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# Development of a Green and Sustainable Manufacturing Process for Gefapixant Citrate (MK-7264) Part 2: Development of a Robust Process for Phenol Synthesis

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**ABSTRACT:** Various synthetic routes to 2-isopropyl-4-methoxyphenol **3**, the phenol core of Gefapixant citrate (MK-7264), are described, which provide better alternatives to the initial four-step supply route. These new routes include a coumarin fragmentation approach in flow, a rhenium-catalyzed isopropylation of mequinol, and a bromination/methoxylation of 2-isopropylphenol. After exploring several approaches, a robust two-step process for the preparation of **3** from the commodity starting material 2-isopropylphenol was developed. The optimized route employs a highly regioselective bromination. After isolating the bromophenol DABCO cocrystal, a copper-catalyzed methoxylation delivers **3** in high yield. This route is successfully demonstrated at the plant scale with low process mass intensity and cost.

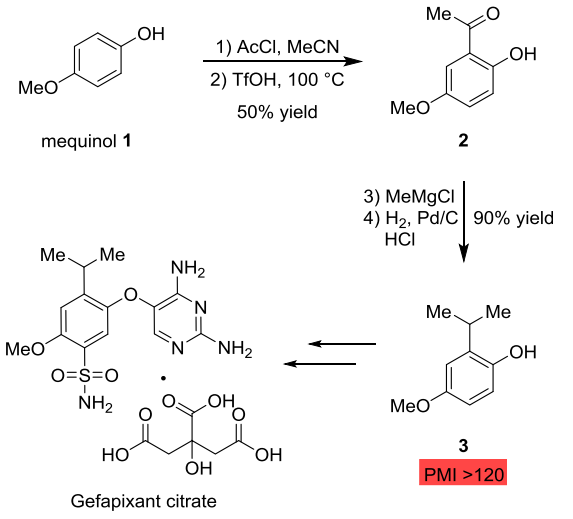
**KEYWORDS:** *alkylation, methoxylation, phenol derivatization, copper catalysis, Gefapixant*



## 1. INTRODUCTION

A popular literature method of synthesizing 2-isopropyl-4-methoxy phenol **3**,[1] a key building block in Gefapixant citrate (MK-7264), is to perform a methyl Grignard addition to 2′-hydroxy-5′-methoxyacetophenone **2** and a subsequent hydrogenation on the resulting tertiary alcohol (Scheme 1).[2] This approach represents a common strategy to install an isopropyl group on electron-rich aromatic rings via hydrogenation of an aryl dimethyl tertiary alcohol.[3] However, 2′-hydroxy-5′-methoxyacetophenone **2** is not a commodity chemical, and it requires two additional steps from commodity mequinol **1** using a Fries rearrangement (Scheme 1). Overall, this process delivers phenol **3** with a process mass intensity (PMI)[4] of more than 120. In addition to this, the handling of TfOH at high temperatures for the Fries rearrangement adds a significant safety concern to this approach. Herein, we described a newly developed low-cost, concise, and safe process of synthesizing phenol **3** from commodity chemicals.

**Scheme 1. Synthesis of 2-Isopropyl-4-methoxyphenol and Structure of Gefapixant Citrate (MK-7264)**




## 2. RESULTS AND DISCUSSION

**2.1. Route Scouting.** Although the criteria for a commercial route vary from one company to another, there are several common principles such as low cost, ease of operation, safety, ease of supply, robustness, and sustainability that are typically considered important.[5] Guided by these principles, we sought to define a concise, protecting-group-free, and precious-metal-free route to achieve a cost-effective and environmentally benign process to synthesize phenol **3** from commodity chemicals. Herein, we describe our route scouting efforts to phenol **3** with three different approaches.

The first approach (Scheme 2A) uses 6-methoxy-4-methylcoumarin **4** as the starting material, which provides 2-isopropyl-4-methoxyphenol **3** in a single step with good yield under high-

