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Lewis Acid Catalyzed Addition of Benzophenone Imine to Epoxides Enables the Selective Synthesis and Derivatization of Primary 1,2-Amino Alcohols

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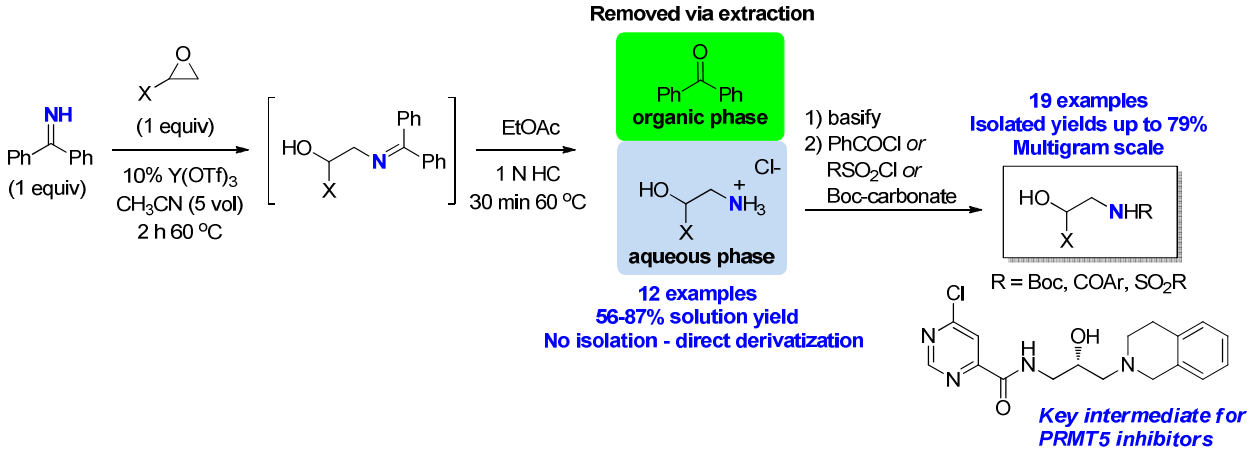


ABSTRACT. Benzophenone imine was found to be an effective ammonia surrogate to selectively prepare primary 1,2-amino alcohols from epoxides, including enantiopure epichlorohydrin, in the presence of catalytic $Y(OTf)_3$. High-throughput screening of 48 Lewis acids quickly identified $Y(OTf)_3$ as an effective mediator of the addition reaction under mild conditions. Following acidic hydrolysis, the primary amino alcohol salt is revealed and partitions into the aqueous solution, while the benzophenone byproduct is easily removed by simple extraction with ethyl acetate. These ammonium salts can be directly Boc-protected or further derivatized without isolation to form benzamides and sulfonamides under Schotten-Baumann type conditions in up to 79% isolated yield over three steps. This methodology has been used to prepare key intermediates for the synthesis of PRMT5 inhibitors with high enantiopurity, as well as numerous other amide and sulfonamide derivatives.

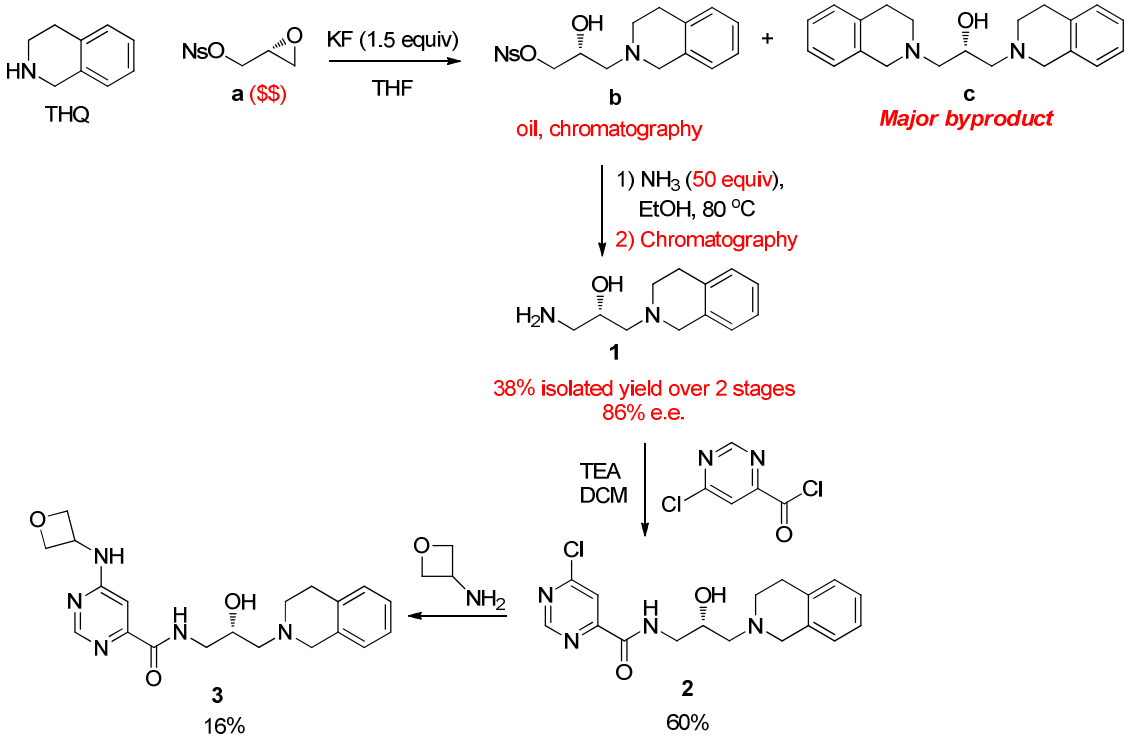
Introduction.

1,2-Amino alcohols are a well reviewed class of organic compounds with a variety of pharmaceutical and industrial uses.[1] Because of this importance, many synthetic methods have been devised to access structurally diverse analogs. Classic routes to access primary 1,2-amino alcohols proceed via either Strecker (cyanide)[2] or Henry (nitromethane)[3] additions to aldehydes, followed by reduction. While there is a plethora of literature devoted to implementation of these transformations, the need for toxic or high-energy reactants (cyanide sources and nitromethane, respectively) can be a significant safety concern when working on larger scales. Amination of epoxides is an attractive alternative strategy for the synthesis of 1,2-amino alcohols; however, direct access to primary 1,2-amino alcohols from epoxides and ammonia often results in overalkylation even with large excesses of NH_3, as the primary amine product reacts further with the epoxide electrophile.[4] Use of an appropriately protected ammonia surrogate can circumvent this overalkylation, but this often requires a subsequent and separate deprotection step.[5] Addition of azide to an epoxide followed by reduction is a commonly employed strategy;[6] however, safety concerns around the use of azide are even more severe than the aforementioned Strecker or Henry routes. Finally, regardless of the synthetic strategy employed, the desired primary amino alcohol products are often very water soluble and thus can be difficult to isolate, typically requiring precipitation of an appropriate ammonium salt or fractional distillation.

