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## Just Accepted



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# Anchimerically Assisted Selective Cleavage of Acid-labile Aryl Alkyl Ethers by Aluminum Triiodide and *N*,*N*-Dimethylformamide Dimethyl Acetal

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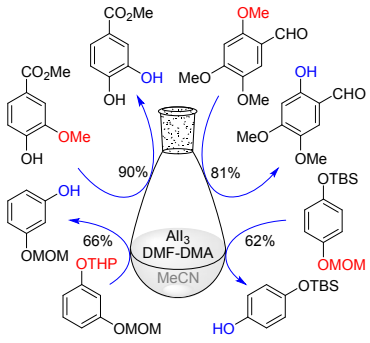
*Supporting Information Placeholder*




**ABSTRACT:** Aluminum triiodide is tamed by *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) for selective cleavage of ethers with the assistance of neighboring group participation effect. Various acid-labile functional groups, including carboxylate, allyl, *tert*-butyldimethylsilyl (TBS) and *tert*-butoxycarbonyl (Boc), suffer the conditions intact. The method offers an efficient approach to cleaving catechol monoalkyl ethers and to uncovering phenols from acetal-type protecting groups such as methoxymethyl (MOM), methoxyethoxymethyl (MEM) and tetrahydropyranyl (THP) chemoselectively.

## INTRODUCTION

Ether cleavage is a transformation with significant applications in synthesis for uncovering hydroxyl groups.[1] A variety of approaches have been established to effect selective ether cleavages by taking advantage of the steric hindrance, electronic character,[2] adjacent substitution patterns[3] or other features[4] of the ether linkage.[5] However, due to some typical drawbacks such as harsh conditions, hazardous reagents and unsatisfactory yields,[5a] mild conditions remain to be developed for selective and efficient cleavage of labile aryl alkyl ethers.

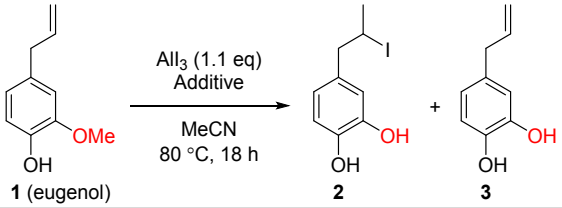
Aluminum triiodide, a strong Lewis acid reactive toward various oxygen-containing functional groups,[6] has been extensively exploited for cleaving aryl alkyl ethers.[7] Whereas the efficiency could be improved by using tetrabutylammonium iodide (TBAI)[7b] and ethanethiol[8] as promoters, its effect in cleaving acid-labile ethers is sometimes challenging due to either its untamed reactivity or unintended *in situ* generation of HI. The demethylation of eugenol (4-allyl-2-methoxyphenol) by $AlI_3$-TBAI, for instance, suffered from an unexpected hydrogenation of the allyl group that afforded 4-propylcatechol as the sole product.[9]

We have used pyridine,[10] dimethyl sulfoxide,[11] CaO[12] and 1,3-diisopropylcarbodiimide (DIC)[13] to counteract HI, but noted the power of $AlI_3$ affected to various extent. It was thus reasoned that $AlI_3$ might be tuned for selective cleavage of ethers upon adequate deactivation by proper additives. We report herein that *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) suits as the additive for harnessing $AlI_3$ in selective ether cleavages with the assistance of anchimeric effect.

## RESULTS AND DISCUSSION

**Optimization of conditions**. Acetals, known to be acid-labile, were tentatively employed as acid scavengers. Eugenol (**1**)[14] was selected as the model substrate for optimizing the demethylation conditions (Table 1) due to the labile character of the allyl toward hydrogen halides.[10,15] When slight excess DMF-DMA (1.1 eq) was used, demethylation of **1** by $AlI_3$ (1.1 eq) afforded a mixture of 4-(2-iodopropyl)catechol (**2**) and hydroxychavicol (**3**) in ratio **2**/**3** = 0.12:1 after stirring for 18 h at 80 °C in MeCN (entry 1). The adduct **2** turned negligible (~5%) with the increase of the additive (entry 2). The side-reaction was eventually obviated when 1.5 equivalent of DMF-DMA was applied (entry 3). Further increase of DMF-DMA resulted in lower yields (entries 4 – 6). Other additives, such as 2,2-dimethoxypropane (2,2-DMP), 1,1,3,3-tetramethoxypropane (1,1,3,3-TMP), formaldehyde dimethyl acetal (formal), DMF and *N*-methylformamide dimethyl acetal (MF-DMA) were less satisfactory (entries 7 – 11). Trimethyl orthoformate (TMOF) was similarly incompetent (entry 12).

Table 1. Optimization of demethylation conditions

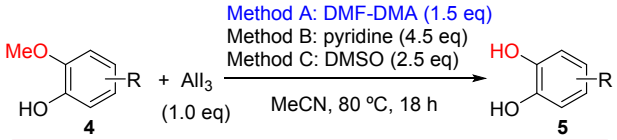



**1** (eugenol) **2** **3**

| Entry | Additive (eq) | Ratio **2**/**3** | Isolated yield **3** (%) |
|---|---|---|---|
| 1 | DMF-DMA (1.1) | 0.12:1 | / |
| 2 | DMF-DMA (1.3) | 0.05:1 | / |
| 3 | DMF-DMA (1.5) | 0:1 | 82 |
| 4 | DMF-DMA (1.6) | 0:1 | 82 |
| 5 | DMF-DMA (1.7) | 0:1 | 68 |
| 6 | DMF-DMA (2) | 0:1 | 58 |
| 7 | 2,2-DMP (1.5) | 0:1 | 45 |
| 8 | 1,1,3,3-TMP (1) | 0:1 | 43 |
| 9 | Formal (1.5) | 0.14:1 | / |
| 10 | DMF (1.5) | 1.9:1 | / |
| 11 | MF-DMA (1.5) | 0:1 | 79 |
| 12 | TMOF (1.1) | 0.02:1 | / |

**Validation of concept**. The deactivation-selectivity reasoning was then examined in the selective cleavage of the ester/ether C-O bonds, and the results were compared with those by our previous methods (Table 2). Pleasingly, methyl vanillate (**4a**), methyl isovanillate (**4a'**) and ethyl vanillate (**4b**) were all selectively cleaved that afforded 3,4-dihydroxybenzoates **5a** and **5b** in excellent yields. Demethylation of methyl ferulate (**4c**) afforded methyl caffeate (**5c**) in 65% yield, and the yield was increased to 81% using *N*,*N*-dimethylformamide diethyl acetal (DMF-DEA) as the additive.

Table 2. Selective demethylation of vanillates and ferulates[a]




**4** **5**

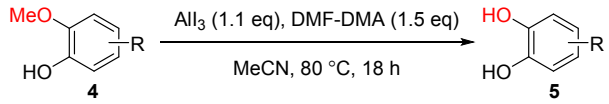
| | **5a** | **5a** | **5b** | **5c** | **5d** |
|---|---|---|---|---|---|
| A: | 90 | 98 | 94 | 65 (81[b]) | 37 (43[c]) |
| B: | 78[d] | 86 | 69 | 56 | 62 |
| C: | 65 | 93 | 88 | 74[d] | 62[e] |
| | 31,[f] 82[g] | 68[g] | 93[g] | 60[g] | |

[a] Isolated yield (%). [b] RT, 18 h, using DMF-DEA as the additive. [c] 40 °C, 18 h, using DMF-DEA as the additive. [d] Reaction was conducted at rt. [e] Stirred for 0.5 h. [f] Demethylated by $AlI_3$-DIC.[13] [g] Demethylated by $AlI_3$-DIC using ethyl acetate as a co-solvent and sacrificial ester.[16]

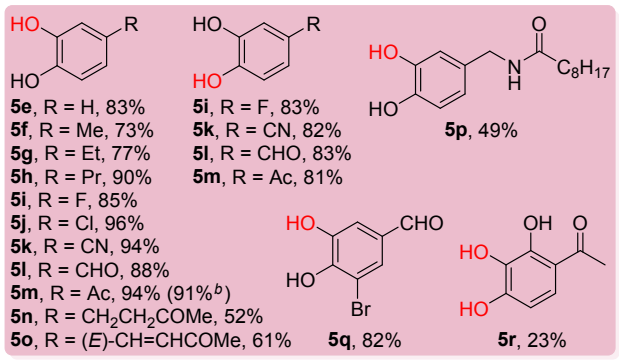
**Substrate scope exploration**. In comparison, demethylation of these substrates by $AlI_3$-pyridine and $AlI_3$-DMSO was less efficient except for ethyl ferulate (**4d**), which afforded ethyl caffeate (**5d**) in moderate yields. We had noted that demethylation of methyl vanillate (**4a**) by $AlI_3$-DIC afforded **5a** as a minor product (31%) due to non-hydrolytic ester cleavage by $AlI_3$.[13] $AlI_3$-DMF-DMA was also superior to $AlI_3$-DIC-ethyl acetate[16] in the term of efficiency.

Next, the substrate scope was investigated (Table 3). For catechol monomethyl ethers **4e** – **4m'**, the methyl was removed to afford the corresponding catechols **5e** – **5m** in good to excellent yields. Whereas fluorine and chlorine (**4i**, **4i'**, and **4j**) tolerated the conditions intact, hydrodebromination had occurred during an attempted demethylation of 4-bromo-2-methoxyphenol, giving a mixture of 4-bromocatechol and catechol. Ethers bearing butanone (**4n**), α,β-enone (**4o**) and amido (**4p**) moieties were demethylated less efficiently, and afforded the corresponding catechols (**5n** – **5p**) in moderate yields. Demethylation of 5-bromovanillin (**4q**) afforded 3-bromo-4,5-dihydroxybenzaldehyde (**5q**) in 83% yield. 2'-Hydroxy-3',4'-dimethoxyacetophenone (**4r**) was exhaustively demethylated that afforded 2',3',4'-trihydroxyacetophenone (**5r**) as the major product presumably after a series of ring-opening/ring-closing events, though in a low (23%) yield. To evaluate the scalability of this method, the demethylation of acetovanillone (**4m**) was performed on a gram-scale following the optimum conditions, which afforded 3',4'-dihydroxyacetophenone (**5m**) in 91% isolated yield.

