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Insertion of arynes into the carbon–oxygen double bond of amides and its application into the sequential reactions

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ABSTRACT

The reaction of arynes, generated from *ortho*-(trimethylsilyl)aryl triflates, with the C=O bond of formamides gave salicylaldehyde derivatives via the formation of formal [2+2] adducts. The sequential transformation of arynes into *ortho*-disubstituted arenes, *o*-aminoalkylphenols or *o*-hydroxyalkylphenols, was achieved by one-pot procedure using dialkylzincs.

1. Introduction

Arynes are highly strained and kinetically unstable intermediates that have been wildly employed in organic synthesis since the 1950s.[1] In recent years, aryne chemistry has reemerged and made great advances in synthetic chemistry.[2,3] Particularly, the development of *ortho*-(trimethylsilyl)aryl triflates as mild aryne precursors led to a rapid growth of this research area.[4] It is noteworthy that this mild method for generating arynes provides a highly general solution to the fundamental problems that are associated with the traditional harsh methods. Initially, the utility of arynes, derived in this manner, was found in transition metal-catalyzed reactions involving cross-coupling processes.[3f,5–7] More recently, considerable effort has been directed toward the transition metal-free reactions.[3g,8–11] In most cases, these new aryne-based reactions comprise the initial addition of nucleophiles to arynes and the subsequent trapping of intermediates with electrophiles under transition metal-free conditions.

When nucleophile and electrophile belong to the same molecule, most of reactions are classified into the insertion of arynes **A** into the σ-bond (X–Y) giving *ortho*-disubstituted arenes **B**[10] and the [2+3] cycloaddition of 1,3-dipolars to arynes giving the [2+3] adducts **C**[11] (Fig. 1). As a rare insertion of arynes **A** into the π-bond, Suzuki's group has extensively studied the insertion into the C=C bond, which gave the benzocyclobutenes **D** as relatively stable products.[12,13] However, less is known about the insertion into the carbon–heteroatom double bond (C=X) giving the formal [2+2] cycloaddition-type adducts **E**.[14] As a relative study, in 1965,

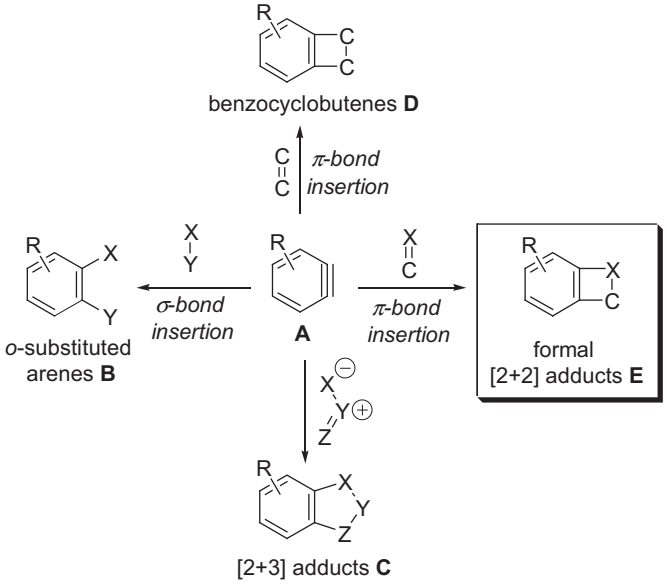

Fig. 1. Insertion of arynes giving *ortho*-disubstituted arenes.

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Yaroslavsky reported that the reaction of benzenediazonium chloride or benzenediazonium-2-carboxylate with *N*,*N*-dimethylformamide (DMF) gave the low yields of salicylaldehyde.[15] The synthetically useful insertion into the π-bond of carbonyl compounds was recently achieved by Yoshida and co-workers.[16a] In their study, the 2/1 coupling reaction of arynes and aldehydes proceeds probably through the formation of unstable [2+2] adducts **E**. Our laboratory is interested in developing the sequential reactions induced by the insertion of arynes into the carbonyl group of amides. As our successful examples, we recently reported the sequential transformation involving trapping process of the intermediates, such as adducts **E** with dialkylzincs[17a] and the multicomponent coupling reaction involving trapping process with the active methylene compounds.[17b] More recently, Yoshida's group also reported the three-component coupling using arynes and DMF.[16b] In this paper, we describe in detail the study on the insertion of arynes, generated from *ortho*-(trimethylsilyl)aryl triflates, into the carbon–oxygen double bond of amides.

Amides are the attractive nucleophiles for researching the reactivity of aryne, since they have nitrogen and oxygen atoms as nucleophilic sites. However, in general, the diversity in the reaction of arynes with amides is limited to the N–C σ-bond bond insertion starting form the addition of amide nitrogen atom to arynes, although the reactions of arynes with various amides including sulfinamide, enamide, and urea, have been investigated (Fig. 2).[18] Therefore, the development of the C=O π-bond insertion starting form the addition of amide oxygen atom to arynes is challenging task. Arynes exhibit extraordinary electrophilicity mainly due to their low-lying LUMO; thus, we surmised that the enhanced electrophilicity would allow for the attack of the weakly nucleophilic amide oxygen atom on arynes to give the formal [2+2] adducts **G**. In particular, the substituents R^1 and R^2 of amides are assumed to play a pivotal role for directing two competitive attacks between nitrogen and oxygen atoms.