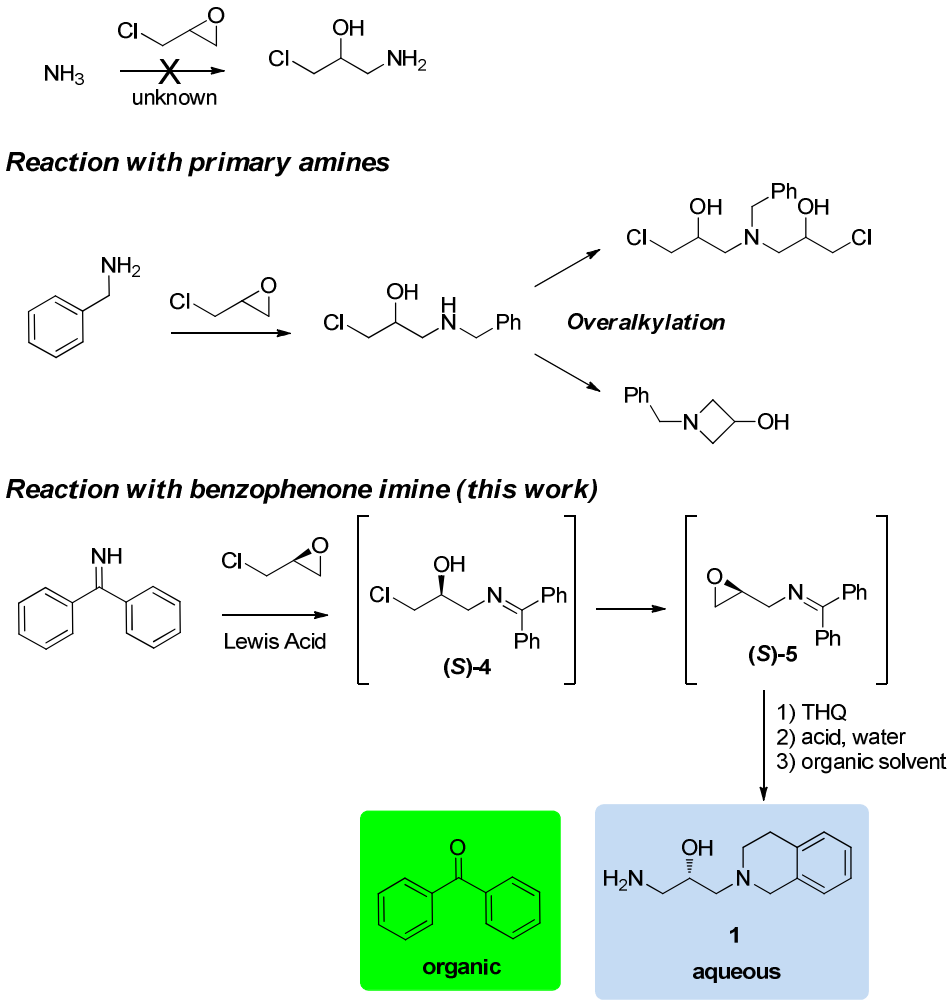
As part of synthetic efforts toward a key amino alcohol intermediate (**1**) for oncology target **3**, a protein arginine methyltransferase-5 (PRMT5) inhibitor[7], we sought to evaluate the use of alternative ammonia surrogates able to react selectively with epoxides (Scheme 1). The synthesis for **1** required the use of an expensive epoxide (**a**), yield loss due to overalkylation (formation of **c**), large volumes of ethanolic ammonia at high temperature in a pressure vessel for

the second step, and the use of chromatography for two isolations. A loss of stereochemical purity was also observed in this sequence, giving **1** with only 86% enantiomeric excess. We hoped to remedy these issues by developing a new synthesis that relied on reacting inexpensive, enantiopure epichlorohydrin with an ammonia surrogate, and then directly reacting the addition intermediate with tetrahydroisoquinoline (THQ, Scheme 2).

Scheme 1. Reported synthesis of **3,** using ammonia to prepare **1**.[7]



Scheme 2. Proposed synthesis of **1** via benzophenone imine addition to epichlorohydrin.



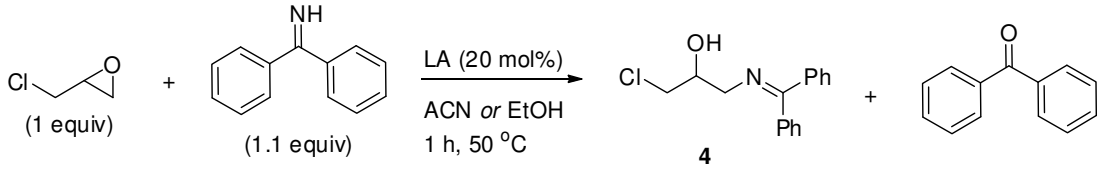
The direct reaction of ammonia with epichlorohydrin is unknown in the literature, and would likely result in a complex mixture of oligo/polymeric amine products. Use of a mono-protected ammonia equivalent such as benzylamine poses the risk of overalkylation, either intermolecularly with another equivalent of epoxide, or through cyclization to form an azetidine.[8] In contrast, use of an ammonia-derived imine as a nucleophile would prevent overalkylation, and provide an easy method to reveal the primary amine through hydrolysis. There are examples of reacting epoxides with *in-situ* generated aldimine nucleophiles in the patent literature;[9] however,

ammonia-derived aldimine formation can be problematic due to low solubility of the imine itself, and the competitive formation of oxazolidines via cyclization after addition to the epoxide. Benzophenone imine is a stable, inexpensive, readily available, and highly organic soluble compound that is frequently used as an ammonia surrogate in Pd-catalyzed amination chemistry;[10-11] however, its use as a nucleophile in reactions with epoxides is almost completely unexplored. To the best of our knowledge, there is a single report of benzophenone imine addition to epoxides, using chiral scandium and indium bipyridine catalysts,[12] though these transformations require long reaction times (5 days) and use of the undesirable process solvent DCM. Furthermore, the reaction scope was not explored beyond a few symmetric 1,2-diarylepoxides, giving no indication of the degree of regioselectivity possible with non-symmetric epoxides.

Herein, we report that Lewis acids can effectively catalyze the regioselective addition of benzophenone imine to a variety of substituted epoxides, including epichlorohydrin, with $Y(OTf)_3$ as the preferred catalyst. Simple hydrolysis of the intermediate alkylated imine and extraction with organic solvent removes the benzophenone, giving an aqueous solution of the desired primary amino alcohol as its ammonium salt; no overalkylated byproducts are observed. These ammonium salts can then be directly acylated or sulfonylated using biphasic Schotten-Baumann conditions to give an array of functionalized products in good yield over multiple steps in a simple, rapid, and scalable protocol. Importantly, stereochemical purity is retained when (*S*)-epichlorohydrin is employed in the synthesis of **2**, providing an efficient route to access homochiral primary amino alcohol derivatives from simple, inexpensive precursors.

Results and Discussion.

Based on the aforementioned report of Lewis acid catalyzed addition of benzophenone imine to select 1,2-diarylepoxides,[12] as well as reports of Lewis acid catalyzed addition of amines to epoxides,[13] we sought to identify an appropriate Lewis acid to effect the regioselective addition of benzophenone imine to epichlorohydrin under mild conditions. In order to achieve this, we designed a high-throughput screen drawn from our in-house catalyst library. This screen included 48 Lewis acids (20 mol%) and 2 solvents (5 vol of acetonitrile or ethanol) for a total of 96 reactions, using benzophenone imine (22 μmol) and racemic epichlorohydrin (20 μmol); the plate was run for one hour at 50 °C to form the racemic diphenylmethylene amino alcohol **4**, which was identified by HPLC analysis (Figure 1).



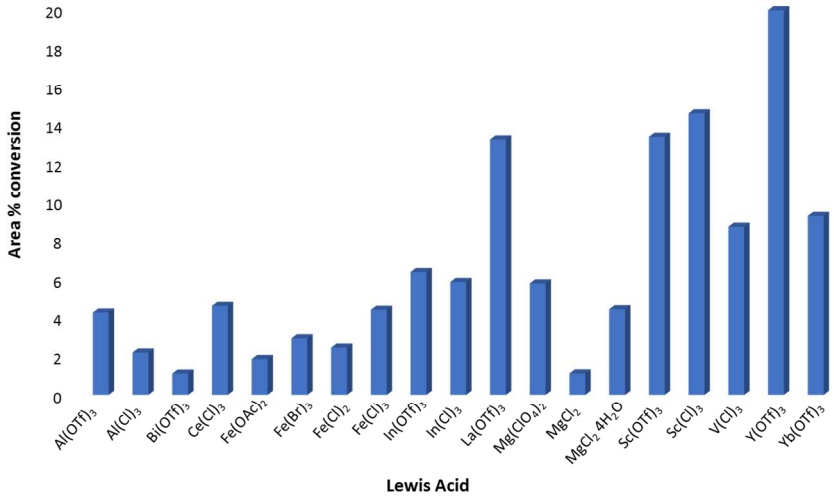
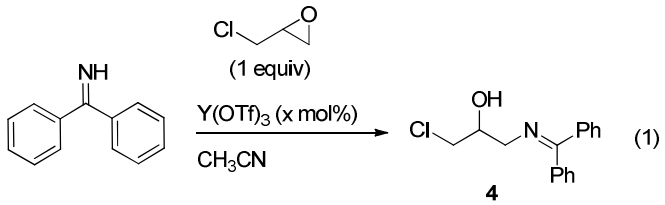


Figure 1. Selected results from Lewis acid screen with CH_3CN as solvent, showing only those reactions with >1% conversion (judged by LC area%). See Supporting Information for further details.

