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Acceleration of Petasis Reactions of Salicylaldehyde Derivatives with Molecular Sieves

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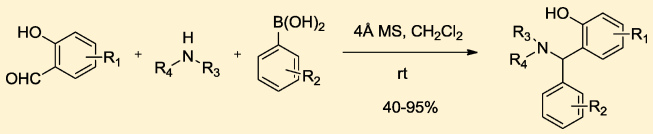
Supporting Information

ABSTRACT: Mild reaction conditions for Petasis reactions of substituted salicylaldehydes with various amines and arylboronic acids in the presence of molecular sieves were developed. Molecular sieves (MS) significantly accelerated the reaction rates and drove the reactions to high conversions. The conditions were applied to the synthesis of the core structure of BIIB042, a γ-secretase modulator, without stereochemical erosion of a stereogenic center in the salicylaldehyde intermediate.



Three-component Petasis reactions of boronic acids, amines, and aldehydes yield several types of important structures and have received significant attention recently, largely due to the efficiency in synthesizing these structures from readily available building blocks.[1,2] Applications of Petasis reactions in the synthesis of highly functionalized natural and unnatural products of importance for medicinal research and Petasis reactions that proceed with high stereoselectivity and minimal protection of functional groups were exemplified recently by Petasis,[3] Wong,[4] and Pyne.[5] Also, a Petasis reaction was successfully used in a concise synthesis of FTY720, a novel S1P1 agonist (Gilenya) recently approved for the treatment of multiple sclerosis.[6]

Besides actual structural effects of the reactants, the aspects of the reaction conditions including solvents,[7] microwave irradiation,[8] temperature, and catalysts[9] can alter performance of a Petasis reaction significantly. Often, specific conditions need to be developed to achieve satisfactory results for a desired set of reactants.[1] The subject of this article is the study of general effects of molecular sieves on Petasis reaction rates and extends of conversions[10,11] and a Petasis reaction developed to synthesize BIIB042, a γ-secretase modulator that was pursued for the treatment of Alzheimer's Disease (Scheme 1).[12]

The Petasis reaction employed to synthesize **2** involved reaction of the slightly electron deficient 4-fluorophenylboronic acid. The reaction was found to be sluggish, and heating was necessary under typical literature conditions.[3] The reaction only proceeded to 70−80% conversion after 2−3 days. The enantiomeric purities (by HPLC) in both recovered starting material **1** and isolated product **2** were significantly lower than that in the starting material **1** when the reaction was carried out at ≥45 °C.[13] Therefore, identification of milder Petasis reaction conditions became an essential goal to preserve the integrity of the stereogenic center and to achieve an acceptable conversion and yield for the reaction.

The first parameter explored was solvents because they can play a critical role in Petasis reactions and sometimes allow the reactions to proceed well at ambient temperature.[3,7,14] For preparation of **2** without racemization, however, in all solvents screened the reaction was slow and stalled at low conversions of **1** at ambient temperature (Table 1).

According to the proposed mechanism,[1] a Petasis reaction occurs via an iminium intermediate, which is generated from dehydration of a hemiaminal formed by reaction of an aldehyde with an amine (see discussion below). We suspected the rate and yield of the Petasis reaction of **1** would increase if formation of the iminium intermediate was enhanced, and removal of H_2O from the reaction system could provide this outcome. The effect of drying agents on the reaction was thus studied, and the results are shown in Table 2. Molecular sieves (MS) and $MgCl_2$ dramatically improved the reaction rate and the extent of reaction conversion at ambient temperature. The conversion of **1** in the presence of MS reached 64% in just 4 h (Table 2) and >98% in 2 days. $MgCl_2$ gave comparable results in the early stages of the reaction; however, the reaction mixture formed a gel and the reaction rate slowed significantly.

To further investigate the effect of the MS, the kinetic profiles of a series of reactions of salicylaldehyde, a model compound for **1**, with 4-fluorophenylboronic acid and piperidine in several solvents were monitored. Figure 1 shows the conversion data obtained with toluene, CH_2Cl_2, THF, and EtOH as the reaction solvents. In the absence of the MS (data in broken lines), the reactions were sluggish and stalled at low conversions, particularly in EtOH and THF. Even with the

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Scheme 1. Proposed Synthesis of BIIB042 Using a Petasis Reaction

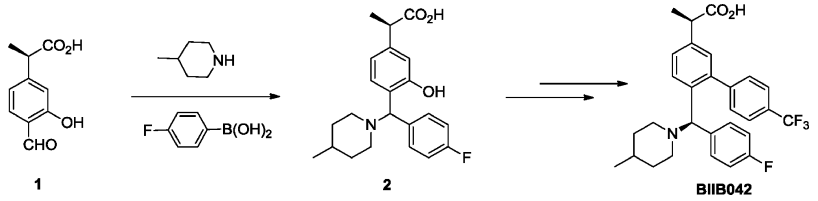
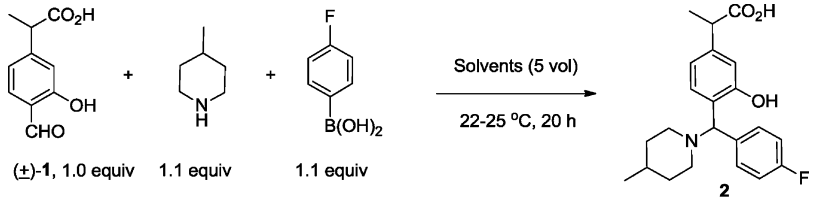


