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Advanced Synthesis & Catalysis

Ruthenium-Catalyzed Aminomethylation and Methylation of Phenol Derivatives Utilizing Methanol as the C_1 Source

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Abstract: A reaction involving *ortho*-aminomethylation of phenol was developed *via* ruthenium-catalyzed dehydrogenation of methanol, an environmentally benign C_1 building block, without the use of reactive reagents. The reaction was successfully applied to a range of substrates. When naphthol was employed instead of phenol, only methylation was observed. On the basis of various mechanistic studies, we propose that formamide barely participates in the reaction, which mainly occurs through an iminium cation intermediate. The difference in the reactivities of phenol and naphthol is attributable to stronger basicity of naphtholate as a conjugate base owing to its lower aromaticity. Plausible reaction pathways were proposed for both reactions.

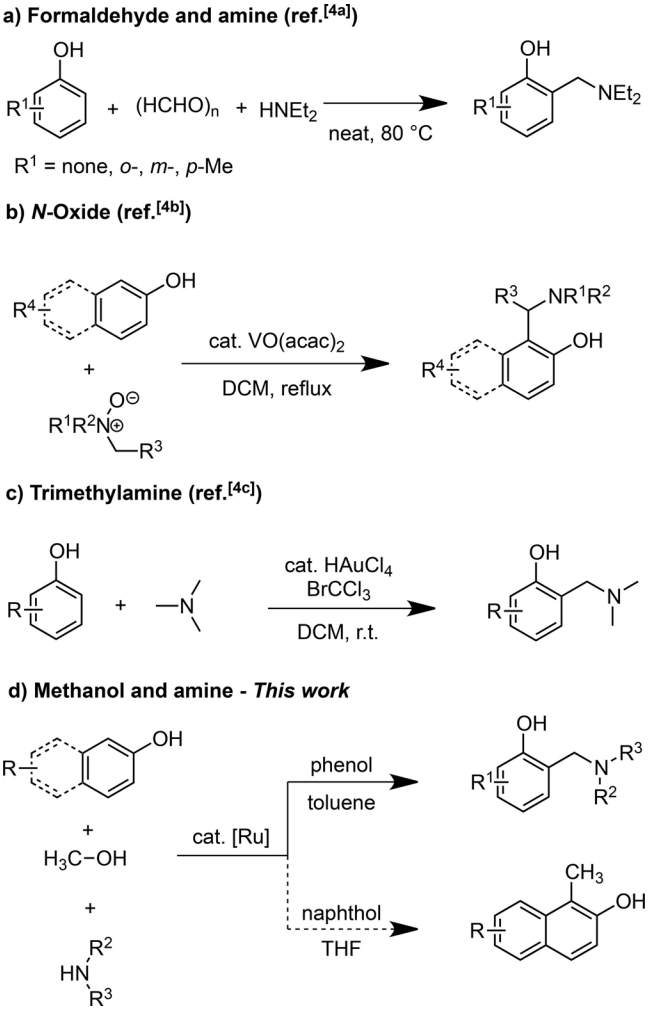
Keywords: aminomethylation; dehydrogenation; methanol; phenols; ruthenium

Introduction

Since the discovery of the Friedel–Crafts reaction,[1] a number of phenol functionalization methods has been extensively developed. Among those transformations, preparation of *ortho*-aminomethylated phenol structures, which can be found in various compounds such as pharmaceuticals[2] and ligands for transition metals,[3] is one of the most important types of phenol functionalization. Classically, this structure could be obtained by utilizing Eschenmoser's salt as a common intermediate,[4] but unfortunately, stoichiometric amounts of reactive species such as pre-generated salt itself, *N*-oxide, or $BrCCl_3$ are required for the reaction to proceed (Scheme 1).

In pursuit of environmentally benign synthesis[5] without pre-activation of substrates,[6] we designed a catalytic *ortho*-aminomethylation of phenol utilizing methanol as the methylation source. Methanol has emerged as a potential renewable resource[7] as the development of CO_2 reduction[8] and biomass conversion chemistry.[9] In the utilization of methanol as a C_1 source, a commonly used strategy is *in situ* generation of formaldehyde *via* dehydrogenative activation of methanol. The formaldehyde intermediate generated, which acts as an electrophile, can be transformed to a hydroxymethyl group through nucleophilic attack.[10] Further dehydrogenation could afford compounds containing carbonyl groups.[11] If dehydration is facilitated rather than dehydrogenation, an $X{=}CH_2$ ($X{=}CR_2$, NR, NR_2^+) type of intermediate is formed, which could be further converted to a methyl[12] or methylene group.[13]

In this context, we envisioned that *ortho*-aminomethylation of phenol can be achieved by using methanol and an amine through an activated intermediate such as an iminium cation formed by successive dehydrogenation and dehydration reactions.[14] Formaldehyde generated *in situ* from methanol can be captured by two nucleophiles, phenol and the amine. Reactions between nucleophiles and formaldehyde often suffer from unwanted side reactions such as dimerization or oligomerization through bridging methylene groups.[13b,15] In this case, the desired 3-component reaction was successfully controlled without significant formation of possible side products such as 2,2′-methylenediphenol. The recently developed hydroaminomethylation and dehydrogenation sequence can also be considered as a possible reaction pathway for this transformation.[16] In the case of naphthol, we observed methylation instead of aminomethylation. Only a few methods were reported for the catalytic methylation of naphthol with methanol, using heterogeneous catalysts under harsh reaction conditions ($\geq$ 200 °C).[17] Plausible intermediates and reaction pathways were proposed for each reaction on the basis of the mechanistic studies.



Scheme 1. Classical and developed synthetic methods for *ortho*-aminomethylation of phenol derivatives.

Results and Discussion

ortho-Aminomethylation of Phenol

We began our study on the *ortho*-aminomethylation of phenol with *in situ* generated (I*i*Pr)-$RuH_2(CO)(PPh_3)_2$, which was used as a dehydrogenation catalyst in our previous report.[18] In the initial attempt, **4a** was obtained in 8% yield (Table 1, entry 1). *N*-Methyl-*N*-benzylformamide (**7**) was observed as the major by-product. Various dehydrogenation catalysts were then tested (Table 1, entries 2–9). The iridium complex, which is highly active for the dehydrogenation of alcohols, did not afford the desired product,[19] while Milstein's catalyst[14f] and Shvo's catalyst[20] did not catalyze the reaction at all (Table 1, entries 2–4). $Ru(acac)_3$ as catalyst with triphos as ligand system[21] gave a 49% yield (Table 1, entry 8). Among the catalysts tested, Ru-MACHO-BH exhibited the highest efficiency (Table 1, entry 9). When increased equivalents of the amine and elevated temperatures were used, 78% of **4a** could be obtained (Table 1, entry 10). The developed reaction showed exclusive *ortho*-selectivity, no other regioisomers being formed. Other tested solvents did not show better reactivity than toluene (Table 1, entries 11–14). We also confirmed that the reaction was tolerant to moisture (Table 1, entry 15). Lower temperature gave a moderate yield of **4a** (Table 1, entry 16). The reaction under air exhibited lower efficiency (Table 1, entry 17).

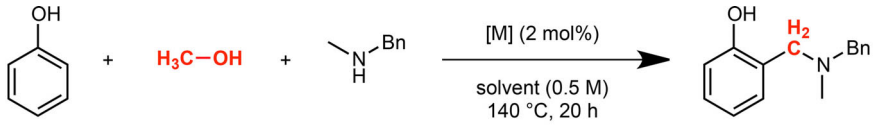
The substrate scope was subsequently explored (Table 2). Electron-rich phenols as well as a conjugated phenol smoothly participate in the developed reaction (**4b**–**4e**). The reaction efficiency was not significantly affected by halide substituents on phenol (**4f**–**4h**). The *ortho*-aminomethylated product of *ortho*-substituted phenol could also be obtained in a moderate yield (**4i**). When anisole was employed as a substrate, the desired transformation was not observed, indicating that deprotonation of the acidic proton by the amine is an important step in the reaction. The reactions involving various acyclic secondary amines were also efficient (**4j**–**4l**). Unfortunately, when the steric hindrance of the amine was increased, the desired product was not observed (**4m**). Diverse cyclic secondary amines were tested with from 5- to 7-membered rings (**4n**–**4t**). Regardless of the ring size, good yields of the desired products were obtained. When a primary amine was employed, poor reactivity was observed (**4u**). The formation of the imine rather than the iminium cation might be the reason for this observation, which could be attributed to the low electrophilicity of the former (Scheme 5). In low yielding cases such as **4h**, **4s**, **4u**, poor conversion of starting materials was observed.

