batey, R. A. Copper(II)-Catalyzed Ether Synthesis from Aliphatic Alcohols and Potassium Organotrifluoroborate Salts. *Org. Lett.* **2003**, *5*, 1381−1384.

(14) Sueki, S.; Kuninobu, Y. Copper-Catalyzed N- and O-Alkylation of Amines and Phenols using Alkylborane Reagents. *Org. Lett.* **2013**, *15*, 1544−1547.

(15) Blakemore, D. C.; Doyle, P. M.; Fobian, Y. M. *Synthetic Methods in Drug Discovery*; Royal Society of Chemistry, 2016.

(16) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. Copper-catalyzed general C-N and C-O bond cross-coupling with arylboronic acid. *Tetrahedron Lett.* **2001**, *42*, 3415−3418.

(17) Simon, J.; Salzbrunn, S.; Surya Prakash, G. K.; Petasis, N. A.; Olah, G. A. Regioselective Conversion of Arylboronic Acids to Phenols and Subsequent Coupling to Symmetrical Diaryl Ethers. *J. Org. Chem.* **2001**, *66*, 633−634.

(18) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. Copper-promoted/catalyzed C-N and C-O bond cross-coupling with vinylboronic acid and its utilities. *Tetrahedron Lett.* **2003**, *44*, 4927−4931.

(19) Decicco, C. P.; Song, Y.; Evans, D. A. Intramolecular O-Arylation of Phenols with Phenylboronic Acids: Application to the Synthesis of Macrocyclic Metalloproteinase Inhibitors. *Org. Lett.* **2001**, *3*, 1029−1032.

(20) Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. Total Synthesis of Teicoplanin Aglycon. *J. Am. Chem. Soc.* **2001**, *123*, 12411−12413.

(21) Tzschucke, C. C.; Murphy, J. M.; Hartwig, J. F. Arenes to Anilines and Aryl Ethers by Sequential Iridium-Catalyzed Borylation and Copper-Catalyzed Coupling. *Org. Lett.* **2007**, *9*, 761−764.

(22) Hitotsuyanagi, Y.; Ishikawa, H.; Naito, S.; Takeya, K. Synthesis of l,l-cycloisodityrosines by copper(II) acetate-DMAP-mediated intramolecular O-arylation of phenols with phenylboronic acids. *Tetrahedron Lett.* **2003**, *44*, 5901−5903.

(23) Cherney, R. J.; Duan, J. J. W.; Voss, M. E.; Chen, L.; Wang, L.; Meyer, D. T.; Wasserman, Z. R.; Hardman, K. D.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Mandlekar, S.; Christ, D. D.; Trzaskos, J. M.; Newton, R. C.; Magolda, R. L.; Wexler, R. R.; Decicco, C. P. Design, Synthesis, and Evaluation of Benzothiadiazepine Hydrox-