Table 3. Cleavage of catechol monomethyl ethers[a]



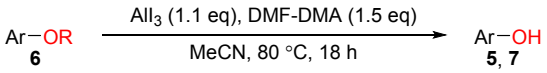

**4** **5**

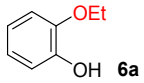
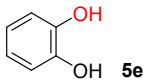
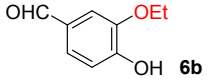
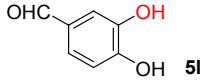
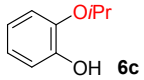
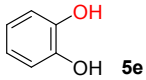
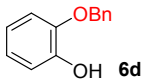
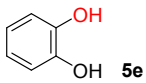


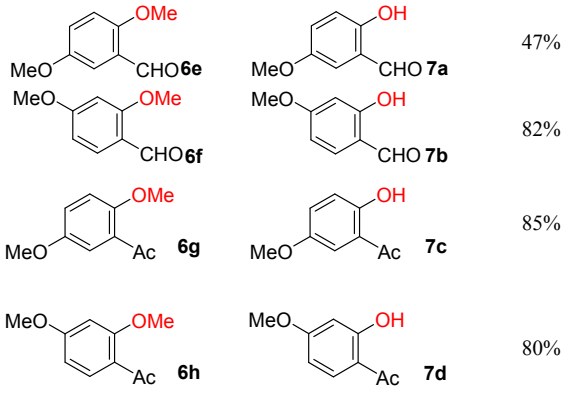

[a] Isolated yield. [b] On a gram scale.

Next, the power of $AlI_3$-DMF-DMA in removing bulkier alkyl groups bearing a neighboring phenolic hydroxyl group (**6a** – **6d**), and demethylation of aryl ethers adjacent to a carbonyl (**6e** – **6h**) was evaluated, as summarized in Table 4. The removal of bulkier ethyl (**6a** and **6b**), isopropyl (**6c**) and benzyl (**6d**) was less efficient compared to demethylation of related catechol ethers (**4e** and **4l**).

Table 4. Anchimerically facilitated cleavage of other ethers

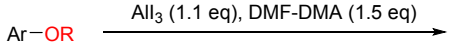


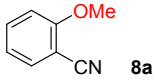
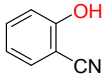
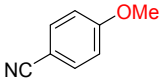
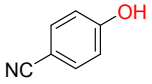
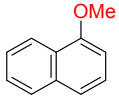
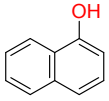
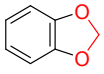
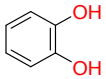
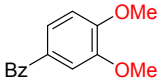
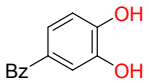
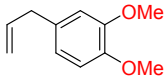
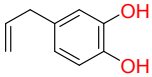
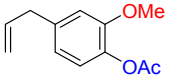
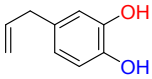

| Substrate **6** | Product **5**, **7** | Isolated yield |
|---|---|---|
|  **6a** |  **5e** | 72% |
|  **6b** |  **5l** | 60% |
|  **6c** |  **5e** | 44% |
|  **6d** |  **5e** | 63% |

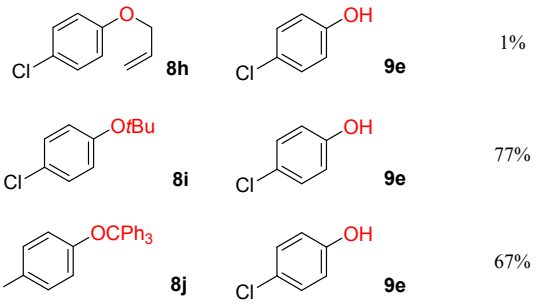



**Limitation study**. The limitation of the method was well represented by the generally inefficient cleavage of typical aryl ethers (Table 5). The cleavages of both electron-deficient and electron-rich ethers (**8a** – **8c**) were sluggish and low-yielding. Demethylenation of 1,3-benzodioxole (**8d**) was also inefficient that afforded catechol (**5e**) in 22% yield. Exhaustive demethylation of catechol dimethyl ethers (**8e** and **8f**) was observed, albeit in poor yields. Interestingly, deprotection of eugenol acetate (**8g**) afforded hydroxychavicol (**3**) as the sole product without any hint of Fries rearrangement.[6e] The allyl group (**8h**) remained essentially intact after treating with $AlI_3$-DMF-DMA. Sterically bulky *t*Bu and trityl (**8i** and **8j**), however, were readily removed that afforded 4-chlorophenol (**9e**) in good yields. The ease of cleaving tertiary alkyl ethers compared to the sluggish demethylation (**8a** – **8c**) and deallylation (**8d**) was due to a shift of the cleavage mechanism from $S_N2$ to $S_N1$.

Table 5. Cleavage of typical aryl alkyl ethers

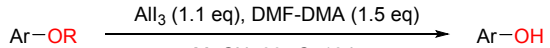


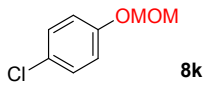
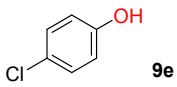
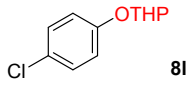
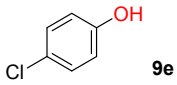
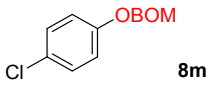
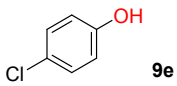
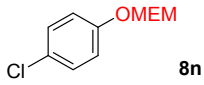
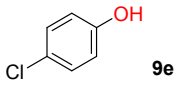
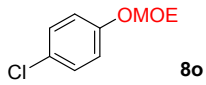
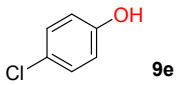
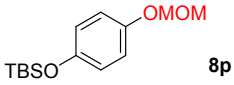
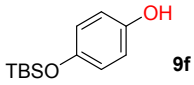
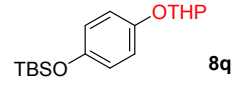
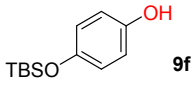
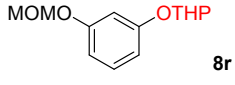
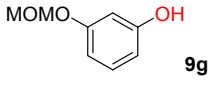
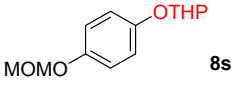
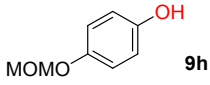
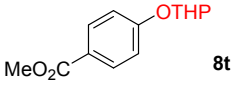
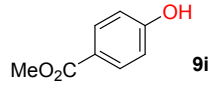
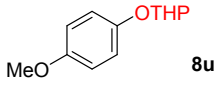
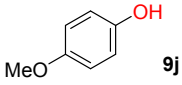

| Substrate **8** | Product **3, 5** | Isolated yield |
|---|---|---|
|  **8a** |  **9a** | 10% |
|  **8b** |  **9b** | 8% |
|  **8c** |  **9c** | 18% |
|  **8d** |  **5e** | 22% |
|  **8e** |  **9d** | 39% |
|  **8f** |  **3** | 34% |
|  **8g** |  **3** | 27% |

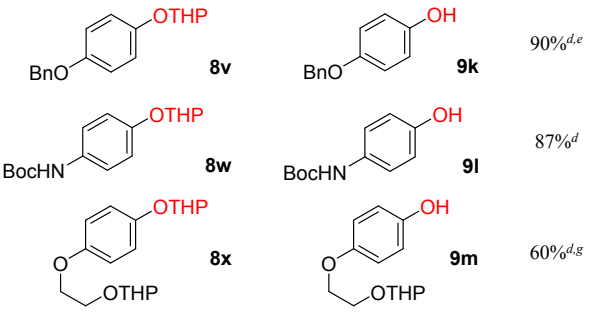



**Removal of acetal-type functional groups**. It was anticipated that acetal-type protecting groups might be removed due to the presence of an additional oxygen adjacent to the ether bond. Typically, these ethers are easily deprotected under acidic conditions *via* oxonium ion intermediates. An efficient and selective non-acidic protocol is favorable[5a,19] for protecting acid-labile groups. As expected, methoxymethyl (MOM), tetrahydropyranyl (THP), benzyloxymethyl (BOM) and methoxyethoxymethyl (MEM) were readily cleaved off from ethers **8k** – **8n**. Methoxyethyl (MOE) was similarly removed but in a lower yield from ether **8o** (Table 6).

Table 6. Cleavage of acetal-type ethers[a]




| Substrate **8** | Product **9** | Yield |
|---|---|---|
|  **8k** |  **9e** | 91% |
|  **8l** |  **9e** | 96% |
|  **8m** |  **9e** | 93% |
|  **8n** |  **9e** | 94% |
|  **8o** |  **9e** | 16%[b] |
|  **8p** |  **9f** | 62%[c] |
|  **8q** |  **9f** | 93%[d,e] |
|  **8r** |  **9g** | 66%[d,f] |
|  **8s** |  **9h** | 56%[d,f] |
|  **8t** |  **9i** | 85%[d,f] |
|  **8u** |  **9j** | 87%[d] |

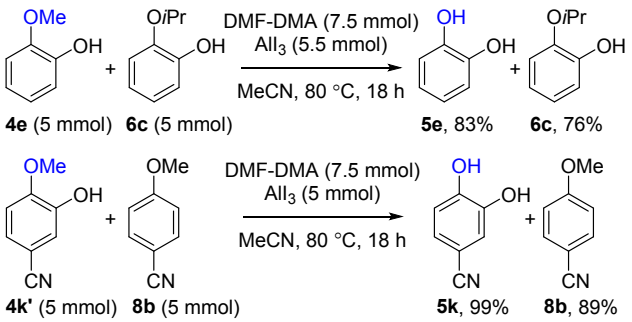



[a] Isolated yield; [b] stirred for 2 d, unreacted **8o** (76%) was recovered; [c] $AlI_3$ (1.0 eq), DMF-DMA (1.5 eq), 1.5 h, 40 °C; [d] $AlI_3$ (1.0 eq), DMF-DMA (1.5 eq), rt; [e] stirred for 2 h; [f] 1 h; [g] 0.5 h.

MOM and THP were selectively removed in the presence of TBS (**8p** and **8q**), see Table 6. It is noteworthy that the removal of THP was achieved selectively without affecting MOM (**8r** and **8s**), ester (**8t**), methoxy (**8u**), benzyloxy (**8v**) and *N*-Boc (**8w**) group. Interestingly, for ether **8x** where THP was used for protecting both phenolic and alcoholic hydroxyl group, the former was selectively and efficiently deprotected.

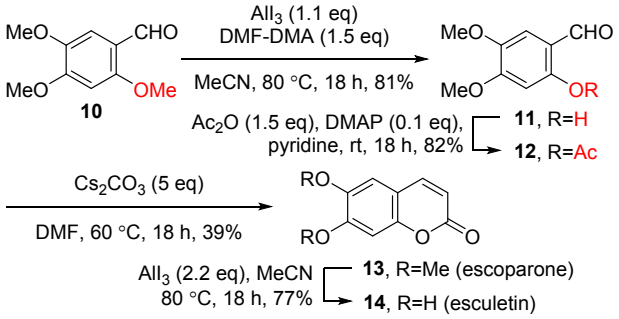
The preference for anchimerically assisted demethylation of aryl ethers provides a chance for selective ether cleavages. For example, deprotection of an equimolar mixture of guaiacol (**4e**) and 2-isopropoxyphenol (**6c**) by $AlI_3$ (1.1 eq) and DMF-DMA (1.5 eq) afforded catechol (**5e**) in 83% yield (Scheme 1) along with the unreacted **6c** (76% recovery). The importance of anchimeric effect was also exemplified by the efficient demethylated of 3-hydroxy-4-methoxybenzonitrile (**4k'**) using stoichiometric $AlI_3$-DMF-DMA that afforded 4-cyanocatechol (**5k**) in essentially quantitative yield without affecting 4-methoxybenzonitrile (**8b**).