Methylation of Naphthol

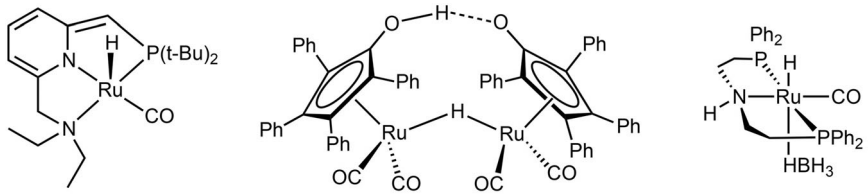
Interestingly, when similar reaction conditions were applied to 2-naphthol, 1-methyl-2-naphthol (**6a**) was obtained almost quantitatively, with the production of **7** from **3a** (Table 3, entry 2). The reaction without methanol did not give **6a** (Table 3, entry 3). This result implies that methanol, rather than **3a**, is the methyl source for the product. The yield significantly dropped when a reduced temperature was applied (Table 3, entry 4). Surprisingly, **3a** showed superior efficiency compared to other inorganic bases (Table 3, entries 5–7). When the more economical pyrrolidine was introduced as a base, a quantitative yield was obtained, while the tertiary amine showed no reactivity (Table 3, entries 8 and 10). Substoichiometric amounts of pyrrolidine gave a reasonable, but slightly decreased, yield of the product (Table 3, entry 11).

We then investigated the substrate scope for the methylation of 2-naphthol (Table 4). Biaryl substrates

Table 1. Optimization of the reaction conditions.[a]



1a 2 3a 4a



Milstein's catalyst Shvo's catalyst Ru-MACHO-BH

Entry	[M]	Base	Solvent	Yield[b] [%]
1	$RuH_2(CO)(PPh_3)_3$/*Ii*Pr·HBr	2 NaH	toluene	8
2	$[Cp^*IrCl_2]_2$	NaOAc	toluene	0
3	Milstein's catalyst	–	toluene	0
4	Shvo's catalyst	–	toluene	0
5	$[Ru(p\text{-cymene})Cl]_2$/2 dppb	KO-*t*-Bu	toluene	5
6	$RuH_2(PPh_3)_4$	–	toluene	5
7	$RuHCl(CO)(PPh_3)_4$	KO-*t*-Bu	toluene	10
8	$Ru(acac)_3$/2 triphos	–	THF	49
9	Ru-MACHO-BH	–	toluene	61
10[c]	Ru-MACHO-BH	–	toluene	78
11[c]	Ru-MACHO-BH	–	THF	65
12[c]	Ru-MACHO-BH	–	DCE	0
13[c]	Ru-MACHO-BH	–	MeCN	0
14[c]	Ru-MACHO-BH	–	neat	46
15[c,d]	Ru-MACHO-BH	–	toluene	72
16[e]	Ru-MACHO-BH	–	toluene	56
17[c,f]	Ru-MACHO-BH	–	toluene	37

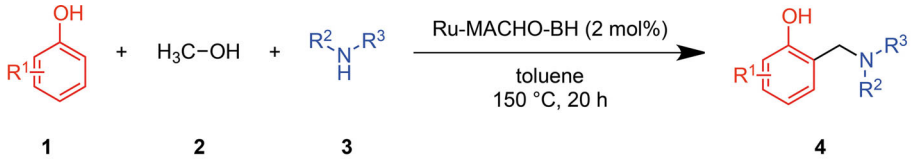
[a] *Reaction conditions:* **1a** (0.50 mmol, 1.0 equiv.), **2** (2.50 mmol, 5.0 equiv.), **3a** (0.50 mmol, 1.0 equiv.), [M] (0.01 mmol per metal center, 2 mol%), base (0.01 mmol, 2 mol%), 140 °C, 20 h in toluene (1.0 mL, 0.5 M), in a sealed tube. *Ii*Pr·HBr = 1,3-diisopropylimidazolium bromide.
[b] Yields were determined by ^1H NMR with CH_3NO_2 as an internal standard.
[c] 2.0 equiv. of **3a** were used at 150 °C.
[d] 1.0 equiv. of H_2O was added.
[e] 2.0 equiv. of **3a** were used at 130 °C.
[f] Under air.

with various kinds of substituents gave good yields of the desired products (**6b–6e**). When 1-naphthol was employed with an increased amount of **2**, a moderate yield of the dimethylated product was obtained (**6f**). Compared to the previous catalytic methods utilizing methanol for the methylation of naphthols, our method operates under relatively milder reaction conditions and shows better substrate scope.[17] Furthermore, the overall reaction yields were better than for those methods utilizing stoichiometric amount of methyl iodide or diiodomethane.[22]

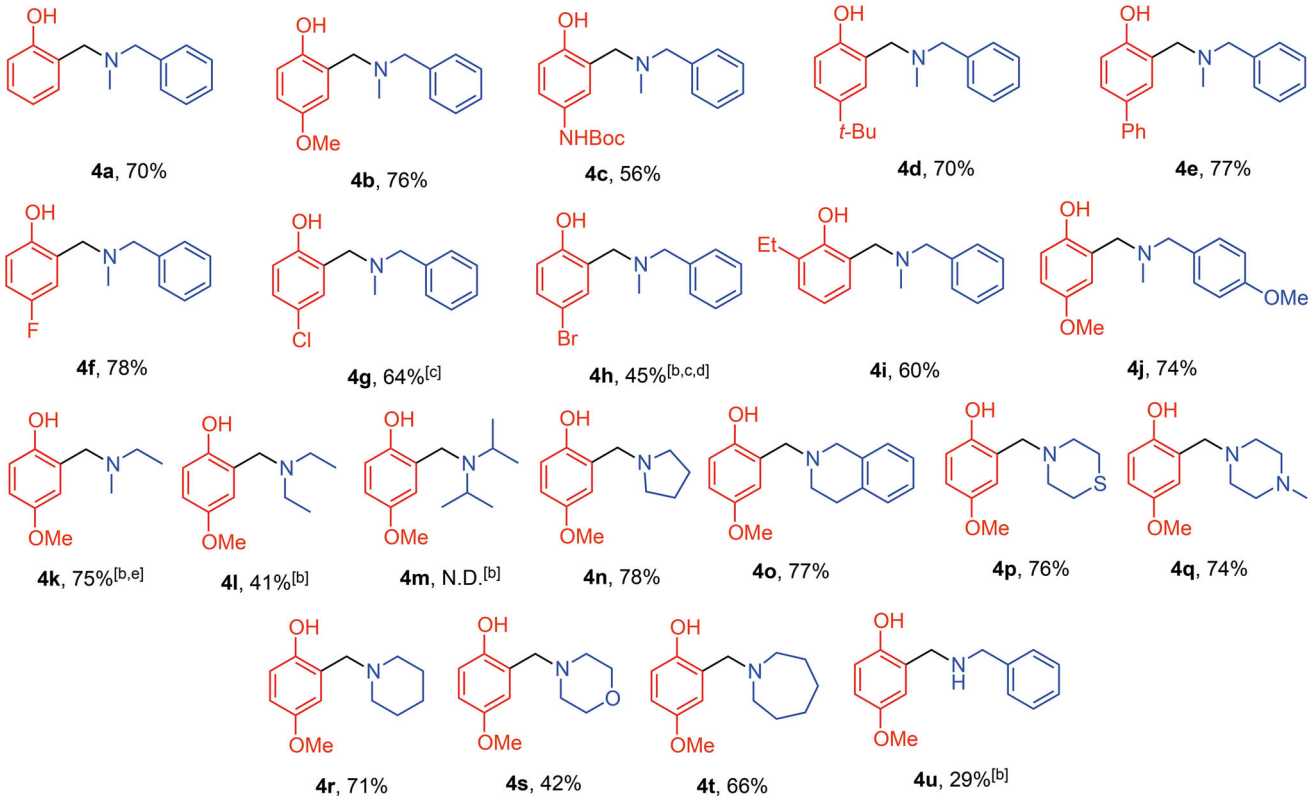
Mechanistic Study

The possible reaction pathways for each reaction were investigated by observing the reactivities of phenol and naphthol. First, changes in the levels of each substrate and product in the *ortho*-aminomethylation of phenol over time were measured by ^1H NMR spectroscopy (Figure 1). The production of **4b** was observed as **1b** and **3a** were consumed. At the same time, the gradual accumulation of formamide **7** was observed.