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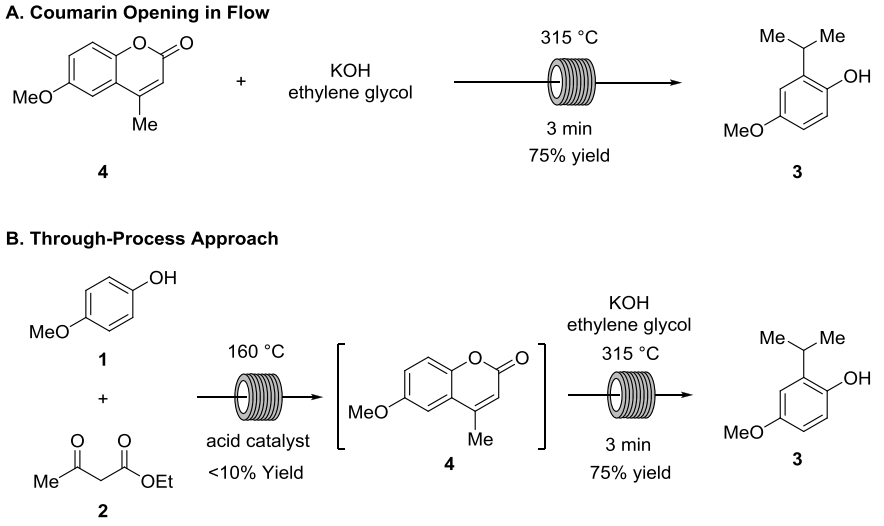
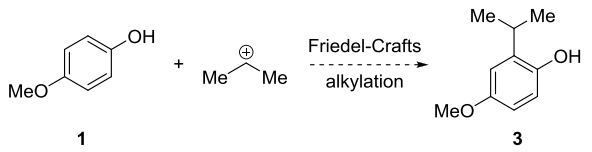
**Scheme 2. Coumarin Fragmentation Reaction to Provide Phenol 3**




temperature flow conditions.[6] 6-Methoxy-4-methylcoumarin **4** is not a commodity and cost-effective building block, and Pechmann condensation[7] using **1** and **2** provided a low yield of **3** in batch conditions in hand. In order to further improve process efficiency, we also investigated the possibility to synthesize **4** in flow and telescope the formation of coumarin **4** with the phenol synthesis (Scheme 2B). This approach was complicated by the low yield in the coumarin formation step, which provides a low conversion reaction in flow.

Our second approach uses mequinol **1** as the starting material. Retrosynthetically, a Friedel−Crafts reaction between mequinol and an isopropyl cation would provide 2-isopropyl-4-methoxyphenol (Scheme 3). Not surprisingly, this reaction was

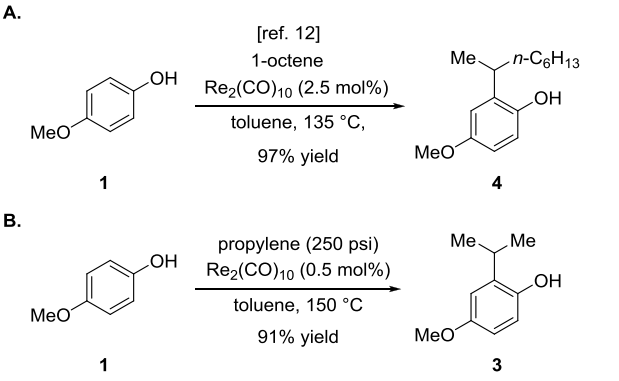
**Scheme 3. Synthesis of 3 via Friedel−Crafts Isopropylation of Mequinol 1**




reported to afford a complex reaction profile and low yield due to an overalkylation side reaction of **3**.[8] However, we were inspired by the simplicity of this proposal and quickly leveraged high-throughput experimentation (HTE) to evaluate this approach.[9]

Our initial screening of Lewis acids, isopropyl cation precursors, solvents, and different reaction temperatures did not provide a clean reaction profile for isopropylation of mequinol.[10] In most cases, overalkylation products dominated the product mixture. This observation is consistent with literature reports since phenol **3** is more electronically rich than mequinol, and product **3** would also react with the isopropyl cation to provide overalkylation products.[8] In order to achieve a clean isopropylation of mequinol, it was thought that conditions not involving a classic isopropyl cation mechanism could provide better results. We therefore tested transition-metal catalysts, hoping that a C−H activation and hydroarylation would provide the desired phenol product.[11] Despite broad screening of transition-metal catalysts, rhenium-based catalysts, specifically $Re_2(CO)_{10}$, proved uniquely effective. Previously, Takai and co-workers reported $Re_2(CO)_{10}$ as an effective catalyst for the *ortho*-monoalkylation of phenols using terminal alkenes such as 1-octene to afford the branched hydroarylation product **4** (Scheme 4A).[12] Intrigued by Takai's

**Scheme 4. Recatalyzed Isopropylation of Mequinol**




report with high-boiling alkenes (*e.g.*, bp of 1-octene = 122 °C), we explored isopropylation using low-boiling alkenes, in particular using propene (bp, −48 °C). Indeed, this approach proved successful in affording **3** directly from mequinol and propene and provided a very clean reaction profile. Upon further optimization of the reaction temperature and pressure, guided by our recent study of the reaction mechanism,[13] we demonstrated a 100 g isopropylation of mequinol with 91% yield and 0.5 mol % catalyst loading (Scheme 4B).