Scheme 1. Competitive experiments



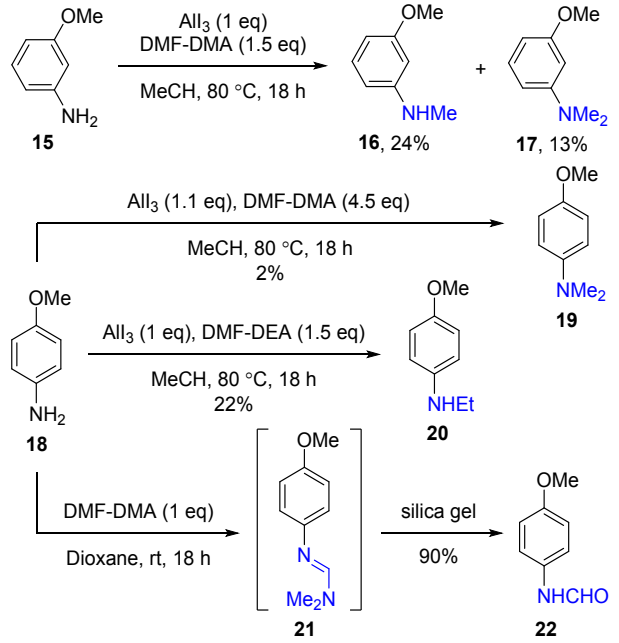

**An application**. This protocol was successfully employed in the syntheses of escoparone and esculetin,[20] two natural coumarins of pharmacological importance (Scheme 2).[21] Selective demethylation of 2,4,5-trimethoxybenzaldehyde (**10**) afforded 4,5-dimethoxysalicylaldehyde (**11**) in 81% yield. Aldehyde **11** was then acetylated by acetic anhydride in pyridine to afford acetate **12**, which underwent intramolecular aldol condensation upon base treatment, and afforded escoparone (**13**). Exhaustive demethylation of **13** by $AlI_3$ furnished esculetin (**14**). Notably, the low cyclization yield was due to unintended ester cleavage that afforded **11** as the major by-product. Several routes have been developed in the literature for these syntheses.[20] Aldehyde **11** is a useful building block achievable by a number of methods including $CeCl_3$-NaI[22], $AlI_3$-NaI,[7b] $BBr_3$[23] and $BCl_3$.[24] This synthesis featured the utilization of $AlI_3$ in selective and exhaustive cleavages of ethers.

Scheme 2. Syntheses of escoparone and esculetin




**Unexpected *N*-alkylation and *N*-formylation**. During an attempted demethylation of 3-methoxyaniline (**15**) with $AlI_3$-DMF-DMA, the unexpected formation of 3-methylaminoanisole (**16**) and 3-dimethylaminoanisole (**17**) was observed under the optimum demethylation conditions (Scheme 3). It is worth noting that DMF-DMA has been widely applied in methylation of heterocyclic secondary amines, amides, phenols and carboxylic acids,[25] but direct *N*-methylation of aryl amines has not been previously achieved. When 4-methoxyaniline (**18**) was subjected to $AlI_3$ treatment in the presence of excess DMF-DMA (4.5 eq) in anticipation of improved *N*-dimethylation, however, only trace amount of the desired 4-dimethylaminoanisole (**19**) was isolated. *N*-ethylation was also observed when DMF-DEA was used, which afforded 4-ethylaminoanisole (**20**) in 22% yield. The contradictory reaction modes of DMF-DMA in the presence and absence of $AlI_3$ toward anilines, and the marked difference between $AlI_3$-DMF-DMA and $AlI_3$-DMSO in the cleavage of typical aryl alkyl ethers implied that a reaction between $AlI_3$ and DMF-DMA should have occurred, giving likely aluminum methoxide iodide as the reactive species.

Scheme 3. Unintended *N*-alkylation and *N*-formylation of anilines




The poor yields for *N*-methylation and *N*-ethylation were due to the formation of some unidentified polar by-products. To determine the enamine **21** as a possible by-product, direct condensation of **18** with DMF-DMA was performed. Unexpectedly, 4-methoxyaniline formate (**22**) was isolated in 90% yield as a mixture of stereoisomers in a ratio of approximately *cis*/*trans* = 0.9:1. This *N*-formylation was due to silica gel catalyzed hydrolyzation[26] of **21**.

**Mechanism investigation**. To gain insight into the demethylation mechanism, a set of NMR experiments were conducted (Figure 1). The methoxy of DMF-DMA appeared as a singlet at 3.24 ppm, and the *N*-Me at 2.20 ppm in $CD_3CN$ (Figure 1A). After treating with $AlI_3$, the methoxy and the tertiary C-H (4.35 ppm) peaks disappeared (Figure 1B). Acetovanillone (**4m**) was then introduced, and after stirring overnight at 80 °C the reaction mixture showed clearly the methoxy and methyl of unreacted **4m** at 3.90 and 2.50 ppm (Figure 1C, marked with red dots), respectively. After hydrolyzation with $CF_3CO_2H$ and $D_2O$, the acetyl of product **5m** appeared at 2.46 ppm (marked with a reversed triangle) along with two new peaks at 2.91 and 2.78 (marked with black diamonds) and an additional peak at 7.89 ppm, which were recognized as DMF (Figure 1D).

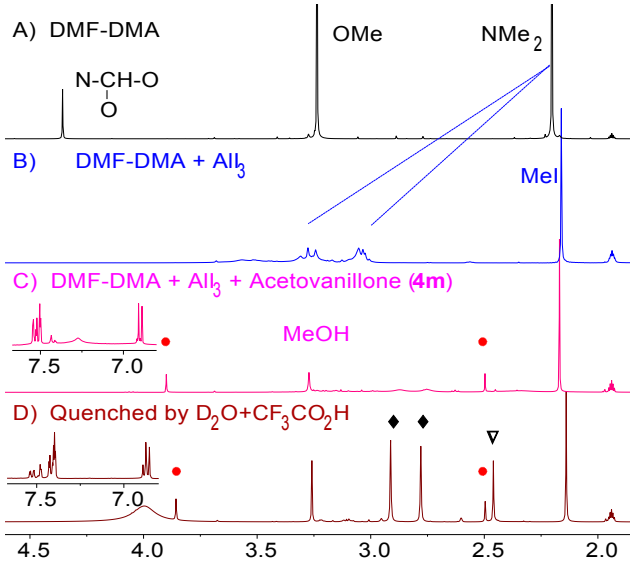



Figure 1. NMR experiments (400 MHz, $CD_3CN$). A) DMF-DMA; B) DMF-DMA and $AlI_3$; C) treatment of acetovanillone (**4m**) by $AlI_3$-DMF-DMA; D) reaction mixture was hydrolyzed by $D_2O$ and $CF_3CO_2H$. Peaks marked with ● were recognized as the methoxy and acetyl of unreacted **4m** (3.90 and 2.50 ppm); the peak (2.46 ppm) marked with ▽ was the acetyl of **5m**; peaks (2.91 and 2.78) marked with ◆ were attributed to the $NMe_2$ of DMF.

The conversion rate was about 75% based on integration analysis of the acetyl of **4m** and **5m** observed in Figure 1D. The peak at 3.26 ppm (Figure 1C) during the demethylation was ascribed to the *in situ* generated MeOH. An increased ratio of MeOH to the unreacted **4m** after acidification (Figure 1D) indicated that additional MeOH was released upon hydrolysis of the Al-OMe moiety. This reasoning and the disappearance of the dimethyl acetal moiety suggested that the acetal was indeed cleaved by $AlI_3$, which afforded aluminum methoxide iodide, $AlI_n(OMe)_{3-n}$ (n = 1 or 2), as the reactive ether cleaving species.

In considering that the *in situ* generated DMF might coordinate to aluminum methoxide iodide, the effect of $AlI_3$ on DMF was evaluated by $^1H$ NMR. Thus, a sample was prepared by dissolving DMF in $CD_3CN$ along with an equimolar toluene as an internal reference. The $NMe_2$ group appeared as two singlets at 2.80 and 2.68 ppm (Figure 2A). When $AlI_3$ was introduced into the mixture, the $NMe_2$ down-field shifted to around 3.4 and 3.1 ppm and splitted as two clusters of peaks (Figure 2B). The similar shapes and chemical shifts of these peaks to those observed at around 3.2 ppm in Figure 1B confirmed that DMF was generated directly after mixing $AlI_3$ and DMF-DMA in MeCN prior to acidification, and that the $NMe_2$ moiety was affected by the *in situ* generated aluminum methoxide iodide. Thus, the multiplet at 3.3~3.0 ppm in Figure 1B was recognized as the $Me_2N$ group of DMF.

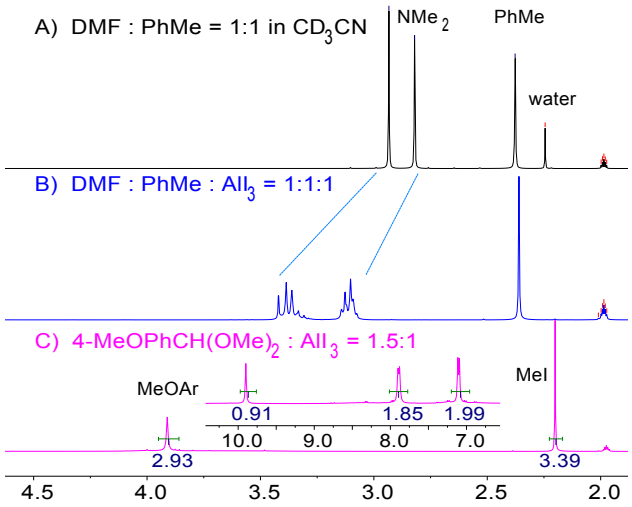
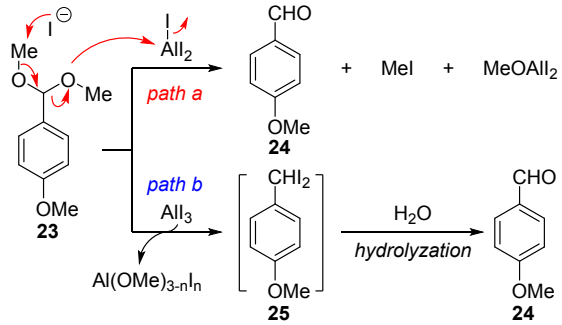



Figure 2. NMR experiments (400 MHz, $CD_3CN$). A) equimolar mixture of DMF and toluene; B) $AlI_3$ was introduced; C) cleavage of 4-methoxybenzaldehyde dimethyl acetal (**23**) by $AlI_3$ at rt for 3 h afforded 4-methoxybenzaldehyde (**24**) and MeI prior to acidification.