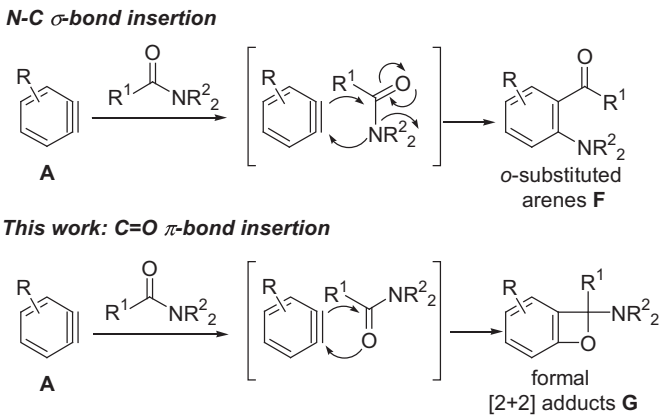
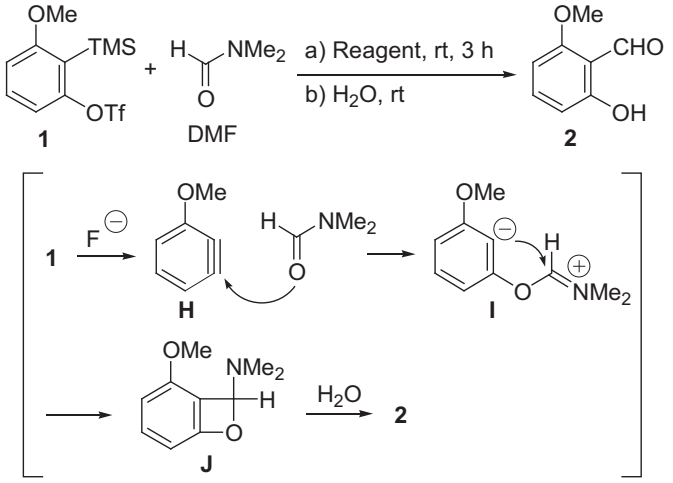


Fig. 2. Two reaction paths with amides.

2. Results and discussion

2.1. Insertion of aryne into the carbon–oxygen double bond of DMF

In organic synthesis, DMF can react as either an electrophilic or nucleophilic agent.[19] At first, we examined the insertion of arynes into the C=O π-bond of sterically less hindered DMF (R^1=H, R^2=Me in Fig. 2). We were gratified to observe the sufficient nucleophilicity of carbonyl oxygen atom of DMF toward aryne (Scheme 1). 3-Methoxy-2-(trimethylsilyl)phenyl triflate **1** was employed as an aryne precursor. All reactions were evaluated at room temperature in the presence of fluoride ion source for 3 h (Table 1). Initially, the reaction of triflate **1** with 3 equiv of DMF was run in CH_3CN in the presence of 3 equiv of TBAF·$3H_2O$ (entry 1). As expected, the desired salicylaldehyde derivative **2** was obtained in 31% yield probably via the zwitterion **I** and the four-membered intermediate **J**, accompanied by 31% yield of the recovered starting material **1** (entry 1). The presence of water had an impact on the chemical efficiency. The isolated yield of **2** increased to 56% yield by changing TBAF·$3H_2O$ into anhydrous TBAF (entry 2). Additionally, the concentration influenced the chemical efficiency; 0.3 M solution of triflate **1** gave a better result (entry 3). In these reactions, the competitive attack of the amide nitrogen atom on aryne **H** was suppressed. In regard to the solvent effect, the replacement of CH_3CN with THF, CH_2Cl_2 or toluene led to a decrease in the chemical yields (entries 4–6). The protic solvents, such as CH_3OH and CH_3CO_2H were not suitable for the present reaction (entries 7 and 8). Decreasing the amount of DMF to 1 equiv resulted in a low chemical yield (entry 9). In contrast, the use of 10 equiv of DMF improved the chemical yield into 70% (entry 10). It is noteworthy that the high regioselectivity was achieved due to the electronic effect by the methoxy group on triflate **1**. The reaction of polarized aryne **H** gave the salicylaldehyde derivative **2** as a single regioisomer.[20]



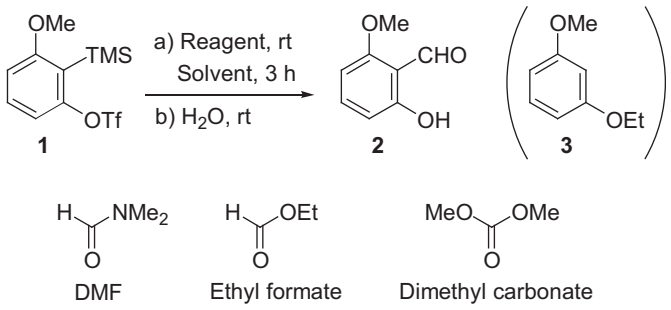
Scheme 1. Insertion of aryne into DMF.

