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Nucleophilic Aromatic Substitutions of 2-Halo-5-(sulfamoyl)benzoic Acids and *N,O*-Bis-alkylation via Phase Transfer Catalysis: Synthesis of RoRγ Inverse Agonist GSK2981278A

Gregg A. Barcan,[†] Jose J. Conde,[†] Mohamed K. Mokhallalati,[†] Mark G. Nilson,[†] Shiping Xie,[†,*] C. Liana Allen,[‡] Yemane W. Andemichael,[†] Nicholas A. Calandra,[§] David C. Leitch,[||] Ling Li,[†] and Michael, J. Morris[†]

[†]Product Development and Supply, GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, Pennsylvania 19426, United States.

[‡]Vertex Pharmaceuticals Inc., 50 Northern Avenue, Boston, Massachusetts 02210.

[§]H3 Biomedicine, 300 Technology Square, Cambridge, Massachusetts 02139.

[||]University of Victoria, P.O. Box 3065, Victoria, British Columbia, Canada V8W 3V6.

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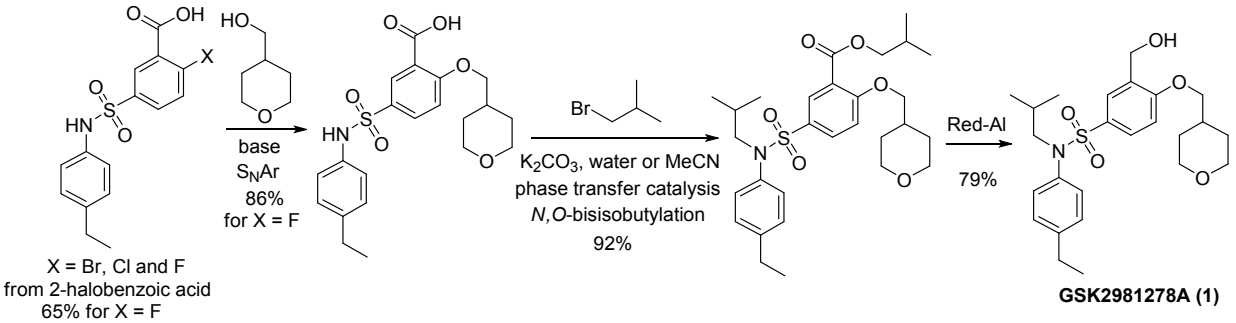
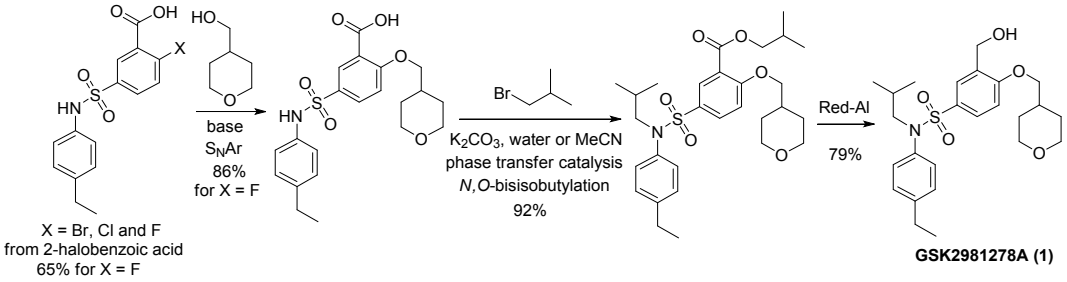


ABSTRACT

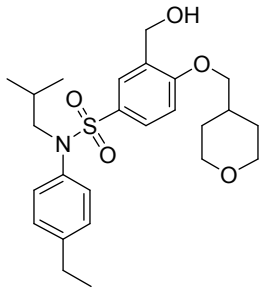


GSK2981278A (**1**) is a RORγ inverse agonist as a potential topical non-steroidal therapy for psoriasis. New synthesis of **1** was developed based on a S_NAr reaction of (tetrahydro-2*H*-pyran-4-yl)methanol with an aryl halide intermediate, prepared from 2-halobenzoic acids. The dianion underwent *in situ N,O*-bis-isobutylated, followed by a reduction to provide **1**. The new route eliminated a genotoxic tosylate of (tetrahydro-2*H*-pyran-4-yl)methanol and a difficult reductive amination from the original synthesis starting from methyl salicylate. A primary version of the route has been scaled up to deliver 125 kg of **1**. However, the heating of a strong base in DMSO for an extended period during the bis-alkylation was found to be a safety concern for manufacturing. A safer and greener process was then developed utilizing a facile *N,O*-bis-alkylation, which was conducted under phase transfer conditions with mild bases such as potassium carbonate and in green solvents such as water. The concise four stage sequence from 2-halobenzoic acids to GSK2981278A (**1**) had an overall yield of 41%.

Key words: RORγ, S_NAr, *N,O*-bisalkylations, phase transfer catalysis.

Introduction

Psoriasis vulgaris is a chronic autoimmune inflammatory skin condition resulting from an interaction of genetic, environmental and systemic factors and it affects 2–3% of the Caucasian population.[1] IL-17-targeting biologics have been successful in reducing the disease burden of psoriasis patients with moderate-to-severe disease.[2,3] Unfortunately, the stratum corneum prevents penetration of proteins with large molecule weights, including monoclonal antibodies. For most of psoriasis patients ineligible for systemic treatments, a small molecule targeting RORγ, the master regulator of IL-17 family cytokines, may represent an alternative topical medicine with biologic-like efficacy.[4] GSK2981278A (**1**), shown in Figure 1, is a potent RORγ inverse agonist. The program required a very large quantity of the drug substance to support development of a topical formulation and clinical studies. The synthetic target can be viewed as 2-(hydroxymethyl)phenol (salicylic alcohol), with the phenol capped as the (tetrahydro-2*H*-pyran-4-yl)methyl ether and the *para* position functionalized as the sulfonamide with 4-ethyl-*N*-isobutylaniline.

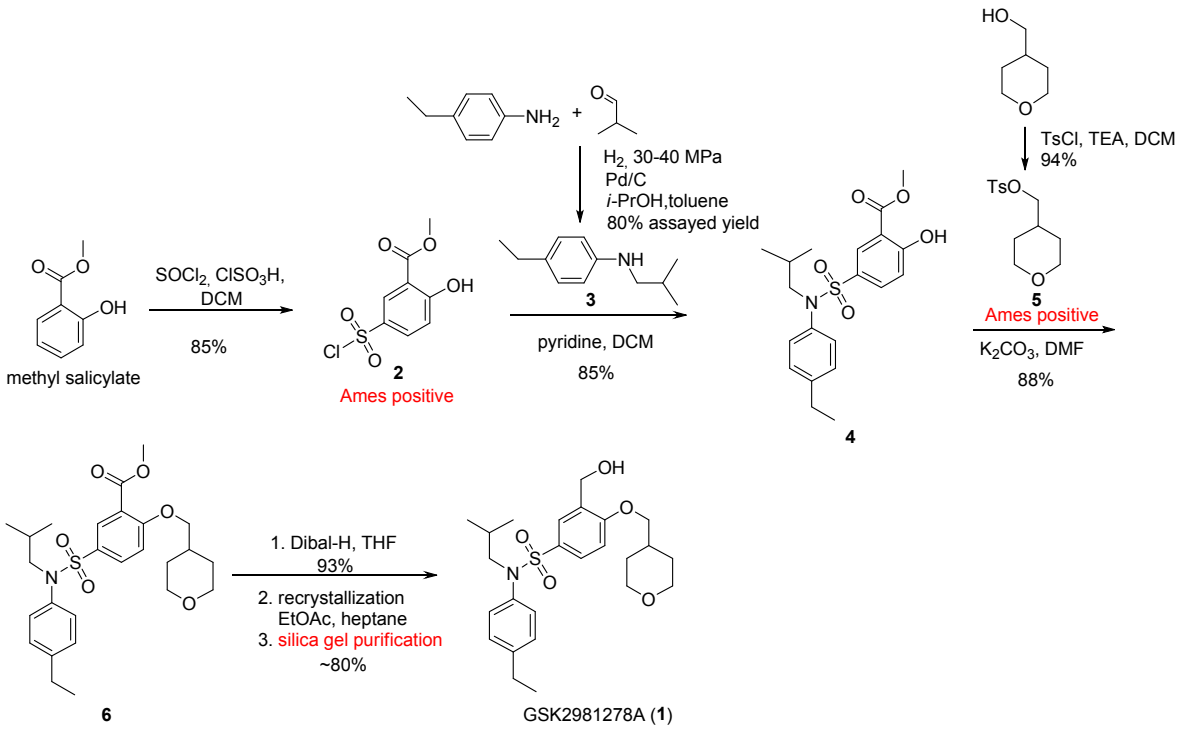


GSK2981278A (**1**)

Figure 1. Structure of RORγ inverse agonist GSK2981278A (**1**).

The original synthesis of **1** is shown in Scheme 1. The synthesis started with the *p*-chlorosulfonylation of methyl salicylate to give aryl sulfonyl chloride **2**, which reacted with 4-ethyl-*N*-isobutylaniline **3** to provide sulfonamide **4**. Alkylation of the phenol with tosylate **5**, derived from (tetrahydro-2*H*-pyran-4-yl)methyl alcohol, led to ether **6**. Finally, reduction of the methyl ester followed by recrystallization gave **1**. While the overall yield of the synthesis was high, chromatography had to be employed at the end of the synthesis in the delivery of 25 kg of **1** to remove an amine impurity derived from the reductive amination of butyraldehyde and 4-ethylaniline in the preparation of the 4-ethyl-*N*-isobutylaniline **3**. The reductive amination could not be cleaned up readily on scale, so the crude product in ~80% assayed yield was used directly. Additionally, compounds **2** and **5** were Ames positive and were subject to strict control in the analytical release of the drug substance based on the predicted treatment dose and duration.