The synthesis of **3** as described in Scheme 4B is a synthetically attractive route since it utilizes commodity feedstock materials and provides the desired phenol in one step; however, the use of expensive $Re_2(CO)_{10}$ significantly increased the cost of this route.[14] In addition, this route requires high temperature and high pressure, which limits its execution to manufacturing sites with specialized equipment to handle these conditions. In view of these limitations, we sought a new approach for the synthesis of phenol **3**.

While the first two approaches described above prepare phenol **3** through installation of the isopropyl group on a fully functionalized aromatic ring, the third approach that we considered features methoxylation of isopropylphenol **5**, a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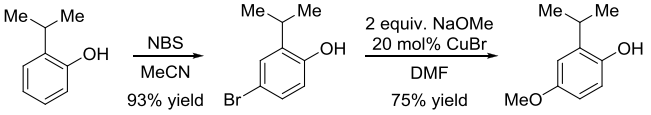
commodity chemical (Scheme 5). As such, a regioselective bromination of phenol **5** provides *para*-bromoisopropylphenol

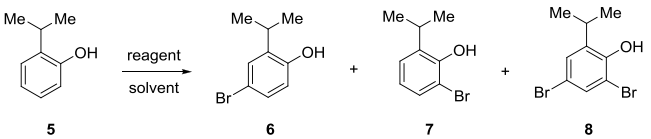
**Scheme 5. Bromination and Methoxylation of 2-Isopropylphenol 5**




**6** in high yield. Cu-catalyzed methoxylation (formally an Ullmann methyl aryl ether synthesis) provides our desired phenol in about 75% yield.[15] In addition, these two steps could be telescoped in a one-pot process.[16] Since this approach appears to meet several criteria for a manufacturing route, such as cheap commodity starting materials, inexpensive reagents, and promising levels of efficiency, we decided to investigate it in greater detail.

**2.2. Process Optimization.** Our first objective was to identify the best conditions for preparing *para*-bromophenol **6**. A quick survey of popular bromination conditions in different solvents revealed that several brominating reagents provide *para*-bromophenol **6** with excellent yields (Table 1).[17] For

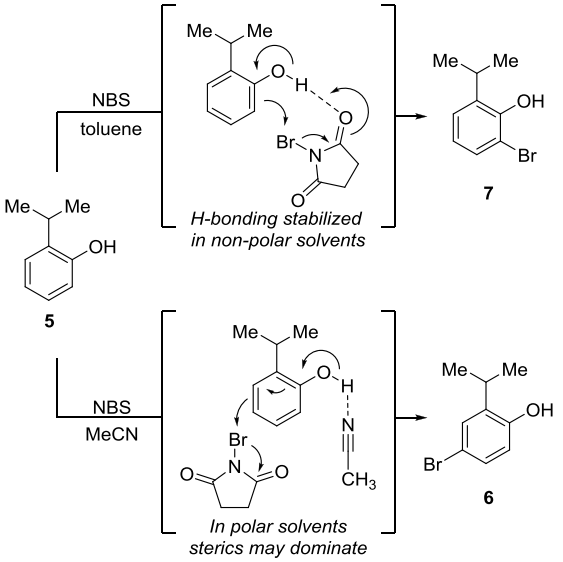
**Table 1. Summary of Bromination Outcomes Using Phenol 5**




| entry | reagent | solvent | **6** (LCAP) | **7** (LCAP) | **8** (LCAP) |
|---|---|---|---|---|---|
| 1 | $Br_2$ | $CH_2Cl_2$ | 85 | 7 | 8 |
| 2 | NBS | MeCN | 96 | 1.8 | 2.2 |
| 3 | NBS | toluene | 25 | 73 | 2 |
| 4 | HBr + $H_2O_2$ | MeCN | 93 | 1 | 6 |
| 5 | PyHBr3 | toluene | 94 | 4 | 2 |
| 6 | PyHBr3 | MeCN | 88 | 1.5 | 10.5 |