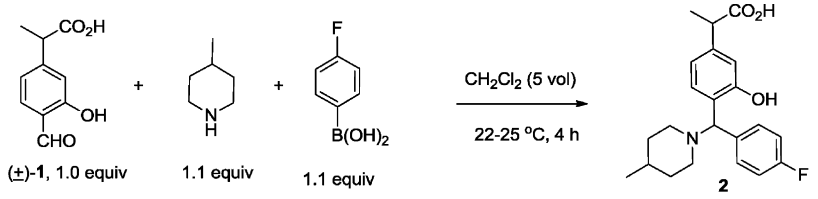
Table 1. Extent of Conversion in Different Solvents at Ambient Temperature



solvents	PhMe	$PhCF_3$	CH_2Cl_2	$(ClCH_2)_2$	dioxane	CH_3CN	THF	EtOH
conv[a] (%)	25	38	43	33	20	16	13	10

[a]Conversion of **1** to **2** determined by LC–MS detection at 214 nm.

Table 2. Effect of Drying Agents on the Reaction Rates



drying agents	none	$MgSO_4$	$MgCl_2$	molecular sieves[a]
conv[b] (%)	28	28	62	64

[a]Aldrich 4 Å, activated, powdered, 2.5 μm molecular sieves were used for the experiments described in this paper. [b]Conversion of **1** to **2** determined by LC–MS detection at 214 nm.

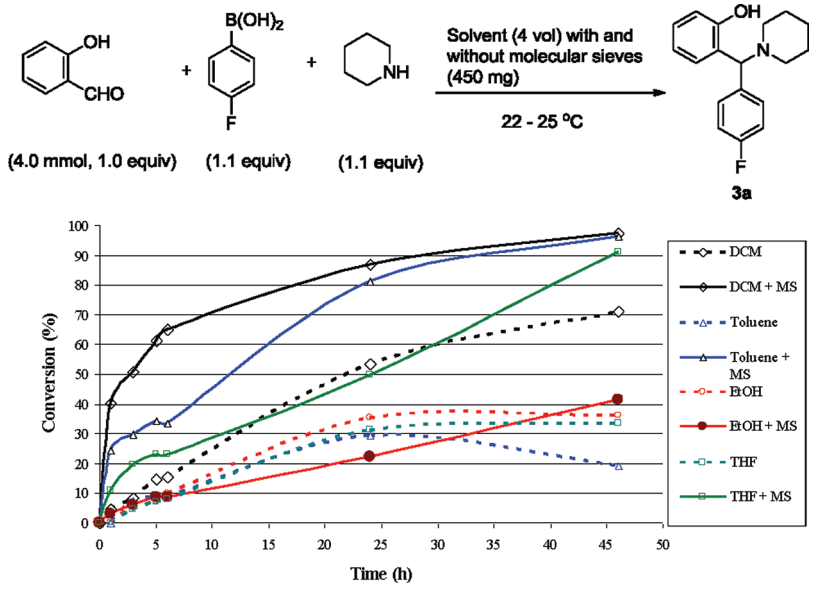


Figure 1. Effect of molecular sieves on Petasis reaction rates and conversions of salicylaldehyde in various solvents.

optimal reaction solvent, CH_2Cl_2, conversion of salicylaldehyde into **3a** reached only ~55 and 80% after 24 and 100 h, respectively. However, when the MS were added, the reaction rates accelerated significantly (data in solid lines). Moreover, addition of the MS essentially drove reactions in CH_2Cl_2 (46 h), toluene (46 h), and THF (72 h) to completion. The effect of the MS to the reaction in EtOH did not follow this trend. Initially the reaction rate was similar to the reaction without the

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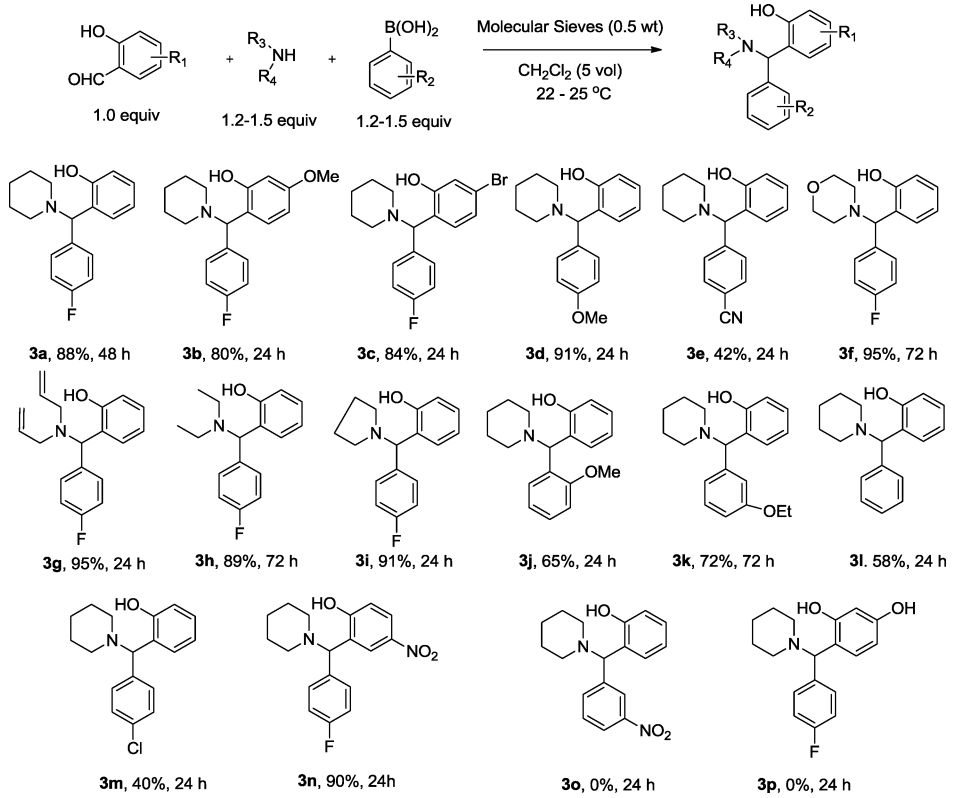
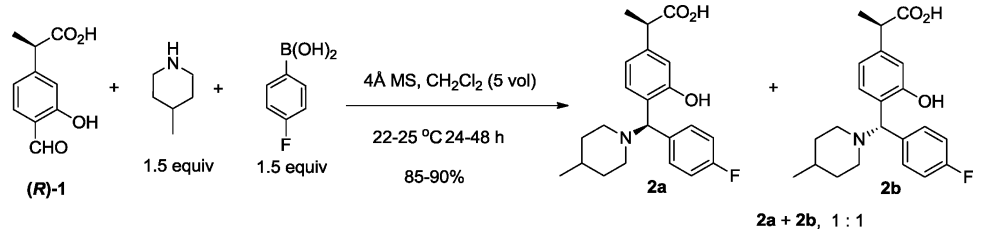
Table 3. Petasis Reactions of Salicylaldehyde Derivatives with Arylboronic Acids and Secondary Amines in the Presence of Molecular Sieves[a]