Table 1
Reaction of aryne precursor **1** with DMF[a]

Entry	Reagent (3.0 equiv)	DMF (equiv)	Solvent	Yield[b] (%)
1[c]	TBAF·$3H_2O$	3.0	CH_3CN	31[d]
2[c]	TBAF	3.0	CH_3CN	56
3[e]	TBAF	3.0	CH_3CN	61
4[c]	TBAF	3.0	THF	46
5[c]	TBAF	3.0	CH_2Cl_2	43
6[c]	TBAF	3.0	Toluene	40
7[c]	TBAF	3.0	CH_3OH	No reaction
8[c]	TBAF	3.0	CH_3CO_2H	No reaction
9[c]	TBAF	1.0	CH_3CN	29
10[c]	TBAF	10.0	CH_3CN	70

[a] Reactions were carried out at rt for 3 h in the presence of 3.0 equiv of TBAF·$3H_2O$ or anhydrous TBAF.
[b] Isolated yield.
[c] Solution (0.1 M) of **1**.
[d] The starting material **1** was recovered in 31% yield.
[e] Solution (0.3 M) of **1**.

The best result was obtained, when DMF was employed as a solvent (Scheme 2, Table 2). In the presence of anhydrous TBAF, treatment of triflate **1** in DMF gave the desired product **2** in 84% yield (entry 1). Under the similar reaction conditions, the effect of fluoride ion sources was studied (entries 2–5). The use of CsF or tetrabutylammonium bifluoride ($TBAHF_2$) promoted the insertion into the C=O π-bond to give the product **2** in reasonable yields (entries 2 and 3). In contrast, the replacement of anhydrous TBAF with tetrabutylammonium difluorotriphenylsilicate (TBAT) or $TBAF{\cdot}3H_2O$ led to a decrease in the chemical yields (entries 4 and 5). In these studies, the fluoride ion sources did not affect the regioselectivity to give the product **2** as a single regioisomer. The scope of carbonyl compounds was tested by employing ethyl formate and dimethyl carbonate instead of DMF (entries 6 and 7). However, the corresponding *ortho*-disubstituted arenes were not obtained. In the case of ethyl formate, the formation of simple adduct **3** was observed (entry 6). At the present stage, the carbonyl oxygen atom of amides was the solitary nucleophile to bring about π-bond insertion into arynes.



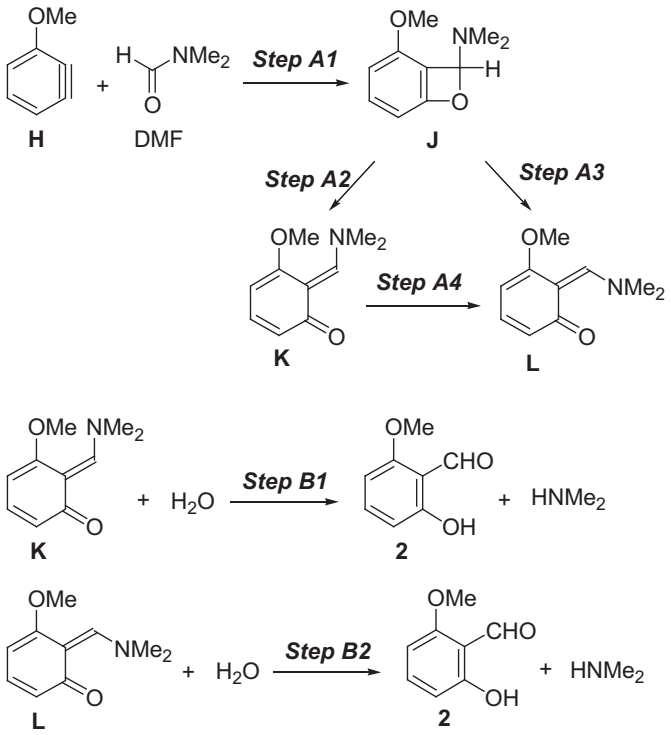
Scheme 2. Insertion of aryne into C=O bond.

Table 2
Reaction of aryne precursor **1** with C=O bond[a]

Entry	Reagent (3.0 equiv)	Solvent	Product (% yield)[b]
1	TBAF	DMF	**2** (84)
2	CsF	DMF	**2** (72)
3	$TBAHF_2$	DMF	**2** (67)
4	TBAT	DMF	**2** (31)
5	$TBAF{\cdot}3H_2O$	DMF	**2** (37)
6	TBAF	Ethyl formate	**3** (25)
7	TBAF	Dimethyl carbonate	Complex mixture

[a] Reactions were carried out at rt for 3 h in the presence of 3.0 equiv of fluoride ion source.
[b] Isolated yield.