Scheme 1. Original Synthesis of GSK2981278A (1)



Two new routes to **1** were explored as shown in Figure 2. The first approach would need the selective mono α-hydroxymethylation via a phenol formaldehyde reaction. The phenol substrate would be prepared from commercially available sodium 4-hydroxybenzenesulfonate or the less stable 4-hydroxybenzenesulfonyl chloride. The other approach would introduce the (tetrahydro-2*H*-pyran-4-yl)methyl ether via a nucleophilic aromatic substitution (S_NAr) on an aryl halide. Palladium catalyzed C-O bond formation would be another possibility for this substrate. 2-Halobenzoic acids are readily available for this approach.

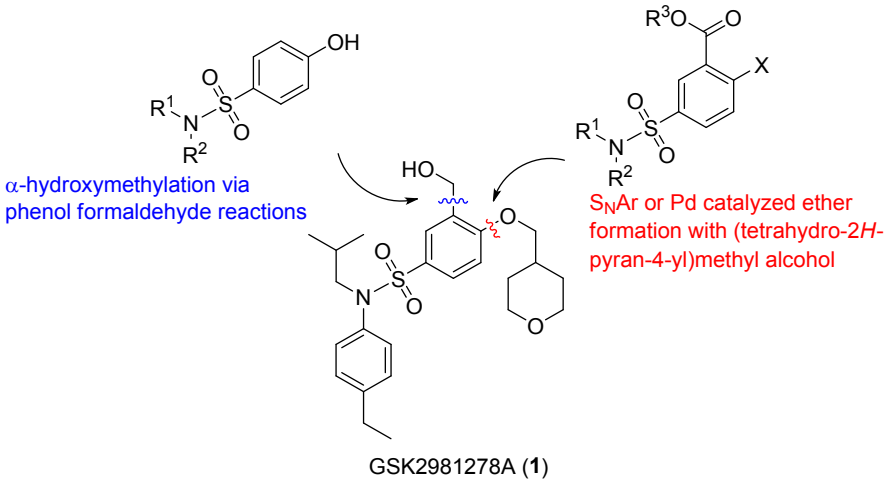


Figure 2. New approaches to **1** based on phenol formaldehyde reactions or S_NAr reactions.

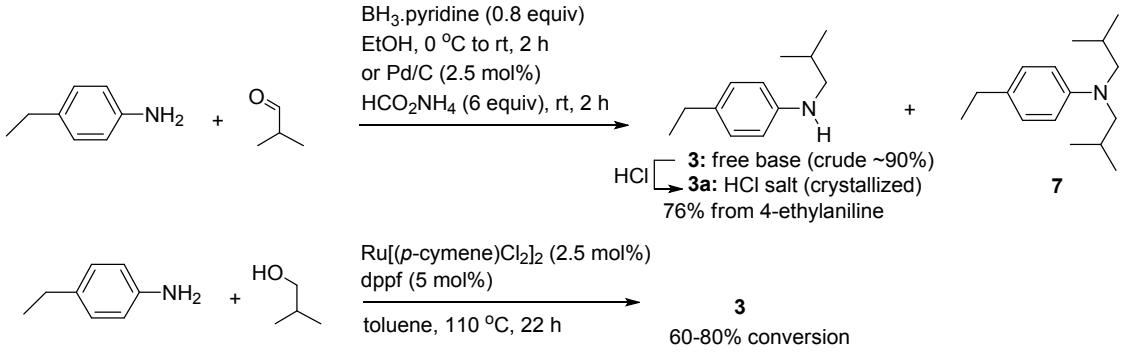
We herein report our findings in the execution of the new synthetic strategies, which led to a significantly improved synthesis. Over 125 kg of **1** was delivered with the new route utilizing the efficient S_NAr reactions of 2-halo-5-(sulfamoyl)benzoic acids. The synthesis was further optimized with the principles of process safety and green chemistry to provide an even more practical solution with phase transfer catalysis to enable a *N,O*-bis-alkylation under very mild conditions.

Results and Discussion

To avoid the byproduct formations and the conditions under high pressure in the preparation of 4-ethyl-*N*-isobutylaniline (**3**) from isobutyraldehyde and 4-ethylaniline, we sought alternative approach shown in Scheme 2. Reductive amination with borane pyridine complex was reported to be generally very rapid.[5] Over alkylation to **7** occurred to some degree. Fortunately, amine **7** was

not reactive for the next step, so the crude product containing up to 8% of **7** could be used without chromatographic purification. Transfer hydrogenation worked well to avoid the use of hydrogen.[6] Free base **3** was converted to the HCl salt **3a** as a solid for higher purity and easier handling. To solve the problem of over-alkylation, a borrowing hydrogen approach was tested with isobutyl alcohol and 4-ethylaniline.[7] Under the condition shown with 2.5 mol% of the Ru catalyst, the reaction was clean without over-alkylation to tertiary amine **7**, but conversion was only 60%. Addition of extra catalyst or longer heating time was able to achieve higher conversion of 80%, albeit with a less clean reaction profile. Ultimately, the optimization was not carried out for the borrowing hydrogen method.

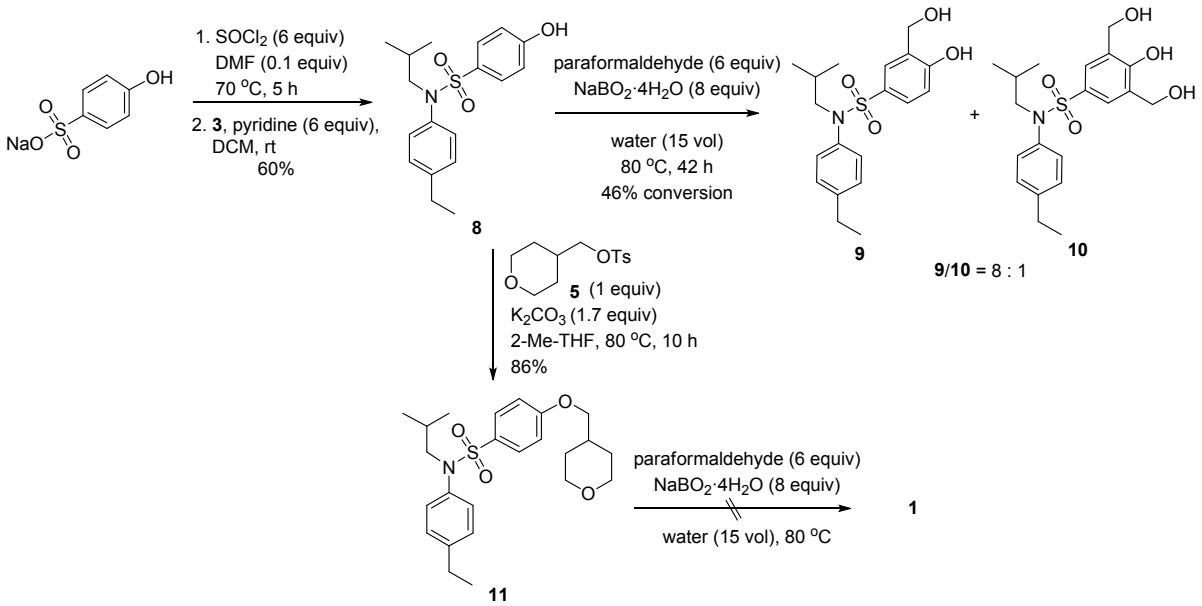
Scheme 2. Preparation of 4-Ethyl-*N*-isobutylaniline 3 by Reductive Amination with Isobutyraldehyde and Borrowing Hydrogen Methodology with Isobutyl Alcohol



The α-hydroxymethylation of a phenol via Friedel-Crafts reaction (Figure 2) was very attractive to us as it would only take three steps from the readily available 4-hydroxybenzenesulfonyl chloride to obtain target **1**. The synthesis of salicylic alcohol templates from a phenol via this approach is reported.[8] Our result from this effort is shown in Scheme 3. Sulfonamide **8** was

prepared from amine **3** and 4-hydroxybenzenesulfonyl chloride prepared in situ from the reaction of the sodium salt precursor and $SOCl_2$ with a catalytic amount of DMF. Caution is warranted due to the potential formation of carcinogenic *N,N*-dimethyl carbamoyl chloride (DMCC) from the use of DMF with $SOCl_2$.[9] Reaction of **8** with paraformaldehyde, catalyzed by sodium metaborate, provided an 8:1 mixture of the desired mono-hydroxymethylated product **9** and the bis-hydroxymethylated side product **10** in only 46% conversion. Optimization for higher conversion led to even more of **10** from the bis-hydroxymethylation. Alternatively, phenol **8** was reacted with tosylate **5** in 85% yield to give ether **11**. Hydroxymethylation of **11** did not proceed to yield product **1**.