In EtOH, only $La(OTf)_3$ showed >8% conversion to product **4**, whereas all of the other catalysts promoted hydrolysis of the benzophenone imine instead of alkylation. In CH_3CN, $InCl_3$, $La(OTf)_3$, $Sc(OTf)_3$, $ScCl_3$, VCl_3, $Y(OTf)_3$ and $Yb(OTf)_3$ all showed 8-20% conversion, and were therefore chosen for confirmation experiments on larger scale. In every case, the addition occurs exclusively at the unhindered position of the epoxide, and no displacement of the alkyl chloride was observed. In the absence of catalyst, benzophenone imine reacts very slowly with epichlorohydrin in CH_3CN, giving <2% conversion to product after 20 hours at 65 ^oC. A second control experiment using 30 mol% triflic acid in the absence of yttrium showed no conversion to **4,** indicating that adventituous protons are likely not responsible for promoting the epoxide activation. In our scale-up experiments, $ScCl_3$ gave similar results as $Y(OTf)_3$; however, $Y(OTf)_3$ has the added benefit of lower cost and wider availability.[14] The lower conversions observed in our screening panel compared to the higher conversions observed in scale-up experiments were most likely due to order of addition. The screening panel contained pre-weighed Lewis acids to which were added stock solutions of benzophenone imine followed by epichlorohydrin. The Lewis acids thus had opportunity to hydrolyze the benzophenone imine prior to the addition of epichlorohydrin. The procedure was refined so that the catalyst was added last.

In addition to identifying several possible Lewis acid catalysts, our screening results indicated a distinct solvent preference for CH_3CN over EtOH. With $Y(OTf)_3$ as the Lewis acid, we evaluted several other aprotic solvents under otherwise identical conditions. The addition

reaction performs well in a number of alternative solvents, including 2-MeTHF, TBME, iPrOAc, toluene, and diethylcarbonate, though CH_3CN did still provide the best results.[14] Thus, $Y(OTf)_3$ in CH_3CN exhibits the best combination of short reaction time and minimal hydrolysis of the benzophenone imine when reacting with epichlorohydrin, giving up to 80% conversion to **4** at 65 °C after only one hour. Notably, this catalyst/solvent combination is even able to perform at room temperature (equation 1)

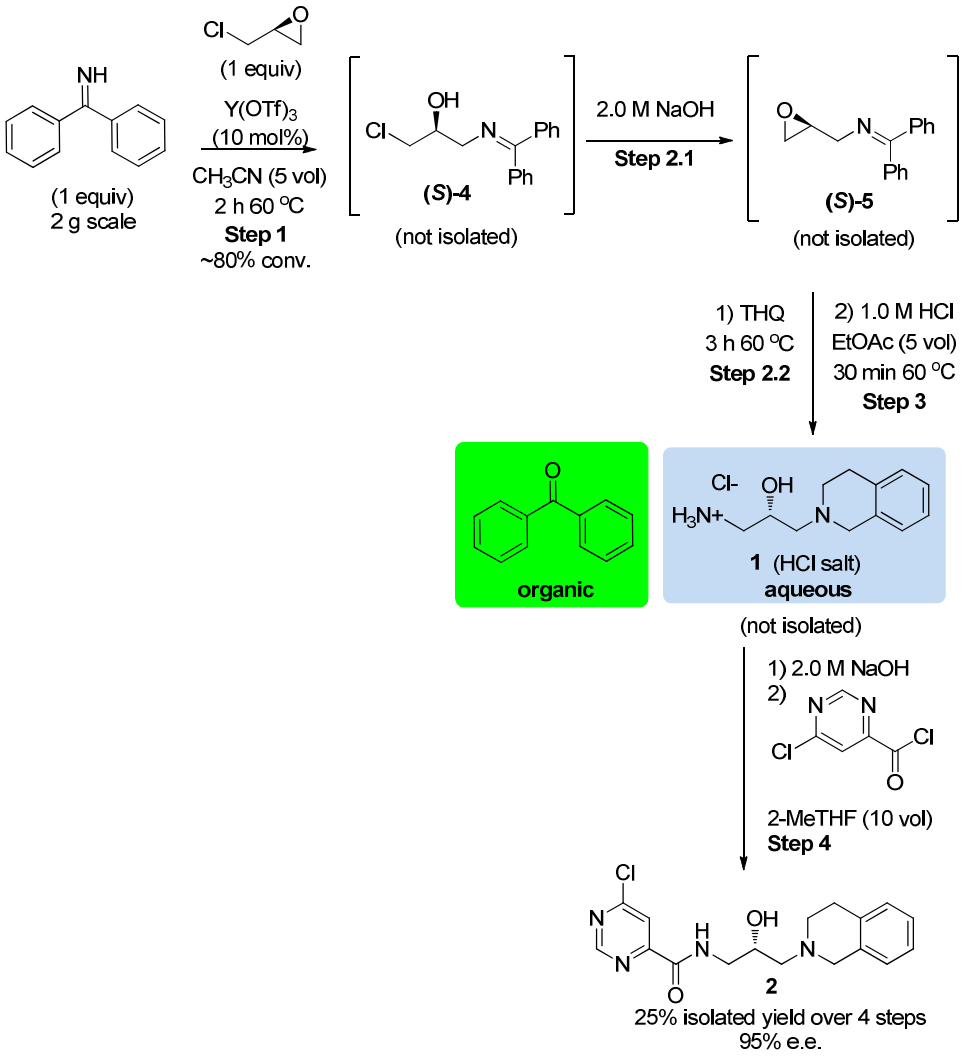


20 mol% cat., 1 h, 65 °C: 80% conversion
10 mol% cat., 23 h, room temp.: 74% conversion

With an improved catalyst/solvent system identified, we applied this strategy to the gram-scale synthesis of enantioenriched intermediate **2** (Scheme 3). In Step 1, the catalyst loading could be reduced to 10 mol%, and the reaction run at 60 °C for 2 h. The Step 1 solution output of **(*S*)-4** can be telescoped directly into Step 2.1 by the addition of 2 M NaOH to form **(*S*)-5** followed by treatment with THQ in Step 2.2. The Step 2 solution output was then treated with 1 M HCl and EtOAc to effect imine hydrolysis and separation of the benzophenone in Step 3. After 30 minutes, the amino alcohol **1** had partitioned exclusively into the aqueous phase while the benzophenone protecting group remained in the organic phase. Following removal of the organic phase, the acidic solution of **1** was basified with 2 M NaOH, and then added to a slurry of the 6-chloropyrimidine-4-carbonyl chloride in 2-MeTHF to effect the amidation under Schotten-Baumann conditions. Following purification, **2** was obtained in 25% isolated yield (average 70% per transformation) and 95% enantiomeric excess, with no isolation of any intermediates. This streamlined sequence can be conducted in a single day, does not require the

use of pressure equipment, affords an equivalent yield to that previously reported for the multi-step route (Scheme 1), and achieves higher enantiopurity of **2** prior to any crystallization.