The possible reaction pathway is shown in Scheme 3. The present reaction is assumed to be driven by high reactivity related to the strain energy of reactants. In other words, this success reflects the overall difference in the strain energy of aryne, the four-membered intermediate, quinone methide, and product. To explore the validity of the mechanistic hypothesis, the thermodynamic data were obtained by an ab initio molecular orbital calculation (Table 3). These data indicate that the insertion of aryne **H** into the C=O π-bond (Step A1) is remarkably exothermic ($\Delta H=-177$ kJ/mol at 325.15 K and −177 kJ/mol at 298.15 K) mainly due to the release of the strain energy of aryne **H** by reacting with DMF. It is important to stress that this enthalpy change sufficiently overcomes the entropy loss of the bimolecular coupling process ($T\Delta S=-71$ kJ/mol at 325.15 K and −65 kJ/mol at 298.15 K). Totally, the changes in Gibbs energy of Step A1 represent that the insertion of aryne **H** into the C=O π-bond of DMF is thermodynamically favorable ($\Delta G<0$ kJ/mol). The resulting [2+2] adduct **J** is also considerably unstable due to strain energy. Therefore, we anticipated that the quinone methide *E*- and *Z*-forms **K** and **L** should be formed from the [2+2] adduct **J**. As expected, the calculation supports that these transformations (Step A2 and Step A3) are thermodynamically favorable processes ($\Delta G<0$ kJ/mol). Additionally, the isomerization of the quinone methide *E*-form **K** into *Z*-form **L** (Step A4) is supported as a reasonable pathway. Finally, the hydrolysis of the quinone methides **K** and **L** giving the salicylaldehyde derivative **2** (Step B1 and Step B2) is favorable to proceed in view of thermodynamics.



Scheme 3. Possible reaction pathway.

Table 3
Change in Gibbs free energy, enthalpy, and entropy

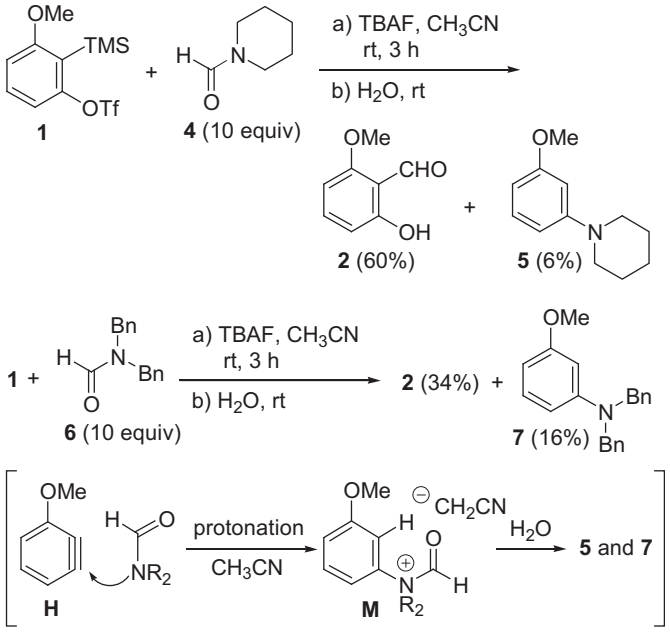
Step	Change	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J/mol K)
A1	**J**–(**H**+DMF)	−106[a] (−111)[b]	−177[a] (−177)[b]	−219[a] (−218)[b]
A2	**K**–**J**	−67[a] (−67)[b]	−63[a] (−63)[b]	13[a] (12)[b]
A3	**L**–**J**	−74[a] (−74)[b]	−71[a] (−71)[b]	12[a] (11)[b]
A4	**L**–**K**	−7.3[a] (−7.4)[b]	−7.6[a] (−7.6)[b]	−0.9[a] (−1.0)[b]
B1	(**2**+$HNMe_2$)–(**K**+H_2O)	−93[a] (−93)[b]	−87[a] (−87)[b]	19[a] (20)[b]
B2	(**2**+$HNMe_2$)–(**L**+H_2O)	−86[a] (−85)[b]	−80[a] (−79)[b]	20[a] (21)[b]

[a] At 325.15 K.
[b] The numerical values in parentheses are at 298.15 K.

2.2. Reaction of aryne with several amides

We next investigated the effect of two substituents at nitrogen atom of formamides on the C=O π-bond insertion reaction (see: R^2 of amides in Fig. 2). Initially, we allowed triflate **1** to react with 10 equiv of 1-formylpiperidine **4** and 3 equiv of anhydrous TBAF in CH_3CN for 3 h (Scheme 4). As expected, the desired salicylaldehyde