[a]All yields are isolated yields, and typical purity of the isolated products was >97% by HPLC (area %).

Scheme 2. Synthesis of the Core Structure 2 of BIIB042 via Petasis Reaction



MS. However, the extent of conversion eventually surpassed the conversion reached by the reaction without MS.[15]

Having shown that addition of the MS was beneficial, effects of reaction concentrations and reagent stoichiometries of piperidine and 4-fluorophenylboronic acid were then studied in reactions with salicylaldehyde to prepare **3a**. Higher reaction rates at higher concentrations were observed.[16] For studies on the scope of the reactions discussed below, the reaction concentrations (typically 5 vol relative to salicylaldehyde derivatives) chosen were based on handling convenience. Also, the reaction rates slowed near reaction completion. An excess of the amines and arylbronic acids were used to limit the reaction times to 24 h. These conditions were then applied to a variety of reactants to determine the scope of the reactions under these mild conditions (Table 3). Typically, 1.2−1.5 equiv of the amines and boronic acids were used; reactions were worked up after 24 h, and the products were isolated. In some instances, on the basis of HPLC analysis, the reaction times were extended to 72 h to achieve higher conversions. In general, however, the conditions were not optimized for each individual reaction. Structures and yields of the isolated products are shown in Table 3.

As the data in Table 3 showed, these mild reaction conditions have broad substrate generality.[17] Most reactions using secondary amines gave products in high yields. Regarding the use of arylboronic acids, only the extremely electron deficient 3-nitrophenylboronic acids failed to participate in the reaction to form product **3o**. This result is consistent with the few literature examples using highly electron-deficient boronic acids and is likely because these groups do not migrate well from boron to the iminium carbon (see Scheme 3).[18] 3-Nitrophenylboronic acid was reported to participate in a Petasis reaction under harsher solvent-free conditions, i.e., by microwave irradiation at 120 °C.[8] The less electron-deficient 4-cyanophenylboronic acid and 4-chlorophenylboronic acid successfully reacted to produce the desired products **3e** and **3m**. For salicylaldehyde derivatives, observations similar to those reported in the literature, substituents on salicylaldehyde were generally well tolerated, except for an additional hydroxyl group, which inhibited the formation of product **3p**.[19]

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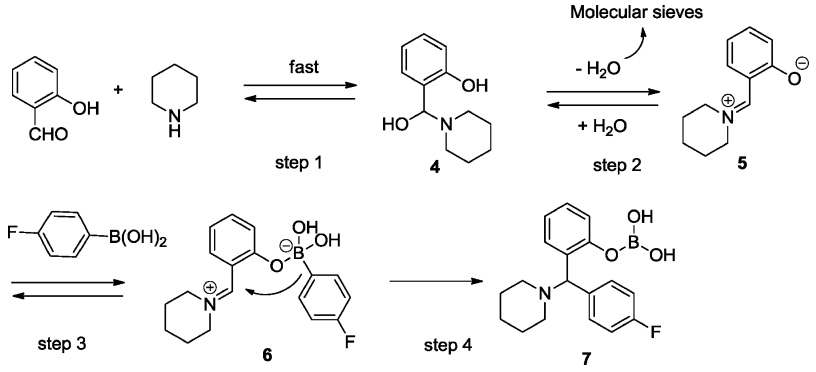
Scheme 3. Possible Mechanism for the Molecular Sieves Effect



The reactions produced few impurities. Product purifications were accomplished by sequential washing of the reaction mixtures with a slight excess of aqueous HCl and NaOH to remove remaining amines and boronic acids, respectively, followed by washing with brine, drying, and concentration. Purities of the compounds obtained were typically >97% on the basis of HPLC (area %) analysis and acquired NMR spectra.