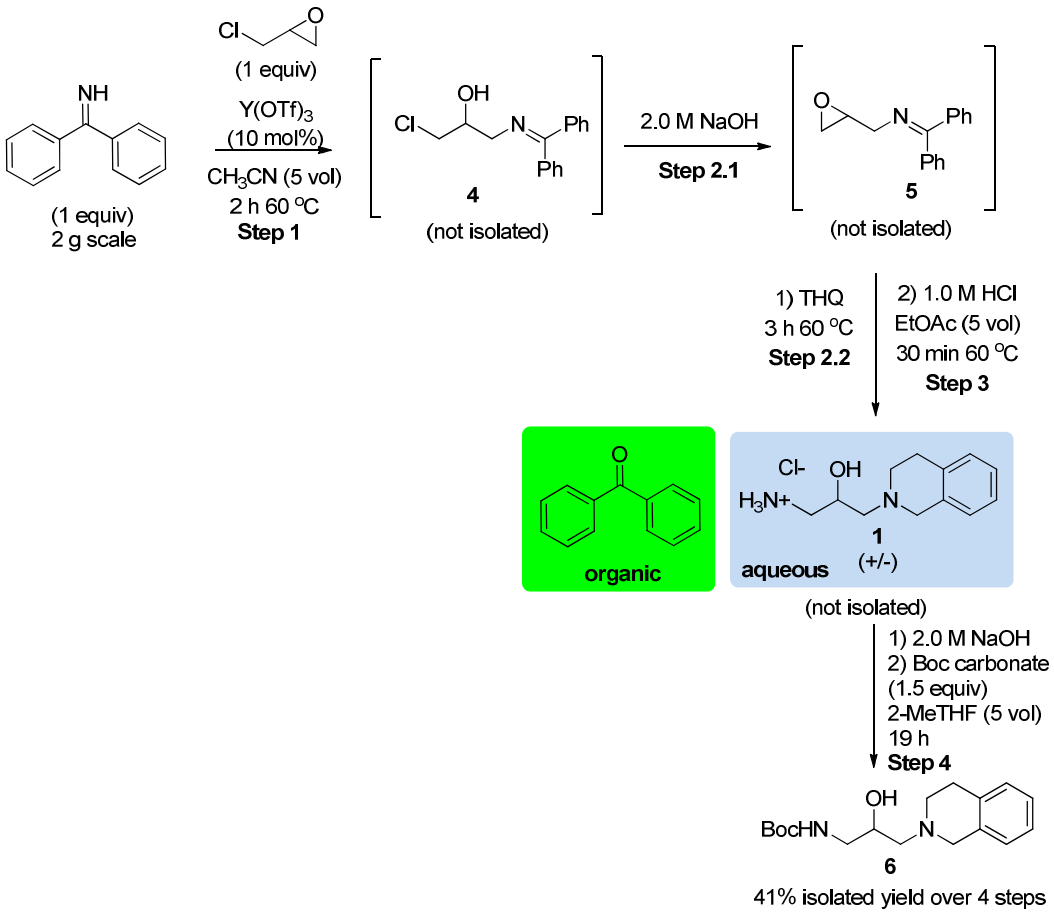
Scheme 3. Synthesis of **2** in a two-pot telescoped sequence.



While this method provides rapid access to gram-quantities of **2**, we sought to further investigate the suitability of this approach toward a more general synthesis of amino alcohol

derivatives. Using racemic epichlorohydrin, we evaluated several points for isolation of key intermediates to enable synthetic diversification (Scheme 4). Unfortunately, attempts to isolate **4** via chromatography did not give a pure product. We suspect that hydrolysis of the imine, cyclization to the oxazolidine, and/or formation of the epoxide can occur during the chromatographic separation; therefore, progressing **4** as a solution into the subsequent steps is advisable. We were able to hydrolyze **4** to obtain amino alcohol **7** in 80% solution yield as its HCl salt (Scheme 5); however, **7** was not further derivatized. In order to access an easily isolated intermediate capable of diversification, we have prepared the Boc-protected analogue **6** in 41% isolated yield by treating a basified solution of racemic **1** with Boc-carbonate.

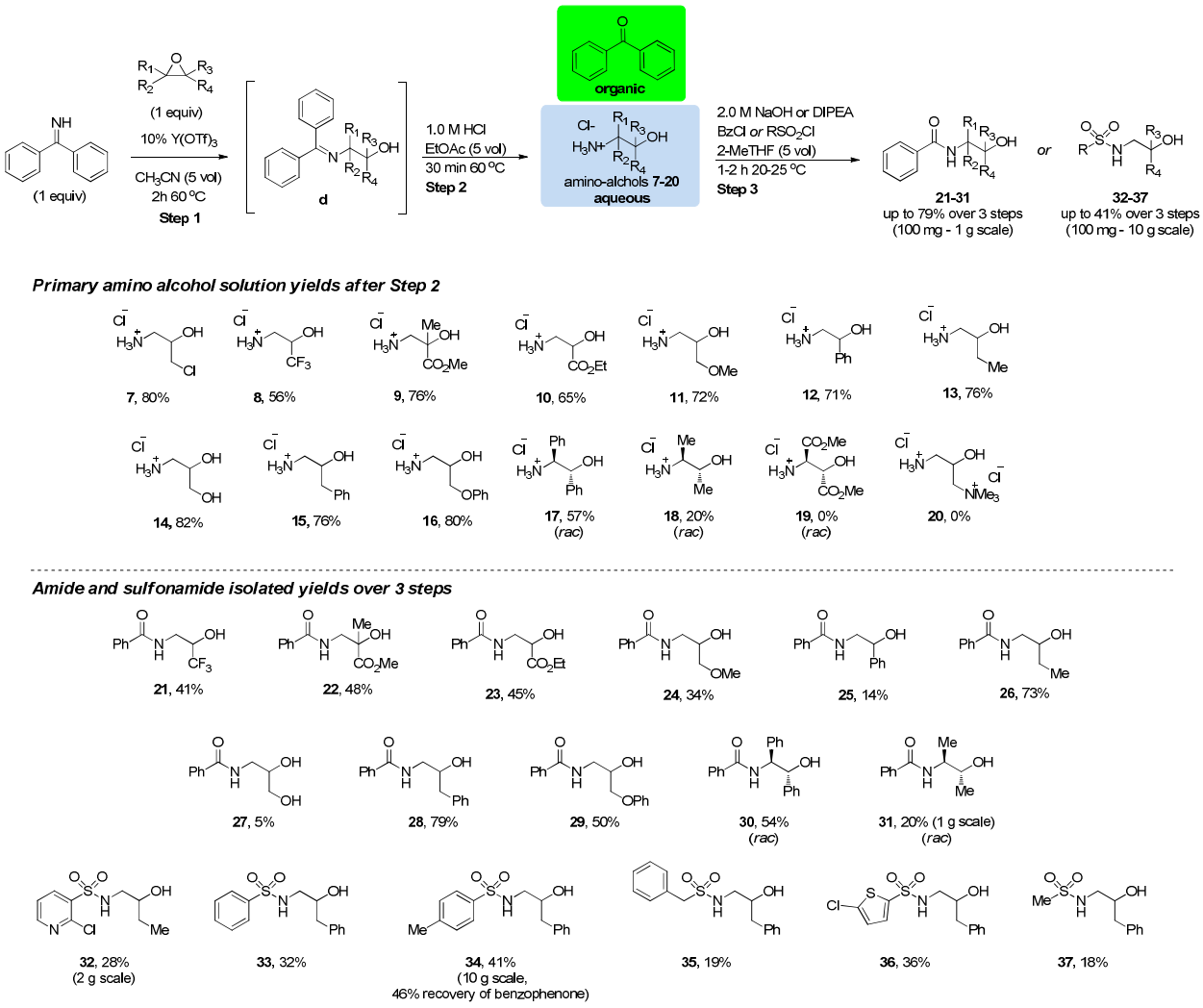
Scheme 4. Preparation and isolation of **6**.



Given the success observed with epichlorohydrin, we have further expanded the scope of the $Y(OTf)_3$ catalyzed addition of benzophenone imine to epoxides into a general two-pot, three-step process as shown in Scheme 5. In Step 1, various epoxides can be reacted to form benzophenone-protected amino alcohols of type **d**, which are then hydrolyzed and separated from the benzophenone by extraction with EtOAc in Step 2. We have used this method to generate amino alcohol salts **7**-**20**; solution yields for these intermediates ranged from 56-87% (determined using 40 mol% BHT as internal standard), except for compounds **18**, **19**, and **20**. The poor results for the synthesis of **18** and **19** are likely due to steric hindrance, while the

epoxide used for **20** likely decomposed under the reaction conditions. In Step 3, the aqueous solution of the ammonium salt is basified with either 2 M NaOH or Hunig's base, followed by the addition of 2-MeTHF and the desired electrophile. Amidation or sulfonylation is thus effected under Schotten-Baumann conditions, generally reaching completion within 1-2 h. The organic layer was separated and purified by chromatography to afford a variety of benzamides and sulfonamides in up to 79% isolated yield over 3 steps (Scheme 5). The poor yield of **27** is probably due to the high aqueous solubility of the product, especially given the high solution yield of **14**. While most of these examples were conducted on 100 mg scale to test the methodology, we also performed several multi-gram runs to confirm the practicality of this approach toward preparative synthesis. Compounds **31** and **32** were thus prepared using 1-2 g of benzophenone imine as the input material in 20% and 28% isolated yield respectively. While the isolated yields of the final products are modest in many cases, we note that each example was prepared using the same general set of conditions over three steps; specific process optimization for a desired product, particularly with respect to isolation, would undoubtedly result in higher isolated yields.