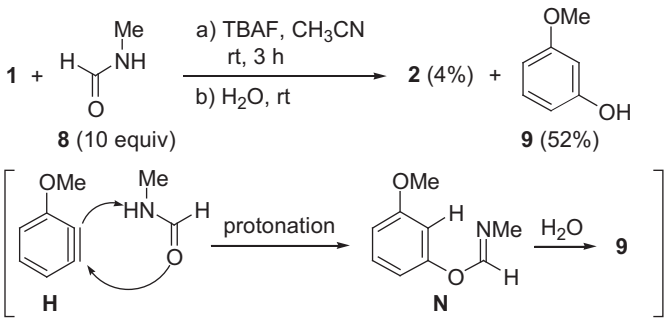
derivative **2** was obtained in 60% yield. Interestingly, the simply aminated product **5** was also formed in 6% yield as a by-product. When the bulky formamide **6** was employed, the chemical yield of **2** diminished to 34%; instead, the formation of the simply aminated product **7** increased to 16% yield. In the case of DMF, the formation of the corresponding aminated product was not observed under the similar reaction conditions (see: entry 10 in Table 1). As one of the possible suppositions, the steric factor of substituents at nitrogen atom might affect the C=O π-bond insertion process from the zwitterion **I** into the four-membered intermediate **J** as shown in Scheme 1. Probably, the aminated products **5** and **7** would be formed by hydrolysis of the ammonium salt **M**, which was generated by the attack of the amide nitrogen atom on aryne **H** followed by the protonation with the acetonitrile component of the reaction solvent. The protonation by the acetonitrile was verified by Greaney's studies on aryne chemistry.[21] However, as an alternative pathway giving the aminated products **5** and **7**, the reaction of aryne **H** with *N*,*N*-dialkylamines, generated by the hydrolysis of quinone methide intermediates, would not be rigorously excluded, although the reactions were carefully conducted under anhydrous conditions.



Scheme 4. Reaction of **1** with formamides **4** and **6**.

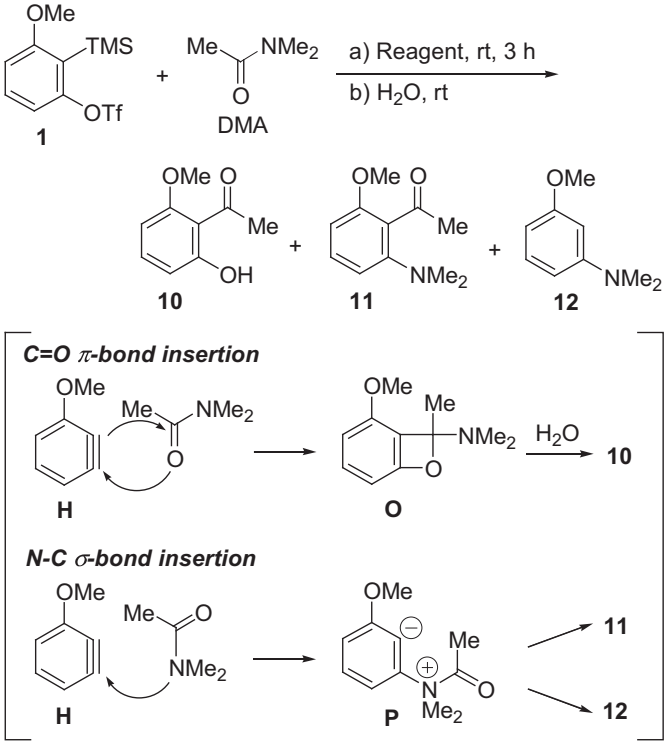
We next studied the reaction using *N*-monoalkylated formamide **8** (Scheme 5). As expected, *N*-methylformamide **8** worked well as an oxygen atom nucleophile. However, the undesired product **9** was predominantly formed probably through the intermediate **N** as a result of the rapid protonation by protic formamide **8**. In a consequence, the sterically less hindered and fully substituted DMF is a highly efficient oxygen atom nucleophile for the present C=O π-bond insertion reaction.

Next, two competitive attacks between nitrogen and oxygen atoms of amides were investigated by changing amides from formamide to acetamide (Scheme 6, Table 4). In comparison with DMF, the insertion into the C=O π-bond of *N*,*N*-dimethylacetamide (DMA) giving ketone **10** was apparently suppressed, since the steric factor of DMA gave rise to destabilizing the [2+2] adduct **O**. Instead, the formation of the N–C σ-bond bond insertion product **11** and the aminated product **12** was observed, except for entry 1. The products **11** and **12** were formed via the intermediate **P** generated by the addition of amide nitrogen atom into aryne **H**. Because the reaction



Scheme 5. Reaction of **1** with *N*-methylformamide **8**.

in CH_3CN was less effective (entry 1), DMA was employed as a solvent. In the presence of anhydrous TBAF, treatment of **1** with DMA gave the desired product **10** in 34% yield, accompanied by the product **11** in 10% yield and the aminated product **12** in 5% yield (entry 2). The three products **10**–**12** were also obtained, when CsF and $TBAHF_2$ were employed (entries 3 and 4). In the light of the fact that the reported reactions of arynes with amides have concentrated on the N–C σ-bond insertion,[18] the formation of the N–C σ-bond insertion product **11** is reasonable.



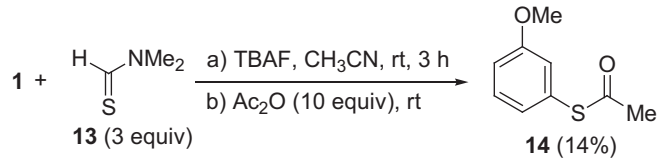
Scheme 6. Two competitive insertions into DMA.