example, HBr in DMSO, $Br_2$, NBS, and PyH-$Br_3$ all provide desired bromophenol **6** with good yields. Considering the cost and ease of reagent handling, we chose NBS as the bromination reagent. During this investigation, it was also found that solvent plays a critical role in the regioselectivity of bromination. For example, with NBS in MeCN, the desired *para*-bromophenol **6** was obtained in 96% yield. On the other hand, when performing the reaction in toluene, the undesired *ortho*-bromophenol **7** was the major product. This interesting observation could be explained by hydrogen bonding between phenol and NBS in nonpolar solvents (such as toluene), which facilitates a closed transition state to brominate *ortho* to the hydroxy group (Scheme 6). On the other hand, when MeCN is used, a hydrogen bonding interaction between the phenol and MeCN causes the bromination to occur at the less-hindered *para*-position as sterics become the dominant factor.[18] The quality of NBS also played a critical role as some new batches of NBS provided significant dibrominated side product **8**. This side reaction was suppressed by the addition of 1 mol % methanesulfonic acid (MSA) in the reaction medium.[19] We hypothesize that MSA disables the path to *ortho*-bromination due to it being a better hydrogen bond donor than the phenol

**Scheme 6. Rational for Regioselective Outcome Dependent on Solvent**




hydroxyl, thus preventing the phenol−NBS interaction shown in Scheme 6 that leads to *ortho*-bromination. With these optimized conditions in hand, the bromination reaction robustly provides desired bromophenol **6** in 95% assay yield (AY), along with 1−2% dibromophenol **8** and 1% *ortho*-bromophenol **7**.

Our next objective was to develop a robust Cu-catalyzed methoxylation process to provide highly pure 2-isopropyl-4-methoxyphenol **3**. Our initial conditions (Scheme 5) provided 2-isopropyl-4-methoxyphenol in about 75% yield in which dimer **9** and isopropylphenol **5** were generated in high levels, up to 20% total. Oxidative dimer **9** is probably formed via a Cu-catalyzed phenol oxidative coupling of the electron-rich phenol by trace oxygen.[20] We wondered if these side reactions could be suppressed by tuning the reaction conditions. To test this hypothesis, we screened a range of different solvents, copper precatalysts, additives, and ligands.[21] Several conditions were identified as leads due to their favorable product distribution observed at a screening scale (20 $\mu$mol). For example, additives—such as methyl formate, ethyl acetate, and DMF (entries 1−5)—were found to suppress isopropylphenol **5** from 22% down to 4% (entry 5). CuBr performed better than CuCl and CuI under the same conditions (entry 1 vs entry2, entry 3 vs entry 4, entry 8 vs entry 13 vs entry 14). Ligands,[22] particularly dicarbonyl compound **L2** (entry 8), were discovered to decrease the formation of oxidative dimer **9** from 18% down to 4% (entries 6−13) and NaOMe was demonstrated as the best base (entries 15−20). Combining these findings, the methoxylation reaction provided greater than 90% yield of **3** when the reaction was run inside a $N_2$-filled glovebox (entry 16).

**2.3. First Generation of Cu-Methoxylation Process.** With the lead conditions in hand (Table 2, entry 16), we scaled up the Cu-catalyzed methoxylation reaction to a 50 g scale inside a fume hood (*i.e.*, outside of a glovebox). To our surprise, the dimer impurity increased significantly, even when taking extreme precautions to degas the reaction mixture by sparging (30 min of heavy sparging with $N_2$ per 20 mL of reaction mixture) prior to addition of the NaOMe. Additionally, the end of the reaction stream was discovered to be unstable as the level of the oxidative dimer **9** continued to increase during storage. Since the formation of oxidative dimer **9** likely involves


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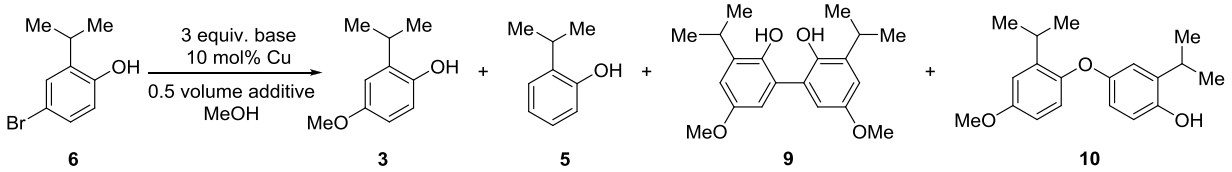
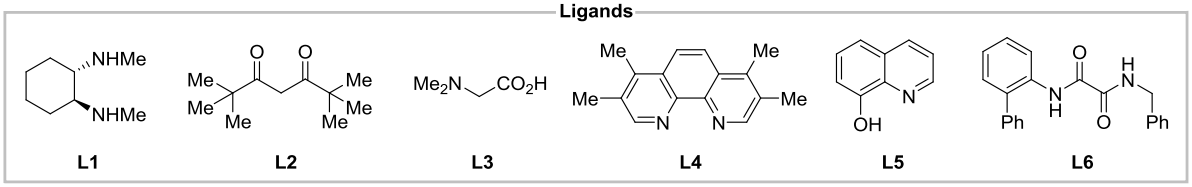
**Table 2. Summary of Cu-Catalyzed Methoxylation of 2-Isopropyl-4-bromophenol Screens**