Table 2. Scope of the *ortho*-aminomethylation reaction.[a]



1 2 3 4

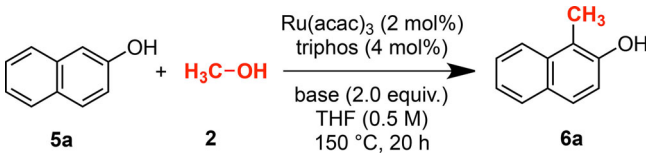


[a] *Reaction conditions:* **1** (0.50 mmol, 1.0 equiv.), **2** (2.50 mmol, 5.0 equiv.), **3** (1.0 mmol, 2.0 equiv.), Ru-MACHO-BH (0.01 mmol, 2 mol%), 150 °C, 20 h in toluene (1.0 mL, 0.5 M), in a sealed tube. N. D. = not determined. Isolated yields repoprted.
[b] For 44 h.
[c] 15 mol% of NaOMe were added.
[d] 5 mol% of catalyst was used.
[e] 4 equiv. of amine were used.

The reactions between the nucleophiles and **7** were performed to determine if formamide **7** acts as an electrophile in the reaction (Table 5 and Table 6). For each reaction, the remaining amount of **7**, and yields of **3a** and the desired products were measured *via* ^{1}H NMR spectroscopy. When **1a** was employed without base or with DIPEA, only marginal conversion of **7** was observed, with a poor yields of **4a** (Table 5, entries 1 and 2). When piperidine was added, the *ortho*-aminomethylated product and the formamide of piperidine were obtained in 60% and 27% yields, respectively. However, production of **4a** was still poor (Table 5, entry 3). The reactions between **5a** and **7** also gave poor yield of **6a** without significant conversion of **7** (Table 6, entry 1). When pyrrolidine was added, the yield of **6a** significantly increased (Table 6, entry 2). These experimental results strongly support our hypothesis that free secondary amine, and not formamide, is involved in both reactions.

The involvement of formamide was further examined by deuterium labelling (Scheme 2). When reactions were conducted with deuterated methanol (**2-D**) in the presence of **7**, the deuterated products, **8-D** and **6a-D**, were obtained without formation of **8** and **6a**. Concurrently, deuterium scrambling on **7** occurred to a minimal extent. These results demonstrate that formamide formation is almost irreversible under the developed reaction conditions. Based on the control experiments and the deuterium labelling study, we conclude that formamide forms almost irreversibly and barely participates in both alkylation reactions.

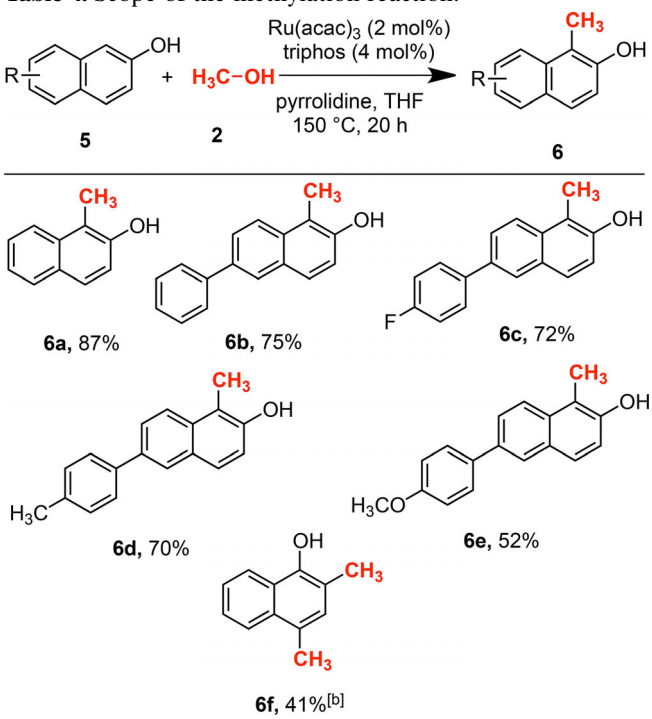
Table 3. Effect of base on the methylation of 2-naphthol.[a]



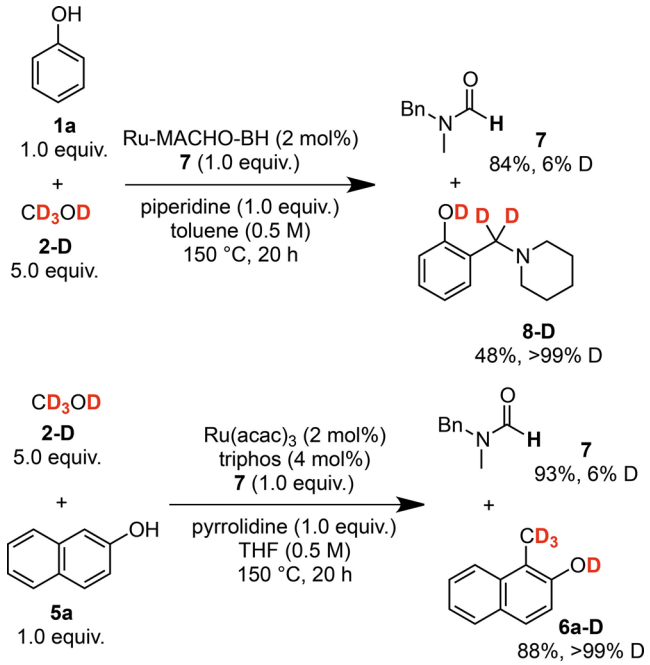
Entry	Base	Yield[b] [%]
1[c]	BnMeNH (**3a**)	24
2	BnMeNH (**3a**)	98
3[d]	BnMeNH (**3a**)	0
4[e]	BnMeNH (**3a**)	39
5	K_2CO_3	0
6	KOH	8
7	$NaHCO_3$	16
8	DIPEA	0
9	hexamethyleneimine	49
10[f]	pyrrolidine	>99
11[g]	pyrrolidine	92

[a] *Reaction conditions:* **5a** (0.50 mmol, 1.0 equiv.), **2** (2.50 mmol, 5.0 equiv.), $Ru(acac)_3$ (0.01 mmol, 2 mol%), triphos (0.02 mmol, 4 mol%), base (1.00 mmol, 2.0 equiv.), 150 °C, 20 h in THF (1.0 mL, 0.5 M), in a sealed tube.
[b] Yields were determined by ^1H NMR with CH_3NO_2 as an internal standard.
[c] Ru-MACHO-BH (2 mol%) and toluene (1.0 mL, 0.5 M) were used instead of $Ru(acac)_3$, triphos, and THF.
[d] **2** was not added.
[e] At 140 °C.
[f] 1.0 equiv. of amine and 4.0 equiv. of **2** were used.
[g] 0.5 equiv of amine and 4.0 equiv of **2** were used.

Table 4. Scope of the methylation reaction.[a]



[a] *Reaction conditions:* **5** (0.50 mmol, 1.0 equiv.), **2** (2.00 mmol, 4.0 equiv.), $Ru(acac)_3$ (0.01 mmol, 2 mol%), triphos (0.02 mmol, 4 mol%), pyrrolidine (0.50 mmol, 1.0 equiv.), 150 °C, 20 h in THF (1.0 mL, 0.5 M), in a sealed tube. Isolated yields reported.
[b] 10.0 equiv. of **2** were used.