amates as Selective Tumor Necrosis Factor-α Converting Enzyme Inhibitors. *J. Med. Chem.* **2003**, *46*, 1811−1823.
(24) Deng, H.; Jung, J.-K.; Liu, T.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. Total Synthesis of Anti-HIV Agent Chloropeptin I. *J. Am. Chem. Soc.* **2003**, *125*, 9032−9034.
(25) McKinley, N. F.; O'Shea, D. F. Efficient Synthesis of Aryl Vinyl Ethers Exploiting 2,4,6-Trivinylcyclotriboroxane as a Vinylboronic Acid Equivalent. *J. Org. Chem.* **2004**, *69*, 5087−5092.
(26) Voisin, A. S.; Bouillon, A.; Lancelot, J.-C.; Lesnard, A.; Rault, S. Synthesis of novel halo-oxybispyridines, new building blocks in cholinergic medicinal chemistry. *Tetrahedron* **2006**, *62*, 6000−6005.
(27) Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. $Cu(OTf)_2$-Mediated Chan−Lam Reaction of Carboxylic Acids to Access Phenolic Esters. *J. Org. Chem.* **2010**, *75*, 7472−7474.
(28) Vantourout, J. C.; Li, L.; Bendito-Moll, E.; Chabbra, S.; Arrington, K.; Bode, B. E.; Isidro-Llobet, A.; Kowalski, J. A.; Nilson, M. G.; Wheelhouse, K. M. P.; Woodard, J. L.; Xie, S.; Leitch, D. C.; Watson, A. J. B. Mechanistic Insight Enables Practical, Scalable, Room Temperature Chan−Lam N-Arylation of N-Aryl Sulfonamides. *ACS Catal.* **2018**, *8*, 9560−9566.
(29) Chan, D. G.; Winternheimer, D. J.; Merlic, C. A. Enol Silyl Ethers via Copper(II)-Catalyzed C−O Bond Formation. *Org. Lett.* **2011**, *13*, 2778−2781.
(30) Feng, X.-H.; Zhang, G.-Z.; Chen, C.-Q.; Yang, M.-Y.; Xu, X.-Y.; Huang, G.-S. Copper(II) Acetate−Mediated Cross-Coupling of Phenylboronic Acids with Aryloximes: Synthesis of O-Aryloximes. *Synth. Commun.* **2009**, *39*, 1768−1780.
(31) Petrassi, H. M.; Sharpless, K. B.; Kelly, J. W. The Copper-Mediated Cross-Coupling of Phenylboronic Acids and N-Hydroxyphthalimide at Room Temperature: Synthesis of Aryloxyamines. *Org. Lett.* **2001**, *3*, 139−142.
(32) Wang, Z.; Zhang, J. Synthesis of phenoxyquinolin-4(*1H*)-one through copper(II)-mediated cross-coupling of phenylboronic acid and hydroxyquinolin-4(*1H*)-one. *Tetrahedron Lett.* **2005**, *46*, 4997−4999.
(33) Cazorla, C.; Métay, E.; Lemaire, M. Oxidative nucleophilic substitution: transformation of alkylboronic derivatives. *Tetrahedron* **2011**, *67*, 8615−8621.
(34) Yang, T.; Zhu, F.; Walczak, M. A. Stereoselective oxidative glycosylation of anomeric nucleophiles with alcohols and carboxylic acids. *Nat. Commun.* **2018**, *9*, 3650.
(35) Snider, B. B. Manganese(III)-Based Oxidative Free-Radical Cyclizations. *Chem. Rev.* **1996**, *96*, 339−364.
(36) Demir, A. S.; Reis, Ö.; Emrullahoglu, M. Generation of Aryl Radicals from Arylboronic Acids by Manganese(III) Acetate: Synthesis of Biaryls and Heterobiaryls. *J. Org. Chem.* **2003**, *68*, 578−580.
(37) Richert, S. A.; Tsang, P. K. S.; Sawyer, D. T. Ligand-centered redox processes for manganese, iron and cobalt, MnL_3, FeL_3, and CoL_3, complexes (L = acetylacetonate, 8-quinolinate, picolinate, 2,2′-bipyridyl, 1,10-phenanthroline) and for their tetrakis(2,6-dichlorophenyl)porphinato complexes[M(Por)]. *Inorg. Chem.* **1989**, *28*, 2471−2475.
(38) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. [Hydroxy(organosulfonyloxy)iodo]arenes in Organic Synthesis. *Synlett* **1990**, *1990*, 365−383.
(39) Tamura, Y.; Yakura, T.; Tohma, H.; Ki-kuchi, K.; Kita, Y. Hypervalent Iodine Oxidation of p-Alkoxy- and Related Phenols: A Facile and Efficient Synthesis of p-Quinones. *Synthesis* **1989**, *1989*, 126−127.
(40) Xu, Y.-C.; Lebeau, E.; Gillard, J. W.; Attardo, G. Regio- and stereoselective DDQ-induced oxidative coupling of isochromans and isothiochroman with alcohols. *Tetrahedron Lett.* **1993**, *34*, 3841−3844.
(41) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, *16*, 1200−16.
(42) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451−3479.
(43) Demont, E. H.; Redshaw, S.; Walter, D. S. Hydroxyethylamine compounds having asp2 inhibitory activity for the treatment of Alzheimer's disease. WO2004080376A2, 23 September 2004.
(44) Eickmeier, C.; Fuchs, K.; Peters, S.; Dorner-Ciossek, C.; Handschuh, N. H. S.; Klinder, K.; Kostka, M. Substituted 1,2-ethylendiamines, medicaments comprising said compound; their use and their method of manufacture. WO2006103038A1, 5 October 2006.