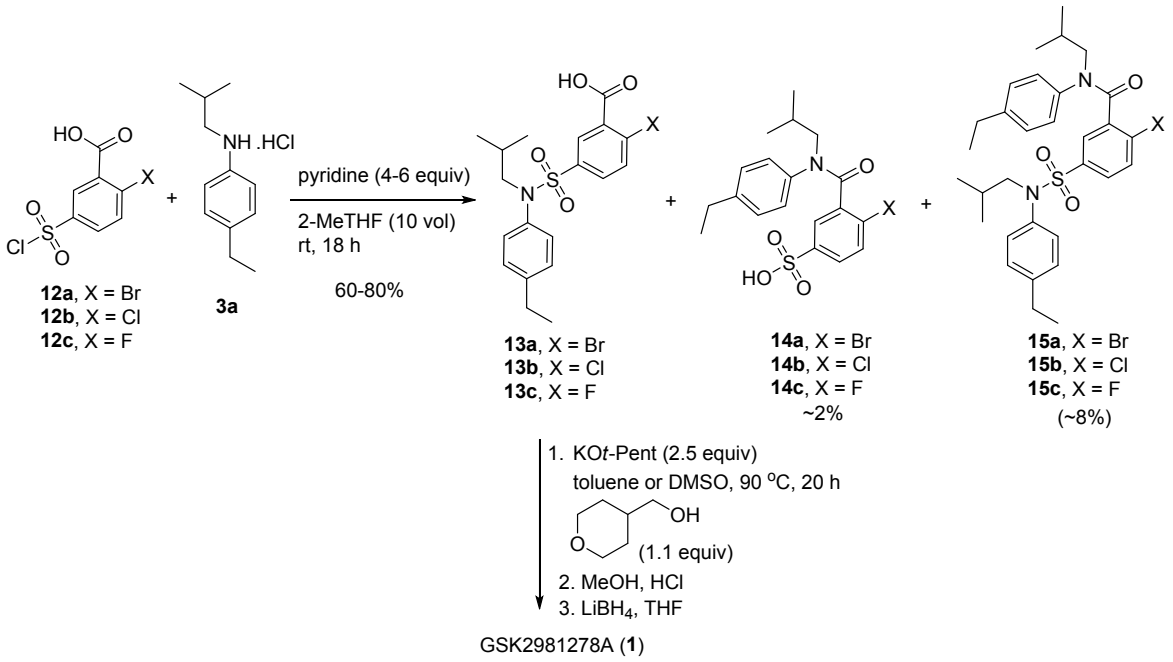
Scheme 3. **α-Hydroxymethylation Approach via Friedel-Crafts Reactions**



We next explored the S_NAr approach shown in Figure 2 to install the ether moiety through reaction of an aryl halide with (tetrahydro-2*H*-pyran-4-yl)methanol as the nucleophile.[10] Genotoxic tosylate **5**, utilized in the original synthesis, should be avoided. The aryl sulfonyl chlorides **12a-c** are commercially available in small quantities, and they could be readily prepared from the corresponding 2-halobenzoic acids and chlorosulfonic acid.[11]

The sulfonamide formation between 4-ethyl-*N*-isobutylaniline **3** or its HCl salt **3a** and 5-(chlorosulfonyl)-2-halobenzoic acids **12a-c** proved more challenging than anticipated as shown in Scheme 4. In addition to the desired sulfonamide **13a-c**, the reaction yielded amide byproducts **14** and **15** in significant quantities, requiring careful purifications. These byproducts likely derived from mixed anhydrides formed from the starting carboxylic acid and sulfonyl chloride in **12**. The mixed anhydrides reacted with the amine **3** to generate **14** and **15**. Significant efforts including use of Design of Experiments (DOE) tool were not able to minimize the formation of **14** and **15** to a level suitable for isolation by crystallization on scale. Bases such as pyridine, ethyl nicotinate and sodium bicarbonate favored the generation of the desired sulfonamide **13**, while tertiary amine bases such as triethylamine and Hünig's base led to mostly the byproducts. The S_NAr reactions of **13a-c** with (tetrahydro-2*H*-pyran-4-yl)methanol with potassium t-pentoxide were clean. The ether product was converted to **1** by ester formation (MeOH and HCl) and reduction of the methyl ester by $LiBH_4$ as shown in Scheme 4. However, the difficulty in preparation and purification of **13a-**c led us to pursue an alternative sequence shown in Scheme 5. It is worth mentioning that the chloride **13b** was also successful for use in coupling with (tetrahydro-2*H*-pyran-4-yl)methanol through Pd-catalyzed ether formation, as an alternative to the S_NAr reaction.

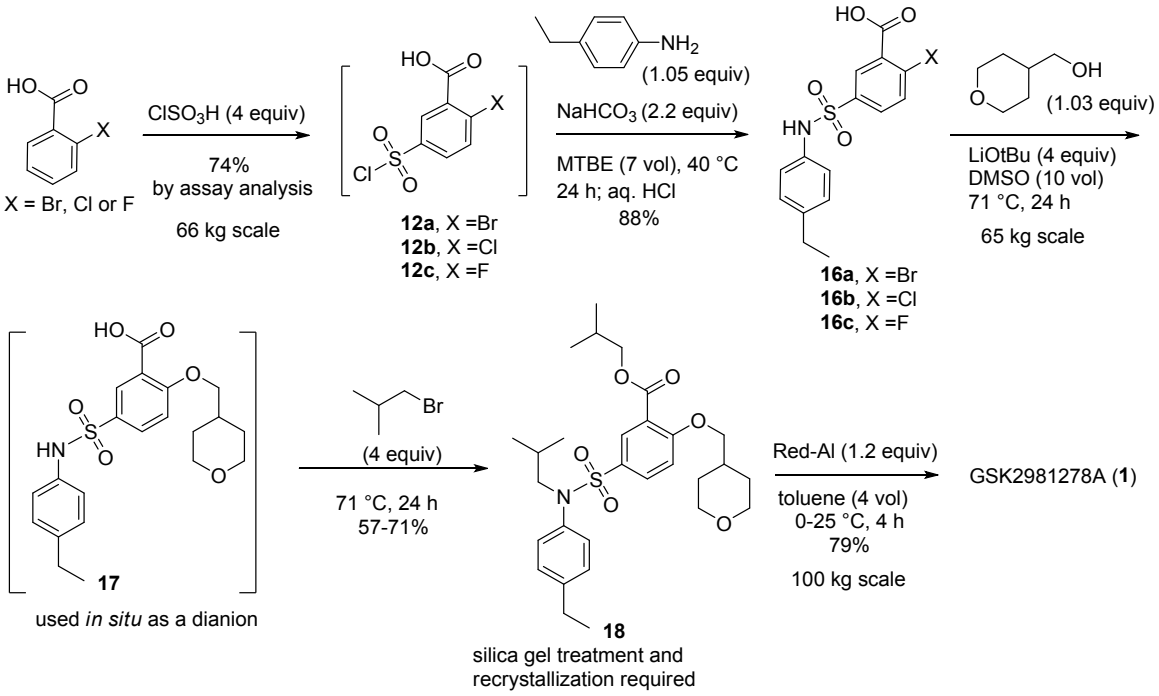
Scheme 4. **Unexpected Byproduct Formation in Preparation of Arylsulfonamide 13a-c**



We were interested in compounds such as **16** shown in Scheme 5 as a substrate for the S_NAr reaction. Several potential benefits were envisioned with this sequence: elimination of the need for reductive amination to prepare secondary amine **3**, sulfonamide formation with less basic 4-ethylaniline to avoid the formation of the corresponding byproducts similar to **14** and **15**, and one-pot preparation of **18** by sequential ether formation to **17** via the S_NAr reaction and *in situ N,O*-bis-isobutylation of the dianion of **17**. The new route turned out to be successful with all three compounds **13a-c**, and all the anticipated benefits were realized. The sequence starting with 2-fluorobenzoic acid shown in Scheme 5 was selected for successful scale up to deliver >125 kg of GSK2981278A (**1**). This decision was made before a much milder process for the bis-alkylation via phase transfer catalysis was developed and became available, due to the urgent need of a large

quantity of drug substance **1** to support the program. Aryl fluoride **16c** was preferred because of the slightly lower temperature and shorter reaction time required relative to the bromide **16a** and chloride **16b** for the S_NAr reactions.

Scheme 5. Synthesis of 1 on Scale and with Conditions and Yields Shown for the Fluoro Series



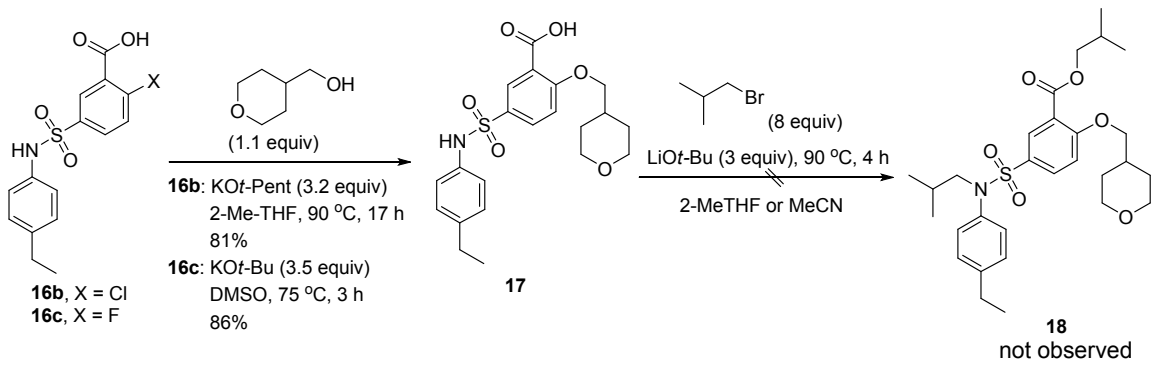
5-(Chlorosulfonyl)-2-fluorobenzoic acid **12c** was commercially available but the relatively low stability and the high cost made it more practical to prepare from 2-fluorobenzoic acid for the large campaign to supply >100 kg of **1**. The solution of crude **12c** in MTBE was used directly in the amide formation with 4-ethylaniline to form sulfonamide **16c** in 88% yield. As expected, the reaction with 4-ethylaniline was cleaner than the analogous reaction with 4-ethyl-*N*-isobutylaniline