Scheme 2. Deuterium labelling study

We then hypothesized that formaldehyde or the iminium cation might react with nucleophiles in both reactions. If phenol reacts with the iminium cation, the aminomethylated product can be formed directly. Hence, in the case of phenol, involvement of formaldehyde was considered *via* control experiments (Scheme 3). Firstly, we examined the reactivity of 2-hydroxybenzyl alcohol (**9**) which can be formed from formaldehyde and phenol; **9** could be transformed to **4a** quantitatively under the standard reaction conditions (Scheme 3A). Noticeably, a significant amount of **4a** was still formed in the absence of Ru catalyst and methanol, possibly through dehydrative transformation to *ortho*-quinone methide.[23] Accordingly, we assumed that both the dehydrogenative pathway *via* reductive amination[24] and the dehydrative pathway *via ortho*-quinone methide[23] can significantly contribute to the reaction if **9** is generated during the reaction. The dehydrogenative pathway was previously reported,[24] and the feasibility of the dehydrative pathway was investigated by capturing *ortho*-quinone methide (**A**) from **9** *via* the Diels–Alder reaction (Scheme 3B).[25] However, when we started from **1a**, attempts to capture **A** with ethyl vinyl ether (Scheme 3C) or several nucleophiles, such as imida-

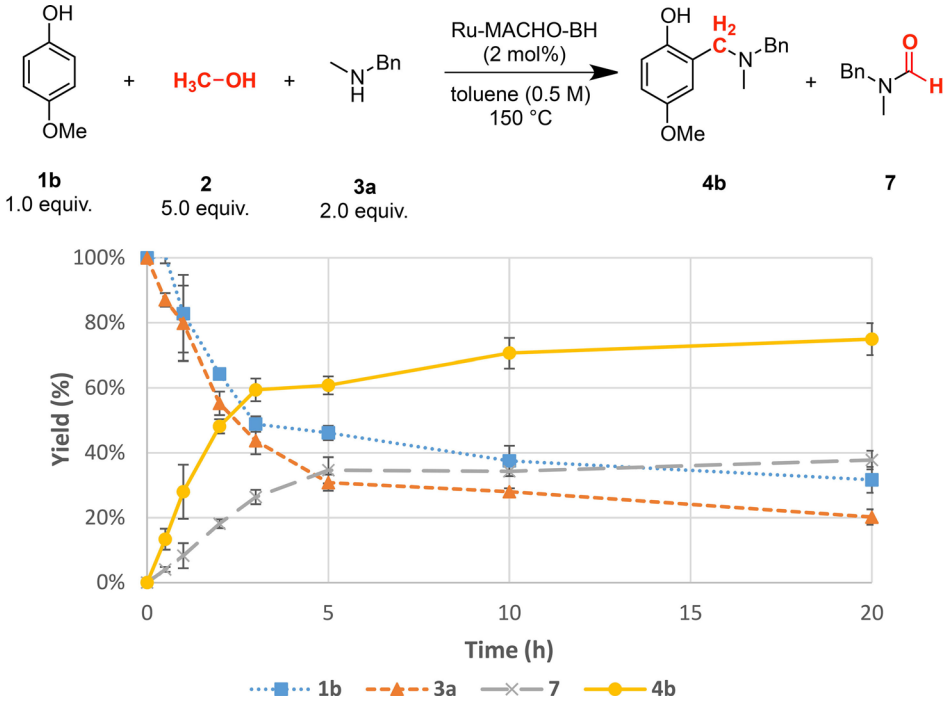
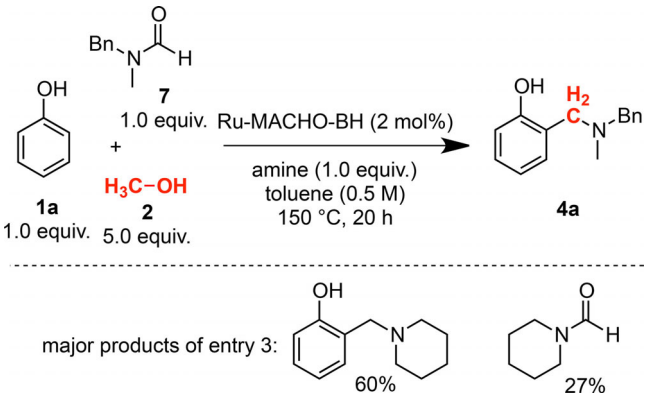


Figure 1. Kinetic profile of *ortho*-aminomethylation of **1b**. Error bars were calculated from three repetitions.

zole, 2-phenylethanethiol and 2,5-dimethylpyrrole, all failed, contrary to the reaction involving naphthol (Scheme 4D). In addition, we could not observe **9** and 2-methylphenol *via* the spectroscopic analyses done during the reaction. Reaction between phenol and formaldehyde also did not give any meaningful product such as **9**. Thus, we conclude that involvement of **9** is not likely in the case of phenol.

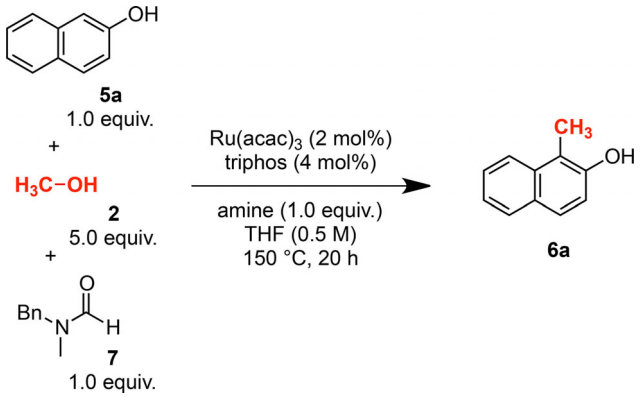
In the case of 2-naphthol, it is known that the reaction between formaldehyde and 2-naphthol forms 1-hydroxymethyl-2-naphthol (**10**) in the presence of base.[26] However, transformation of **10** into **6a** gave only 38% yield under the standard reaction conditions (Scheme 4A). In contrast, **11**, which can be formed from naphthol and iminium cation,[27] gave a quantitative yield of **6a** (Scheme 4B). We postulated that a deaminative pathway occurs *via ortho*-naphthoquinone methide (**B**) as an intermediate. Indeed, it could be captured by ethyl vinyl ether (Scheme 4C).[25] **B** can also be captured during the reaction (Scheme 4D), which further proves that **B** acts as a real intermediate.

Table 5. Reaction between phenol and formamide.