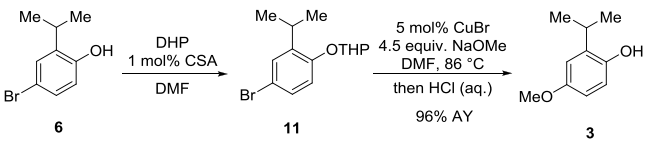



| entry | Cu source | ligand | additive | base | **3** (LCAP) | **5** (LCAP) | **9** (LCAP) | **10** (LCAP) |
|---|---|---|---|---|---|---|---|---|
| 1 | CuCl | N/A | none | NaOMe | 42 | 26 | 28 | 2 |
| 2 | CuBr | N/A | none | NaOMe | 57 | 22 | 18 | 3 |
| 3 | CuCl | N/A | $HCO_2Me$ | NaOMe | 69 | 7 | 22 | 2 |
| 4 | CuBr | N/A | $HCO_2Me$ | NaOMe | 74 | 5 | 18 | 3 |
| 5 | CuBr | **L1** | DMF | NaOMe | 80 | 4 | 14 | 2 |
| 6 | CuBr | **L1** | none | NaOMe | 42 | 27 | 28 | 3 |
| 7 | CuBr | **L2** | $HCO_2Me$ | NaOMe | 84 | 4 | 11 | 1 |
| 8 | CuBr | **L3** | $HCO_2Me$ | NaOMe | 91 | 4 | 4 | 1 |
| 9 | CuBr | **L4** | $HCO_2Me$ | NaOMe | 80 | 6 | 12 | 2 |
| 10 | CuBr | **L5** | $HCO_2Me$ | NaOMe | 75 | 9 | 13 | 3 |
| 11 | CuBr | **L6** | $HCO_2Me$ | NaOMe | 79 | 7 | 12 | 2 |
| 12 | CuBr | **L2** | $HCO_2Me$ | NaOMe | 82 | 8 | 8 | 2 |
| 13 | CuI | **L2** | $HCO_2Me$ | NaOMe | 87 | 5 | 8 | 2 |
| 14 | CuCl | **L2** | $HCO_2Me$ | NaOMe | 85 | 6 | 8 | 3 |
| 15 | CuBr | **L2** | $HCO_2Me$ | $K_3PO_4$ | 51 | 22 | 24 | 3 |
| 16 | CuBr | **L2** | $HCO_2Me$ | NaOMe | 94 | 3 | 2 | 1 |
| 17 | CuBr | **L2** | DMF | $K_3PO_4$ | 56 | 18 | 23 | 3 |
| 18 | CuBr | **L2** | DMF | $Cs_2CO_3$ | 62 | 15 | 20 | 3 |
| 19 | CuBr | **L2** | DMF | LiOMe | 75 | 19 | 5 | 1 |
| 20 | CuBr | **L2** | DMF | KOMe | 93 | 4 | 2 | 1 |

coordination between Cu and the *para*-methoxyphenoxide anion, we postulated that a protecting group on the phenol may prevent this coordination, which would suppress the formation of dimer **9**. Indeed, the use of an *in situ* protection with a THP group enabled a ligand-free Cu-catalyzed methoxylation of bromophenol **6** in high yield with the formation of the dimer being suppressed to less than 0.1%[23] and the THP can be deprotected during an aqueous HCl workup, without the need for an additional step (Scheme 7). This three-step transformation was telescoped in a one-pot process, providing the desired phenol in 96% yield at the 50 g scale with less than 0.1% of the phenol oxidative dimer byproduct being formed.