Scheme 5. General approach to derivatized 1,2-diamino alcohols from $Y(OTf)_3$-catalyzed addition of benzophenone imine to epoxides (reactions run using 100 mg of benzophenone imine unless otherwise noted).



The mass efficiency of the process can be improved by recovering the benzophenone protecting group and eliminating chromatography, both of which would be desirable for larger scale applications. The synthesis of compound **34** was chosen for a 10 g scale up demonstration, and to assess the feasibility of benzophenone recovery and a simplified purification procedure. In Step 1, an extra 0.4 equiv of the epoxide was charged after 2 h at 60 °C followed by stirring

for an additional hour at 60 ^{o}C. Following Step 2, the organic layer containing the benzophenone protecting group was concentrated under reduced pressure, seeded with pure benzophenone, and then filtered to afford 4.6 g (46%) of recovered benzophenone. Following Step 3, the organic layer was washed with water to remove inorganic impurities. The organic layer was then concentrated and recrystallized from MeOH to afford 6.6 g of **34** for an isolated yield of 41% over three steps with no chromatographic purifications.

Conclusions.

Benzophenone imine was found to be an effective ammonia surrogate for the selective synthesis of primary 1,2-amino alcohols from epoxides, including epichlorohydrin. Several Lewis acids are capable of promoting this reaction, with $Y(OTf)_3$ identified as the best catalyst from a panel of 48 different Lewis acids. The aqueous amino alcohol solutions generated after imine hydrolysis are easily derivatized without the need for isolation. We have demonstrated that this chemistry is amenable for both rapid small-scale analogue synthesis and multi-gram scale-up without the need for chromatography. Importantly, we have shown that the enantiopurity of the starting epoxide can be carried through these steps with little erosion, as in the synthesis of **2**. From a practicality standpoint, both benzophenone imine and $Y(OTf)_3$ are air stable and readily available from a variety of vendors at low cost. If desired, extraction of the benzophenone byproduct provides an opportunity for recycling; we have demonstrated the feasibility of this by simple crystallization of benzophenone on larger scale. Thus, this operationally simple procedure should have broad applicability in the synthesis and derivatization of primary amino alcohols from readily available precursor materials.

Experimental Section.

General information:

All solvents and reagents were obtained from commercial sources and were used as they were received. All reactions were carried out in oven-dried reaction vessels or glass vials. TLC analysis was performed on silica gel TLC plates. Column chromatography was carried out on prepacked ISCO columns on Combiflash purification unit. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer, and are reported as chemical shifts (δ) in parts per million (ppm), and multiplicities are abbreviated as s= singlet, d = doublet, t = triplet, m = multiplet, b = broad, dd = doublet of doublets, ddd = doublet of doublet of doublets. Residual solvent signals were used as reference. HRMS (m/z) was measured using a LTQ Discovery Orbitrap (Thermo) mass spectrometer equipped with a heated electrospray ionization (HESI) ion source. LRMS (m/z) was measured using a Water Acquity SQD mass spectrometer on a Waters CSH column (C18, 30mm x 2.1 mm, 1.7 µm particle size).

Procedure for synthesis of **2** (S)-6-chloro-N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)pyrimidine-4-carboxamide.[7]

All reagent charges based on 1 equiv of benzophenone imine charged in Step 1.

Step 1: To a vial containing a magnetic stirbar were charged the following materials in this order: CH_3CN (10.0 mL, 5 vol), benzophenone imine (2.00 g, 1.94 mL, 11.0 mmol), (*S*) epichlorohydrin (1.02 g, 0.86 mL, 11.0 mmol), and finally $Y(OTf)_3$ (0.59 g, 1.10 mmol). The reaction vial was capped and placed on a heating block set for 60 ^{o}C. The reaction mixture was stirred for 2 hours.

Step 2: The vial was removed from the heating block, allowed to cool to room temperature, and then charged with 2.0 M NaOH (5.5 mL, 1.0 equiv). The vial was returned to heating block and stirred for 1-2 min. THQ (1.17 g, 1.12 mL, 0.8 equiv) was then added, and the biphasic mixture stirred at 60 ^{o}C for 3 h.

Step 3: The reaction mixture was allowed to cool to room temperature, and then transferred to a 125 mL Erlenmeyer flask. 2.0 M HCl (12.5 mL, 2.4 equiv) was added, followed by iPrOAc (10.0 mL, 5 vol), ensuring the mixture is acidic to litmus (pH < 4). This biphasic mixture was stirred vigorously for 30 min at 60 ^{o}C. The mixture was then allowed to cool to room temperature, the layers were separated using a separatory funnel, and the aqueous layer transferred to a 100 mL flask.

Step 4: To the aqueous layer was charged 2.0 M NaOH (22.0 mL, 4.0 equiv), ensuring pH > 10. In a separate flask, 6-chloropyrimidine-4-carbonyl chloride (1.46 g, 0.75 equiv) was suspended in 2-MeTHF (20.0 mL, 10 vol). This organic solution was added to the basified aqueous amino alcohol solution. The biphasic reaction mixture was stirred vigorously at room temperature for 2 h. Mixing was stopped, and the layers allowed to settle. The layers were separated, the organic phase was concentrated under reduced pressure before directly loading the material onto a silica gel column. Elution using a gradient of 0% to 100% EtOAc/hexanes yielded **2** as a white solid (950 mg, 25% yield over 4 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.93 (s, 1 H), 8.53 (br. s. 1 H), 8.14 (d, *J*=0.78 Hz, 1 H), 7.08 - 7.23 (m, 3 H), 7.01 (d, *J*=6.26 Hz, 1 H), 4.52 (br. s. 1 H), 4.03 - 4.16 (m, 1 H), 3.87 (d, *J*=14.87 Hz, 1 H), 3.61 - 3.80 (m, 2 H), 3.45 - 3.58 (m, 1 H), 2.86 - 3.06 (m, 3 H), 2.75 - 2.86 (m, 1 H), 2.55 - 2.72 (m, 2 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{17}H_{19}ClN_4O_2$: 347.2

Procedure for synthesis of compound **6** (*tert*-butyl (3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)carbamate).

Step 1: To a vial containing a magnetic stirbar were charged the following materials in this order: CH_3CN (10.0 mL, 5 vol), benzophenone imine (2.00 g, 1.94 mL, 11.0 mmol), epichlorohydrin (racemic) (1.02 g, 0.86 mL, 11.0 mmol), and $Y(OTf)_3$ (0.59 g, 1.10 mmol). The reaction vial was capped and placed on a heating block set for 60 ^oC. The reaction mixture was stirred for 2 hours. The presence of **4** was confirmed by HRMS; however, **4** was not isolated and the Step 1 output was carried forward directly to Step 2.

HRMS (ESI) *m/z* $[M+H]^+$: Calcd for $C_{16}H_{16}ClNO$: 274.0993; Found 274.0987.

Step 2.1: The vial was removed from the heating block, allowed to cool to room temperature, and then charged with 2.0 M NaOH (5.5 mL, 1.0 equiv). The vial was returned to the heating block and stirred for 1-2 min. The presence of **5** was confirmed by LRMS; however, **5** was not isolated.

LRMS (*m/z*) $[M+H]^+$: Found for $C_{16}H_{15}NO$: 238.1

Step 2.2: THQ (1.17 g, 1.12 mL, 0.8 equiv) was then added, and the biphasic mixture stirred at 60 ^oC for 3 h.

Step 3: The reaction mixture was allowed to cool to room temperature before transferring to a 125 mL Erlenmeyer flask. 1 M HCl (25.0 mL, 2.4 equiv) and EtOAc (20.0 mL, 10 vol) were charged, and the biphasic mixture stirred vigorously for 30 min at 60 ^oC, ensuring the mixture is acidic to litmus (pH < 4). The mixture was then allowed to cool to room temperature, the layers were separated using a separatory funnel, and the aqueous layer transferred to a 100 mL flask.