3. The ether **17** was successfully installed via the key S_NAr reaction of the aryl fluoride **16c** with the lithium salt of (tetrahydro-2*H*-pyran-4-yl)methanol. However, DMSO and elevated temperature (>90 °C) had to be used in the presence of a large amount (4 equiv) of a strong base to achieve a clean and complete S_NAr reaction for yields ranging 90-95%. The strong condition was needed likely due to decreased activity of the Ar-X, as a dianion derived from **17** by the deprotonation, towards the S_NAr reaction. This step was telescoped with a double *N*-, *O*-alkylation with isobutyl bromide to provide ester **18**, which was isolated by filtration after addition of water to the reaction mixture. Process safety test showed that the combination of DMSO and lithium *t*-butoxide was a significant safety risk at 90 °C for an extended period. Thus, only up to 71 °C was allowed for this reaction in the scaleup in the plant as shown in Scheme 5. This led to incomplete reaction and byproduct formation derived from the degradation during the long heating including formation of methylpropene. Rework of intermediate **18** by treatment with silica gel, followed by recrystallization, was needed. This ultimately led to lower yield of **18** in the scaleup (57-71% for the three runs in the plant). Ester **18** was readily reduced with Red-Al (sodium bis(2-methoxyethoxy)aluminum hydride) to give the API GSK2981278A (**1**) in 79% yield. The Red-Al was much more economical and practical than the Dibal-H in the original reduction of the same substrate. The overall yield for the sequence shown in Scheme 5 was 29-37%. This route was short but the safety concern of heating lithium *t*-butoxide and DMSO over a prolonged period prevented us from designating this route as the manufacturing route. The degradation of isobutyl bromide in the heated t-butoxide was also a major concern.

To reduce the amount of time DMSO was exposed to a strong base with heating (up to two days from **16** to **18**, see Scheme 5), we divided the one-pot process from **16** to **18** into two discreet stages, with isolation of **17** as shown in Scheme 6. This would be followed by bis-isobutylation in another solvent such as THF and MeCN, safer than an aprotic polar solvent like DMSO in the presence of a strong base.[12]

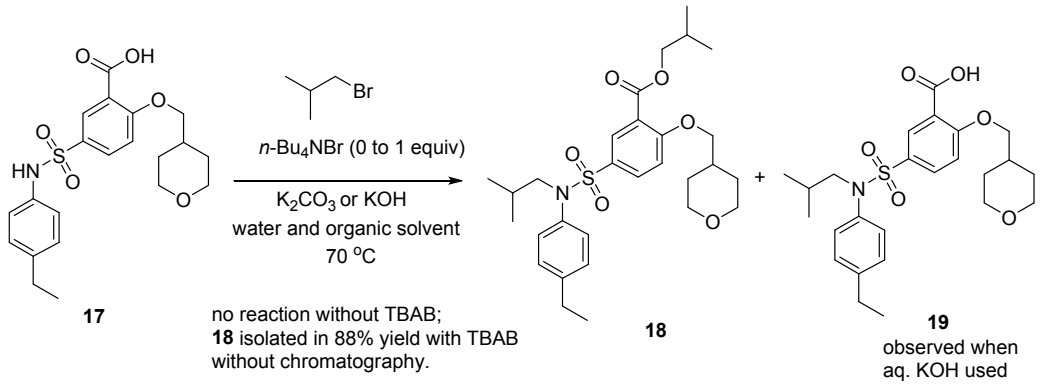
The S_NAr process on **16**, as shown in Scheme 6, provided **17** smoothly as a crystalline solid in 81% and 86% yield, resepctively from **16b** and **16c**. Aryl fluoride **16c** was again preferred for the process to provide **17** as an isolated intermediate at 75 ^oC. Analogous chemistry with aryl chloride **16b** required 90 ^oC and 14 hours longer. The safety issue of heating DMSO in the presence of a strong base is well known.[13] Use of the lowest temperature and heating time is warranted, when a strong base cannot be avoided as in our S_NAr reactions. For the subsequent bis-alkylation, contrary to our expectation, we found that there was no product observed even with 8 equivalents of isobutyl bromide and 3 equivalents of lithium *t*-butoxide in 2-MeTHF or MeCN. It appeared that the dianion from reaction of a strong base and **17** precipitated out unless an aprotic polar solvent like DMSO or DMF was used. This likely inhibited the alkylations in solvents other than DMSO and DMF.

Scheme 6. Two-stage Approach from 16 to 18 with 17 Isolated

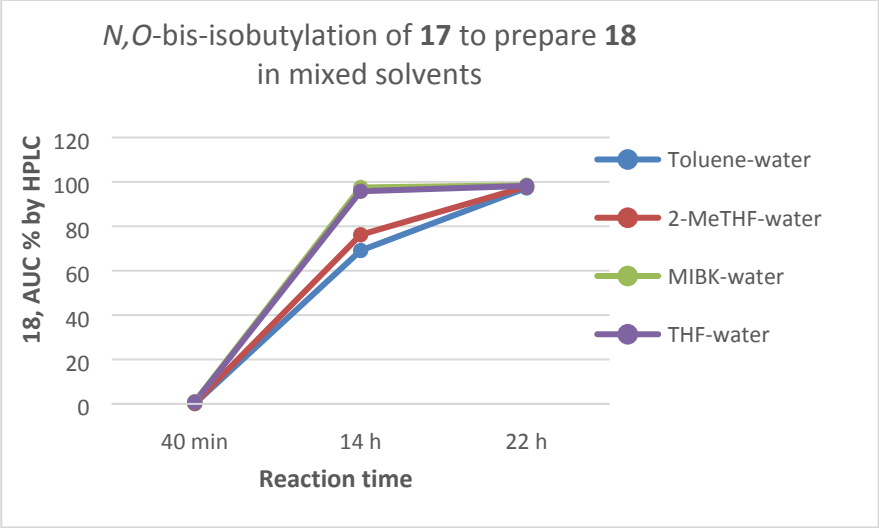


It was postulated that a phase transfer catalysis (PTC) would be suitable for alkylation or bis-alkylation of the dianion of **17**.[14] As a proof of concept (Scheme 7), **17** was dissolved in THF (15 vol) and treated with a stoichiometric amount of tetrabutylammonium bromide (TBAB) and isobutyl bromide (6 equiv) in two reactions with K_2CO_3 and KOH, respectively. Gratifyingly, the bis-isobutylated product **18** was detected by HPLC after just 30 min at ambient temperature. The reaction with K_2CO_3 was complete and very clean after 10 h at 70 °C, while the reaction with KOH afforded 45% of the targeted *N,O*-bis-isobutylation product **18**, along with 55% of the *N*-isobutyl product **19** (Scheme 7). The mono-alkylated product in aqueous KOH was probably caused by the competitive ester hydrolysis. While KOH may have been adopted with optimization of the aqueous *p*H in the manner described by King and co-authors,[15] we chose K_2CO_3 for the next phase of optimization. In contrast, there was no alkylated product in the absence of TBAB. In a test run with 0.4 equivalent of TBAB and 50 wt% aqueous K_2CO_3 (2 vol) in 2-MeTHF (9 vol) at 70 °C, product **18** was isolated in 88% yield without chromatography as shown in Scheme 7. The mild conditions contrasted with the harsh and failed conditions in Schemes 5 and 6 for the bis-alkylation with lithium *t*-butoxide at up to 90 °C.

Scheme 7. Proof of Concept for Green *N,O*-Bis-isobutylation of 17 by Phase Transfer Catalysis (PTC)



A solvent screening was then carried out with K_2CO_3 as the base as shown by the area under curve (AUC%) of product **18** in Figure 3. With a 9:1 v/v mixture of an organic solvent and water, the reaction was fastest with THF and MIBK, but slower in toluene. All reactions reached completion after just 22 h. Screening on single solvents was then carried out as shown on the bottom chart of Figure 3 All reactions were clean with the reaction in MeCN slightly faster than the three other solvents. The reaction in water was worked up by acidification and direct filtration to give **18** as a crystalline solid of 100% purity. No product was detected in the aqueous mother liquor by HPLC analysis, indicating a clean reaction and excellent recovery with water as the solvent.