**Scheme 7. First Generation Approach to Phenol 3 Enabled by a THP Protecting Group**




**2.4. Impurity Control and Second Generation Cu-Catalyzed Methoxylation Process.** With the optimized process shown in Scheme 7, we then evaluated if phenol **3** from this new process could be used to produce API in good quality. To our disappointment, this investigation indicated that several impurities that were present in small amounts in **3** could not be rejected well in the downstream steps (*e.g.*, *ortho*-bromophenol **7**, dibromophenol **8**, and 2-isopropylphenol **5**), which suggests that these impurities need to be controlled to lower levels as part of the phenol synthesis. In view of the need for higher purity materials, a robust crystallization of 2-isopropyl-4-methoxylphenol **3**, or one of its derivatives, would be an ideal solution to this challenge. However, although it was soon found that phenol **3** itself is a crystalline solid with an m.p. of 35 °C, unfortunately, attempts to recrystallize this material directly suffered from high mother liquor losses under all isolation conditions examined (*e.g.*, heptane/toluene, hexane/toluene, and MeOH/water). In addition, the low melting point of **3** also frequently caused oiling-out of the product on the filter during isolation. Thus, to achieve this objective, we sought to identify a more suitable crystalline solid form of phenol **3**. A crystalline potassium salt was discovered; however, this type of phenol derivative was found to be unstable in the presence of oxygen. In addition, several oxidative impurities were identified upon stress studies of these crystallization conditions. This highlights that a robust crystallization process is challenging to achieve with electron-rich 2-isopropyl-4-methoxyphenol. To our delight, we eventually discovered that crystallization of phenol with DABCO, corresponding to a bromophenol-DABCO cocrystal **12** (mp = 95−97 °C),[24] provided a robust isolation point and stable,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highly crystalline intermediate.[25] This process upgrades the purity of bromophenol to 99.8 LCAP, which reproducibly controls the problematic impurities to low levels. As a result, phenol **3** from the new process can be used to produce API with good quality. This bromophenol-DABCO cocrystal tends to have a large particle size ($D_{50}$ = 370 $\mu$m) and is observed to have dense packing ($d$ = 0.9 g/mL). These properties provide heavy solid particles, which raised the risk of difficulty dispersing suspensions that could cause plugging concerns at the plant scale when piping the slurry. To mitigate this risk, we found that by lowering the crystallization temperature from 60 to 30 °C, smaller particle size crystals ($D_{50}$ = 180 $\mu$m) can be obtained as a result of reducing growth rate kinetics while maintaining a high supersaturation (Figure 1).[26]

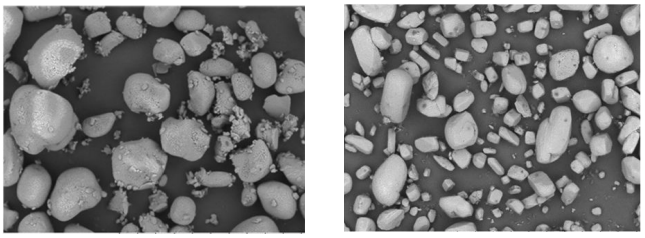



**Figure 1.** Controlling bromophenol-DABCO crystal particle size through temperature.

With a robust process for isolating the bromophenol-DABCO salt **12**, we sought to convert this species to the THP-protected bromophenol **11** to bridge with the previous phenol process (Scheme 7). We initially subjected the bromophenol-DABCO cocrystal intermediate to the standard protection conditions of 1 equiv DHP and a catalytic amount of camphorsulfonic acid (CSA, 5 mol %). Not surprisingly, this transformation provided poor conversion since CSA is neutralized by DABCO. In contrast, when the bromphenol-DABCO complex was first subjected to an acidic workup (using aq HCl) to provide free bromophenol **6** in toluene, the DHP protection step proceeded as expected to cleanly deliver THP-protected bromophenol **11**. However, this approach adds one more operation to the process. For the sake of simplicity and cost, it was deemed optimal that the bromophenol-DABCO cocrystal undergoes methoxylation directly without the use of THP protection. While this was a very attractive proposal, we realized that generation of a free phenoxide anion[27] under NaOMe conditions could potentially provide oxidative dimer **9** via coordination with a high valent copper catalyst. Nevertheless, to our delight, the methoxylation reaction of the bromophenol-DABCO cocrystal **12** provides **3** with a clean reaction profile, in up to 98.8 LCAP. Using **12** as the starting material led to formation of less than 0.1 LCAP of the oxidative dimer without the need for rigorously air-free conditions or the use of a glovebox. This new process was ultimately demonstrated successfully at the plant scale with the same yield and profile as the lab scale (Scheme 8). Overall, the new process delivered phenol **3** with a PMI of 23, which significantly reduces waste generation compared with the initial four-step process (PMI = 127) and provides a shorter, simpler process. To date, 3 tons of phenol **3** has been prepared through this new process.