Step 4: To the aqueous layer was charged 2 M NaOH (11.0 mL, 2.0 equiv) and 2-MeTHF (20.0 mL, 10 vol), ensuring pH > 10 by litmus. Boc-carbonate (3.60 g, 1.5 equiv) was charged and the reaction mixture stirred vigorously overnight. Mixing was stopped, and the layers allowed to settle. The layers were separated, and the organic phase was concentrated under reduced pressure before directly loading the material onto a silica gel column. Elution using a gradient of 0% to 90% TBME/hexanes yielded **6** as a clear oil (1.4 g, 41% yield over 4 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.07 - 7.22 (m, 3 H), 6.98 - 7.07 (m, 1 H), 5.05 (br. s. 1 H), 4.96 (dd, *J*=6.06, 4.50 Hz, 1 H), 3.85 (d, *J*=14.87 Hz, 1 H), 3.62 (d, *J*=14.87 Hz, 1 H), 3.47 - 3.57 (m, 1 H), 3.41 (d, *J*=6.26 Hz, 1 H), 2.85 - 3.04 (m, 3 H), 2.69 - 2.85 (m, 2 H), 2.57 - 2.69 (m, 1 H), 2.49 - 2.57 (m, 1 H), 1.41 - 1.52 (m, 9 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 156.43 (s, 1 C), 134.27 (s, 1 C), 134.04 (s, 1 C), 128.72 (s, 1 C), 126.53 (s, 1 C), 125.80 (s, 1 C), 125.69 (s, 1C), 71.31 (s, 1 C), 66.31 (s, 1 C), 60.76 (s, 1 C), 56.04 (s, 1 C), 51.12 (s, 1 C), 44.15 (s, 1 C), 29.08 (s, 1 C), 28.43 (s, 1 C)

HRMS (ESI) *m/z* $[M+H]^+$: Calcd for $C_{17}H_{26}N_2O_3$: 307.2011; Found 307.2011.

General procedure for synthesis of benzamides **21-31**. All reagent charges based on 1 equiv of benzophenone imine charged in Step 1 (100 mg unless otherwise noted).

Step 1: To a vial containing a magnetic stirbar were charged the following materials in this order: CH_3CN (0.5 mL, 5 vol), benzophenone imine (100 mg, 1 equiv), epoxide (1 equiv), BHT (48.6 mg, 40 mol %), and $Y(OTf)_3$ (29.6 mg, 10 mol %). Note – BHT may be omitted if Step 1 will not be assayed. The reaction vial was capped and placed on a heating block set for 60 ^{o}C. The reaction mixture was stirred for 2 hours. If assaying Step 1, 5 uL of the reaction mixture was then diluted in 1.0 mL of CH_3CN and analyzed by HPLC.

Note – for Compounds **17** and **18**, Step 1 was allowed to proceed for 20 h @ 60 ^{o}C.

Step 2: The reaction mixture was allowed to cool to room temperature. 1 M HCl (0.550 mL) and EtOAc (0.5 mL, 5 vol) were charged, and the biphasic mixture stirred vigorously for 30 min

at 60 °C, ensuring the mixture is acidic to litmus (pH < 4). The mixture was then allowed to cool to room temperature, the layers were separated using a separatory funnel, and the aqueous layer transferred to a vial containing a magnetic stirbar.

Step 3: The aqueous layer was charged with either 2 M NaOH or Hunig's base until basic to litmus (usually 1 equiv based on benzophenone imine charge in Step 1) and 2-MeTHF (0.5 mL, 5 vol). To the resultant white slurry was charged benzoyl chloride (0.75 equiv based on benzophenone imine charge in Step 1) and the mixture was stirred vigorously for 1-2 h @ 20-25 °C, at which point most of the solids have dissolved. The agitation was stopped and the layers were allowed to separate. The aqueous layer was removed via pipet and the organic layer was loaded directly onto a silica gel column and eluted using a gradient of EtOAc/hex to yield the desired product, except Compound **30** – see below.

Compound **21** (N-(3,3,3-trifluoro-2-hydroxypropyl)benzamide)

29.4 mg collected as a white solid (40.8% over 3 steps).

^{1}H NMR (400 MHz, CD_3CN) δ ppm 7.81 - 7.90 (m, 2 H), 7.57 - 7.64 (m, 1 H), 7.46 - 7.57 (m, 2 H), 7.42 (br. s. 1 H), 4.88 (br. s. 1 H), 4.26 (br. s. 1 H), 3.78 (ddd, *J*=13.99, 5.97, 3.52 Hz, 1 H), 3.50 (ddd, *J*=13.99, 7.92, 5.87 Hz, 1 H)

^{13}C NMR (101 MHz, CD_3CN) δ ppm 168.89 (s, 1 C), 134.44 (s, 1 C), 132.31 (s, 1 C), 129.13 (s, 1 C), 127.69 (s, 1 C), 117.92 (s, 1 C), 69.52 (s, 1 C), 40.72 (s, 1 C)

HRMS (ESI) *m*/*z* $[M+H]^+$: Calcd for $C_{10}H_{10}F_3NO_2$: 234.0736; Found 234.0734.

Compound **22** (methyl 3-benzamido-2-hydroxy-2-methylpropanoate)

47.4 mg collected as a light yellow oil (47.9% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.72 - 7.83 (m, 2 H), 7.49 - 7.56 (m, 1 H), 7.39 - 7.49 (m, 2 H), 6.66 (br. s. 1 H), 3.80 (s, 3 H), 2.32 - 2.53 (m, 2 H), 1.49 (s, 3 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 170.70 (s, 1 C), 168.17 (s, 1 C), 134.07 (s, 1 C), 131.73 (s, 1 C), 128.60 (s, 1 C), 127.04 (s, 1 C), 53.20 (s, 1 C), 47.64 (s, 1 C), 30.86 (s, 1 C), 23.62 (s, 1 C)
HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{15}NO_4$: 238.0174; Found 238.1067

Compound **23** (ethyl 3-benzamido-2-hydroxypropanoate)[15]

45.0 mg collected as a white solid (45.0% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 - 7.88 (m, 2 H), 7.51 - 7.59 (m, 1 H), 7.39 - 7.51 (m, 2 H), 6.67 (br. s., 1 H), 4.41 (dd, *J*=5.48, 3.91 Hz, 1 H), 4.29 (q, *J*=7.30 Hz, 2 H), 3.76 - 3.95 (m, 2 H), 1.32 (t, *J*=7.04 Hz, 3 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{12}H_{15}NO_4$: 238.1

Compound **24** (N-(2-hydroxy-3-methoxypropyl)benzamide)

28.6 mg collected as a white solid (34.2% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.69 - 7.79 (m, 2 H), 7.43 - 7.51 (m, 1 H), 7.31 - 7.43 (m, 2 H), 6.67 (br. s. 1 H), 3.86 - 4.01 (m, 1 H), 3.67 (ddd, *J*=14.09, 6.26, 3.52 Hz, 1 H), 3.37 - 3.49 (m, 2 H), 3.26 - 3.37 (m, 4 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.38 (s, 1 C), 134.17 (s, 1 C), 131.66 (s, 1 C), 128.61 (s, 1 C), 127.00 (s, 1 C), 69.66 (s, 1 C), 59.27 (s, 1 C), 43.01 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{15}NO_3$: 210.1125; Found 210.1123

Compound **25** (N-(2-hydroxy-2-phenylethyl)benzamide)[16]

13.2 mg collected as a white solid (13.9% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79 - 7.90 (m, 2 H), 7.51 - 7.60 (m, 1 H), 7.44 - 7.51 (m, 2 H), 7.37 - 7.44 (m, 3 H), 7.31 - 7.37 (m, 1 H), 6.87 (b, 1H), 5.25 - 5.41 (m, 1 H), 4.05 (br. s. 2 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{15}H_{15}NO_2$: 242.2

Compound **26** (N-(2-hydroxybutyl)benzamide)[16]

63.9 mg collected as a white solid (73.0% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 - 7.86 (m, 2 H), 7.49 - 7.58 (m, 1 H), 7.35 - 7.49 (m, 2 H), 6.76 (br. s. 1 H), 3.64 - 3.85 (m, 2 H), 3.23 - 3.41 (m, 1 H), 1.45 - 1.65 (m, 2 H), 0.91 - 1.08 (m, 3 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{11}H_{15}NO_2$: 194.1

Compound **27** (N-(2,3-dihydroxypropyl)benzamide)[17]
3.2 mg collected as a white solid (4.5% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 - 7.88 (m, 2 H), 7.52 - 7.61 (m, 1 H), 7.41 - 7.52 (m, 2 H), 7.41 - 7.52 (m, 2 H), 6.65 (br. s. 1 H), 3.92 (d, *J*=4.70 Hz, 1 H), 3.56 - 3.79 (m, 3 H), 2.96 (br. s. 2 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{10}H_{13}NO_3$: 196.0