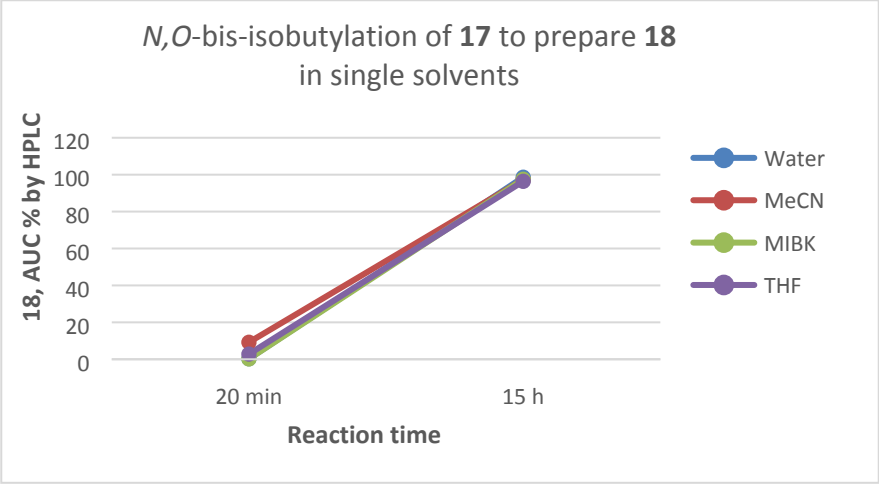


Figure 3. Solvent screening for PTC: TBAB (0.2 equiv), *i*-BuBr (4 equiv), K_2CO_3 (4 equiv), 70 °C. Top chart: mixed organic solvents and water. Bottom chart: single solvents.

In the scaleup with water as a single solvent, it was noted that isobutyl bromide (bp 90-92 °C) was partially lost to evaporation due to its high volatility. The poor immiscibility with water was another factor, leaving isobutyl bromide on top of the reaction mixture when not well agitated.

This led to incomplete reaction, unless a closed system was used as in the screening in tubes equipped with a screw cap. It was predicted that MeCN as the single solvent should not have this issue as MeCN is fully miscible with isobutyl bromide. This proved to be the case as shown in Figure 4. The reaction kinetics in MeCN were compared for two reactions: one in a round bottle flask connected to a nitrogen line and the other in a sealed tube. Clearly the sealed reaction was faster at the 4th hour. After 17 h, both reactions reached completion and was very clean as shown by the amount of product **18** by HPLC.

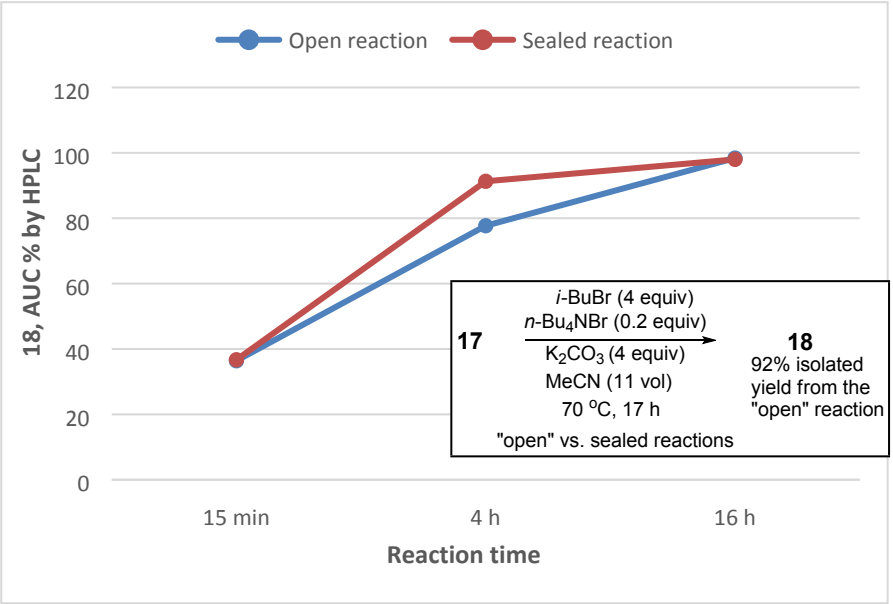


Figure 4. *N,O*-Bis-isobutylation of **17** to **18,** sealed tube vs. flask "open" to nitrogen line.

The conditions shown in Figure 4 were run in 2 g scale in a regular round bottle flask (10 vol of MeCN, 70 °C, 15 h) to provide 92% isolated yield of product **18** in 100% purity by HPLC, avoiding the need of silica gel chromatographic purification in the previous bis-alkylation with lithium *t*-butoxide in DMSO as shown in Scheme 5. The workup consisted of a simple addition of water to

dissolve K_2CO_3 for discharge as a concentrated homogeneous aqueous solution in the bottom layer. The top MeCN layer was partially concentrated to provide crystalline **18** for direct filtration. For water to be the single solvent for the bis-isobutylation, a closed vessel had to be used and the isolated yield of **18** was 87% without optimization.

The PTC reaction worked equally well for the related 2-halo-5-(sulfamoyl)benzoic substrates **16b** and **16c**, indicating some substrate scope for the PTC catalyzed *N, O*-bis-alkylation.

Intermediate **18** from the safe PTC process was converted to GSK2981278A (**1)** under the same reduction conditions with Red-Al as shown in Scheme 5. Although the PTC process has not been scaled up in the plant, it has demonstrated consistency from milligram scale in screening in tubes to gram scale in flasks for both reaction profile and purity of isolated product. Ultimately, we expect to use water as the solvent on scale for this reaction with easier containment of the volatile *i*-BuBr in a plant setting and truly achieve "green" status for the alkylation. This route was expected to be designated as the manufacturing route for the much safer and cleaner *N,O*-bis-isobutylation. The overall yield from 2-fluorobenzoic acid was 41% (65% for sulfonylation/sulfonamidation from 2-F-PhCO_2H to **16**, 86% for S_NAr from **16** to **17**, 92% for the PTC bis-alkylation from **17** to **18**, and 79% for reduction of **18** to **1**). Despite being one stage longer for the isolation of **17**, the overall yield for the new route including the PTC bis-alkylation was higher than the 29-37% yield for the 3-stage sequence shown in Scheme 5, which required lengthy heating of lithium *t*-butoxide in DMSO and purification with silica gel and recrystallization.

Conclusion

GSK2981278A (**1**) was synthesized in four stages by the new route starting from 2-halobenzoic acids in ~41% overall yield. The high efficiency was attributed to the well-chosen nucleophile (4-ethylaniline) for the formation of the 2-halo-5-(sulfamoyl)benzoic acids, the dianions of which were excellent substrates for S_NAr reactions with (tetrahydro-2*H*-pyran-4-yl)methanol. Mild and efficient *N,O*-bis-isobutylation via phase transfer catalysis was successfully developed for the *N,O*-bis-alkylations of the S_NAr products. Compared to the original synthesis starting from methyl salicylate, the new synthesis eliminated a reductive amination for amine **3**, a genotoxic tosylate intermediate (**5**) and chromatographic purifications. A version of the new route has been utilized to deliver >125 kg of GSK2981278A (**1**) in the plant, with one example of the S_NAr reactions scaled up to 60-70 kg three times. The facile S_NAr reactions and the mild *N,O*-bis-alkylations should find applications in a wider scope of substrates.

Experimental Section

General Procedures. All reactions were run under nitrogen. Unless otherwise specified, concentration by rotary evaporation or distillation was carried out under house vacuum of 12-50 torr. Melting points were measured in Mettler Toledo MP 90 Melting Point System at 3 °C/min ramp, and the results were not corrected. All NMR spectra were acquired at ambient temperature on a Bruker 400 MHz spectrometer. Solvents and frequencies for specific data acquisitions are noted for each case in the following sections. Chemical shifts were calibrated relative to residual protio solvent (^{1}H and ^{13}C). Data were processed using ACD Spectrus. HPLC analysis was

performed on Agilent 1260 or 1290 series instruments with diode array detectors, though analysis was typically done with traces from a single wavelength. Two HPLC methods were utilized during this work: Method A: Column: Zorbax SB-C18, 1.8 μm, 3 mm x 50 mm; column temperature: 60 °C; flow rate: 1.5 mL/min; solvent gradient: ACN (0.05% TFA v/v) / H_2O (0.05% TFA v/v), from 100/0 to 5/95 over 2.7 min; detection wavelength: 220 nm. Method B: Column: Phenomenex Luna C18(2), 3.0 μm, 5 mm x 20 mm; column temperature: 40 °C; flow rate: 1.0 mL/min; solvent gradient: ACN (0.05% TFA v/v) / H_2O (0.05% TFA v/v), from 100/0 to 5/95 over 8 min; detection wavelength: 220 nm. HRMS (m/z) was measured using an Exactive Plus (Thermo) orbitrap mass spectrometer equipped with a heated electrospray ionization (HESI) ion source.

4-Ethyl-N-isobutylaniline and the Hydrochloride Salt (3/3a). A. Through Reductive Amination of Isobutyraldehyde with Borane Pyridine Complex. To a 500 mL flask was added 12.0 g (99 mmol) of 4-ethylaniline and 10.7 g (149 mmol) of isobutyraldehyde. The mixture was stirred for 10 min with visible solids from the formation of the imine, followed by addition of 60 mL of EtOH. The mixture was cooled to 20 °C, and 7.36 g (79.2 mmol) of pyridine borane complex was added over about 10 min. At the end of the addition, generic HPLC Method A showed 94% of product **3a** at retention time of 1.9 min and 1.9% of the over-alkylated 7 at retention time of 2.4 min. However, the amounts of **3** and **7** changed to 88% and 8%, respectively after stirring for 2 h at ambient temperature. The reaction was quenched with 40 mL of water, treated with 20 mL of 1 N HCl and stirred for 10 min.[16] The mixture was extracted with 100 mL of DCM, and the organic layer was successively washed with 50 mL each of 0.5 N HCl, saturated $NaHCO_3$ and 25 wt%

NaCl, dried over anhydrous Na_2SO_4 and evaporated to 18.7 g of crude **3**, which was used directly for the next step as a free base or further purified as the HCl salt **3a** as shown in *method B* below.