To understand the role of DABCO and DMF in this process, we studied the control reactions in toluene without DABCO and DMF. The kinetic data indicates that both DMF and DABCO accelerate the C−O coupling compared to the reaction without these additives (Figure 2). Interestingly, the data also suggests

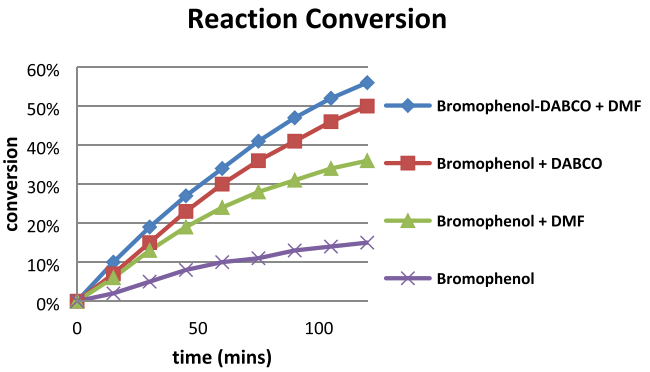


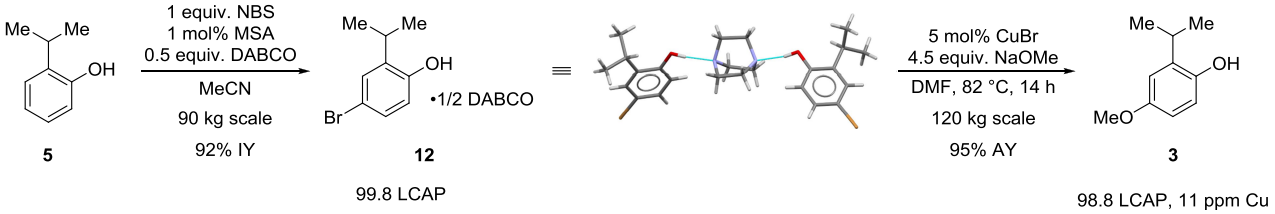

**Figure 2.** Impact of DABCO on reaction conversion.

that DABCO suppresses dimer formation, regardless of whether running the reaction in a glovebox or in a fume hood. Without DABCO, reactions tend to provide high levels of dimer **9**, namely, 6 and 18 LCAP for reactions carried out in the glovebox and fume hood, respectively. Based on these observations, we propose that DABCO serves as a unique ligand for Cu.[28] Upon coordination with Cu, DABCO not only facilitates the C−O bond formation reaction but also suppresses coordination of the phenoxide to Cu due to the steric hindrance between DABCO and the isopropyl group. As such, the resulting C−O formation reaction provides low levels of dimer **9**.

## 3. CONCLUSIONS

In summary, we utilized a blend of rational design and HTE to develop a green and robust two-step process for synthesizing phenol **3** from commodity chemicals. The key discovery was bromophenol-DABCO cocrystal **12**, which not only provided an efficient impurity control point but also enabled a robust Cu-catalyzed methoxylation reaction by suppressing the formation of the phenol dimer. The new process was demonstrated successfully at several different sites on the plant scale with almost 2 times improvement in yield and an 80% reduction in PMI compared with the initial four-step process.[29]

**Scheme 8. Plant Demonstration of a New 2-Isopropyl-4-methoxylphenol Process**



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**3.1. Experimental Section.** Unless otherwise noted, all reactions were performed under a nitrogen atmosphere. All reagents and solvents were commercially available and used without further purification unless indicated otherwise. Yields reported are for isolated, spectroscopically pure compounds. NMR spectra were recorded on Bruker 400 or 500 MHz instruments. The residual solvent protons ($^1$H) or the solvent carbons ($^{13}$C) were used as internal standards. $^1$H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; and m, multiplet. High-resolution mass spectra were recorded by the on a Waters Xevo G2 Qtof spectrometer. Assay yield was measured via the external pure standard.

*3.1.1. Preparation of Phenol **3** Using Rhenium Catalyst.* To a high-pressure vessel were charged 400 mL of anhydrous toluene, $Re_2(CO)_{10}$ (3.16 g, 4.84 mmol), and mequinol **1** (100 g, 806 mmol) at RT. The vessel was then degassed with propylene and charged with propylene (85.0 g, 2.02 mol). The vessel was sealed and heated to 170 °C. Internal pressure was measured near 250 psi. The reaction was stirred under these conditions for 72 h. The vessel was then allowed to cool down to 23 °C. The internal pressure was carefully released to 1 atmosphere pressure, and the toluene solution was assayed as 91 wt % of phenol **3**.