Compound **28** (N-(2-hydroxy-3-phenylpropyl)benzamide)

79.1 mg collected as a white solid (79.0% over 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.63 - 7.77 (m, 2 H), 7.40 - 7.49 (m, 1 H), 7.33 - 7.40 (m, 2 H), 7.23 - 7.33 (m, 2 H), 7.12 - 7.22 (m, 3 H), 6.51 (br. s. 1 H), 3.96 - 4.08 (m, 1 H), 3.65 - 3.82 (m, 1 H), 3.33 (ddd, *J*=13.99, 7.73, 4.89 Hz, 1 H), 2.83 (dd, *J*=13.69, 5.48 Hz, 1 H), 2.73 (dd, *J*=13.69, 8.22 Hz, 1 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.37 (s, 1 C), 137.55 (s, 1 C), 131.63 (s, 1 C), 129.40 (s, 1 C), 128.76 (s, 1 C), 128.60 (s, 1 C), 127.00 (s, 1 C), 126.76 (s, 1 C), 60.44 (s, 1 C), 45.45 (s, 1 C), 41.63 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{17}NO_2$: 256.1332; Found 256.1328

Compound **29** (N-(2-hydroxy-3-phenoxypropyl)benzamide)

61.2 mg collected as a white solid (50.3% over 3 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 - 7.89 (m, 2 H), 7.53 - 7.59 (m, 1 H), 7.42 - 7.53 (m, 2 H), 7.26 - 7.37 (m, 2 H), 7.00 (tt, *J*=7.34, 1.08 Hz, 1 H), 6.89 - 6.97 (m, 2 H), 6.74 (br. s. 1 H), 4.20 - 4.35 (m, 1 H), 4.04 (qd, *J*=9.19, 5.67 Hz, 2 H), 3.79 - 3.95 (m, 1 H), 3.66 (ddd, *J*=14.09, 6.65, 5.48 Hz, 1 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 168.91 (s, 1 C), 158.28 (s, 1 C), 133.90 (s, 1 C), 131.85 (s, 1 C), 129.63 (s, 1 C), 128.70 (s, 1 C), 127.04 (s, 1 C), 121.38 (s, 1 C), 114.52 (s, 1 C), 69.85 (s, 1 C), 69.39 (s, 1 C), 43.18 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{17}NO_3$: 272.1281; Found 272.1276

Compound **30** (racemic N-((1S,2R)-2-hydroxy-1,2-diphenylethyl)benzamide)

32.3 mg collected as a white solid (precipitated out of solution, 54.4% over 3 steps).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.67 (d, *J*=9.39 Hz, 1 H), 7.58 - 7.69 (m, 2 H), 7.33 - 7.52 (m, 6 H), 7.23 - 7.33 (m, 4 H), 7.12 - 7.23 (m, 2 H), 5.48 (d, *J*=5.48 Hz, 1 H), 5.12 (t, *J*=9.00 Hz, 1 H), 4.92 (dd, *J*=8.41, 5.28 Hz, 1 H)

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 165.68 (s, 1 C), 144.15 (s, 1 C), 141.91 (s, 1 C), 135.07 (s, 1 C), 131.51 (s, 1 C), 128.86 (s, 1 C), 128.60 (s, 1 C), 128.10 (s, 1 C), 128.02 (s, 1 C), 127.64 (s, 1 C), 127.48 (s, 1 C), 127.37 (s, 1 C), 127.12 (s, 1 C), 75.02 (s, 1 C), 59.53 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{19}NO_2$: 318.1489; Found 318.1483

Compound **31** (N-((2R,3S)-3-hydroxybutan-2-yl)benzamide)[18]

211 mg collected as a white solid (19.8% over 3 steps, 1.0 g of benzophenone imine charged in Step 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.76 - 7.87 (m, 2 H), 7.53 - 7.60 (m, 1 H), 7.40 - 7.53 (m, 3 H), 6.36 (br. s., 1 H), 4.26 (ddd, *J*=7.83, 6.85, 2.93 Hz, 1 H), 4.02 (td, *J*=6.06, 2.74 Hz, 1 H), 2.62 (d, *J*=5.48 Hz, 1 H), 1.16 - 1.33 (m, 6 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{11}H_{15}NO_2$:194.0

General procedure for synthesis of sulfonamides **32-37.** All reagent charges based on 1 equiv of benzophenone imine charged in Step 1 (100 mg unless otherwise noted).

Step 1: To a vial containing a magnetic stirbar were charged the following materials in this order: CH_3CN (0.5 mL, 5 vol), benzophenone imine (100 mg, 1 equiv), epoxide (1 equiv), BHT (48.6 mg, 40 mol %), and $Y(OTf)_3$ (29.6 mg, 10 mol %). Note – BHT may be omitted if Step 1 will not be assayed. The reaction vial was capped and placed in a heating block set for 60 °C. The reaction mixture was stirred for 2 hours.

Step 2: The reaction mixture was allowed to cool to room. 1 M HCl (0.550 mL) and EtOAc (0.5 mL, 5 vol) were charged, and the biphasic mixture stirred vigorously for 30 min at 60 °C, ensuring the mixture is acidic to litmus (pH < 4). The mixture was then allowed to cool to room temperature, the layers were separated using a separatory funnel, and the aqueous layer transferred to a vial containing a magnetic stirbar.

Step 3: The aqueous layer was charged with either 2 M NaOH or Hunig's base until basic to litmus (usually 1 equiv based on benzophenone imine charge in Step 1) and 2-MeTHF (0.5 mL, 5 vol). To the resultant white slurry was charged sulfonyl chloride (0.75 equiv based on benzophenone imine charge in Step 1) and the mixture was stirred vigorously for 1-2 h @ 20-25 °C, at which point most of the solids have dissolved. The agitation was stopped and the layers allowed to separate. The aqueous layer was removed via pipet and the organic layer was loaded directly onto a silica gel column and eluted using a gradient of EtOAc/hex to yield the desired product.

Compound **32** (2-chloro-N-(2-hydroxybutyl)pyridine-3-sulfonamide)[19]

828 mg collected as a clear oil (28.0% over 3 steps, 2 g of benzophenone imine charged in Step 1).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.60 (dd, *J*=4.70, 1.96 Hz, 1 H), 8.43 (dd, *J*=7.82, 1.56 Hz, 1 H), 7.47 (dd, *J*=7.63, 4.89 Hz, 1 H), 5.68 (br. s. 1 H), 3.59 - 3.74 (m, 1 H), 3.15 (ddd, *J*=12.91, 7.04, 3.13 Hz, 1 H), 2.85 (ddd, *J*=12.91, 8.02, 4.89 Hz, 1 H), 2.03 (d, *J*=3.91 Hz, 1 H), 1.41 - 1.55 (m, 2 H), 0.93 (t, *J*=7.43 Hz, 3 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_9H_{13}ClN_2O_3S$: 265.1

Compound **33** (N-(2-hydroxy-3-phenylpropyl)benzenesulfonamide)

49 mg collected as a white solid (32.2% over 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.81 - 7.93 (m, 2 H), 7.60 - 7.68 (m, 1 H), 7.49 - 7.60 (m, 2 H), 7.30 - 7.39 (m, 2 H), 7.21 - 7.30 (m, 1 H), 7.10 - 7.21 (m, 2 H), 4.87 - 5.05 (m, 1 H), 3.95 (dd, *J*=7.63, 3.33 Hz, 1 H), 3.20 (ddd, *J*=12.91, 7.43, 3.13 Hz, 1 H), 2.92 (ddd, *J*=12.72, 7.63, 5.09 Hz, 1 H), 2.81 (dd, *J*=13.69, 4.70 Hz, 1 H), 2.70 (dd, *J*=13.69, 8.61 Hz, 1 H),1.97 (d, *J*=3.52 Hz, 1 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 136.90 (s, 1 C), 132.79 (s, 1 C), 129.32 (s, 1 C), 129.22 (s, 1 C), 128.84 (s, 1 C), 127.06 (s, 1 C), 126.95 (s, 1 C), 71.23 (s, 1 C), 47.98 (s, 1 C), 41.14 (s, 1 C)
HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{17}NO_3S$: 292.1002; Found 292.0998

Compound **34** (N-(2-hydroxy-3-phenylpropyl)-4-methylbenzenesulfonamide)[20]