Table 4
Reaction of aryne precursor **1** with DMA[a]

Entry	Reagent	Solvent	Product (% yield)[b]		
			10	**11**	**12**
1	TBAF, DMA (3 equiv)	CH_3CN	3	ND[c]	Trace
2	TBAF	DMA	34	10	5
3	CsF	DMA	31	6	8
4	$TBAHF_2$	DMA	19	6	3

[a] Reactions were carried out at rt for 3 h in the presence of 3.0 equiv of fluoride ion source.
[b] Isolated yield.
[c] Not detected.

The reaction of triflate **1** with *N*,*N*-dimethylthioformamide **13** was next tested (Scheme 7). However, the insertion of aryne into the C=S π-bond of **13** could not be observed. After being stirred for 3 h, the reaction mixture was treated with Ac_2O, because the *S*-incorporated product was difficult to isolate as a pure compound. We confirmed the formation of product **14** in 14% yield, accompanied with the recovered triflate **1** in 77% yield.



Scheme 7. Reaction using *N*,*N*-dimethylthioformamide **13**.

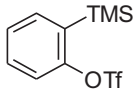
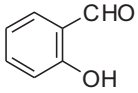
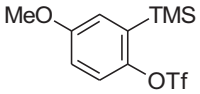
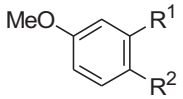
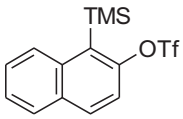
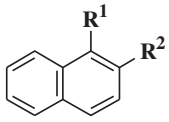
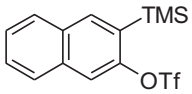
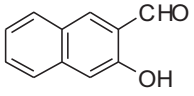
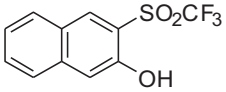
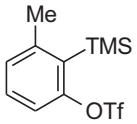
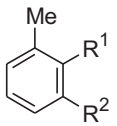
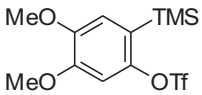
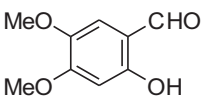
2.3. Reaction of several arynes with DMF giving salicylaldehyde derivatives

With these results in mind, we next examined the effect of varying the substituents on the aryne precursors (Table 5). The simple triflate **15** reacted well to afford the salicylaldehyde **21** (entry 1). The reaction of the unsymmetrical aryne, generated from triflate **16** having a methoxy group at 4-position, gave the regioisomers **22a** and **22b** in a 7/5 ratio on ^{1}H NMR (entry 2).[20] The formation of regioisomers supports that the present reaction proceeds via aryne intermediates. The nucleophilicity of DMF toward aryne, generated from bulky unsymmetrical naphthalene triflate **17**, was sufficient to bring about the C=O π-bond insertion (entry 3). The adducts **23a** and **23b** were obtained in 73% combined yield and a 2/1 ratio, accompanied by 11% yield of the recovered starting material **17**. The observed regioisomeric ratio revealed the preferential attack of carbonyl oxygen atom of DMF at the less sterically hindered carbon atom of aryne. In the case of symmetrical naphthalene triflate **18**, the chemical yield of the desired naphthaldehyde **24** decreased to 49%, because of the competitive formation of thia-Fries rearrangement product **25** and the recover of triflate **18** (entry 4).[22] In contrast to triflate **1** having a 3-methoxy group, the use of triflate **19** having a 3-methyl group led to a decrease in regioselectivity to give the products **26a** and **26b** in a 7/5 ratio (entry 5). The reaction of triflate **20** resulted in the formation of product **27** in 73% yield (entry 6).