Finally, these new mild conditions were applied to the synthesis of **2**. In the presence of the MS, a ~97% conversion of **1** at ambient temperature was observed within 48 h (Scheme 2), and the reaction was very clean. With simple aqueous acid and base washings to remove excess of the starting amine and arylboronic acid, **2** was obtained in 85−90% yield as a 1:1 mixture of diastereomers (**2a** and **2b**) and ~99% purity (HPLC area %). It is important to note that when enantioenriched (*R*)-**1** (~80% ee) was used, product **2** was obtained as a 1:1 diastereomeric mixture with each diastereomer having the same enantiomeric purity as **1** at the α-methyl stereogenic center. Intermediate **2** was then converted into BIIB042 by a Suzuki coupling reaction of the triflate intermediate[20] following an established methodology in our laboratory that preserved the integrity of the α-methyl stereogenic center.[12]

The generally accepted mechanism for the Petasis reaction is outlined in Scheme 3.[1] All steps from hemiaminal (**4**) formation through the iminium borate ester (**6**) are reversible, followed by the irreversible and likely rate-limiting aryl migration (step 4). The accelerating effect of MS on the reaction may occur in step 2 of the proposed mechanism (Scheme 3).[1] By removing water from the reaction matrix, added MS should drive the equilibrium from hemiaminal **4** to iminium **5**. Shift of the equilibrium should increase the concentration of **5** and accelerate the overall reaction rate. Furthermore, removal of water from the reaction matrix should reduce the chance for hydrolysis of **6** before the desired rearrangement to **7**. Observations of a similar effect on the reaction rate by drying agent $MgCl_2$ and inhibition of the reaction by H_2O support this explanation.[21]

Additional characterization data from in situ ATR-FTIR spectroscopy monitoring of the reaction supported the role of MS in the reaction mechanism described in Scheme 3. A ReactIR probe was placed into the reaction vessel, and monitoring was started when CH_2Cl_2 was added to the reaction vessel, continued, and extended as salicylaldehyde, piperidine, molecular sieves, and 4-fluorophenylboronic acid were added, respectively. The reaction of salicylaldehyde and piperidine occurred quickly to produce an intermediate, likely hemiaminal **4**, which persisted in solution in the absence of MS. Upon addition of the MS, the concentration of this intermediate rapidly diminished, and formation of a new species (presumably iminium **5**) was observed. Observation of an infrared absorption band at 1650 cm^{-1} for C═N bond (characteristic C═N stretch of iminium ions is 1640−1700 cm^{-1})[22] using the iC IR software for data interpretation supported formation of **5**.

After addition of 4-fluorophenylboronic acid, the IR data showed disappearance of intermediate **5** and formation of a new intermediate (**6**, probably) at a low concentration and a product (**7**). The intermediate reached maximum concentration 5 h after addition of the boronic acid and also displayed an infrared absorption band at 1650 cm^{-1} corresponding to a C═N bond, which is present in an intermediate like **6**. The low concentration of **6** may indicate it exists mostly not as an iminium ion but as a species more stable, for example, a hemiaminal, which might be formed by reversible migration of OH^- from the B atom to the iminium ion C atom. Formation of the presumed terminal compound **7** continued for 22 h after addition of the boronic acid.

In summary, 4 Å activated MS significantly improved the reaction rates and the degrees of conversions of Petasis reactions of salicylaldehyde derivatives at ambient temperature. Use of the MS allowed the reactions to be carried out under mild conditions, which eliminated side reactions and permitted facile isolation and purification of products by simple aqueous workup.

■ EXPERIMENTAL SECTION

General Procedures. All reagents and solvents were purchased from commercial sources and used as received. Both racemic and enantio-enriched 2-(4-formyl-3-hydroxyphenyl)propanoic acid were purchased from Adesis and used as received. Molecular sieves (4 Å, activated, 2.5 μm, powdered) were purchased from Aldrich and used as received. NMR spectra were recorded for ^{1}H NMR at 400 MHz, for ^{13}C NMR at 100 MHz, and for HSQC at 500 MHz (128 MHz for C), and data were processed using ACDLABSv12 software. Chemical shifts are expressed as δ (ppm) values using TMS or the residual signals of the solvents as the internal standard. HPLC data were collected with UV detection at 235 nm or as specified using Sunfire column (C18, 3.6 μm, 150 × 4.6 mm) and mobile phase A (water with 0.1% TFA) and B (acetonitrile with 0.1% TFA) with a linear gradient from 30 to 70% B in 15 min and a flow rate of 1 mL per minute. Chiral HPLC data were collected with UV detection at 285 nm using Diacel Chiralpak AD-H column (5 μm, 25 cm × 4.6 mm) and mobile phase *n*-hexane/isopropanol/ethanol/trifluoroacetic acid/triethylamine (250:50:5:0.5:0.25, v/v/v/v/v), with a flow rate of 0.3 mL per minute. Real-time and postprocessing reaction IR data analysis was done using the software iC IR 4.1 and ConcIRT.

Representative Procedure for Data Presented in Figure 1. To a 10 mL vial were added 2-hydroxybenzaldehyde (0.5 g, 4.0

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mmol), 4-fluorophenylboronic acid (0.618 g, 4.4 mmol, 1.1 equiv), molecular sieves (Aldrich, 4 Å, activated, powdered, 2.5 μm, 0.45 g), CH_2Cl_2 (2.0 mL), and piperidine (0.45 mL, 4.6 mmol, 1.15 equiv). The mixture was stirred at 22−25 °C, and reaction conversions (based on area percent) were determined by HPLC analysis at the indicated times.