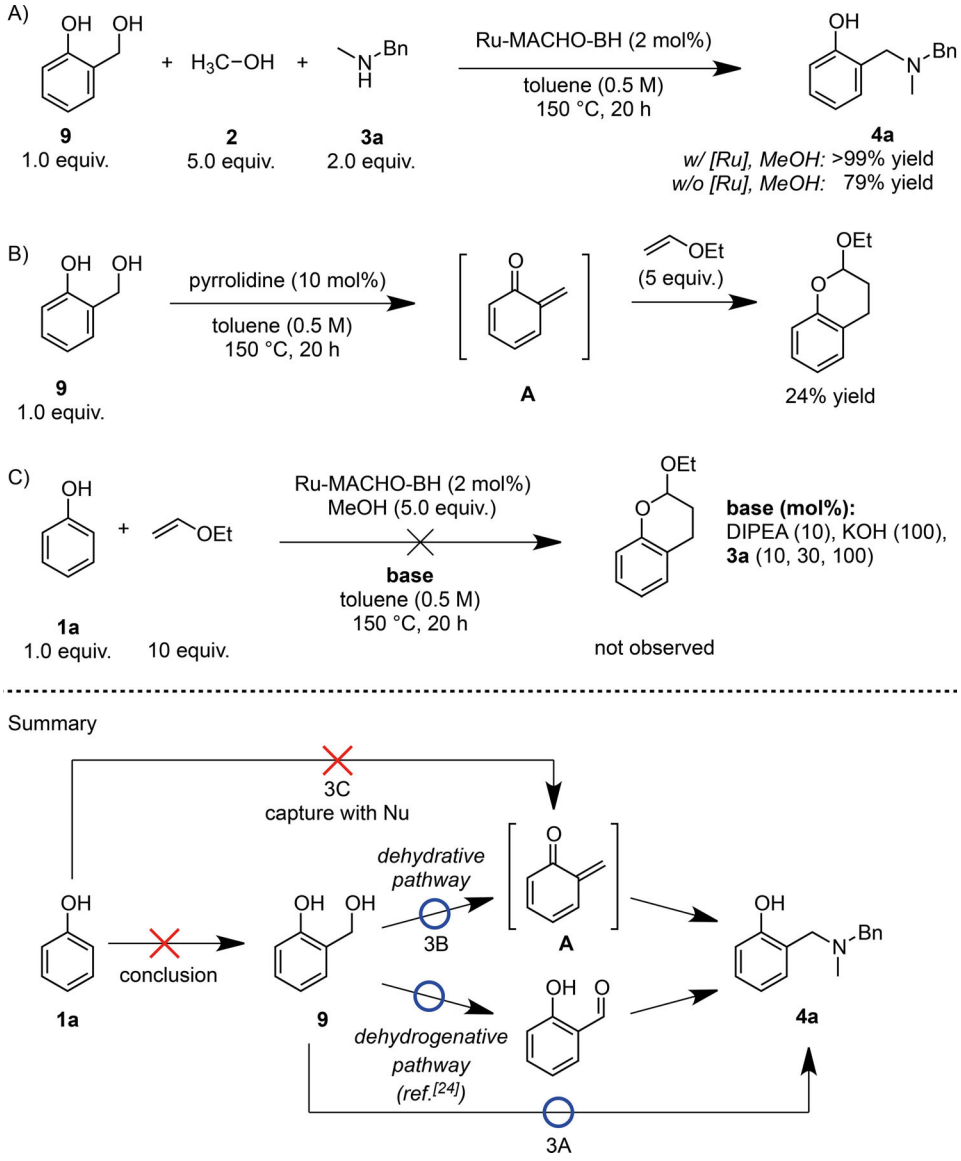


Entry	Amine	7	3a	4a
1	none	93%	1%	6%
2	DIPEA	94%	0%	6%
3	piperidine	84%	4%	3%

Table 6. Reaction between naphthol and formamide.



Entry	Amine	7	3a	6a
1	none	100%	0%	20%
2	pyrrolidine	90%	10%	89%

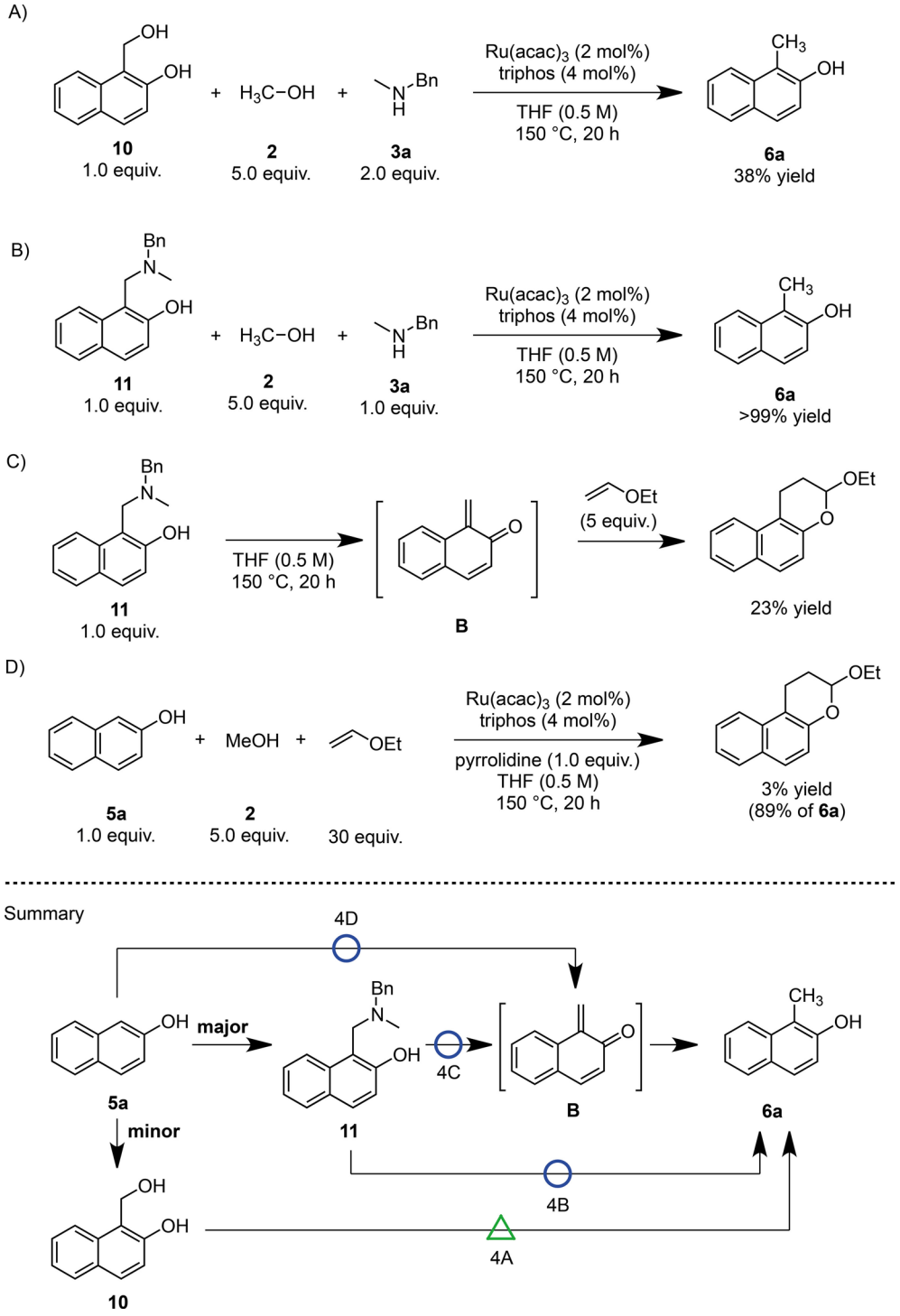


Scheme 3. Possible intermediates in *ortho*-aminomethylation of phenol.

Notably, deamination occurred only with **11** and not with **4a**, presumably due to the stronger basicity of naphtholate as a conjugate base, which in turn results from its lower aromaticity. Capturing of *ortho*-quinone methide (**A**) from **4a** by ethyl vinyl ether did not occur.

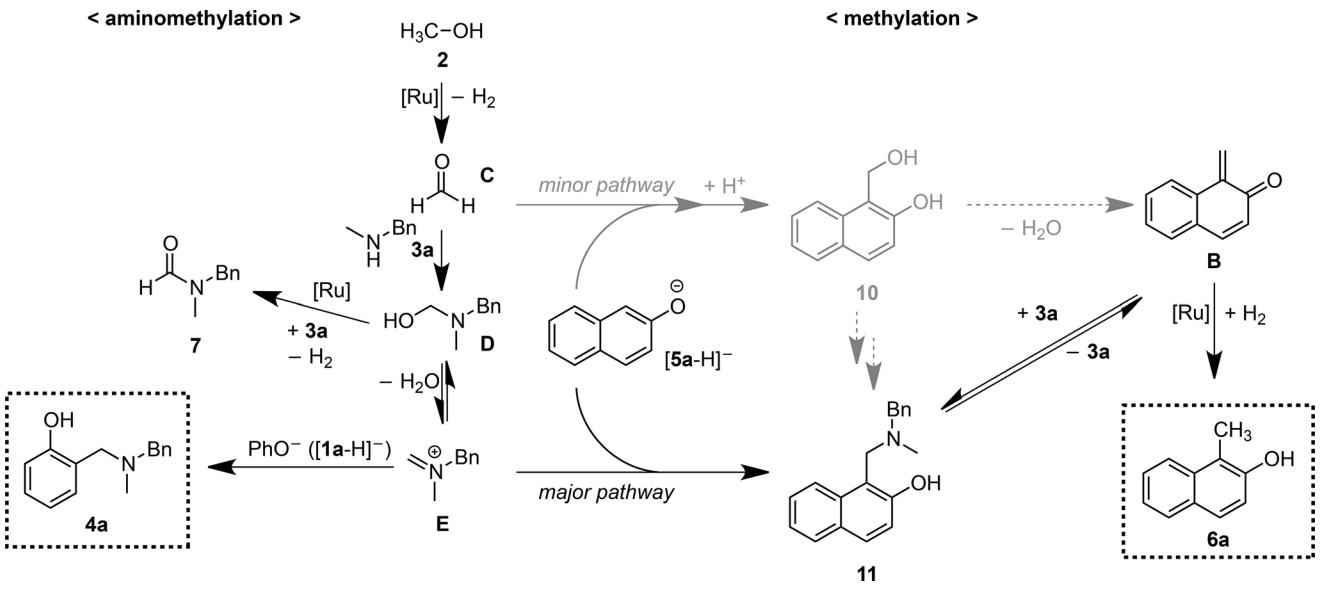
Since an iminium cation is a plausible intermediate in both transformations, involvement of the ruthenium catalyst in the reaction between nucleophiles and iminium cation, such as hydroaminomethylation and dehydrogenation sequence, could be considered. However, the ruthenium-catalyzed hydroaminomethylation reaction occurs usually with terminal olefins,[16b–e] and only a few examples are known with internal olefins.[16f,g] Furthermore, reactivity with the aromatic multiple bond was not observed in the previous reports even though the applied reaction temperatures were as high (up to 140 °C) as in our reaction conditions.[16] Hence, we believe that an enolate-involved nucleophilic attack operates in our case rather than ruthenium-catalyzed sequential reactions.