2.4. Trapping reaction using dialkylzincs

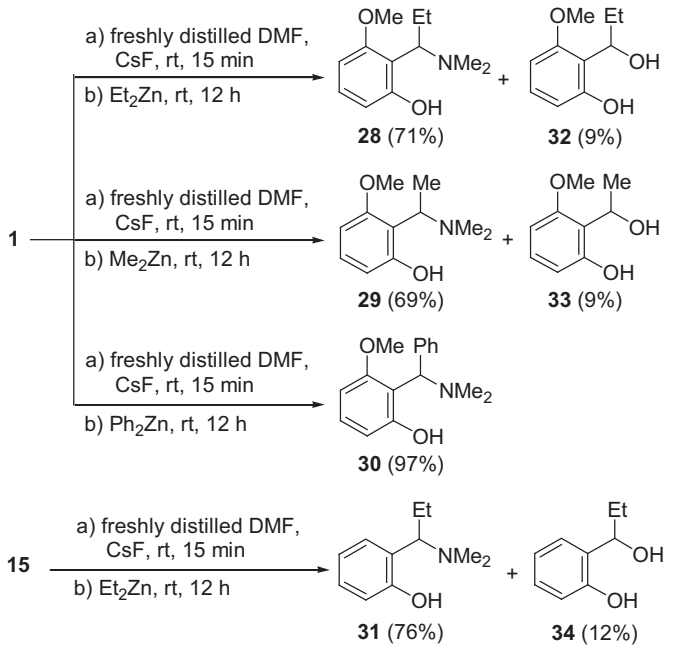
We next investigated the trapping reaction of the unstable intermediates, the formal [2+2] adduct **J** or the quinone methide *E*- and *Z*-forms **K** and **L**, with organometallic reagents. We found that dialkylzincs have the sufficient reactivity toward these intermediates and the compatibility of DMF as a solvent (Scheme 8). After a solution of triflate **1** in freshly distilled DMF was stirred in the presence of CsF at room temperature for 15 min, dialkylzincs were added to the reaction mixture, and then the reaction mixture was stirred at the same temperature for 12 h. When a solution of Et_2Zn in hexane (1.05 M, 5 equiv) was employed, the desired *o*-aminoalkylphenol **28** was obtained in 71% yield by simple one-pot procedure. In this transformation, a small amount of *o*-hydroxyalkylphenol **32** was also isolated as a by-product, which was generated by trapping of salicylaldehyde derivative **2** with Et_2Zn. Under the similar conditions, Me_2Zn reacted well to give *o*-aminoalkylphenol **29**, accompanied by *o*-hydroxyalkylphenol **33** in 9% yield. Interestingly, Ph_2Zn trapped the intermediates with high activity to form the aminophenol **30** in 97% yield without the formation of the corresponding *o*-hydroxyalkylphenol. Similar result was observed when simple triflate **15** was employed as an aryne precursor. As reported in our communication,[17a] we assumed that dialkylzincs added to not the formal [2+2] adduct **J** but the thermodynamically stable quinone methide *E*- or *Z*-forms **K** or **L** based on the calculation study.

Table 5
Variation of aryne precursors[a]

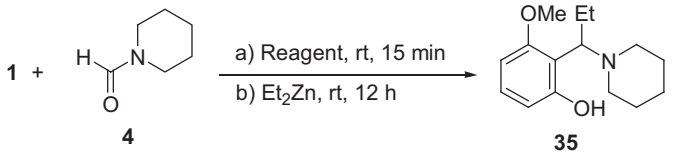
Entry	Precursor	Product (Yield,[b] ratio)
1	 **15**	 **21** (68%)
2	 **16**	 **22a:** R^1=CHO, R^2=OH **22b:** R^1=OH, R^2=CHO (81%, **22a:22b** = 7:5)
3[c]	 **17**	 **23a:** R^1=CHO, R^2=OH **23b:** R^1=OH, R^2=CHO (73%, **23a:23b** = 2:1)
4[d]	 **18**	 **24** (49%)  **25** (13%)
5	 **19**	 **26a:** R1=OH, R2=CHO **26b:** R1=CHO, R2=OH (57%, **26a:26b** = 7:5)
6	 **20**	 **27** (73%)

[a] Reactions were carried out in DMF at rt in the presence of 3.0 equiv of anhydrous TBAF.
[b] Isolated yield.
[c] The starting material **17** was recovered in 11% yield.
[d] The starting material **18** was recovered in 26% yield.

We next investigated the one-pot procedure for the sequential transformation using 1-formylpiperidine **4** (Scheme 9). The reaction using 10 equiv of 1-formylpiperidine **4** and 3 equiv of CsF in CH_3CN gave the desired adduct **35** in 11% (Table 6, entry 1). Slight improvement in the chemical yield was observed when the reaction was carried out in the presence of 30 equiv of **4** (entry 2). The yield of **35** increased to 40% when anhydrous TBAF was employed



Scheme 8. Trapping reaction of the unstable intermediates with R_2Zn.



Scheme 9. Trapping reaction using amide **4**.

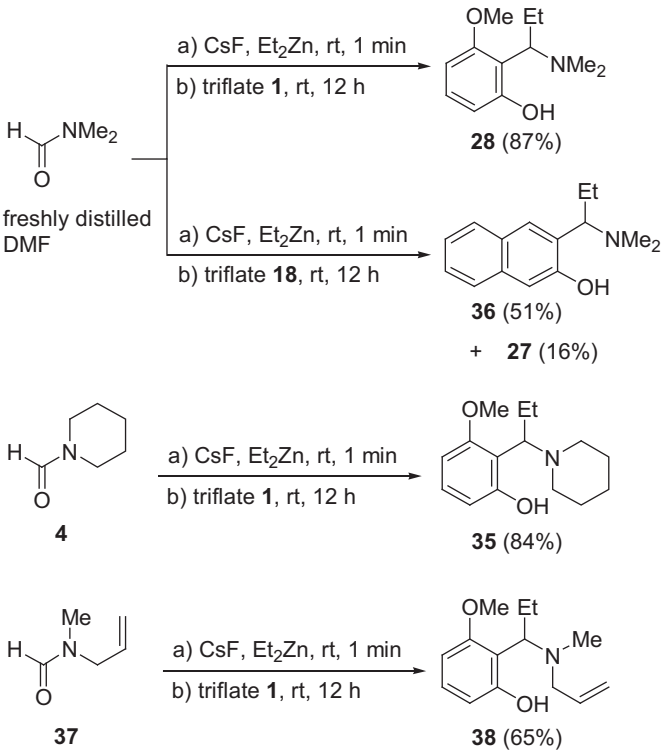
Table 6
Trapping reaction using aryne precursor **1** and 1-formylpiperidine **4**[a]