Representative Procedure for the Petasis Reactions in the Presence of Molecular Sieves: Preparation of 2-((4-Fluorophenyl)(piperidin-1-yl)methyl)-4-nitrophenol (3n). To a magnetically stirred mixture of 2-hydroxy-5-nitrobenzaldehyde (200.0 mg, 1.20 mmol), 4-fluorophenylboronic acid (200.9 mg, 1.43 mmol, 1.2 equiv), molecular sieves (160 mg), and CH_2Cl_2 (2 mL) was added piperidine (177 μL, 1.80 mmol, 1.5 equiv). The mixture was stirred at 22 °C for 24 h and filtered through a Celite bed. The filter cake was washed with EtOAc (3 × 5 mL). The combined filtrates were washed with 0.15 N HCl (5 mL, 1.5 equiv of the excess piperidine), 0.1 N NaOH (3 mL, 1.5 equiv of the excess 4-fluorophenylboronic acid), and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated on a rotary evaporator. The residue was dried under high vacuum at 22 °C overnight to give **3n** as yellow oil, which slowly turned into solid (0.36 g, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.2 (br, 1H), 7.96 (dd, J = 2.76, 9.04 Hz, 1H), 7.74 (d, J = 2.51 Hz, 1H), 7.26 (br, s, 2H), 6.97 (dd, J_{H-H} = 8.66 Hz, J_{H-F} = 8.66 Hz, 2H), 6.81 (d, J = 9.04 Hz, 1H), 4.55 (s, 1H), 2.00−2.97 (br, 4H), 1.40−1.80 (br, m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 162.7 (d, J = 247 Hz), 139.9, 133.0 (d, J = 4 Hz), 130.6, 125.5, 125.1 (2C), 117.5, 116.1 (d, J = 19 Hz), 74.8, 52.0 (br, w), 25.8, 23.7; HRMS calcd for $C_{18}H_{20}FN_2O_3$ $(M + H^+)$ 331.14580, found 331.14534.

Signals for hydrogens on the piperidine ring of compounds **3a**, **3b**, **3c**, **3d**, **3e**, **3j**, **3k**, **3m**, and **3n** in the ^{1}H NMR spectra obtained in $CDCl_3$ are very broad, and the integrations show less than the required number of hydrogens. However, the spectra of **3a**, **3b**, **3c**, **3j**, and **3n** acquired in DMSO-d_6 are normal (the NMR experiments in DMSO-d_6 were not repeated for **3d**, **3e**, **3k**, and **3m**). The broadening of the signals in $CDCl_3$ is probably due to restricted rotation of the piperidine ring,[23] likely because of intramolecular H-bonding between the N in the piperidine ring and the OH group on the phenyl group. In DMSO, the H-bonding is disrupted and the rotation is less restricted. Therefore, the NMR spectra are normal. For the same reason, the signals of $\underline{C}H_2$−N in ^{13}C NMR ($CDCl_3$) spectra of **3a**, **3b**, **3c**, **3d**, **3e**, **3j**, **3k**, **3m**, and **3n** appear at ∼δ 52 ppm as weak and broad peaks but normal (∼δ 52 ppm) in the spectra acquired in DMSO-d_6. Assignment of the $\underline{C}H_2$−N signal was confirmed by HSQC (DMSO-d_6) experiments on **2j** and **2n**. The NMR data discussed here indicate DMSO is a more appropriate solvent for ^{1}H and ^{13}C NMR spectra of these compounds. ^{1}H and ^{13}C NMR spectra of **3a**, **3b**, **3c**, **3j**, and **3n** acquired in both solvents are provided in the Supporting Information to demonstrate this point.

2-((4-Fluorophenyl)(piperidin-1-yl)methyl)phenol (3a). Reaction of 2-hydroxybenzaldehyde (1.0 g, 8.0 mmol), 4-fluorophenylboronic acid (1.36 g, 9.6 mmol, 1.2 equiv), molecular sieves (330 mg), and piperidine (0.96 mL, 9.6 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL), 22 °C for 48 h gave product **3a** (2.0 g, 88%), purity ∼100% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.44 (br, 1 H), 7.36 (br, 2 H), 7.03−7.14 (m, 1 H), 6.98 (dd, J_{H-F} = 8 Hz, J_{H-H} = 8 Hz, 2 H), 6.84 (m, 2 H), 6.69 (dt, J = 1.3, 7.4 Hz, 1 H), 4.45 (s, 1 H), 2.16−2.51 (br, 4 H), 1.57−1.69 (m, 4 H), 1.40−1.53 (br, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J = 245 Hz), 156.9, 135.4 (d, J = 3 Hz), 130.4, 129.1, 128.5, 125.4, 119.1, 117.0, 115.6 (d, J = 22 Hz), 75.7, 52.5 (br, w), 26.1, 24.1; ESI-HRMS calcd for $C_{18}H_{21}FNO$ $(M + H)^+$ 286.16072, found 286.16021.