Another NMR experiment was designed to gain insight into the cleavage mode of the dimethyl acetal by $AlI_3$ (Figure 1B). In a precedent treatment of ethylene acetal of ketone by $AlCl_3$-NaI, the ketone was cleanly unmasked.[27] It remained unclear whether the ketone was formed during acidification of the corresponding dihaloalkyl intermediate, or was directly generated *in situ* prior to work-up. 4-Methoxybenzaldehyde dimethyl acetal (**23**) was selected as a model substrate for the ease of interpretation of intermediates by NMR spectroscopy. Two cleavage paths were imagined for the process (Scheme 4). Abstraction of one methoxy of the acetal by the Lewis acidic center and the subsequent attack of the other methoxy by an iodide ion afforded 4-methoxybenzaldehyde (**24**) along with $MeOAlI_2$ and MeI (path a). The reaction might also proceed *via* consecutive methoxy/iodide exchange to afford 4-diiodomethylanisole (**25**) as an intermediate, which underwent hydrolyzation to afford aldehyde **24** (path b).

Scheme 4. Two possible paths for the cleavage of acetals by $AlI_3$

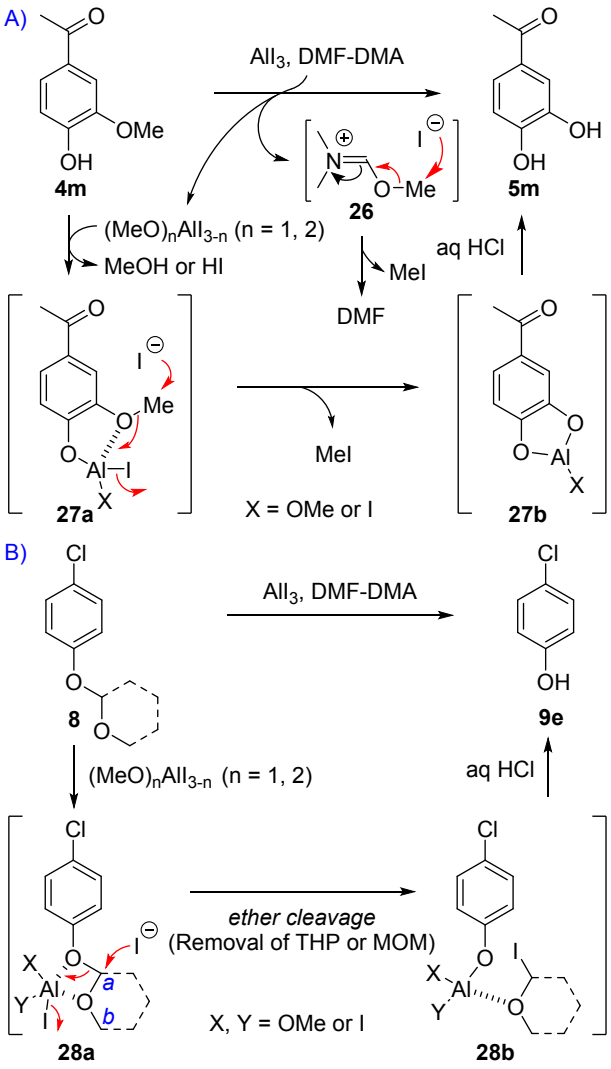



After stirring for 3 hours at room temperature, the dimethyl acetal moiety disappeared completely (Figure 2C), and typical peaks of formyl and methoxy at 9.90 and 3.91 ppm were observed prior to acidification. The singlet at 2.19 ppm was thus recognized as MeI, which also appeared in Figure 1C and Figure 1B, with the chemical shift moved to the lower field by about 0.1 ppm (Figure 1C). The integration ratio of $NMe_2$ to MeI was about 2.4 (Figure 1B), and the ratio to the acetyl of the unreacted acetovanillone (**4m**) in Figure 1B and 1C was $I_{MeI}/I_{Ac} \approx 5$. The direct formation of MeI during the cleavage of dimethyl acetals by $AlI_3$ was in accord with the unexpected *N*-alkylation (Scheme 3), which seemingly

proceeded *via* direct alkylation of anilines by the *in situ* generated alkyl iodides.

Based on these observations, and inspired by the demethylation mechanism of $AlCl_3$-pyridine suggested by Lange,[28] the ether cleavage was proposed to proceed as shown below. Treatment of DMF-DMA by $AlI_3$ led to the generation of aluminum methoxide iodide in concurrent with ion pair **26** (Scheme 5A). Attack of **26** by iodide ion afforded DMF (coordinated to the aluminum Lewis acidic center) and MeI.

Scheme 5. Proposed demethylation mechanism

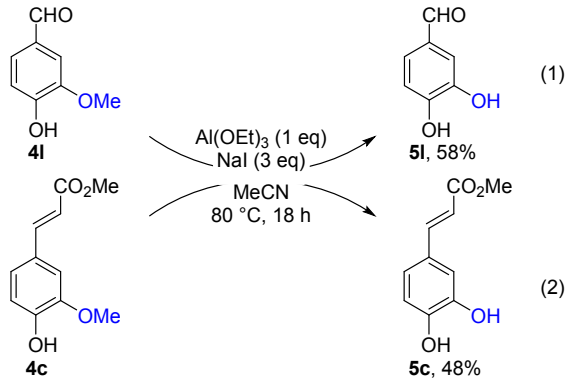



The anchimerically assisted demethylation was then initiated with the release of MeOH and HI. The $NMe_2$ and MeO-Al moieties served as the acid scavengers. Thus, treating acetovanillone **4m** with $AlI_3$ and DMF-DMA in hot acetonitrile afforded aluminum phenolate **27a** *via* ligand exchange, which then gave a solvated, five-membered cyclic aluminum catecholate **27b** along with the release of MeI. Acidification of **27b** furnished 3',4'-dihydroxyacetophenone (**5m**). Analogously, cleavage of acetal-type ethers (**8k** or **8l**) occurred by coordination to the aluminum methoxide iodide Lewis acidic center to afford complex **28a** (Scheme 5B). Attack of the carbon *a* by iodide led to the ether cleavage that afforded aluminum phenolate **28b**. Hydrolysis of **28b** afforded 4-chlorophenol (**9e**). This reasoning was supported by an NMR study of the deprotection of MOM ether **8k**. The typical MeI peak was not observed during the cleavage, suggesting that the possibility of attacking the terminal methyl (carbon *b*) by iodide and the following fragmentation to **9e** could be negated. It is worth noting that THP could be readily cleaved off at room temperature whereas the removal of MOM required heating. The difference might be due to the flexibility of MOM compared to the rigid THP group.

**Aluminum ethoxide iodide from $Al(OEt)_3$-NaI**. To support the validity of aluminum methoxide iodide as the reactive species for demethylation in $AlI_3$-DMF-DMA, a different approach to its formation was pursued. $Al(OMe)_3$ is not commercially available; thus, $Al(OEt)_3$, a widely used reductant in Meerwein-Ponndorf-Verley reaction for reducing aldehydes[29] and a catalyst for esterification of aldehydes,[30] was employed to mimic the demethylation process.

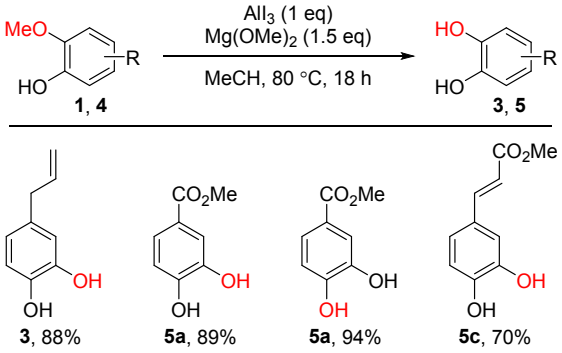
Being similar to the demethylation of eugenol by $Al(OiPr)_3$-KI,[11] it was not surprising that $Al(OEt)_3$ was effective in ether cleavages in the presence of NaI. Thus, vanillin (**4l**) was subjected to the treatment, which afforded protocatechualdehyde (**5l**) in 58% yield (Scheme 6). Its application in demethylating methyl ferulate (**4c**) was also investigated that afforded methyl caffeate (**5c**) in 48% yield. No demethylation was observed in the absence of NaI. Hence, a displacement between $Al(OEt)_3$ an NaI might occur to afford $Al(OEt)_{3-n}I_n$ as the reactive species for demethylation.

Scheme 6. Demethylation by $Al(OEt)_3$-NaI



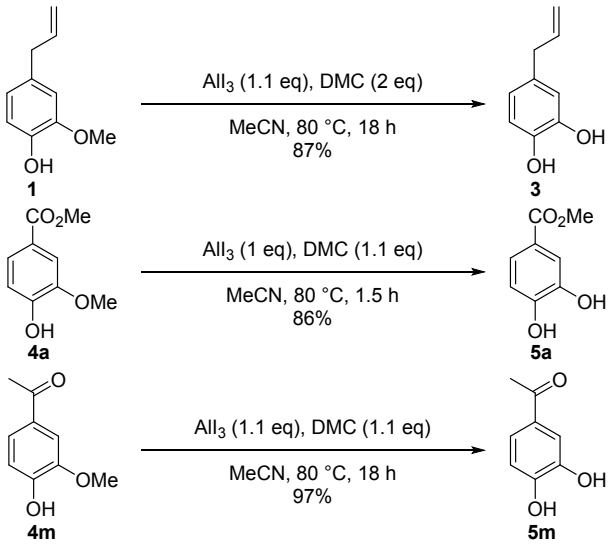

**Aluminum methoxide iodide from $AlI_3$-$Mg(OMe)_2$**. To confirm the contribution of aluminum methoxide iodide in $AlI_3$-DMF-DMA mediated ether cleavages, $Mg(OMe)_2$ was used as an alternative methoxy source, which after ligand exchange with $AlI_3$ might afford $AlI_{3-n}(OMe)_n$ and MeOMgI or $MgI_2$. Four catechol monomethyl ethers (**1**, **4a**, **4a'** and **4c**)were subjected to the treatments (Table 7), and the corresponding catechols (**3**, **5a** and **5c**) were obtained in yields comparable to those by $AlI_3$-DMF-DMA. It should be addressed that magnesium iodide constitutes another species that might contribute to the ether cleavages.