6.6 g collected as a white solid (41.0% over 3 steps, 10 g benzophenone imine charged in Step 1)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 - 7.80 (m, 2 H), 7.31 - 7.39 (m, 3 H), 7.22 - 7.31 (m, 2 H), 7.11 - 7.21 (m, 2 H), 4.90 (br. s. 1 H), 3.86 - 4.00 (m, 1 H), 3.09 - 3.24 (m, 1 H), 2.85 - 2.97 (m, 1 H), 2.80 (dd, *J*=13.69, 4.70 Hz, 1 H), 2.70 (dd, *J*=13.69, 8.61 Hz, 1 H), 2.46 (s, 3 H)

LRMS (*m*/*z*) $[M+H]^+$: Found for $C_{16}H_{19}NO_3S$: 306.2

Compound **35** (N-(2-hydroxy-3-phenylpropyl)-1-phenylmethanesulfonamide)

74 mg collected as a white solid (18.5% over 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29 - 7.39 (m, 4 H), 7.22 - 7.29 (m, 2 H), 7.13 - 7.22 (m, 2 H), 7.02 - 7.13 (m, 2 H), 4.62 (br. s. 1 H), 4.21 (s, 2 H), 3.71 - 3.86 (m, 1 H), 3.02 (dd, *J*=7.04, 3.13 Hz, 1 H), 2.87 (dd, *J*=8.02, 4.89 Hz, 1 H), 2.67 (dd, *J*=13.69, 4.70 Hz, 1 H), 2.58 (dd, *J*=13.69, 8.61 Hz, 1 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 136.92 (s, 1 C), 130.67 (s, 1 C), 129.33 (s, 1 C), 129.25 (s, 1 C), 128.89 (s, 1 C), 128.84 (s, 1 C), 126.95 (s, 1 C), 71.76 (s, 1 C), 58.99 (s, 1 C), 48.56 (s, 1 C), 41.03 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{19}NO_3S$: 306.1158; Found 306.1152

Compound **36** (5-chloro-N-(2-hydroxy-3-phenylpropyl)thiophene-2-sulfonamide)

155 mg collected as a white solid (35.7% over 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.30 (d, *J*=3.91 Hz, 1 H), 7.23 - 7.28 (m, 2 H), 7.14 - 7.23 (m, 1 H), 7.05 - 7.14 (m, 2 H), 6.85 (d, *J*=3.91 Hz, 1 H), 5.13 (br. s.1 H), 3.78 - 3.98 (m, 1 H),

3.09 - 3.24 (m, 1 H), 2.92 (dd, *J*=8.22, 3.91 Hz, 1 H), 2.74 (dd, *J*=13.69, 5.09 Hz, 1 H), 2.63 (dd, *J*=13.69, 8.22 Hz, 1 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 137.38 (s, 1 C), 136.71 (s, 1 C), 131.61 (s, 1 C), 129.33 (s, 1 C), 128.90 (s, 1 C), 127.06 (s, 1 C), 126.84 (s, 1 C), 71.11 (s, 1 C), 48.13 (s, 1 C), 41.18 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{13}H_{14}ClNO_3S_2$: 332.0176; Found 332.0173

Compound **37** (N-(2-hydroxy-3-phenylpropyl)methanesulfonamide)

53 mg collected as a white solid (17.6% over 3 steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.31 - 7.39 (m, 2 H), 7.17 - 7.31 (m, 3 H), 5.17 (br. s. 1 H), 3.92 - 4.05 (m, 1 H), 3.25 - 3.39 (m, 1 H), 3.02 - 3.15 (m, 1 H), 2.91 - 3.02 (m, 3 H), 2.69 - 2.88 (m, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$) δ ppm 133.26 (s, 1 C), 129.78 (s, 1 C), 129.35 (s, 1 C), 128.90 (s, 1 C), 71.55 (s, 1 C), 48.11 (s, 1 C), 41.18 (s, 1 C), 40.38 (s, 1 C)

HMRS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_{15}NO_3S$: 230.0845; Found 230.0844

ASSOCIATED CONTENT

Supporting Information. Table of Lewis acid screening data, solution yield determinations, and characterization data for all isolated compounds. This material is available free of charge via the internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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REFERENCES

(1) (a) Ferrara, S.J.; Meinig, J.M.; Placzek, A.T.; Banerji, T.; McTique, P.; Hartley, M.D.; Sanford-Crane, H.S.; Bourdette, D.; Scanlan, T.S. *Bioorg. Med. Chem*., **2017**, *25*, 2743. (b) Gilmore, J.L.; Sheppeck, J.E. 2nd; Watterson, S.H.; et. al. *J. Med. Chem*., **2016**, *59*, 6248.

(c) Barzagli, F.; Mani, F.; Peruzzini, M. *Environ. Sci. Technol*., **2016**, *50*, 7239.

(d) Ager, D.J.; Prakash, I.; Schaad, D.R. *Chem. Rev*., **1996**, *96*, 835-875.

(e) Bergmeier, S.C. *Tetrahedron*, **2000**, *56*, 2561-2576.

(f) Lee, H.S.; Kang, S.H. *Synlett*., **2004**, 10, 1673-1685.

(g) Donohoe, T.J., Callens, C.K., Flores, A., Lacy, A.R., Rathi, A.H. *Chem. Eur. J*., **2010**, *17*, 58-76.

(2) (a) Groger, H. *Chem. Rev*. **2003**, 103, 2795.
(b) Wang, J.; Liu, X.; Feng, X. *Chem. Rev*., **2011**, *111,* 6947.

(3) (a) Westermann, B. *Angew. Chem. Int. Ed*., **2003**, *42*, 151.
(b) Luzzio, F. *Tetrahedron*, **2001**, *57*, 915.

(4) Srivastava, R.P.; McChesney, J.D. *Natural Product Letters*, **1995**, *6*, 147.

(5) (a) Habtemariam, A.; Watchman, B.; Potter, B. S.; Palmer, R.; Parsons, S.; Parkin, A.; Sadler, P.J. *Journal of the Chemical Society, Dalton Transactions*, **2001**, *8*, 1306.
(b) Soroka, M.; Goldeman, W. *ARKIVOC*. **2003**, *xii*, 31.

(c) Trost, B.M.; Bunt, R.C.; Lemoine, R.C.; Calkins, T.L. *J. Am. Chem. Soc*., **2000**, *122*, 5968.

(6) Yamashita, H. *Bulletin of the Chemical Society of Japan*, **1988**, *61*, 1213.

(7) Chan-Penebre, E.; Kuplast, K.; Duncan, K.; et.al.; *Nature Chemical Biology*. **2015**, *11*, 432.

(8) Reddy, V.K.; Udakiran, D.; Chintamani, U.S.; Reddy, E.M.; Kameswararao, C.; Madhusudhan. *Org. Process Res. Dev.*, **2011**, *15*, 462.

(9) Li, K.; Cao, Z.; Hu, J.; Liu, F.; Zhang, Y. Method for preparation of Rivaroxaban and its intermediate. Chinese Patent Application CN 2012-10536633, Dec 13, 2012.

(10) Wolfe, J.P.; Ahman, J.; Sadighi, J.P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997,** *38,* 6367.

(11) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998,** *120,* 827.

(12) Mai, E.; Schneider, C. *ARKIVOC*. **2008**, *xvi*, 216.

(13) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994,** *35,* 433.

(14) See Supporting Information for details.

(15) Williams, T.; Crumbie, R.; Mosher, H. *J. Org. Chem*. **1985**, *50,* 91

(16) Lee, M.; Sanford, M. *Org. Lett*. **2017**, *19,* 572

(17) Azhayev, A.; Antopolsky, M. *Tetrahedron.* **2001**. *57,* 4977

(18) Wappes, E.; Nakafuku, K.; Nagib, D. *J. Am. Chem. Soc*. **2017**. *139(30),* 10204.

(19) Boehm, J.; Davies, T.; Woolford, J.; Griffiths-Jones, C.; Willems, H.; Norton, D.; Saxty, G.; Heightman, T.; Li, T.; Kerns, J.; Davis, R.; Yan, H. Preparation of

sulonylaminophenylpropanoic acid derivatives as Nrf2 regulators. PCT International Patent Application WO 2015092713, Jun 25, 2015

(20) Kang, T.; Kim, H.; Kim, J.; Chang, S. *Chem. Comm*. **2014**. *50(81),* 12073.