2-((4-Fluorophenyl)(piperidin-1-yl)methyl)-4-methoxyphenol (3b). Reaction of 2-hydroxy-4-methoxybenzaldehyde (100 mg, 0.66 mmol), 4-fluorophenylboronic acid (101 mg, 0.72 mmol, 1.1 equiv), molecular sieves (54 mg), and piperidine (71 μL, 0.72 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL), 22 °C for 24 h gave product **3b** (165 mg, 80%), purity ∼97% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.34 (br, 1H), 7.24 (br, s, 2H), 6.89 (dd, J_{H-H} = 8.66 Hz, J_{H-F} = 8.66 Hz, 2H), 6.63 (d, J = 8.53 Hz, 1H), 6.34 (d, J = 2.76 Hz, 1H), 6.17 (dd, J = 2.51, 8.28 Hz, 1H), 4.36 (s, 1H), 3.64 (s, 3H), 1.99−2.77 (br, 4H), 1.43−1.72 (br, m, 4H), 1.19−1.42 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 245 Hz), 160.1, 158.3, 135.4 (d, J = 3 Hz), 130.4, 129.7, 117.7, 115.5 (d, J = 21 Hz), 105.3, 102.2, 74.9, 55.1, 52.3 (br, w), 26.1, 24.1; ESI-HRMS calcd for $C_{19}H_{23}FNO_2$ $(M + H)^+$ 316.17128, found 316.17078.

4-Bromo-2-((4-fluorophenyl)(piperidin-1-yl)methyl)phenol (3c). Reaction of 2-hydroxy-4-bromobenzaldehyde (100 mg, 0.50 mmol), 4-fluorophenylboronic acid (76 mg, 0.55 mmol, 1.1 equiv), molecular sieves (41 mg), and piperidine (54 μL, 0.55 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL), 22 °C for 24 h gave product **3c** (152 mg, 84%), purity ∼100% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.79 (br, 1H), 7.24 (br, s., 2H), 6.83−6.98 (m, 3H), 6.73 (dd, J = 1.88, 8.16 Hz, 1H), 6.61 (d, J = 8.28 Hz, 1H), 4.37 (s, 1H), 1.23 (br, 4H), 1.47−1.70 (m, 4H), 1.38 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 246 Hz), 158.3, 134.5 (d, J = 3 Hz), 130.4, 130.3, 124.4, 122.1, 121.8, 120.2, 115.7 (d, J = 21 Hz), 75.1, 52.3 (br, w), 26.0, 24.0; ESI-HRMS calcd for $C_{18}H_{20}BrFNO$ $(M + H)^+$ 364.07123, found 364.07090.

2-((4-Methoxyphenyl)(piperidin-1-yl)methyl)phenol (3d). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-methoxyphenylboronic acid (292 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and piperidine (0.24 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3d** (435 mg, 91%), purity ∼98% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.64 (br, 1H), 7.23−7.44 (m, 2H), 7.05−7.18 (m, 1H), 6.80−6.96 (m, 4H), 6.73−6.74 (m, 1H), 4.48 (s, 1H), 3.79 (s, 3H), 2.43 (br, 4H), 1.56−1.89 (m, 4H), 1.47 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.2, 131.4, 130.1, 129.2, 128.2, 125.8, 119.0, 116.8, 114.0, 75.6, 55.2, 52.4 (br, w), 26.1, 24.2; ESI-HRMS calcd for $C_{19}H_{23}NO_2$ $(M + H)^+$ 298.18070, found 298.18019.

4-((2-Hydroxyphenyl)(piperidin-1-yl)methyl)benzonitrile (3e). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-cyanophenylboronic acid (283 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and piperidine (0.24 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3e** (195 mg, 42%), purity ∼90% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (br, 1H), 7.41−7.53 (m, 4H), 6.99−7.09 (m, 1H), 6.74−6.83 (m, 2H), 6.63 (dt, J = 0.88, 7.47 Hz, 1H), 4.38 (s, 1H), 2.09−2.83 (br, m, 4H), 1.49−1.74 (m, 4H), 1.42 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 145.4, 132.6, 129.2, 128.9, 124.5, 119.5, 118.6, 117.3, 111.7, 76.3, 52.9 (br, w), 26.0, 24.0; ESI-HRMS calcd for $C_{19}H_{20}N_2O$ $(M + H)^+$ 298.18070, found 293.16486.

2-((4-Fluorophenyl)(morpholino)methyl)phenol (3f). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-fluorophenylboronic acid (269 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and morpholine (0.21 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 72 h gave product **3f** (436 mg, 95%), purity ∼100% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (br. s., 1H), 7.33−7.53 (m, 2H), 7.11−7.19 (m, 1H), 7.01 (dd, J_{H-H} = 8.66 Hz, J_{H-F} = 8.66 Hz, 2H), 6.91−6.96 (m, 1H), 6.89 (d, J = 8.03 Hz, 1H), 6.72−6.78 (m, 1H), 4.41 (s, 1H), 3.57−3.93 (m, 4H), 2.61 (br, 2H), 2.27−2.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J = 245 Hz), 156.0, 135.2 (d, J = 3 Hz), 130.2 (d, J = 7 Hz), 129.3, 128.9, 124.7, 119.7, 117.2, 115.8 (d, J = 21 Hz), 76.0, 66.9, 52.2; ESI-HRMS calcd for $C_{17}H_{18}FNO_2$ $(M + H)^+$ 288.13998, found 288.13947.