B. Through Reductive Amination of Isobutyraldehyde by Transfer Hydrogenation. To a 500 mL 3-neck flask fitted with a magnetic stir bar and an immersion thermometer was charged 180 mL of isopropanol, followed by 20 mL of water. The flask was sealed except for the middle neck and flushed through with nitrogen for 5 min. To the mixture was added 8.78 g (4.15 mmol) of 5 wt% Pd/C, followed by portion-wise addition of 62.4 g (990 mmol) of ammonium formate. After being cooled to 16 ^oC, the mixture was treated with 20.5 mL (165 mmol) of 4-ethylaniline, followed by 19.6 mL (215 mmol) of isobutyraldehyde in one portion. The flask was sealed under nitrogen and stirred at ambient temperature for 1.5 h, at that point the reaction was deemed complete by complete consumption of the starting aniline by HPLC Method A (1.52 min). The reaction was filtered over Celite, and the flask was successively rinsed with 40 mL of toluene, 40 mL of water and 360 mL of toluene until no product was observed in the effluent by HPLC Method A (2.01 min). The biphasic solution was transferred to a separatory funnel and washed with 2 x 200 mL of water. The layers were split, and the organic layer was washed with 2x70 mL of saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated on a rotovap to give free base **3** as an oil.

An anhydrous solution of HCl in EtOAc was prepared by addition of 14.1 mL (198 mmol) of acetyl chloride to 10.0 mL (248 mmol) of methanol in 110 mL of ethyl acetate. The free base **3** prepared above was dissolved in 70 mL of EtOAc, followed by the slow addition of the above anhydrous HCl solution. The reaction darkened immediately, and a white precipitate formed about

half way through the addition. Addition of 50 mL of MeOH and heating to near reflux dissolved the solids. After being cooled to ambient temperature, the mixture was seeded with granules of 4-ethyl-*N*-isobutylaniline hydrochloride (**3a**). Crystallization was so rapid that 50 mL of 1:1 solution of EtOAc and heptane was added to aid the stirring. After being cooled to 0 °C, the mixture was treated with 30 mL of heptane, filtered, washed with 100 mL of 1:1 EtOAc-heptane and dried at 40 °C to give 26.83 g (76%) of the title compound **3a** as an off-white solid: mp. 147.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.2 (br s, 2 H), 7.52 (d, J = 7.5 Hz, 2 H), 7.18 (d, J = 7.7 Hz, 2 H), 3.05 (d, J = 7.1 Hz, 2 H), 2.62 (q, J = 7.6 Hz, 2 H), 2.12 (dquin, J = 13.5, 6.8 Hz, 1 H), 1.20 (t, J = 7.6 Hz, 3 H) 1.02 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.4, 133.4, 129.2, 123.4, 60.4, 28.5, 25.3, 20.4, 15.4. HRMS (ESI) *m/z* calcd for $C_{12}H_{20}N$ (MH^+ for free base **3**) 178.1590, found 178.1589.

C. Through Amination of Isobutyl Alcohol by Hydrogen Borrowing Method. To a 50 mL tube was successively added 253 mg (0.413 mmol) of $[Ru(p\text{-cymene})Cl_2]_2$, 457 mg (0.825 mmol) of dppf, 2.06 ml (16.5 mmol) of 4-ethylaniline, 3.06 ml (33.0 mmol) of isobutyl alcohol, and 16.5 mL of degassed toluene. The mixture was stirred under nitrogen at 110 °C for 22 h. After being cooled to ambient temperature, the reaction was analyzed by generic HPLC Method A which showed 60% conversion based on the ratio of **3** (2.01 min) to 4-ethylaniline (1.52 min). Additional 126 mg (0.206 mmol) of the $[Ru(p\text{-cymene})Cl_2]_2$ and 230 mg (0.415 mmol) of dppf was added and the reaction was stirred under nitrogen for additional 22 h at 110 °C. The reaction was cooled and sampled for analysis by generic HPLC Method A, which showed 80% conversion. This

reaction was run as a part of the screening of conditions for the hydrogen borrowing reaction and it was not worked up for product isolation.

(Tetrahydro-2H-pyran-4-yl)methyl 4-Methylbenzenesulfonate (5). To a 500 mL flask was added 14.0 g (121 mmol) of (tetrahydro-2*H*-pyran-4-yl)methanol, 112 mL of DCM and 25.2 mL (181 mmol) of triethylamine, followed by 29.9 g (157 mmol) of *p*-toluenesulfonyl chloride at room temperature. The reaction was slightly exothermic. After being stirred for 20 h at room temperature, the mixture was cooled with an ice batch and quenched with 120 mL of water. The layers were split, and the aqueous layer was back extracted with 50 mL of DCM. The combined organic layer was successively washed with 120 mL of water and 125 mL of 13 wt% NaCl and evaporated to 120 mL. Crystallization was occurred during the evaporation, and 40 mL of heptane was added for further crystallization. The mixture was cooled for 1 h, filtered, washed with 3x10 mL of heptane and dried at 60 ^{o}C to give 26.9 g (83 %) of **5** as a white crystalline solid: mp. 99.8 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 7.7 Hz, 2 H), 7.26 (d, J = 7.7 Hz, 2 H), 6.74 (m, 4 H), 3.78 (m, 2 H), 3.76 (d, J = 6.4 Hz, 2 H), 3.23 (td, J = 11.9, 2.2 Hz, 2 H), 2.35 (s, 3 H), 1.83 (m, 1 H), 1.48 (m, 2 H), 1.17 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 132.9, 129.9, 127.8, 74.2, 67.1, 34.6, 28.9, 21.6. HRMS (ESI) *m/z* calcd for $C_{13}H_{19}O_4S$ (MH^+) 271.0999, found 271.0997.

N-(4-Ethylphenyl)-4-hydroxy-N-isobutylbenzenesulfonamide (8). To a 100 mL flask was added 9.80 g (45.8 mmol) of 4-hydroxybenzenesulfonic acid sodium salt hydrate and 0.35 ml (4.58

mmol) of DMF, followed by 20.0 ml (275 mmol) of thionyl chloride at room temperature. The mixture was heated to 60-70 °C and stirred for 5 h. Excess thionyl chloride was removed by evaporation under vacuum (~15 torr) at 45 °C to produce a gel-like residue. After addition of 50 mL of toluene, the mixture was further evaporated under vacuum at 50 °C, followed by addition of 40 mL of DCM. Further evaporation gave a yellow oil, which was diluted with 30 mL of DCM to make a white slurry for direct use in the next step as 4-hydroxybenzenesulfonyl chloride.

To a 500 mL flask was successively added 9.91 g (50.3 mmol) of crude **3**, 30 mL of DCM and 21.7 g (275 mmol) of pyridine. After being stirred for 2 min at room temperature, 4-hydroxybenzenesulfonyl chloride in DCM as prepared above was added. The mixture was stirred for 30 min, cooled with an ice batch and quenched with 50 mL of 1 N HCl. The layers were split, and the DCM layer was successively washed with 50 mL of 1 N HCl and 50 mL saturated $NaHCO_3$ and 25 wt% NaCl, dried over anhydrous Na_2SO_4 and evaporated to give an oil. Crystallization was achieved by slow addition of about 30 mL each of DCM and heptane over 3 h and stirring overnight. The mixture was filtered, and the cake was washed with 3x5 mL of 3:1 heptane/DCM and dried at 65 °C to give 9.10 g (60 %) of **8** as a white crystalline solid: mp. 142.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 8.0 Hz, 2 H), 6.96 (d, J = 7.2 Hz, 2 H), 6.74 (m, 4 H), 3.10 (d, J = 7.3 Hz, 2 H), 2.47 (q, J = 7.6 Hz, 2 H), 1.39 (m, 1 H), 1.07 (t, J = 7.7 Hz, 3 H) 0.74 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 144.1, 136.7, 129.9, 129.4, 128.5, 128.4, 115.6, 58.0, 28.4, 26.7, 19.9, 15.3. HRMS (ESI) *m/z* calcd for $C_{18}H_{24}NO_3S$ (MH^+) 334.1468, found 334.1468.

N-(4-Ethylphenyl)-N-isobutyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (11): To a 100 mL flask was successively added 2.00 g (6.00 mmol) of phenol **8**, 1.62 g (6.00 mmol) of tosylate **5**, 16.0 mL of DMF and 1.33 g (9.60 mmol) of potassium carbonate. The mixture was heated at 100 °C for 18 h. After being cooled to room temperature, the reaction was quenched with 28 mL of water. The resultant white solids were filtered, washed with 3x10 mL of water and dried at 70 °C to give 2.22 g (86%) of **11** as an off-white crystalline solid: mp. 146.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 8.0 Hz, 2 H), 7.11 (m, 2 H), 6.92 (m, 4 H), 4.03 (dd, *J* = 11.3, 3.2 Hz, 2 H), 3.84 (d, *J* = 6.4 Hz, 2 H), 3.45 (td, *J* = 11.8, 2.1 Hz, 2 H), 3.25 (d, *J* = 7.3 Hz, 2 H), 2.63 (q, *J* = 7.6 Hz, 2 H), 2.08 (m, 1 H), 1.76 (br dd, *J* = 13.0, 2.0 Hz, 2 H), 1.51 (m, 3 H), 1.22 (t, *J* = 7.7 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 143.8, 137.0, 130.2, 129.8, 128.5, 128.3, 114.2, 72.8, 67.6, 57.9, 35.1, 29.6, 28.4, 26.7, 19.9, 15.3. HRMS (ESI) *m/z* calcd for $C_{24}H_{34}NO_4S$ (MH^+) 432.2203, found 432.2203.