On the basis of the experimental results, possible reaction pathways were proposed (Scheme 5). It is well known that methanol (**2**) can be dehydrogenated by ruthenium catalysts.[28] The generated formaldehyde (**C**) is attacked by **3a** to form the hemiaminal intermediate (**D**). *Via* subsequent dehydration, the iminium cation (**E**) is formed. Formamide **7** is also produced from dehydrogenation of **D**.[11a,b] However, formamide does not directly participate in the reaction. In the case of the *ortho*-aminomethylation of phenol, the iminium cation is attacked by the phenolate anion



Scheme 4. Possible intermediates in methylation of naphthol.

([**1a**-H]$^-$), generating **4a**. In the case of the methylation of 2-naphthol, both formaldehyde and the iminium cation react with the 2-naphtholate anion ([**5a**-H]$^-$). However, compound **10**, resulting from formaldehyde and [**5a**-H]$^-$, is not efficiently converted to **6a**. On the other hand, compound **11** undergoes reversible deamination *via* an E1cB mechanism and reduction to successfully form **6a**.[29] In this pathway, **3a** is liberated and can participate in the generation of **11**. The amine acts as a catalyst as well as a base in the methylation of naphthol, and this suggestion is consistent with the previous experimental results (Table 3, entry 11).



Scheme 5. Plausible mechanism

Conclusions

We have developed novel alkylation reactions of phenol derivatives by using methanol as the C_1 source. Initiated by dehydrogenation of methanol and subsequent nucleophilic attack on formaldehyde, methanol could be directly incorporated into the organic molecules, phenol and naphthol. The developed reactions could be applied to a range of substrates with good yields. Based on our mechanistic studies, the iminium cation is proposed to be the key electrophile in both reactions. In the case of the methylation of naphthol, an *ortho*-naphthoquinone methide intermediate and the dual role of the amine as a catalyst and a base, were suggested.

Experimental Section

General Information

Unless otherwise noted, all reactions were carried out using standard Schlenk techniques or in an argon-filled glove box. All anhydrous solvents were purchased from commercial suppliers and degassed with dry argon before usage. **1c**,[30] **5b**–**5e**,[31] **10**,[26] and **11**[27] were prepared by the methods reported in the literature, and all other substrates and catalysts were purchased from commercial suppliers and used as received without purification. HR-MS analyses were performed at the Organic Chemistry Research Center of Sogang University.

General Procedure for *ortho*-Aminomethylation of Phenol

To an oven-dried, 50-mL, screw capped round-bottom flask equipped with a stirring bar, Ru-MACHO-BH (5.9 mg, 0.01 mmol), **1** (0.50 mmol), **2** (101 μL, 2.50 mmol), **3** (1.00 mmol) and anhydrous toluene (1.0 mL) were added inside a glovebox. The reaction tube was then taken out of the box and the mixture stirred for 20–44 h at 150 °C. The resulting reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude products were purified *via* silica gel column chromatography.

General Procedure for Methylation of Naphthol

To an oven-dried, 50-mL, screw capped round-bottom flask equipped with a stirring bar, $Ru(acac)_3$ (4.0 mg, 0.01 mmol), triphos (12.5 mg, 0.02 mmol), **5** (0.50 mmol), **2** (81 μL, 2.00 mmol), pyrrolidine (42 μL, 0.50 mmol) and anhydrous toluene (1.0 mL) were added inside a glovebox. The reaction tube was then taken out of the box and the mixture stirred for 20 h at 150 °C. The resulting reaction mixture was cooled to room temperature and concentrated under reduced pressure. The crude products were purified *via* silica gel column chromatography.

General Procedure for the Capture of *ortho*-Quinone Methide (Scheme 3B)

To an oven-dried 50-mL, screw capped round-bottom flask equipped with a stirring bar, **9** (62.1 mg, 0.50 mmol), ethyl vinyl ether (239 μL, 2.50 mmol), pyrrolidine (4.2 μL, 0.05 mmol) and anhydrous toluene (1.0 mL) were added inside a glovebox. The reaction tube was then taken out of the box and the mixture stirred for 20 h at 150 °C. The resulting reaction mixture was cooled to room temperature and concentrated under reduced pressure. 25 μL of nitromethane were added as an internal standard. The crude mixture was analyzed by ^{1}H NMR spectroscopy. The experiments of Scheme 3C, Scheme 4B and Scheme 4C were conducted analogously to the method described here.

Characterization Data

Reactions were performed in a 0.50 mmol scale. All compounds were identified by ^{1}H, ^{13}C NMR. All new compounds were further identified by HR-MS. All reported compounds–**4l**,[32] **4r**,[33] **4s**,[34] **6a**[35] and **6f**[36]– were also identified by spectral comparison with literature data.

2-{[Benzyl(methyl)amino]methyl}phenol (4a): Colourless liquid; yield: 80 mg (70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.12 (br s, 1H), 7.45–7.29 (m, 5H), 7.23 (dt, J = 0.9, 7.3 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 6.92 (dd, J = 0.8, 8.1 Hz, 1H), 6.84 (dt, J = 1.1, 7.3 Hz, 1H), 3.79 (s, 2H), 3.63 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 136.9, 129.4, 128.8, 128.6, 128.6, 127.7, 121.9, 119.2, 116.1, 61.5, 60.9, 41.3; HR-MS-ESI: m/z = 228.1385 $[M+H]^+$, calcd. for $C_{15}H_{18}NO$: 228.1383.

2-{[Benzyl(methyl)amino]methyl}-4-methoxyphenol (4b): Light yellow liquid; yield: 98 mg (76%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.44 (br. s., 1H), 7.40–7.27 (m, 5H), 6.87–6.72 (m, 2H), 6.62 (d, J = 2.6 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 2H), 3.60 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 151.6, 136.9, 129.4, 128.6, 127.7, 122.6, 116.4, 114.5, 113.6, 61.4, 61.0, 55.7, 41.3; HR-MS-ESI: m/z = 258.1488 $[M+H]^+$, calcd. for $C_{16}H_{20}NO_2$: 258.1489.

***tert*-Butyl {3-[benzyl(methyl)amino]methyl}-4-hydroxyphenyl)carbamate (4c):** Beige solid; yield: 95 mg (56%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.30 (br. s., 1H), 7.38–7.26 (m, 5H), 7.23 (br. s., 1H), 6.99 (dd, J = 2.5, 8.6 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 6.51 (s, 1H), 3.71 (s, 2H), 3.57 (s, 2H), 2.21 (s, 3H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.8, 153.4, 136.9, 130.1, 129.4, 128.6, 127.7, 122.2, 120.0, 120.0, 116.2, 80.1, 61.5, 61.0, 41.2, 28.5; HR-MS-ESI: m/z = 343.2014 $[M+H]^+$, calcd. for $C_{20}H_{27}N_2O_3$: 343.2016.

2-{[Benzyl(methyl)amino]methyl}-4-(*tert*-butyl)phenol (4d): Light yellow liquid; yield: 99 mg (70%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.65 (br. s., 1H), 7.42–7.29 (m, 5H), 7.25 (dd, J = 2.1, 8.5 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 3.79 (s, 2H), 3.64 (s, 2H), 2.29 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 141.8, 137.1, 129.4, 128.6, 127.7, 125.5, 125.4, 121.1, 115.5, 61.6, 61.4, 41.4, 34.0, 31.7; HR-MS-ESI: m/z = 284.2010 $[M+H]^+$, calcd. for $C_{19}H_{26}NO$: 284.2009.