Table 7. Deprotection of catechol monomethyl ethers




**Aluminum methoxide iodide from $AlI_3$ and dimethyl carbonate**. To evaluate the power of $MeOAlI_2$ in the absence of DMF and magnesium iodide, the species was prepared *in situ* in a cleaner manner. Considering that $AlI_3$ is efficient in cleaving esters, it was envisioned that a controlled cleavage of dimethyl carbonate (DMC) might afford $MeOAlI_2$ along with the evolution of $CO_2$ and MeI. Besides, additional DMC would serve as the acid scavenger to counteract *in situ* generated HI. To verify this reasoning, eugenol (**1**) was used again as the model substrate (Scheme 7). Pleasingly, hydroxychavicol (**3**) was obtained in 87% isolated yield when DMC (2 eq) was used. A mixture of approximately equimolar amount of **3** and HI adduct **2** was produced if the DMC was reduced to 1.1 eq, whereas the yield of **3** decreased to 22% using excess DMC (5 eq). Methyl vanillate (**4a**) was also demethylated by $AlI_3$ (1 eq) and DMC (1.1 eq) that afforded methyl protocatechuate (**5a**) in 86% yield after stirring for 1.5 h at 80 °C. Longer reaction time or higher amount of DMC led to decreased yield. Treatment of acetovanillone (**4m**) under the conditions afforded 3',4'-dihydroxyacetophenone (**5m**) in 97% yield. The improved efficiency for the demethylation of eugenol and acetovanillone by $AlI_3$-DMC compared to that by $AlI_3$-DMF-DMA suggested that the power of $MeOAlI_2$ was higher than $MeOAlI_2$-DMF. These results implied that DMF impairs the cleavage of ethers.

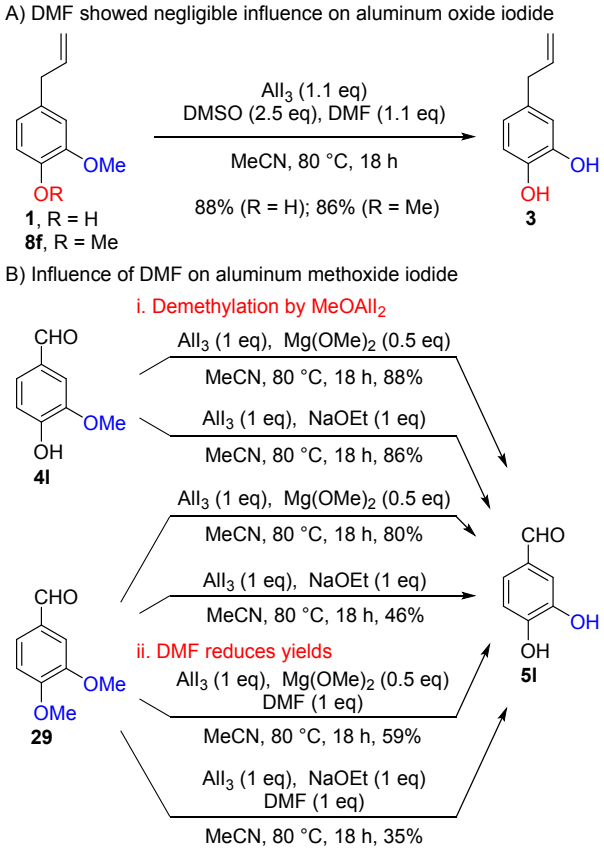
Scheme 7. Demethylation by $MeOAlI_2$ generated from $AlI_3$-DMC




**Influence of DMF on ether cleavages**. The unusual preference of aluminum methoxide iodide toward aryl alkyl ethers bearing an adjacent phenolic hydroxyl or carbonyl group remained to be clarified. It was noted that aluminum oxide iodide (O=Al-I), generated *in situ* by mixing $AlI_3$ and CaO or dimethyl sulfoxide in hot acetonitrile, was reactive toward typical aryl alkyl ethers.[11-12] Thus, an equimolar amount of DMF was added into a suspension of aluminum oxide iodide, and its effect in the demethylation of eugenol (**1**) and eugenol methyl ether (**8f**) was evaluated. The cleavages were influenced only slightly, and hydroxychavicol (**3**) was isolated in very good yield from both substrates (Scheme 8A).

The behavior of aluminum methoxide iodide was also mimicked by mixing $AlI_3$ with $Mg(OMe)_2$ (0.5 eq) and NaOEt (1 eq) in hot MeCN. Exact amount of these two alkoxy sources were employed to guarantee the formation of aluminum alkoxide iodide. Eugenol is inappropriate as the substrate due to the absence of proper acid scavengers. Instead, vanillin (**4l**) and veratraldehyde (**29**) were subjected to the treatments to further evaluate the influence of DMF on demethylation (Scheme 8B). As expected, protocatechualdehyde (**5l**) was obtained in very good yields when vanillin was demethylated by these conditions. The efficiency for the exhaustive demethylation of **29** was lower, and the poor yields were further decreased when DMF was added. The demethylation yields were higher by $Mg(OMe)_2$ than NaOEt, possibly because the *in situ* generated magnesium iodide is also effective in ether cleavages. The markedly lower yield for deprotecting veratraldehyde than vanillin by $AlI_3$-EtONa strongly resembled $AlI_3$-DMF-DMA in preferred cleavage of catechol monomethyl ethers. The contribution of the *in situ* generated magnesium iodide, an agent effective for cleaving ethers, could not be excluded.

Scheme 8. DMF as a nuisance for demethylation




## CONCLUSIONS

In summary, an efficient and selective method was developed for the cleavage of aryl alkyl ethers adjacent to a phenolic hydroxyl or carbonyl using $AlI_3$ and DMF-DMA. Acetal-type protecting groups such as MOM, MEM, BOM and THP were also readily removed. Selective removal of THP was achieved in the presence of a number of functionalities that are reactive toward $AlI_3$. NMR

experiments revealed that aluminum methoxide iodide was the reactive species, and its reactivity was further decreased by the *in situ* generated DMF. The cleavages proceeded with the assistance of neighboring group participation effect. Acid-labile functional groups such as allyl, ester, *N*-Boc and TBS tolerated the conditions intact. A number of lignin related phytochemicals including acetovanillone, eugenol, guaiacol, methyl vanillate, methyl ferulate and vanillin were efficiently deprotected to the corresponding catechols.

## EXPERIMENTAL SECTION

**General Information**. Unless otherwise stated, all reagents and solvents were purchased and used as received without further purification. MeCN was of HPLC grade with less than 500 ppm of water. Thin layer chromatography analyses were performed on precoated GF254 silica gel plates and were visualized under UV 254 nm light or by iodine staining. NMR spectra were recorded using a Bruker Avance-400 FT NMR spectrometer with TMS as the internal standard. Column chromatography was carried out using 200 – 300 mesh silica gel. Melting points were uncorrected. EA = ethyl acetate, PE = petroleum ether (60 – 90 °C).

**Hydroxychavicol** (**4-Allylcatechol**, **3**) **General procedure**. To a suspension of $AlI_3$ (5.5 mmol, 1.1 eq), prepared by stirring a mixture of aluminum powder (0.338 g) and iodine ( 2.094 g, 8.25 mmol) in MeCN (40 mL) at 80 °C in an oil bath for about 0.5 h, was added DMF-DMA (0.894 g, 7.5 mmol, 1.5 eq) in one portion. After stirring for 15 min, eugenol (**1**, 0.821 g, 5 mmol) was added. The mixture was stirred for 18 h at 80 °C before quenching with dilute aqueous HCl (2M, 5 mL). Then the mixture was extracted by EA (50 mL×3). The organic phases were combined, washed with saturated aqueous $Na_2S_2O_3$, and dried over $MgSO_4$. After filtration, the organic solvents were removed by a rotary evaporator, and the residue was purified by column chromatography (eluent: PE/EA = 4:1) to afford **3** as an off-white solid; yield: 0.615 g (82%); mp 44 – 45 °C; $R_f$ = 0.34 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, $J$ = 8.1 Hz, 1H), 6.68 (d, $J$ = 2.1 Hz, 1H), 6.59 (dd, $J_1$ = 8.1 Hz, $J_2$ = 2.0 Hz, 1H), 5.88 (ddt, $J_1$ = 15.6 Hz, $J_2$ = 10.5 Hz, $J_3$ = 6.7 Hz, 1H), 5.72 (br s, 2H), 5.09 – 4.93 (m, 2H), 3.22 (d, $J$ = 6.7 Hz, 2H). Demethylation of **1** by $Mg(OMe)_2$-$AlI_3$; yield: 0.664 g (88%). Demethylation of **1** by DMC-$AlI_3$; yield: 0.667 g (88%). From eugenol methyl ether (**8f**); yield: 0.262 g (34%); unreacted **8f** was recovered: 0.443 g (49%). From eugenol acetate (**8g**); yield: 0.204 g (27%); unreacted **8g** was recovered: 0.668 g (64%).

**Methyl 3,4-dihydroxybenzoate (5a)** Method A; from methyl vanillate (**4a**); white solid; yield: 0.757 g (90%); mp 133 – 135 °C; $R_f$ = 0.21 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.79 (br s, 1H), 9.38 (br s, 1H), 7.36 (d, $J$ = 2.1 Hz, 1H), 7.32 (dd, $J_1$ = 8.3 Hz, $J_2$ = 2.1 Hz, 1H), 6.81 (d, $J$ = 8.3 Hz, 1H), 3.76 (s, 3H). Method A; from methyl isovanillate (**4a'**); yield: 0.827 g (98%). Method B; from **4a** (0.366 g, 2 mmol); yield: 0.265 g (78%). Method B; from **4a'** (0.364 g, 2 mmol); conducted at rt for 18 h; yield: 0.289 g (86%). Method C; from **4a**; yield: 0.553 g (65%). Method C; from **4a'**; yield: 0.782 g (93%). Demethylation by $Mg(OMe)_2$-$AlI_3$; from **4a** (0.365 g, 2 mmol); yield: 0.300 g (89%). Demethylation by DMC-$AlI_3$; from **4a** (0.363 g, 2 mmol); stirred for 1.5 h; yield: 0.289 g (86%). Demethylation by $Mg(OMe)_2$-$AlI_3$; from **4a'** (0.364 g, 2 mmol); yield: 0.317 g (94%).

**Ethyl 3,4-dihydroxybenzoate (5b)** Method A; white solid; yield: 0.859 g (94%); mp 132 – 134 °C; $R_f$ = 0.21 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.56 (br s, 2H), 7.37 (d, $J$ = 2.2 Hz, 1H), 7.32 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.1 Hz, 1H), 6.81 (d, $J$ = 8.3 Hz, 1H), 4.22 (q, $J$ = 7.1 Hz, 2H), 1.28 (t, $J$ = 7.1 Hz, 3H). Method B; yield: 0.630 g (69%). Method C; yield: 0.809 g (88%).