2-Bromo-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)benzoic Acid (13a). To a 50 mL flask was added 1.30 g (4.34 mmol) of **12a** and 11 mL of DCM. The solution was cooled with a water bath of 20 °C, followed by addition of 1.03 g (5.21 mmol) of crude **3** as a solution in 3 mL DCM and 2.11 mL (26.0 mmol) of pyridine over about 3 min. After being stirred at room temperature for 1 h, the reaction was quenched by 20 mL water, diluted with 20 mL DCM and further treated with 30 mL of 1 N HCl (*p*H ~4). Layers were split, and the DCM layer was successively washed with 50 mL of 1 N HCl and 50 mL of 25 wt% NaCl, dried over anhydrous Na_2SO_4, filtered and evaporated under 40 torr at 40 °C to about 30 mL. Crystallization was initiated after about 15 mL

of heptane was added. After being stirred for 30 min, the mixture was filtered, washed with 2x5 mL of 3:1 heptane/DCM and dried at 70 °C under vacuum to give 1.20 g (63%) of **13a** as a white crystalline solid: mp. 176.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 2.0 Hz, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.50 (dd, J = 8.3, 2.2 Hz, 1 H), 7.16 (m, 2 H), 6.97 (m, 2 H), 3.33 (d, J = 7.3 Hz, 2 H), 2.66 (q, J = 7.6 Hz, 2 H), 1.11 (m, 1 H), 1.24 (t, J = 7.6 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 144.5, 138.1, 136.1, 135.4, 131.9, 131.2, 131.0, 128.7, 128.3, 127.3, 58.2, 28.4, 26.8, 19.8, 15.3. HRMS (ESI) *m/z* calcd for $C_{19}H_{23}BrNO_4S$ (MH^+) 440.0526, found 440.0529.

2-Chloro-5-(N-(4-ethylphenyl)-N-isobutylsulfamoyl)benzoic Acid (13b). To a 100 mL flask was successively added 2.64 g (12.4 mmol) of **3a**, 9 mL of DCM and 3.80 mL (47.0 mmol) of pyridine at room temperature, followed by addition of 3.00 g (11.8 mmol) of **12b** as a solution in 20 mL of DCM over about 15 min. After being stirred for 25 min, the reaction was sampled and analyzed by HPLC Method B which showed **13b** (6.16 min), **14b** (5.05 min) and **15b** (8.09 min) in normalized AUC of 92.4%, 1.8% and 5.8%, respectively. After being stirred for additional 30 min, the reaction was quenched with 50 mL of 1 N HCl. Layers were split, and the aqueous layer was extracted with 30 mL of DCM. The combined DCM layers were successively washed with 30 mL of 1 N HCl and 30 mL of 25 wt% NaCl and evaporated under 170 torr at 30 °C. Crystallization began when the volume was reduced to ~30 mL. After addition of 30 mL of hexanes, the mixture was stirred for 30 min, filtered, washed with 2x15 mL of hexanes and dried at 75 °C to give 3.69 g (79%) of **13b** as a crystalline solid: mp. 162.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J =

2.2 Hz, 1 H), 7.59 (m, 2 H), 7.16 (m, 2 H), 6.97 (m, 2 H), 3.33 (d, J = 7.6 Hz, 2 H), 2.66 (q, J = 7.6 Hz, 2 H), 1.61 (dquin, J = 13.6, 6.9 Hz, 1 H), 1.24 (t, J = 7.7 Hz, 3 H), 0.93 (d, J = 6.6 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 144.5, 139.1, 137.5, 136.1, 132.1, 132.0, 131.4, 129.0, 128.7, 128.3, 58.2, 28.4, 26.8, 19.8, 15.3. HRMS (ESI) *m/z* calcd for $C_{19}H_{23}ClNO_4S$ (MH^+) 396.1031, found 396.1031.

2-Chloro-5-(N-(4-ethylphenyl)sulfamoyl)benzoic Acid (16b). To a 100 mL flask was successively added 1.57 g (12.9 mmol) of 4-ethylaniline, 2.85 mL (35.3 mmol) of pyridine and 30 mL of dichloromethane. The mixture was cooled to 0 °C, and 3.00 g (11.8 mmol) of **12b** was added in 5 portions over 5 min. The mixture was warmed to room temperature and stirred for about 30 min. The reaction was quenched with 50 mL 1N HCl, vigorously stirred for 10 min, filtered, washed with 2x30 mL of water and dried at 60 °C to give 3.20 g (80%) of **16b** as a white solid: mp. 205.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.9 (br s, 1 H), 10.3 (s, 1 H), 8.12 (d, J = 2.2 Hz, 1 H), 7.77 (m, 2 H), 7.09 (m, 2 H), 6.99 (m, 2 H), 2.46 (q, J = 7.7 Hz, 2 H), 1.09 (t, J = 7.7 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 140.4, 138.5, 136.4, 134.6, 132.0, 131.9, 130.3, 129.1, 128.5, 121.3, 27.4, 15.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}ClNO_4S$ (MH^+) 340.0400, found 340.0399.

2-Fluoro-5-(N-(4-ethylphenyl)sulfamoyl)benzoic Acid (16c). To a reactor was added 66.0 kg (471 mol) of 2-fluorobenzoic acid and 275 kg (1943 mol) of chlorosulfonic acid under nitrogen. The mixture was heated to 75-85 °C and stirred for 14 h. After being cooled to 15 °C, the reaction

was transferred slowly to 528 L of water, which was pre-cooled to 0 °C in another reactor, maintaining the temperature below 10 °C throughout the quench. The mixture was filtered and washed with water 66 kg of water. The wet cake was dissolved in 462 L of MTBE, and the solution was washed with 66 L of saturated NH_4Cl at 10 °C and then concentrated to about 198 L. Additional 462 L of MTBE was added, and the solution was again concentrated to about 200 L. About 300 L of MTBE was added to make 479 kg of the solution of **12c** in MTBE for use in the next transformation. Assay analysis showed 17.4 w/w% of **12c.** This corresponded to 83.4 kg (74%) of **12c** with purity of 99% by HPLC and water content of 0.09% by KF method.

To a separate reactor was successively added 44.0 kg (363 mol) of 4-ethylaniline, 580 L of MTBE and 64.1 kg (763 mol) of $NaHCO_3$ under nitrogen. The mixture was heated and stirred at 40 °C, then 82.8 kg (347 mol) of **12c,** as the 17.4 w/w% solution in MTBE above, was added slowly over 1.5 h to minimize the risk of sudden gas evolution. The mixture was stirred for 24 h at 40 °C. After being cooled to 15 °C, the reaction was quenched with 414 L of water. The *p*H was adjusted to 1-2 with concentrated HCl at 15 °C, and the mixture was stirred for 30 min. Layers were separated, and the organic layer was treated with 828 L of water. The *p*H was adjusted to about 10 with solid KOH and the mixture was stirred for 30 min. Layers were separated, and the aqueous layer was transferred to another reactor, and the *p*H was adjusted to 1-2 with 2 N HCl. The resultant slurry was stirred for 3 h, filtered, washed with water and dried at 50 °C to give 99.1 kg (88%) of **16c** as a white crystalline solid: mp. 191.9 °C. HPLC retention times for reaction monitoring by Method A: **16c**, 2.18 min; 4-ethylaniline, 1.56 min; **12c**, 1.97 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.75 (br s, 1 H), 10.24 (s, 1 H), 8.27 (dd, J = 6.9, 2.5 Hz, 1 H), 7.90 (m, 1

H), 7.49 (t, *J* = 9.4 Hz, 1 H), 7.07 (m, 2 H), 6.98 (m, 2 H), 2.48 (m, 2 H), 1.07 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.5, 163.7, 161.8, 140.4, 135.9, 134.7, 133.1 (d, *J* = 11 Hz), 131.0 (m), 128.6, 121.3, 120.1 (d, *J* = 12 Hz), 118.6 (d, *J* = 24 Hz), 27.5, 15.4; HRMS (ESI) *m/z* calcd for $C_{15}H_{15}FNO_4S$ (MH^+) 324.0700, found 324.0701.

5-(N-(4-Ethylphenyl)sulfamoyl)-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzoic Acid (17). A. From 16b via S_NAr of the Aryl Chloride. To a flask was successively added 500 mg (1.47 mmol) of 2-chloro-5-(N-(4-ethylphenyl)sulfamoyl)benzoic acid (**16b**), 7.5 mL of 2-MeTHF and 188 mg (1.62 mmol) of (tetrahydro-2*H*-pyran-4-yl)methanol. The mixture was stirred for 5 min and 2.77 mL (4.71 mmol) of potassium t-pentoxide (1.7 M in toluene) was added at room temperature. The thick mixture was heated to 90 °C and stirred for 17 h. After being cooled to room temperature, the reaction was quenched with ~2.5 mL of 2 N HCl. Layers were separated, and the organic layer was successively washed with 2 mL of water and 2 mL of 10 wt % aqueous NaCl, concentrated under vacuum to a yellow oil and treated with 5 mL of MTBE. The resultant slurry was stirred for 1 h, filtered, washed with 2x2 mL of 1:1 TBME-heptane and dried under vacuum at 50 °C overnight to give 501 mg (81%) of **17** as a crystalline solid: solid: mp. 175.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (br s, 1 H), 10.1 (s, 1 H), 8.01 (d, *J* = 2.7 Hz, 1 H), 7.79 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 1 H), 7.06 (m, 2 H), 6.99 (m, 2 H), 3.93 (m, 2 H), 3.84 (m, 2 H), 3.30 (m, 2 H), 2.47 (m, 2 H), 1.98 (br s, 1 H), 1.63 (m, 2 H), 1.34 (m, 2 H), 1.09 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 160.4, 139.7, 135.2, 131.7, 130.7, 129.5, 128.4,

121.5, 120.6, 113.6, 73.0, 66.6, 34.4, 28.9, 27.4, 15.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{26}NO_6S$ (MH^+) 420.1475, found 420.1475.