3-{[Benzyl(methyl)amino]methyl}-[1,1′-biphenyl]-4-ol (4e): Yellow liquid; yield: 118 mg (77%); ^{1}H NMR (499 MHz, $CDCl_3$): δ = 11.05 (br. s., 1H), 7.60 (d, J = 7.3 Hz, 2H), 7.51–7.32 (m, 9H), 7.31 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 3.86 (s, 2H), 3.67 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 141.0, 136.8, 132.3, 129.4, 128.8, 128.7, 127.7, 127.5, 127.3, 126.6, 126.5, 122.1, 116.5, 61.5, 61.0, 41.3; HR-MS-ESI: m/z = 304.1694 $[M+H]^+$, calcd. for $C_{21}H_{22}NO$: 304.1696.

2-{[Benzyl(methyl)amino]methyl}-4-fluorophenol (4f): Light yellow liquid; yield: 92 mg (75%); ^{1}H NMR (499 MHz, $CDCl_3$): δ = 10.45 (br. s., 1H), 7.39–7.35 (m, 2H), 7.33–7.29 (m, 3H), 6.89 (dt, J = 2.9, 8.6 Hz, 1H), 6.80 (dd, J = 4.6, 9.0 Hz, 1H), 6.74 (dd, J = 2.9, 8.8 Hz, 1H), 3.71 (s, 2H), 3.60 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.07 (d, J = 236.4 Hz), 153.84 (d, J = 1.8 Hz), 136.68, 129.40, 128.70, 127.83, 122.82 (d, J = 7.2 Hz), 116.76 (d, J = 7.8 Hz), 115.14 (d, J = 3.6 Hz), 114.83 (d, J = 3.0 Hz), 61.48, 60.53, 41.30; HR-MS-ESI: m/z = 246.1289 $[M+H]^+$, calcd. for $C_{15}H_{17}NO$: 246.1289.

2-{[Benzyl(methyl)amino]methyl}-4-chlorophenol (4g): Off-white solid; yield: 83 mg (64%); ^{1}H NMR (499 MHz, $CDCl_3$): δ = 11.09 (br. s., 1H), 7.40–7.34 (m, 2H), 7.34–7.28 (m, 3H), 7.14 (dd, J = 2.7, 8.6 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 3.71 (s, 2H), 3.60 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.7, 136.6, 129.4, 128.7, 128.6, 128.3, 127.9, 123.7, 123.4, 117.5, 61.5, 60.5, 41.3; HRMS-ESI: m/z = 262.0993 $[M+H]^+$, calcd. for $C_{15}H_{17}ClNO$: 262.0993.

2-{[Benzyl(methyl)amino]methyl}-4-bromophenol (4h): White solid; yield: 69 mg (45%); ^{1}H NMR (499 MHz, $CDCl_3$): δ = 11.24 (br. s., 1H), 7.38–7.33 (m, 2H), 7.33–7.24 (m, 4H), 7.11 (s, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.71 (s, 2H), 3.60 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.2, 136.6, 131.6, 131.2, 129.5, 128.8, 127.9, 124.0, 118.1, 110.9, 61.6, 60.5, 41.4; HR-MS-ESI: m/z = 306.0489 $[M+H]^+$, calcd. for $C_{15}H_{17}BrNO$: 306.0488.

2-{[Benzyl(methyl)amino]methyl}-6-ethylphenol (4i): Light yellow liquid; yield: 64 mg (50%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.16 (br. s, 1H), 7.43–7.29 (m, 5H), 7.13 (dd, J = 1.5, 7.3 Hz, 1H), 6.91 (dd, J = 1.5, 7.3 Hz, 1H), 6.79 (t, J = 7.3 Hz, 1H), 3.79 (s, 2H), 3.63 (s, 2H), 2.74 (q, J = 7.4 Hz, 2H), 2.27 (s, 3H), 1.30 (t, J = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 137.1, 131.0, 129.5, 128.7, 128.3, 127.7, 126.3, 121.4, 118.9, 61.5, 61.2, 41.2, 23.0, 14.3; HR-MS-ESI: m/z = 256.1697, $[M+H]^+$, calcd. for $C_{17}H_{22}NO$: 256.1696.

4-Methoxy-2-{[(4-methoxybenzyl)(methyl)amino]methyl}-phenol (4j): Light yellow liquid; yield: 106 mg (74%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.53 (br. s., 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.86–6.74 (m, 3H), 6.63 (d, J = 2.8 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.72 (s, 2H), 3.56 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.2, 152.6, 151.7, 130.6, 129.0, 122.7, 116.5, 114.6, 114.0, 113.6, 60.8 (2 C), 55.8, 55.3, 41.2; HR-MS-ESI: m/z = 288.1595 $[M+H]^+$, calcd. for $C_{17}H_{22}NO_3$: 288.1594.

2-{[Ethyl(methyl)amino]methyl}-4-methoxyphenol (4k): Yellow liquid; yield: 73 mg (75%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.63 (br. s., 1H), 6.78–6.67 (m, 2H), 6.54 (d, J = 1.7 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 2H), 2.53 (q, J = 7.2 Hz, 2H), 2.27 (s, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 152.0, 122.8, 116.4, 114.4, 113.4, 61.1, 55.9, 50.8, 40.9, 12.2; HR-MS-ESI: m/z = 196.1333 $[M+H]^+$, calcd. for $C_{11}H_{18}NO_2$: 196.1332.

2-[(Diethylamino)methyl]-4-methoxyphenol (4l):[32] Brown liquid; yield: 43 mg (41%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.42 (br. s., 1H), 6.72 (s, 2H), 6.55 (s, 1H), 3.77–3.65 (m, 5H), 2.60 (q, J = 7.1 Hz, 4H), 1.09 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.5, 152.2, 123.0, 116.4, 114.5, 113.3, 57.2, 55.9, 46.4, 11.3.

4-Methoxy-2-(pyrrolidin-1-ylmethyl)phenol (4n): Dark yellow liquid; yield: 81 mg (78%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.56 (br. s., 1H), 6.81–6.66 (m, 2H), 6.55 (s, 1H), 3.76 (s, 2H), 3.72 (s, 3H), 2.68–2.53 (m, 4H), 1.91–1.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.3, 151.8, 123.2, 116.2, 113.8, 113.3, 58.9, 55.7, 53.5, 23.7; HR-MS-ESI: m/z = 208.1333 $[M+H]^+$, calcd. for $C_{12}H_{18}NO_2$: 208.1332.

2-{[3,4-Dihydroisoquinolin-2(1*H*)-yl]methyl}-4-methoxyphenol (4o): Light orange solid; yield: 103 mg (77%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.98 (br. s., 1H), 7.25–7.12 (m, 3H), 7.09–7.00 (m, 1H), 6.87–6.77 (m, 2H), 6.72–6.62 (m, 1H), 3.87 (s, 2H), 3.83–3.74 (m, 5H), 2.98 (t, J = 5.6 Hz,

2H), 2.88 (t, J=5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.6, 151.7, 133.6, 133.4, 128.7, 126.6, 126.6, 126.0, 122.0, 116.6, 114.6, 113.7, 61.2, 55.8, 55.4, 50.0, 28.7; HR-MS-ESI: m/z=270.1491 $[M+H]^+$, calcd. for $C_{17}H_{20}NO_2$: 270.1489.

4-Methoxy-2-(thiomorpholinomethyl)phenol (4p): White solid; yield: 84 mg (76%); ^{1}H NMR (499 MHz, $CDCl_3$): δ= 10.01 (br. s., 1H), 6.75–6.70 (m, 2H), 6.53 (d, J=2.0 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 2H), 2.85–2.76 (m, 4H), 2.72–2.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.6, 151.3, 121.5, 116.5, 114.7, 113.7, 62.3, 55.7, 54.4, 27.9; HR-MS-ESI: m/z= 240.1052, $[M+H]^+$, calcd. for $C_{12}H_{18}NO_2S$: 240.1053.