2-((Diallylamino)(4-fluorophenyl)methyl)phenol (3g). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-fluorophenylboronic acid (269 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and *N*-2-propenyl-2-propen-1-amine (0.30 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3g** (455 mg, 95%), purity ∼97% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.02 (br. s., 1H), 7.43 (dd, J_{H-F} = 5.52, J_{H-H} = 8.28 Hz, 2H), 7.12−7.21 (m, 1H), 7.07 (dd, J_{H-H} = 8.66 Hz, J_{H-F} = 8.66 Hz, 2H), 6.88−6.94 (m, 1H), 6.83 (d, J = 7.28 Hz, 1H), 6.68−6.76 (m, 1H), 5.92 (tdd, J = 6.78, 10.23, 16.88 Hz, 2H), 5.27 (d, J = 10.29 Hz, 2H), 5.17 (d, J = 17.07 Hz, 2H), 5.07 (s, 1H), 3.40 (dd, J = 5.77, 14.05 Hz, 2H), 3.06 (dd, J = 7.53, 14.05 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J = 246 Hz), 157.4, 133.5 (d, J = 3 Hz), 133.3, 131.1 (d, J = 8 Hz), 129.2, 128.8, 124.8, 119.7, 119.2, 117.0, 115.6 (d, J = 21 Hz), 69.2,

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52.3; ESI-HRMS calcd for $C_{19}H_{20}FNO$ $(M + H)^+$ 298.16072, found 298.16020.

2-((Diethylamino)(4-fluorophenyl)methyl)phenol (3h). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-fluorophenylboronic acid (269 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and *N*-ethylethanamine (0.25 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 72 h gave product **3h** (389 mg, 89%), purity ~98% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (br, 1H), 7.37−7.52 (m, 2H), 7.13 (t, J = 7.40 Hz, 1H), 7.03 (dd, J_{H-H} = 8.66 Hz, J_{H-F} = 8.66 Hz, 2H), 6.79−6.92 (m, 2H), 6.64−6.75 (m, 1H), 4.91 (s, 1H), 2.77 (qd, J = 7.06, 13.71 Hz, 2H), 2.59 (qd, J = 6.91, 13.65 Hz, 2H), 1.09 (t, J = 7.03 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J = 246 Hz), 157.4, 134.9 (d, J = 3 Hz), 130.6 (d, J = 7 Hz), 128.9, 128.5, 125.6, 119.0, 117.0, 115.5 (d, J = 22 Hz), 70.3, 42.8, 11.0; ESI-HRMS calcd for $C_{17}H_{20}FNO$ $(M + H)^+$ 274.16072, found 274.16022.

2-((4-Fluorophenyl)(pyrrolidin-1-yl)methyl)phenol (3i). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-fluorophenylboronic acid (269 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and pyrrolidine (0.20 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3i** (397 mg, 91%), purity ~100% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.16 (br, 1H), 7.46 (dd, J_{H-F} = 5.40, J_{H-H} = 8.41 Hz, 2H), 7.08−7.17 (m, 1H), 6.93−7.01 (m, 3H), 6.88 (d, J = 8.28 Hz, 1H), 6.73 (t, J = 7.40 Hz, 1H), 4.39 (s, 1H), 2.65 (br, 2H), 2.49 (br, m, 2H), 1.68−1.99 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 245 Hz), 156.5, 138.1 (d, J = 3 Hz), 129.4 (d, J = 8 Hz), 128.5, 128.2, 126.5, 119.3, 117.0, 115.5 (d, J = 22 Hz), 74.9, 53.2, 23.5; ESI-HRMS calcd for $C_{17}H_{18}FNO$ $(M + H)^+$ 272.14507, found 272.14454.

2-((2-Methoxyphenyl)(piperidin-1-yl)methyl)phenol (3j). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 2-methoxyphenylboronic acid (292 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and piperidine (0.24 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3j** (310 mg, 65%), purity ~100% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (br, 1H), 7.47 (d, J = 7.03 Hz, 1H), 7.20−7.29 (m, 1H), 7.07−7.18 (m, 1H), 6.81−7.00 (m, 4H), 6.70 (t, J = 7.28 Hz, 1H), 5.36 (br, s, 1H), 3.89 (s, 3H), 2.49 (br, 4H), 1.55−1.80 (br, m, 4H), 1.48 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 157.1, 129.7, 129.1, 128.6, 128.1, 127.3, 125.9, 120.9, 118.8, 116.7, 110.8, 65.4, 55.5, 51.5 (br, w), 26.2, 24.2; ESI-HRMS calcd for $C_{19}H_{23}NO_2$ $(M + H)^+$ 298.18070, found 298.18023.

2-((3-Ethoxyphenyl)(piperidin-1-yl)methyl)phenol (3k). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 3-ethoxyphenylboronic acid (532 mg, 3.2 mmol, 2.0 equiv), molecular sieves (160 mg), and piperidine (0.24 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 72 h gave product **3k** (362 mg, 72%), purity ~100% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (br, s, 1H), 7.18−7.26 (m, 1H), 7.08−7.15 (m, 1H), 6.99 (br, s, 2H), 6.91 (d, J = 7.03 Hz, 1H), 6.86 (d, J = 8.03 Hz, 1H), 6.80 (dd, J = 1.88, 8.16 Hz, 1H), 6.70 (t, J = 7.40 Hz, 1H), 4.43 (s, 1H), 4.01 (q, J = 6.94 Hz, 2H), 2.44 (br, 4H), 1.57−1.79 (m, 4H), 1.48 (br, s, 2H), 1.41 (t, J = 7.03 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.1, 141.1, 129.6, 129.2, 128.3, 125.5, 119.0, 116.8, 113.5, 76.5, 63.3, 52.6 (br, w), 26.1, 24.2, 14.8; ESI-HRMS calcd for $C_{20}H_{25}NO_2$ $(M + H)^+$ 312.19635, found 312.19585.