B. From 16c via SNAr of the Aryl Fluoride. To a 100 mL round bottom flask was successively added 3.00 g (9.28 mmol) of **16c**, 1.29 g (11.1 mmol) of (tetrahydro-2*H*-pyran-4-yl)methanol and 24 mL of DMSO. The orange mixture was stirred at room temperature for 3 min, followed by addition of 3.64 g (32.5 mmol) of potassium *t*-butoxide. The mixture was stirred for 5 min and then heated to 75 °C for 3 h. After being cooled to 0 °C, the reaction was quenched with 4.24 mL (74.2 mmol) of acetic acid as a solution in 48 mL of water. The mixture was stirred for 10 min, filtered, washed with 30 mL of water and dried at 70 °C to give 3.33 g (86%) of **17** as an off-white solid. Refer to method A for compound **18** for the procedure run in the plant in which **17** was prepared and used without isolation.

Isobutyl 5-(N-(4-Ethylphenyl)-N-isobutylsulfamoyl)-2-((tetrahydro-2H-pyran-4-yl)methoxy)benzoate (18). A. From 16c through Telescoped S_NAr Reaction and N,O-Bis-isobutylation. A solution of 65.0 kg (201 mol) of **16c** in 260 L of DMSO was prepared in a reactor. The solution was slowly added to another reactor containing 59.5 kg (744 mol) of *t*-BuOLi in 390 L of DMSO, maintaining temperature below 25 °C throughout the addition. To the mixture was slowly added 24.1 kg (207 mol) of (tetrahydro-2*H*-pyran-4-yl)methanol, maintaining temperature below 25 °C. The mixture was heated to 63-71 °C and stirred for 24 h. Addition of 110 kg (803 mol, 4 equiv) of *i*-BuBr was carried below 65 °C, based the schedule as follows to ensure process safety and minimize the base induced degradations: 1) added 0.7 equiv, stirred for 2 h at 63-68

°C; 2) added 1.3 equiv, stirred for 2 h at 63-68 °C; 3) added 2.0 equiv, stirred for 2 h at 63-68 °C. The reaction temperature was then adjusted to 63-71 °C and stirred for 18 h. After being cooled to 35-45 °C, the reaction was quenched with 650 L of water, keeping temperature below 45 °C. After being further cooled to 25 °C, 1.11 kg (8.04 mol) of K_2CO_3 was added and the mixture was stirred for 30 min. The slurry was filtered and washed with 260 L of water. The wet cake was dissolved in 585 L of 2-MeTHF and washed with 325 L of 10w/w% NH_4Cl. The mixture was filtered through a pad of silica gel and elution was made with 260 L of 2-MeTHF. Layers were separated, and the organic layer was solvent exchanged to 390 L of heptane three times. The slurry was heated to 90 °C and stirred for 30 min. After being cooled to 25 °C and stirred for 10 h, the mixture was filtered, washed with 260 L of heptane and dried at 50 °C under vacuum to give 83.8 kg of **18** as a white solid with an assay purity of 90.8%. This corresponded to 76.1 kg (71%) of **18**. In the two previous runs of similar scale, the yields were 57-58% due to some degradation and byproducts as a result of heating over a long time. **18**: mp. 116.9 °C. HPLC retention times for reaction monitoring by Method A: **17**, 2.28 min; **18**, 3.1 min; **16c**, 2.18. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, J = 2.2 Hz, 1 H), 7.61 (dd, J = 8.8, 2.5 Hz, 1 H), 7.12 (d, J = 8.6 Hz, 2 H), 6.99 (m, 3 H), 4.06 (d, J = 7.6 Hz, 2 H), 4.01 (m, 2 H), 3.93 (d, J = 7.6 Hz, 2 H), 3.45 (td, J = 11.7, 2.0 Hz, 2 H), 3.28 (d, J = 7.3 Hz, 2 H), 2.63 (q, J = 7.3 Hz, 2 H), 2.07 (m, 2 H), 1.81 (br d, J = 13.0, 2.0 Hz, 2 H), 1.51 (m, 3 H), 1.22 (t, J = 7.6 Hz, 3 H), 0.97 (d, J = 7.6 Hz, 6 H), 0.90 (d, J = 7.6 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 161.2, 143.9, 136.7, 132.8, 131.3, 129.9, 128.3, 120.6, 112.3, 73.6, 71.2, 67.4, 57.9, 34.9, 29.5, 28.3, 27.7 26.7, 19.8, 19.1, 15.1. HRMS (ESI) *m/z* calcd for $C_{29}H_{42}NO_6S$ (MH^+) 532.2727, found 532.2728.

B. From 17 through Green N,O-Bis-isobutylation Catalyzed by n-Bu$_4$NBr. To a 50 mL flask was successively added 2.00 g (4.77 mmol) of **17**, 0.307 g (0.954 mmol) of tetrabutylammonium bromide, 2.64 g (19.1 mmol) of potassium carbonate and 20 mL of MeCN. The mixture was stirred at room temperature for 3 min, and 2.59 ml (23.8 mmol) of *i*-BuBr was added. The heterogeneous mixture was heated to 70 °C and stirred for 2.5 h at that point there was only 27% **17** left. Heating was continued for 12.5 h and HPLC showed complete reaction. The reaction was cooled to room temperature and 10 mL of water was added, followed by 6 mL of MeCN which was needed to dissolve all the crystalline product **18**. The bottom aqueous layer showed no product by HPLC and was discarded. The organic layer was concentrated to about 10 mL (5 vol) at 40 °C under vacuum. After being cooled to room temperature and stirred for 30 min, the mixture was filtered washed with 25 mL 4:1 water/MeCN and dried at 70 °C to give 1.61 g (64%) of **18** as a white crystalline solid. The filtrate gave rise to more crystals after evaporation to about 10 mL and stirring for 40 min. The mixture was filtered, washed with 2x3 mL of 4:1 water MeCN and dried at 70 °C to give 699 mg (28%) of a second crop of **18** as a white crystalline solid. The total yield from the two crops was 92% of **18**.

N-(4-Ethylphenyl)-3-(hydroxymethyl)-N-isobutyl-4-((tetrahydro-2H-pyran-4-yl)methoxy)benzenesulfonamide (1). A solution of 100 kg (188 mol) of **18** in 400 L toluene was cooled to -10 °C. To the solution was added 70.0 kg (226 mol) of Red-Al (60 wt.% in toluene) slowly, maintaining temperature below 0 °C. The mixture was heated to 25 °C and stirred for 4 h. After being cooled to a range of -10 to 0 °C, the mixture was quenched by slow transfer into 500

L of 2 N HCl in another reactor at below 10 °C. The mixture was diluted with 1000 L of EtOAc and stirred for 30 min at room temperature. Layers were separated. The organic layer was successively washed with 500 L of 10 wt% NaOH and 500 L of 2 N HCl and concentrated to 200 L. The mixture was diluted with 700 L of EtOAc and concentrated to 200 L. This process was repeated with 700 L of EtOAc and concentrated to give crude **1** as a solution in EtOAc. After being diluted with 800 L of EtOAc, the solution was filtered through a CUNO filter containing silica gel at 35-40 °C three times. The solution was concentrated to 300 L and heated to 60 °C, followed by addition of ~700 L of heptane. After being cooled to 45 °C, the solution was seeded with 500 g of **1** and stirred for 4 h at 45 °C. After being further cooled down to -5 °C slowly, the slurry was filtered, washed with 200 L of heptane and dried at 50 °C to give 68.6 kg (79%) of **1** as a white crystalline solid: mp. 96.1 °C. HPLC retention times for reaction monitoring by Method A: **1**, 2.73 min; **18**, 3.1 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 2.5 Hz, 1 H), 7.44 (dd, J = 8.6, 2.5 Hz, 1 H), 7.12 (m, 2 H), 6.97 (m, 2 H), 6.85 (d, J = 8.8 Hz, 1 H), 4.68 (br d, J = 4.9 Hz, 2 H), 4.04 (dd, J = 11.0, 3.4 Hz, 2 H), 3.91 (d, J = 6.4 Hz, 2 H), 3.47 (td, J = 11.9, 2.2 Hz, 2 H), 3.27 (d, J = 7.3 Hz, 2 H), 2.64 (q, J = 7.6 Hz, 2 H), 2.14 (m, 2 H), 1.75 (m, 2 H), 1.52 (m, 3 H), 1.23 (t, J = 7.6 Hz, 3 H), 0.90 (d, J = 7.6 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 143.9, 137.0, 130.3, 129.8, 129.2, 128.5, 128.3, 127.7, 110.4, 72.9, 67.5, 60.9, 57.9, 35.0, 29.6, 28.4, 26.7, 19.9, 15.3. HRMS (ESI) *m/z* calcd for $C_{25}H_{36}NO_5S$ (MH^+) 462.2309, found 462.2306.

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Supporting Information Available: NMR spectra for all new compounds (21 pages). These materials are available free of charge via the Internet at http://pubs.acs.org.

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