(45) Chong, P. Y.; Miller, J. F.; Peat, A. J.; Shotwell, J. B. Benzofuran compounds for the treatment of hepatitis c virus infections. WO2013028371A1, 28 February 2013.
(46) He, L.; Yu, J.; Zhang, J.; Yu, X.-Q. α-Amidation of Cyclic Ethers Catalyzed by Simple Copper Salt and a Mild and Efficient Preparation Method for α,ϖ-Amino Alcohols. *Org. Lett.* **2007**, *9*, 2277−2280.
(47) Muramatsu, W.; Nakano, K. Efficient C(sp^3)−H Bond Functionalization of Isochroman by AZADOL Catalysis. *Org. Lett.* **2015**, *17*, 1549−1552.
(48) Wang, L.; Agnew, D. W.; Yu, X.; Figueroa, J. S.; Cohen, S. M. A Metal−Organic Framework with Exceptional Activity for C−H Bond Amination. *Angew. Chem., Int. Ed.* **2018**, *57*, 511−515.
(49) Johnson, B. K.; Colvin, C. J.; Needle, D. B.; Mba Medie, F.; Champion, P. A. D.; Abramovitch, R. B. The Carbonic Anhydrase Inhibitor Ethoxzolamide Inhibits the *Mycobacterium tuberculosis* PhoPR Regulon and Esx-1 Secretion and Attenuates Virulence. *Antimicrob. Agents Chemother.* **2015**, *59*, 4436−4445.
(50) Clemett, D.; Goa, K. L. Celecoxib: a review of its use in osteoarthritis, rheumatoid arthritis and acute pain. *Drugs* **2000**, *59*, 957−80.
(51) Dickschat, A.; Studer, A. Radical Addition of Arylboronic Acids to Various Olefins under Oxidative Conditions. *Org. Lett.* **2010**, *12*, 3972−3974.
(52) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. Modular Synthesis of Phenanthridine Derivatives by Oxidative Cyclization of 2-Isocyanobiphenyls with Organoboron Reagents. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363−11366.
(53) Moustafa, D.; Sweet, C.; Lim, H.; Calalpa, B.; Kaur, P. Mn/Cu catalyzed addition of arylboronic acid to nitriles: Direct synthesis of arylketones. *Tetrahedron Lett.* **2018**, *59*, 3816−3820.
(54) Heiba, E.-A. I.; Dessau, R. M. Oxidation by metal salts. VII. Syntheses based on the selective oxidation of organic free radicals. *J. Am. Chem. Soc.* **1971**, *93*, 524−527.
(55) Wang, Y. Y.; Du, Z. Y.; Zheng, T. T.; Sun, H. J.; Li, X. Y. Efficient transfer hydrogenation of carbonyl compounds catalyzed by selenophenolato hydrido iron(II) complexes. *Catal. Commun.* **2019**, *124*, 32−35.
(56) Dhar, S.; La Clair, J. J.; León, B.; Hammons, J. C.; Yu, Z.; Kashyap, M. K.; Castro, J. E.; Burkart, M. D. A Carbohydrate-Derived Splice Modulator. *J. Am. Chem. Soc.* **2016**, *138*, 5063−5068.
(57) Widegren, M. B.; Clarke, M. L. Manganese Catalyzed Hydrogenation of Enantiomerically Pure Esters. *Org. Lett.* **2018**, *20*, 2654−2658.
(58) Tota, A.; St. John-Campbell, S.; Briggs, E. L.; Estevez, G. O.; Afonso, M.; Degennaro, L.; Luisi, R.; Bull, J. A. Highly Chemoselective NH- and O-Transfer to Thiols Using Hypervalent Iodine Reagents: Synthesis of Sulfonimidates and Sulfonamides. *Org. Lett.* **2018**, *20*, 2599−2602.
(59) Gurak, J. A.; Engle, K. M. Practical Intermolecular Hydroarylation of Terminal Alkenes via Reductive Heck Coupling. *ACS Catal.* **2018**, *8*, 8987−8992.
(60) Kumar, B.; Aga, M. A.; Mukherjee, D.; Chimni, S. S.; Taneja, S. C. Allyl tetrahydropyranyl ether: a versatile alcohol/thiol protecting reagent. *Tetrahedron Lett.* **2009**, *50*, 6236−6240.
(61) Hohne, A.; Yu, L.; Mu, L.; Reiher, M.; Voigtmann, U.; Klar, U.; Graham, K.; Schubiger, P. A.; Ametamey, S. M. Organofluorosilanes as model compounds for 18F-labeled silicon-based PET tracers and their hydrolytic stability: experimental data and theoretical calcu-

https://dx.doi.org/10.1021/acs.joc.0c00720
J. Org. Chem. 2020, 85, 8230−8239

lations (PET = positron emission tomography). *Chem. - Eur. J.* **2009**, *15*, 3736−43.
(62) Williams, D. B. G.; Simelane, S. B.; Lawton, M.; Kinfe, H. H. Efficient tetrahydropyranyl and tetrahydrofuranyl protection/deprotection of alcohols and phenols with $Al(OTf)_3$ as catalyst. *Tetrahedron* **2010**, *66*, 4573−4576.
(63) Scheuermann, M. L.; Johnson, E. J.; Chirik, P. J. Alkene isomerization-hydroboration promoted by phosphine-ligated cobalt catalysts. *Org. Lett.* **2015**, *17*, 2716−9.

https://dx.doi.org/10.1021/acs.joc.0c00720
J. Org. Chem. 2020, 85, 8230−8239