2-(Phenyl(piperidin-1-yl)methyl)phenol (3l). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), phenylboronic acid (235 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and piperidine (0.24 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3l** (250 mg, 58%), purity ~99% (by HPLC): ^{1}H and ^{13}C NMR data match those reported for this compound.[8]

2-((4-Chlorophenyl)(piperidin-1-yl)methyl)phenol (3m). Reaction of 2-hydroxybenzaldehyde (200 mg, 1.6 mmol), 4-chlorophenylboronic acid (301 mg, 1.9 mmol, 1.2 equiv), molecular sieves (160 mg), and piperidine (0.24 mL, 2.4 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL), 22 °C for 24 h gave product **3m** (193 mg, 40%), purity ~96% (by HPLC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.21 (br, 1H), 7.21−7.32 (m, 2H), 7.11−7.19 (m, 2H), 6.96−7.06 (m, 1H), 6.70−6.82 (m, 2H), 6.59 (dt, J = 0.88, 7.47 Hz, 1H), 4.34 (s, 1H), 2.28 (br, 4H), 1.44−1.71 (m, 4H), 1.36 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 138.1, 133.7, 130.1, 129.1, 128.9, 128.6, 125.2, 119.2, 117.1, 75.8, 52.5 (br, w), 26.1, 24.1; ESI-HRMS calcd for $C_{18}H_{20}ClNO$ $(M + H)^+$ 302.13117, found 302.13070.

Procedure for in Situ ReactIR Spectroscopy Monitoring. To a 100 mL EasyMax glass reactor equipped with mechanical stirring, temperature probe, and ReactIR probe was added CH_2Cl_2 (10 mL), and the IR spectroscopy monitoring was started. The reaction temperature was maintained at 22 °C through the reaction. To the mixture was added salicylaldehyde (1.0 mL, 9.4 mmol), followed by addition of piperidine (1.0 mL, 1.1 equiv). The reaction was allowed to continue for ~2 h, and molecular sieves (1.0 g) were added. After about 1 h, 4-fluorophenylboronic acid (1.45 g, 1.1 equiv) was added to the reaction mixture, and the reaction was continued for ~24 h. Reference IR spectra of salicylaldehyde, 4-fluorophenylboronic acid, and piperidine in CH_2Cl_2 at roughly the same concentrations as in the reaction were taken separately.

2-(4-((4-Fluorophenyl)(4-methylpiperidin-1-yl)methyl)-3-hydroxyphenyl)propanoic acid (2) Disodium Salt. To a mixture of 2-(4-formyl-3-hydroxyphenyl) propanoic acid (388 mg, 2.0 mmol, purity ~95%, 9:1(*R*:*S*) enantiomer ratio), 4-fluorophenylboronic acid (420 mg, 3.0 mmol, 1.5 equiv), and molecular sieves (194 mg) in CH_2Cl_2 (2 mL) was added 4-methyl-piperidine (355 μL, 3.0 mmol, 1.5 equiv). The mixture was stirred at ~22 °C for 44 h (>99% conversion by LC−MS, detection 214 nm). The reaction mixture was diluted with isopropyl acetate and filtered through Celite to remove the molecular sieves. The filtrate was washed with H_2O, dried, and concentrated. The residue was dissolved in isopropyl acetate, and the solution was extracted with aq NaOH (2 N, excess). To the aqueous layer was added NaCl, and the mixture was extracted with isopropyl acetate (2 × 5 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give a white solid (0.70 g, 84%). This material was >98% pure by HPLC and used for the following triflation and Suzuki coupling reactions without further purification. Diastereomer ratio of the isomers [(*R*,*R*) + (*R*,*S*)] to [(*S*,*R*) + (*S*,*S*)] was 9:1, determined by chiral HPLC. Spectral data: ^{1}H NMR (DMSO-d_6) δ 11.15 (br, 1H), 7.37−7.46 (m, 2 H), 7.03−7.15 (dd, J_{H-F} = 8.0 Hz, J_{H-H} = 8.0 Hz, 2 H), 6.92 (d, J = 7.97 Hz, 1 H), 6.77 (dd, J = 4.33, 1.76 Hz, 1 H), 6.57−6.64 (m, 1 H), 4.58−4.59 (2 peaks, 1 H), 3.16 (q, J = 7.13 Hz, 1 H), 2.94 (d, J = 8.0 Hz, 1 H), 2.63 (d, J = 10.85 Hz, 1 H), 1.81−1.92 (m, 2 H), 1.53−1.64 (m, 2 H), 1.35 (br, 1 H), 1.10−1.22 (m, 5 H), 0.88 (d, J = 6.53 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.6, 161.3 (d, J = 241 Hz), 155.1 (2 peaks, 1C), 145.0, 138.2 (d, J = 4 Hz), 129.7 (d, J = 8 Hz, 2C), 127.1, 123.8, 118.3, 115.1, 115.0 (d, J = 20 Hz, 2C), 70.2 (2 peaks, 1C), 51.9, 50.9, 48.2, 33.9 (2C), 30.2, 21.5, 19.8 (2 peaks, 1C); ESI-HRMS calcd for $C_{22}H_{27}FNO_3$ $(M + H)^+$ 372.19706, found 372.19695.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H/^{13}C NMR spectra of the new compounds, HSQC spectra and ^{1}H/^{13}C NMR assignment of **3j**, **3n**, and **2**, HPLC and chiral HPLC chromatograms for compound **2**, and in situ ReactIR Data. This material is available free of charge via the Internet at http://pubs.acs.org.

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