*3.1.2. Preparation of Bromophenol-DABCO **12**.* 2-Isopropylphenol (90 kg, 661 mol) and acetonitrile (270 L) were charged to a 1500 L vessel with jacket, mechanical stirrer, temperature probe, and $N_2$ inlet at RT. To this mixture was charged methanesulfonic acid (429 mL, 6.6 mol). The reaction mixture was cooled to −10 °C, and then NBS (118 kg, 661 mol) was charged as a solid in four portions (each 29.5 kg). The reaction temperature was maintained below −5 °C while charging NBS. The reaction was aged for 1 h and allowed to warm to 0 °C. It was then quenched with 0.5 wt % $NaHSO_3$ in water (540 L) at −5 °C and the product was extracted with toluene (270 L) at 45 °C. The toluene layer was sequentially washed with 5% v/v aq $H_3PO_4$ (180 L) and 5% brine (180 L). The toluene solution was concentrated to remove water and acetonitrile (spec. for water = 5000 ppm; spec. for MeCN = 2%, pure bromophenol m.p. = 43−44 °C). The residual stream was heated to 50 °C and DABCO (36.7 kg, 330 mol) was charged, which provided a homogeneous solution. To this solution were charged heptane (225 L), lecithin (90 g),[30] and seed of product **12** (90 g). This mixture was agitated for additional 1 h at same temperature, and then heptane (225 L) was charged over 1 h. The resulting slurry was allowed to cool to 20 °C over 2 h and the product was isolated by filtration. The cake was washed with heptane (90 L) and dried under vacuum with $N_2$ sweep (165 kg, 92% yield, m.p. = 95−97 °C).$^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 8.75 (s, 1H), 7.28 (d, $J$ = 2.5 Hz, 1H), 7.12 (dd, $J$ = 8.4, 2.5 Hz, 1H), 6.51 (dd, $J$ = 8.5, 0.8 Hz, 1H), 3.32−3.21 (m, 1H), 2.91 (s, 6H), 1.24 (s, 3H), 1.22 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.5, 138.1, 129.4, 129.0, 117.1, 111.8, 46.2, 27.1, 22.5; HR-MS: $[M + H]^+$ calcd for $C_{24}H_{35}Br_2N_2O_2^+$, 543.1024; found, 543.1037.

*3.1.3. Preparation of Phenol **3** Using Cu Catalyst.* At room temperature, a jacketed reactor equipped with an overhead stirrer and $N_2$ inlet was charged with sodium methoxide solution in methanol (25 wt %, 304 L, 1328 mol), DMF (60 L), and 4-bromo-2-isopropylphenol-DABCO cocrystal **12** (120 kg, 442 mol). The reaction mixture was then degassed with $N_2$ at RT. To the reactor was charged CuBr (3.2 kg, 22 mol) and the reaction was agitated at 88 °C overnight. The batch was cooled to 5 °C and 220 L of HCl (6 N in water) was charged over 25 min under $N_2$. The product was extracted with 480 L of toluene (4 V) at room temperature. This stream was directly used in the next step. For characterization, the organic layer was concentrated and the product was isolated as a yellowish oil (71 kg, 98.2 NMR wt %, 95% yield). This oil was further purified via column chromatography. Pure product is a crystalline solid (m.p. = 34−35 °C). $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ 6.82 (dt, $J$ = 3.2, 1.5 Hz, 1H), 6.71 (d, $J$ = 8.6 Hz, 1H), 6.64 (dd, $J$ = 8.6, 3.0 Hz, 1H), 4.50 (s, 1H), 3.80 (t, $J$ = 1.2 Hz, 3H), 3.23 (heptet, $J$ = 10.4, 9.2, 5.2, 1.7 Hz, 1H), 1.28 (s, 3H), 1.27 (s, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$): $\delta$ 153.9, 146.8, 135.9, 115.8, 112.8, 110.9, 55.8, 27.3, 22.6; HR-MS: $[M + H]^+$ calcd for $C_{10}H_{15}O_2^+$, 167.1054; found, 167.1027.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00241.

Additional experimental details, NMR spectra, mass spectrometry data, and HPLC traces (PDF)

Crystallographic data of 4-bromo-2-isopropylphenol-DABCO cocrystal (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS

TLC = thin layer chromatography; NBS = *N*-bromosuccinimide; PMI = process mass intensity; V = volume; LCAP = HPLC/UPLC area percentage; IY = isolated yield; AY = assay yield; CSA = camphorsulfonic acid; DABCO = 1,4-diazabicyclo-[2.2. 2]octane; DHP = 3,4-dihydropyran

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