**Methyl caffeate** (**5c**) Method A; from methyl ferulate (**4c**, 0.416 g, 2 mmol); white solid; yield: 0.256 g (65%); mp 158 – 161 °C; $R_f$ = 0.19 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.57 (br s, 1H), 9.20 (br s, 1H), 7.49 (d, $J$ = 15.9 Hz, 1H), 7.06 (d, $J$ = 2.2 Hz, 1H), 7.01 (dd, $J_1$ = 8.3 Hz, $J_2$ = 2.1 Hz, 1H), 6.77 (d, $J$ = 8.1 Hz, 1H), 6.28 (d, $J$ = 15.9 Hz, 1H), 3.69 (s, 3H). Method A; from **4c** (0.458 g, 2.2 mmol) using $AlI_3$ (1 eq) and DMF-DEA (0.486 g, 3.3 mmol, 1.5 eq), performed at rt for 18 h; yield: 0.347 g (81%). Method B; from **4c** (0.416 g, 2 mmol); yield: 0.219 g (56%). Method C; from **4c**; conducted at rt for 18 h; yield: 0.725 g (74%). From **4c** (0.416 g, 2 mmol) using $Al(OEt)_3$ (0.324 g, 2 mmol, 1 eq) and NaI (0.899 g, 6 mmol, 3 eq); yield: 0.188 g (48%). Demethylation by $Mg(OMe)_2$-$AlI_3$; from **4c** (0.416 g, 2 mmol); yield: 0.275 g (70%).

**Ethyl caffeate** (**5d**) Method A; from ethyl ferulate (**4d**, 0.444 g, 2 mmol) using DMF-DMA (0.365 g, 3 mmol, 1.5 eq); white solid; yield: 0.155 g (37%); mp 142 – 144 °C; $R_f$ = 0.15 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.60 (br s, 1H), 9.16 (br s, 1H), 7.48 (d, $J$ = 15.9 Hz, 1H), 7.05 (d, $J$ = 2.1 Hz, 1H), 7.01 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.1 Hz, 1H), 6.77 (d, $J$ = 8.1 Hz, 1H), 6.26 (d, $J$ = 15.9 Hz, 1H), 4.16 (q, $J$ = 7.1 Hz, 2H), 1.24 (t, $J$ = 7.1 Hz, 3H). Method A; from **4d** (0.445 g, 2 mmol) using DMF-DEA (0.442 g, 3 mmol, 1.5 eq); conducted at 40 °C for 18 h; yield: 0.181 g (43%). Method B; from **4d** (0.444 g, 2 mmol); yield: 0.261 g (62%). Method C; from **4d** (0.444 g, 2 mmol); conducted at 80 °C for 0.5 h; yield: 0.262 g (62%).

**Catechol** (**5e**) From guaiacol (**4e**); white solid; yield: 0.458 g (83%); mp 103 – 105 °C; $R_f$ = 0.25 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.11 – 6.81 (m, 4H), 4.99 (br s, 2H). From 2-ethoxyphenol (**6a**); yield: 0.399 g (72%). From 2-isopropoxyphenol (**6c**, 0.304g, 2mmol); yield: 0.099 g (44%). From 2-benzoxyphenol (**6d**, 0.400g, 2mmol); yield: 0.140 g (63%). From 1,3-benzodioxole (**8d**); yield: 0.124 g (22%).

**4-Methylcatechol (5f)** Yellow liquid; yield: 0.456 g (73%); $R_f$ = 0.46 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.69 (d, $J$ = 8.0 Hz, 1H), 6.61 (d, $J$ = 2.0 Hz, 1H), 6.51 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.0 Hz, 1H), 6.31 (br s, 2H), 2.12 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 143.2, 141.0, 131.4, 121.9, 116.8, 115.9, 20.7.

**4-Ethylcatechol (5g)** Viscous yellow liquid; yield: 0.538 g (77%); $R_f$ = 0.42 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, $J$ = 8.1 Hz, 1H), 6.68 (d, $J$ = 2.0 Hz, 1H), 6.58 (dd, $J_1$ = 8.1 Hz, $J_2$ = 2.1 Hz, 1H), 6.09 (br s, 2H), 2.47 (q, $J$ = 7.6 Hz, 2H), 1.12 (t, $J$ = 7.6 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 143.3, 141.1, 137.9, 120.5, 115.7, 115.4, 28.2, 15.7.

**4-Propylcatechol (5h)** Yellow liquid; yield: 0.690 g (90%); $R_f$ = 0.39 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, $J$ = 8.1 Hz, 1H), 6.66 (d, $J$ = 2.1 Hz, 1H), 6.55 (dd, $J_1$ = 8.1 Hz, $J_2$ = 2.0 Hz, 1H), 6.25 (br s, 2H), 2.39 (t, $J$ = 7.6 Hz, 2H), 1.50 (sextet, $J$ = 7.4 Hz, 2H), 0.86 (t, $J$ = 7.4 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 143.2, 141.1, 136.4, 121.3, 116.0, 115.8, 37.3, 24.6, 13.8.

**4-Fluorocatechol (5i)** From 4-fluoro-2-methoxyphenol (**4i**, 0.283 g, 2 mmol); white solid; yield: 0.218 g (85%); mp 86 – 89 °C; $R_f$ = 0.43 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.78 (dd, $J_1$= 8.8 Hz, $J_2$ = 5.2 Hz, 1H), 6.64 (dd, $J_1$ = 9.2 Hz, $J_2$ = 2.9 Hz, 1H), 6.51 (td, $J_1$ = 8.6 Hz, $J_2$ = 2.9 Hz, 1H), 5.78 (br s, 1H), 5.34 (br s, 1H). From 5-fluoro-2-methoxyphenol (**4i'**); yield: 0.533 g (83%).

**4-Chlorocatechol (5j)** White solid; yield: 0.698 g (96%); mp 90 – 92 °C; $R_f$ = 0.31 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.38 (s, 1H), 9.16 (s, 1H), 6.75 (d, $J$ = 2.5 Hz, 1H), 6.73 (d, $J$ = 8.4 Hz, 1H), 6.64 (dd, $J_1$ = 8.4 Hz, $J_2$ = 2.6 Hz, 1H).

**4-Cyanocatechol** (**5k**) From 2-methoxy-4-cyanophenol (**4k**); off-white solid; yield: 0.641 g (94%); mp 153 – 154 °C; $R_f$ = 0.39 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.11 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.0 Hz, 1H), 7.06 (d, $J$ = 2.1 Hz, 1H), 6.86 (d, $J$ = 8.2 Hz, 1H). From 2-methoxy-5-cyanophenol (**4k'**); yield: 0.559 g (82%).

**Protocatechualdehyde** (**5l**) From vanillin (**4l**); yellow solid; yield: 0.609 g (88%); mp 151 – 152 °C; $R_f$ = 0.38 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.84 (br s, 2H), 9.70 (s, 1H), 7.27 (d, $J$ = 8.0 Hz, 1H), 7.25 (s, 1H), 6.92 (d, $J$ = 8.0 Hz, 1H). From isovanillin (**4l'**); yield: 0.574 g (83%). From ethylvanillin (**6b**); yield: 0.462 g (60%). From vanillin (**4l**, 0.432 g, 2.84 mmol) using Al(OEt)$_3$ (0.461g, 2.84 mmol, 1 eq) and NaI (1.275 g, 8.51 mmol, 3 eq); yield: 0.228 g (58%).

**3',4'-dihydroxyacetophenone** (**5m**) From acetovanillone (**4m**); off-white solid; yield: 0.721 g (94%); mp 118 – 119 °C (lit.[31] 115-117 °C); $R_f$ = 0.35 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.60 (br s, 2H), 7.35 (dd, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz, 1H), 7.34 (d, $J$ = 2.4 Hz, 1H), 6.82 (d, $J$ = 8.8 Hz, 1H), 2.43 (s, 3H). From isoacetovanillone (**4m'**); yield: 0.617 g (81%). Demethylation by DMC-AlI$_3$; from **4m**; yield: 0.740 g (97%).

**Gram-scale synthesis of 3',4'-dihydroxyacetophenone** (**5m**) A mixture of aluminum powder (0.869 g) and iodine (5.443 g, 21.45 mmol) and MeCN (80 mL) was stirred for about 0.5 h at 80 °C in an oil bath to give a suspension AlI$_3$ (14.3 mmol, 1.1 eq). To the mixture was charged DMF-DMA (2.325 g, 19.51 mmol, 1.5 eq) followed by acetovanillone **4m** (2.160 g, 13 mmol). After stirring for 18 h at 80 °C, the mixture was cooled to room temperature, acidified with dilute HCl (2M, 10 mL), extracted with EA (50 mL×3). The organic phases were combined, washed with saturated $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. After filtration, the solvents were removed by rotary evaporator, and the residue was purified by column chromatography (eluent: PE/EA = 1:1). Yield: 1.808 g (91%).

**4-(3,4-Dihydroxyphenyl)butan-2-one** (**5n**) Off-white solid; yield: 0.473 g (52%); mp 78 – 81 °C (lit.[32] 85 – 86 °C); $R_f$ = 0.35 (PE/EA 1:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.76 (d, $J$ = 8.0 Hz, 1H), 6.70 (d, $J$ = 2.1 Hz, 1H), 6.59 (dd, $J_1$ = 8.1 Hz, $J_2$ = 2.1 Hz, 1H), 6.02 (br s, 1H), 5.80 (br s, 1H), 2.84 – 2.67 (m, 4H), 2.15 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) δ 210.1, 143.7, 142.0, 133.6, 120.5, 115.4, 115.4, 45.4, 30.2, 29.1.

**(*E*)-4-(3,4-Dihydroxyphenyl)but-3-en-2-one** (**5o**) Light yellow solid; yield: 0.550 g (61%); mp 172 – 174 °C (lit.[32] 177-178 °C); $R_f$ = 0.30 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.42 (br s, 2H), 7.46 (d, $J$ = 16.2 Hz, 1H), 7.07 (s, 1H), 7.01 (d, $J$ = 7.8 Hz, 1H), 6.78 (d, $J$ = 8.1 Hz, 1H), 6.49 (d, $J$ = 16.2 Hz, 1H), 2.28 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 198.3, 148.9, 146.1, 144.5, 126.2, 124.4, 122.1, 116.3, 115.2, 27.6.

***N*-(3,4-Dihydroxybenzyl)nonanamide** (**5p**) From *N*-vanillylnonanamide (**4p**, 0.587 g, 2 mmol); off-white solid; yield: 0.277 g (49%); mp 97 – 98 °C; $R_f$ = 0.13 (PE/EA 1:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.41 (br s, 1H), 6.80 (d, $J$ = 2.0 Hz, 1H), 6.79 (d, $J$ = 8 Hz, 1H), 6.60 (dd, $J_1$ = 8.0 Hz, $J_2$ = 1.9 Hz, 1H), 6.49 (br s, 1H), 6.07 (t, $J$ = 6.0 Hz, 1H), 4.27 (d, $J$ = 5.9 Hz, 2H), 2.20 (t, $J$ = 7.7 Hz, 2H), 1.61 (q, $J$ = 7.3 Hz, 2H), 1.36 – 1.12 (m, 10H), 0.86 (t, $J$ = 6.8 Hz, 3H).

**3-Bromo-4,5-dihydroxybenzaldehyde (5q)** Yellow solid; yield: 0.894 g (82%); $R_f$ = 0.19 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.46 (br s, 2H), 9.70 (s, 1H), 7.57 (s, 1H), 7.25 (s, 1H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 191.0, 149.8, 147.0, 129.5, 127.8, 113.2, 109.9.