4-Methoxy-2-[(4-methylpiperazin-1-yl)methyl]phenol (4q): Light yellow liquid; yield: 88 mg (74%); ^{1}H NMR (499 MHz, $CDCl_3$): δ=10.23 (br. s., 1H), 6.72–6.66 (m, 2H), 6.52 (d, J=2.4 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 2H), 2.53 (br. s., 8H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.5, 151.4, 121.8, 116.4, 114.4, 113.6, 61.4, 55.7, 54.9, 52.4, 45.8; HR-MS-ESI: m/z=237.1596, $[M+H]^+$, calcd. for $C_{13}H_{21}N_2O_2$: 237.1598.

4-Methoxy-2-(piperidin-1-ylmethyl)phenol (4r):[33] Light brown liquid; yield: 79 mg (71%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.05 (br. s., 1H), 6.77–6.70 (m, 2H), 6.55 (s, 1H), 3.72 (s, 3H), 3.61 (s, 2H), 2.67–2.30 (m, 4H), 1.71–1.55 (m, 4H), 1.55–1.30 (m, 2H).

4-Methoxy-2-(morpholinomethyl)phenol (4s):[34] Colourless liquid; yield: 47 mg (42%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.12 (br. s., 1H), 6.81–6.67 (m, 2H), 6.60–6.50 (m, 1H), 3.76–3.71 (m, 7H), 3.65 (s, 2H), 2.64–2.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.7, 151.3, 121.4, 116.5, 114.7, 113.9, 66.9, 62.0, 55.8, 53.0.

2-(Azepan-1-ylmethyl)-4-methoxyphenol (4t): Light yellow liquid; yield: 78 mg (66%); ^{1}H NMR (499 MHz, $CDCl_3$): δ=9.79 (br. s., 1H), 6.76–6.70 (m, 2H), 6.53 (d, J= 2.9 Hz, 1H), 3.74–3.71 (m, 5H), 2.69 (t, J=4.9 Hz, 4H), 1.71–1.66 (m, 4H), 1.65–1.60 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.4, 152.2, 123.1, 116.4, 114.4, 113.4, 62.2, 55.8, 55.4, 27.8, 26.7; HR-MS-ESI: m/z=236.1645 $[M+H]^+$, calcd. for $C_{14}H_{22}NO_2$: 236.1645.

2-[(Benzylamino)methyl]-4-methoxyphenol (4u): Colourless liquid; yield: 36 mg (29%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.41–7.27 (m, 5H), 6.83–6.70 (m, 2H), 6.58 (d, J=2.8 Hz, 1H), 6.08 (br. s., 2H), 3.97 (s, 2H), 3.81 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=152.6, 152.0, 138.5, 128.8, 128.5, 127.7, 123.0, 116.9, 114.6, 113.8, 55.9, 52.7, 52.1; HR-MS-ESI: m/z=244.1332, $[M+H]^+$, calcd. for $C_{15}H_{18}NO_2$: 244.1332.

1-Methylnaphthalen-2-ol (6a):[35] Light yellow solid; yield: 69 mg (87%); ^{1}H NMR (499 MHz, $CDCl_3$) δ=7.98 (d, J= 8.8 Hz, 1H), 7.83 (d, J=8.3 Hz, 1H), 7.66 (d, J=8.8 Hz, 1H), 7.56 (t, J=8.3 Hz, 1H), 7.42 (t, J=7.3 Hz, 1H), 7.09 (d, J=8.8 Hz, 1H), 5.28 (br. s., 1H), 2.59 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=150.5, 133.9, 129.3, 128.5, 127.4, 126.4, 123.2 (2C), 117.7, 115.5, 10.6.

1-Methyl-6-phenylnaphthalen-2-ol (6b): White solid; yield: 89 mg (75%); ^{1}H NMR (499 MHz, DMSO-d_6): δ= 9.57 (s, 1H), 8.11–8.06 (m, 1H), 7.93 (d, J=8.8 Hz, 1H), 7.80–7.74 (m, 3H), 7.71 (d, J=8.8 Hz, 1H), 7.48 (t, J= 7.6 Hz, 2H), 7.35 (t, J=6.8 Hz, 1H), 7.21 (d, J=8.8 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ= 152.5, 140.1, 133.7, 133.0, 128.9, 128.3, 127.2, 127.0, 126.6, 125.7, 124.9, 123.6, 118.5, 114.6, 10.5; HR-MS-ESI: m/z= 233.0970 $[M-H]^-$, calcd. for $C_{17}H_{13}O$: 233.0972.

6-(4-Fluorophenyl)-1-methylnaphthalen-2-ol (6c): White solid; yield: 91 mg (72%); ^{1}H NMR (499 MHz, DMSO-d_6): δ=9.58 (s, 1H), 8.04 (d, J=2.0 Hz, 1H), 7.91 (d, J=8.8 Hz, 1H), 7.81–7.75 (m, 2H), 7.72 (dd, J=2.0, 8.8 Hz, 1H), 7.69 (d, J=8.8 Hz, 1H), 7.32–7.26 (m, 2H), 7.21 (d, J=8.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ= 161.65 (d, J=244.1 Hz), 152.48, 137.05 (d, J=2.9 Hz), 132.95, 132.72, 128.44 (d, J=7.6 Hz), 128.23, 127.19, 125.60, 124.83, 123.62, 118.54, 115.68 (d, J=21.0 Hz), 114.56, 10.44; HR-MS-ESI: m/z=251.0876, $[M-H]^-$, calcd. for $C_{17}H_{12}FO$: 251.0878.

1-Methyl-6-(*p*-tolyl)naphthalen-2-ol (6d): White solid; yield: 86 mg (70%); ^{1}H NMR (499 MHz, DMSO-d_6): δ= 9.54 (s, 1H), 8.04 (d, J=1.5 Hz, 1H), 7.90 (d, J=8.8 Hz, 1H), 7.74 (dd, J=2.0, 8.8 Hz, 1H), 7.69 (d, J=8.8 Hz, 1H), 7.65 (d, J=7.8 Hz, 2H), 7.27 (d, J=8.3 Hz, 2H), 7.20 (d, J= 8.8 Hz, 1H), 2.44 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ=152.3, 137.2, 136.2, 133.6, 132.9, 129.5, 128.3, 127.1, 126.4, 125.2, 124.8, 123.5, 118.4, 114.5, 20.7, 10.4; HR-MS-ESI: m/z=247.113 $[M-H]^-$, calcd. for $C_{18}H_{15}O$: 247.1128.

6-(4-Methoxyphenyl)-1-methylnaphthalen-2-ol (6e): White solid; yield: 69 mg (52%); ^{1}H NMR (499 MHz, DMSO-d_6): δ=9.51 (s, 1H), 8.00 (d, J=2.0 Hz, 1H), 7.89 (d, J=8.8 Hz, 1H), 7.74–7.65 (m, 4H), 7.19 (d, J=8.8 Hz, 1H), 7.03 (d, J=8.8 Hz, 2H), 3.80 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6): δ=158.6, 152.2, 133.4, 132.6, 132.5, 128.3, 127.6, 127.0, 124.8, 123.5, 118.4, 114.5, 114.4 (2C), 55.1, 10.4; HR-MS-ESI: m/z=263.1078 $[M-H]^-$, calcd. for $C_{18}H_{15}O_2$: 263.1078.

2,4-Dimethylnaphthalen-1-ol (6f):[36] White solid; yield: 35 mg (41%); ^{1}H NMR (499 MHz, $CDCl_3$): δ=8.24–8.19 (m, 1H), 7.99–7.94 (m, 1H), 7.57–7.51 (m, 2H), 7.12 (s, 1H), 5.06 (br. s., 1H), 2.64 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=147.0, 132.2, 129.6, 126.3, 125.3, 125.1, 124.7, 124.3, 121.5, 116.0, 18.8, 15.6.

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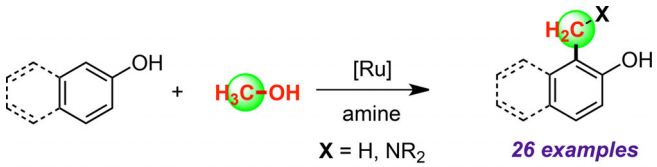

utilization of methanol as an electrophilic C_1 source