**2',3',4'-Trihydroxyacetophenone** (**5r**) Light yellow solid; yield: 0.197g (23%); mp 169 – 170 °C; $R_f$ = 0.26 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.61 (br s, 1H), 10.04 (br s, 1H), 8.71 (brs, 1H), 7.31 (d, $J$ = 8.8 Hz, 1H), 6.41 (d, $J$ = 8.8 Hz, 1H), 2.52 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 204.0, 153.0, 152.6, 132.6, 123.6, 113.6, 108.1, 26.8. Unreacted **4r** was recovered: 0.198 g (20%).

**5-Methoxysalicylaldehyde (7a)** Light yellow liquid; yield: 0.361 g (47%); $R_f$ = 0.58 (PE/EA 10:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 10.65 (s, 1H), 9.83 (s, 1H), 7.13 (dd, $J_1$ = 9.0 Hz, $J_2$ = 3.1 Hz, 1H), 6.98 (d, $J$ = 3.1 Hz, 1H), 6.91 (d, $J$ = 9.0 Hz, 1H), 3.80 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) δ 196.2, 156.0, 152.7, 125.2, 120.0, 118.6, 115.2, 55.9.

**4-Methoxysalicylaldehyde** (**7b**) White solid; yield: 0.631 g (82%); mp 39 – 41 °C; $R_f$ = 0.67 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 11.06 (br s, 1H), 10.00 (s, 1H), 7.62 (d, $J$ = 8.7 Hz, 1H), 6.56 (dd, $J_1$ = 8.7 Hz, $J_2$ = 2.4 Hz, 1H), 6.48 (d, $J$ = 2.4 Hz, 1H), 3.81 (s, 3H).

**2'-Hydroxy-5'-methoxyacetophenone** (**7c**) Light yellow solid; yield: 0.708 g (85%); mp 47 – 48 °C; $R_f$ = 0.81 (PE/EA 3:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 11.86 (s, 1H), 7.16 (d, $J$ = 3.0 Hz, 1H), 7.11 (dd, $J_1$ = 9.0 Hz, $J_2$ = 3.1 Hz, 1H), 6.92 (d, $J$ = 9.0 Hz, 1H), 3.80 (s, 3H), 2.62 (s, 3H).

**2'-Hydroxy-4'-methoxyacetophenone** (**Paeonol**, **7d**) Colorless liquid; yield: 0.670 g (80%); $R_f$ = 0.56 (PE/EA 10:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 12.75 (s, 1H), 7.60 (d, $J$ = 8.8 Hz, 1H), 6.42 (dd, $J_1$ = 8.8 Hz, $J_2$ = 1.1 Hz, 1H), 6.39 (d, $J$ = 1.4 Hz, 1H), 3.81 (s, 3H), 2.53 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, CDCl$_3$) δ 202.6, 166.1, 165.2, 132.3, 113.9, 107.5, 100.8, 55.5, 26.1.

**2-Hydroxybenzonitrile** (**9a**) Off-white solid; yield: 0.060 g (10%); mp 92 – 94 °C; $R_f$ = 0.32 (PE/EA 3:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.51 (dd, $J_1$ = 7.8, 1.7 Hz, 1H), 7.47 (ddd, $J_1$ = 9.0 Hz, $J_2$ = 7.5 Hz, $J_3$ = 1.7 Hz, 1H), 7.02 (d, $J$ = 8.4 Hz, 1H), 6.98 (td, $J_1$ = 7.6 Hz, $J_2$ = 1.0 Hz, 1H), 6.81 (br s, 1H). Unreacted **8a** was recovered: 0.546 g (82%).

**4-Cyanophenol** (**9b**) Off-white solid; yield: 0.051 g (8%); mp 111 – 112 °C; $R_f$ = 0.38 (PE/EA 3:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, $J$ = 8.7 Hz, 2H), 6.95 (d, $J$ = 8.7 Hz, 2H), 6.88 (br s, 1H). Unreacted **8b** was recovered: 0.489 g (73%).

**1-Naphthol** (**9c**) Pale yellow solid; yield: 0.136 g (18%); mp 93 – 95 °C; $R_f$ = 0.84 (PE/EA 3:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.17 (ddt, $J_1$ = 6.1 Hz, $J_2$ = 3.4 Hz, $J_3$ = 0.9 Hz, 1H), 7.86 – 7.75 (m, 1H), 7.53 – 7.46 (m, 2H), 7.44 (d, $J$ = 8.3 Hz, 1H), 7.30 (dd, $J_1$ = 8.3 Hz, $J_2$ = 7.4 Hz, 1H), 6.80 (dd, $J_1$ = 7.5 Hz, $J_2$ = 1.0 Hz, 1H), 5.31 (br s, 1H).

**3,4-Dihydroxybenzophenone** (**9d**) From 3,4-dimethoxybenzophenone (**8e**, 0.485 g, 2 mmol); light yellow solid; yield: 0.168 g (39%); mp 133 – 134 °C (lit.[31] 132 – 134 °C); $R_f$ = 0.47 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.73 (br s, 2H), 7.65 (d, $J$ = 6.7 Hz, 2H), 7.61 (t, $J$ = 7.4 Hz, 1H), 7.52 (t, $J$ = 7.4 Hz, 2H), 7.26 (d, $J$ = 2.1 Hz, 1H), 7.12 (dd, $J_1$ = 8.2 Hz, $J_2$ = 2.1 Hz, 1H), 6.87 (d, $J$ = 8.2 Hz, 1H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 194.9, 151.2, 145.7, 138.8, 132.1, 129.5, 128.7, 128.7, 124.0, 117.4, 115.6. Unreacted **8e** was recovered: 0.218 g (44%).

**4-Chlorophenol** (**9e**) From 4-chlorophenyl allyl ether (**8h**, 0.337 g, 2 mmol); colorless liquid; yield: 0.005 g (1%); $R_f$ = 0.31 (PE/EA 10:1). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.16 (d, $J$ = 8.9 Hz, 2H), 6.75 (d, $J$ = 8.9 Hz, 2H), 6.12 (br s, 1H). $^{13}$C{$^1$H} NMR (101 MHz,

$CDCl_3$) δ 154.0, 129.6, 125.8, 116.8. From 4-chlorophenyl *tert*-butyl ether (**8i**); yield: 0.501 g (77%). From 4-chlorophenyl tripheylmethyl ether (**8j**, 0.371 g, 1 mmol); yield: 0.086 g (67%). From 4-chlorophenyl methoxymethyl ether[33] (**8k**, 0.345 g, 2 mmol); yield: 0.234 g (91%). From 4-chlorophenyl 2-tetrahydropyranyl ether[34] (**8l**, 0.425 g, 2 mmol); yield: 0.249 g (96%). From 4-chlorophenyl benzyloxymethyl ether[35] (**8m**, 0.248 g, 1 mmol); yield: 0.120 g (93%). From 4-chlorophenyl methoxyethoxymethyl ether[36] (**8n**, 0.216 g, 1 mmol); yield: 0.121 g (94%). From 4-chlorophenyl methoxyethyl ether[35] (**8o**, 0.186 g, 1 mmol); stirring for 2 d at 80 °C; yield: 0.020 g (16%); unreacted ether **8o** was recovered: 0.134 g (72%).

**4-(*tert*-Butyldimethylsiloxy)phenol (9f)** From 4-(*tert*-butyldimethylsiloxy)phenyl methoxymethyl ether[37] (**8p**, 0.268 g, 1 mmol); stirred for 1.5 h at 40 °C; off-white solid; yield: 0.141 g (62%); mp 56 – 58 °C; $R_f$ = 0.32 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.94 (s, 1H), 6.67 – 6.57 (m, 4H), 0.92 (s, 9H), 0.12 (s, 6H). From 4-(*tert*-butyldimethylsiloxy)phenyl 2-tetrahydropyranyl ether[37] (**8q**, 0.616 g, 2 mmol); stirred for 2 h at rt; yield: 0.417 g (93%).

**3-(Methoxymethoxy)phenol (9g)** From 3-(methoxymethoxy) phenyl 2-tetrahydropyranyl ether[38] (**8r**, 0.238 g, 1 mmol); stirred for 1 h at rt; colorless liquid; yield: 0.103 g (66%); $R_f$ = 0.56 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, $J$ = 8.1 Hz, 1H), 6.61 (ddd, $J_1$ = 8.2 Hz, $J_2$ = 2.3 Hz, $J_3$ = 0.9 Hz, 1H), 6.56 (t, $J$ = 2.4 Hz, 1H), 6.49 (ddd, $J_1$ = 8.2 Hz, $J_2$ = 2.4 Hz, $J_3$ = 0.9 Hz, 1H), 5.89 (br s, 1H), 5.16 (s, 2H), 3.49 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 158.3, 156.7, 130.3, 109.2, 108.6, 103.7, 94.3, 56.1.

**4-(Methoxymethoxy)phenol (9h)** From 4-(methoxymethoxy)phenyl 2-tetrahydropyranyl ether (**8s**, CAS Reg. No. 130252-97-0, prepared following literature[38] method, 0.237 g, 1 mmol); stirred for 1 h at rt; colorless liquid; yield: 0.087 g (66%); $R_f$ = 0.51 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, $J$ = 9.0 Hz, 2H), 6.72 (d, $J$ = 9.0 Hz, 2H), 5.60 (s, 1H), 5.11 (s, 2H), 3.49 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 151.0, 150.8, 118.0, 116.1, 95.4, 55.9.

**Methyl 4-hydroxybenzoate (9i)** From 4-methoxycarbonylphenyl 2-tetrahydropyranyl ether[39] (**8t**, 0.236 g, 1 mmol); stirred for 1 h at rt; white solid; yield: 0.130 g (85%); mp 124 – 126 °C; $R_f$ = 0.45 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J$ = 8.8 Hz, 2H), 6.90 (d, $J$ = 8.8 Hz, 2H), 6.67 (br s, 1H), 3.91 (s, 3H).

**4-Methoxyphenol (9j)** From 4-methoxyphenyl 2-tetrahydropyranyl ether[40] (**8u**, 0.209 g, 1 mmol); stirred for 18 h at rt; white solid; yield: 0.109 g (87%); mp 53 – 54 °C; $R_f$ = 0.48 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.74 (m, 4H), 5.05 (br s, 1H), 3.77 (s, 3H).

**4-Benzyloxyphenol (9k)** From 4-benzyloxyphenyl 2-tetrahydropyranyl ether[41] (**8v**, 0.284 g, 1 mmol); stirred for 2 h at rt; white solid; yield: 0.180 g (90%); mp 119 – 119 °C; $R_f$ = 0.54 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.38 (ddd, $J_1$ = 7.6 Hz, $J_2$ = 6.6 Hz, $J_3$ = 1.3 Hz, 2H), 7.35 – 7.29 (m, 1H), 6.86 (d, $J$ = 9.0 Hz, 2H), 6.76 (d, $J$ = 9.0 Hz, 2H), 5.01 (s, 2H), 4.63 (br s, 1H).

***N*-Boc-4-hydroxyaniline (9l)** From 4-(*tert*-butoxycarbonylamino)phenyl 2-tetrahydropyranyl ether (**8w**, prepared following literature[42] method, 0.147 g, 0.5 mmol); stirred for 18 h at rt; yellow solid; yield: 0.091 g (87%); mp 141 – 143 °C; $R_f$ = 0.42 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, $J$ = 8.3 Hz, 2H), 6.73 (d, $J$ = 8.9 Hz, 2H), 6.38 (br s, 1H), 5.64 (br s, 1H), 1.51 (s, 9H).

**2-(*p*-Hydroxyphenyl)ethyl 2-tetrahydropyranyl ether (9m)** From bis(2-tetrahydropyranyl) ether of 4-hydroxyethylphenol (**9x**, prepared following literature[40] method, 0.305 g, 1 mmol); stirred 0.5 h at rt; colorless oil; yield: 0.134 g (60%); $R_f$ = 0.53 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.19 (br s, 1H), 7.02 (d, $J$ = 8.4 Hz, 2H), 6.67 (d, $J$ = 8.5 Hz, 2H), 4.58 – 4.51 (m, 1H), 3.73 (dt, $J_1$ = 9.6 Hz, $J_2$ = 7.3 Hz, 1H), 3.64 (ddd, $J_1$ = 11.3 Hz, $J_2$ = 8.2 Hz, $J_3$ = 3.1 Hz, 1H), 3.48 (dt, $J_1$ = 9.6 Hz, $J_2$ = 7.0 Hz, 1H), 3.39 – 3.34 (m, 1H), 2.70 (t, $J$ = 7.1 Hz, 2H), 1.76 – 1.63 (m, 1H), 1.58 (ddt, $J_1$ = 12.3 Hz, $J_2$ = 6.3 Hz, $J_3$ = 3.1 Hz, 1H), 1.51 – 1.33 (m, 4H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 156.0, 130.2, 129.5, 115.4, 98.2, 68.4, 61.6, 35.3, 30.7, 25.5, 19.6.

**Selective experiments** To a suspension of $AlI_3$ (5 mmol, 1 eq) and DMF-DMA (7.5 mmol, 1.5 eq) in MeCN (40 mL) was added a mixture of 5-cyano-2-methoxyphenol (**4k'**, 0.746 g, 5 mmol) and 4-cyanoanisole (**8b**, 0.666 g, 5 mmol). After stirring for 18 h at 80 °C in an oil bath, the reaction mixture was cooled to rt, quenched with dilute 2M HCl (5 mL), and extracted with EA (50 mL×3). The organic phases were combined, washed with saturated aqueous $Na_2S_2O_3$, and dried over $MgSO_4$. After filtration, the solvents were removed by a rotary evaporator, and the residue was purified by column chromatography (eluent: PE/EA = 4:1) to afford 4-cyanocatechol (**5k**, 0.673 g, 99%) along with unreacted **8b** (0.594 g, 89% recovery).

A mixture of 2-isopropoxyphenol (**6c**, 0.762 g, 5 mmol) and guaiacol (**4e**, 0.622 g, 5 mmol) was treated by $AlI_3$ (5 mmol, 1 eq) and DMF-DMA (7.5 mmol, 1.5 eq) in MeCN (40 mL), and the resultant mixture was stirred for 18 h at 80 °C following the above procedure to afford catechol (**5e**, 0.456 g, 83%) and unreacted **6c** (0.580 g, 76% recovery).

**2-Hydroxy-4,5-dimethoxybenzaldehyde (11)** Off-white solid; yield: 0.738 g (81%); mp 104 – 105 °C; $R_f$ = 0.88 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 10.72 (br s, 1H), 10.02 (s, 1H), 7.14 (s, 1H), 6.56 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H).

**2-Acetoxy-4,5-dimethoxybenzaldehyde (12)** A mixture of **11** (0.911 g, 5 mmol), $Ac_2O$ (0.769 g, 7.5 mmol, 1.5 eq), pyridine (6 mL) and DMAP (0.061 g, 0.5 mmol, 0.1 eq) was stirred at rt for 18 h. The reaction was then quenched with water (20 mL), and the mixture was extracted with EA (50 mL×3). The organic phases were combined and dried over $MgSO_4$. After filtration, the organic solvents were removed by a rotary evaporator, and the residue was purified by column chromatography (eluent: PE/EA = 4:1) to afford **12** as an off-white solid; yield: 0.927 g (82%); mp 91 – 93 °C; $R_f$ = 0.40 (PE/EA 3:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.94 (s, 1H), 7.34 (s, 1H), 6.96 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.34 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 188.5, 167.0, 155.1, 147.7, 147.3, 120.8, 110.6, 107.5, 56.8, 56.3, 21.1.

**6,7-Dimethoxycoumarin (13)** A mixture of **12** (0.225 g, 1 mmol), $Cs_2CO_3$ (1.629 g, 5 mmol, 5 eq) was stirred in DMF (10 mL) for 18 h at 60 °C in an oil bath until the disappearance of **12**. The reaction mixture was then partitioned between EA and water, and the organic phases were removed by a rotary evaporator. The residue was purified by column chromatography (eluent: PE/EA = 4:1) to afford **13** as a white solid; yield: 0.082 g (39%); mp 142 – 144 °C; $R_f$ = 0.27 (PE/EA 3:1). Phenol **11**, formed due to unintended hydrolysis of **12**, was isolated as the by-product. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.96 (d, $J$ = 9.5 Hz, 1H), 7.26 (s, 1H), 7.08 (s, 1H), 6.30 (d, $J$ = 9.5 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 161.0, 153.0, 149.9, 146.3, 144.8, 113.1, 111.7, 109.4, 100.5, 56.7, 56.4.

**6,7-Dihydroxycoumarin (Esculetin, 14)** Ether **13** (0.103 g, 0.5

mmol) was added in one portion to a suspension of $AlI_3$ (1.1 mmol, 2.2 eq) in MeCN (10 mL). The mixture was stirred for 18 h at 80 °C in an oil bath before quenching with water. After extracting with EA (3×10 mL), the organic phases were combined, dried over $MgSO_4$, and after evaporation with a rotary evaporator, the residue was purified by column chromatography (eluent: PE/EA = 1:1) to afford **14** as a yellow solid; yield : 0.069 g (77%); mp 273 – 276 °C; $R_f$ = 0.19 (PE/EA 1:1). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.72 (br s, 2H), 7.80 (d, $J$ = 9.4 Hz, 1H), 6.92 (s, 1H), 6.68 (s, 1H), 6.10 (d, $J$ = 9.4 Hz, 1H). $^{13}$C{$^1$H} NMR (101 MHz, DMSO-$d_6$) δ 161.3, 150.9, 149.0, 144.9, 143.3, 112.8, 112.0, 111.2, 103.1.

**3-Methoxy-*N*-methylaniline** (**16**) Isolated during attempted demethylation of 3-methoxyaniline (**15**) following the general procedure. Yellow liquid; yield: 0.171 g (24%); $R_f$ = 0.25 (PE/EA 10:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, $J$ = 8.1 Hz, 1H), 6.26 (ddd, $J_1$ = 8.1 Hz, $J_2$ = 2.4 Hz, $J_3$ = 0.9 Hz, 1H), 6.21 (ddd, $J_1$ = 8.1 Hz, $J_2$ = 2.3 Hz, $J_3$ = 0.9 Hz, 1H), 6.14 (t, $J$ = 2.3 Hz, 1H), 3.75 (s, 3H), 3.63 (br s, 1H), 2.78 (s, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 160.9, 150.9, 130.0, 105.7, 102.4, 98.4, 55.1, 30.7.

**3-Dimethylaminoanisole** (**17**) Yellow liquid; yield: 0.100 g (13%); $R_f$ = 0.41 (PE/EA 10:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, $J$ = 8 Hz, 1H), 6.36 (ddd, $J_1$ = 8.3 Hz, $J_2$ = 2.4 Hz, $J_3$ = 0.9 Hz, 1H), 6.29 (ddd, $J_1$ = 7.6 Hz, $J_2$ = 2.4 Hz, $J_3$ = 0.8 Hz, 1H), 6.27 (t, $J$ = 2.4 Hz, 1H), 3.78 (s, 3H), 2.92 (s, 6H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 160.7, 152.1, 129.8, 105.8, 101.5, 99.2, 55.1, 40.6.

**4-Dimethylaminoanisole** (**19**) Light yellow liquid; yield: 0.016 g (2%); $R_f$ = 0.76 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, $J$ = 9.1 Hz, 2H), 6.75 (d, $J$ = 9.2 Hz, 2H), 3.76 (s, 3H), 2.86 (s, 6H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 152.0, 145.8, 115.0, 114.7, 55.8, 41.9.

**4-Methoxy-*N*-ethylaniline** (**20**) Yellow liquid; yield: 0.069 g (22%); $R_f$ = 0.63 (PE/EA 3:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, $J$ = 8.9 Hz, 2H), 6.57 (d, $J$ = 8.9 Hz, 2H), 3.73 (s, 3H), 3.09 (q, $J$ = 7.1 Hz, 2H), 2.98 (br s, 1H), 1.22 (t, $J$ = 7.1 Hz, 3H). $^{13}$C{$^1$H} NMR (101 MHz, $CDCl_3$) δ 152.1, 142.8, 114.9, 114.2, 55.8, 39.5, 15.0.

**(*E*)-*N*'-(4-Methoxyphenyl)-*N*,*N*-dimethylformimidamide** (**21**)[43] Yield: 0.007 g (0.7 %); $R_f$ = 0.09 (PE/EA 1:1). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.90 (d, $J$ = 8.9 Hz, 2H), 6.82 (d, $J$ = 8.9 Hz, 2H), 3.78 (s, 3H), 3.00 (s, 6H).

**4-Methoxyaniline formate** (**22**) Isolated as a mixture of *cis*/*trans* stereoisomers during attempted isolation of **21** by column chromatography over silica gel. Yellow solid; yield: 0.681 g (90%); mp 77 – 79 °C; $R_f$ = 0.48 (PE/EA 1:1). $^1$H NMR (400 MHz, $CDCl_3$) δ *cis*-**22**: 8.71 (d, $J$ = 11.3 Hz, 1H), 8.52 (d, $J$ = 11.5 Hz, 1H), 7.04 (d, $J$ = 8.9 Hz, 2H), 6.87 (d, $J$ = 8.9 Hz, 2H), 3.79 (s, 3H); *trans*-**22**: 8.28 (d, $J$ = 2.0 Hz, 1H), 8.06 (s, 1H), 7.45 (d, $J$ = 9.0 Hz, 2H), 6.84 (d, $J$ = 9.0 Hz, 2H), 3.77 (s, 3H).

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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