Entry	Reagent	1-Formylpiperidine **4** (equiv)	Solvent	Yield[b] (%)
1	CsF (3.0 equiv)	10	CH_3CN	11
2	CsF (3.0 equiv)	30	CH_3CN	29
3	TBAF (3.0 equiv)	10	CH_3CN	40
4	TBAF (3.0 equiv)	10	Toluene	22

[a] Reactions were carried out by using 3.0 equiv of Et_2Zn (1.0 M in hexane).
[b] Isolated yield.

as a fluoride ion source (entry 3). As shown by entry 4, the use of other solvents led to a decrease in the chemical yield. Under these reaction conditions, the formation of *o*-hydroxyalkylphenol **32** and salicylaldehyde derivative **2** was observed as major by-products due to hydrolysis of intermediates with contaminated water.

To suppress the formation of *o*-hydroxyalkylphenols, generated from salicylaldehyde derivatives, the one-pot procedure was reexamined (Scheme 10). Because CsF is a moisture-sensitive fluoride ion source, Et_2Zn was initially added to a suspension of CsF in freshly distilled DMF to remove a trace amount of water in the reaction mixture. Next, triflate **1** was added to the reaction mixture. As expected, this improved procedure gave the desired *o*-aminoalkylphenol **28** in 87% yield without the formation of *o*-hydroxyalkylphenol **32**, after being stirred at room temperature for 12 h. When the naphthalene triflate **18** was employed, *o*-aminoalkylphenol **36** was obtained, accompanied by thia-Fries rearrangement product **27**. This new procedure was also effective for the one-pot reactions using 1-formylpiperidine **4**. Under the similar reaction conditions using amide **4**, the yield of **35** increased to 84% (vs 40%, entry 3 in Table 6). Additionally, the one-pot reaction using *N*-allyl-*N*-methylformamide **37** gave the desired product **38** in 65%

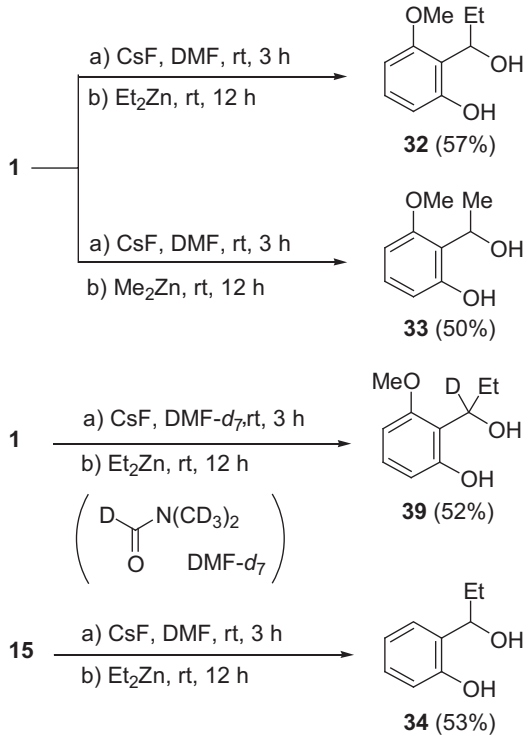


Scheme 10. The improved one-pot procedure for trapping reaction.

yield. In these reactions, 1-formylpiperidine **4** and *N*-allyl-*N*-methylformamide **37** were used without the purification by distillation.

2.5. Trapping reaction giving *o*-hydroxyalkylphenols

As described above, during the study on the trapping reactions synthesizing *o*-aminoalkylphenols, we frequently observed the



Scheme 11. Trapping reaction giving *o*-hydroxyalkylphenols.

formation of the small amount of *o*-hydroxyalkylphenols. Therefore, we finally tried to establish the one-pot procedure for trapping of salicylaldehyde derivatives with dialkylzincs to prepare the *o*-hydroxyalkylphenols (Scheme 11). For this transformation, we allowed triflate **1** to react with commercially available DMF in the presence of moisture-sensitive CsF (5 equiv) for the prolonged time. After the reaction mixture was stirred at room temperature for 3 h, a solution of Et_2Zn in hexane (1.05 M, 10 equiv) was finally added. As expected, the desired *o*-hydroxyalkylphenol **32** was isolated in 57% by this simple procedure, accompanied with a 10% yield of *o*-aminoalkylphenol **28**. When Me_2Zn was used, the *o*-hydroxyalkylphenol **33** was obtained in 50% yield accompanied with a small amount of *o*-aminoalkylphenol **29**. The DMF-d_7 also acted as a nucleophile to give the deuterated product **39**. Under the similar reaction conditions, the aryne precursor **15** worked well, allowing facile incorporation of structural variety. Although the competitive formation of the corresponding *o*-aminoalkylphenols was slightly observed, it is noteworthy that *o*-hydroxyalkylphenols were prepared as major products by simply changing the experimental procedure.

In summary, we have demonstrated that the C=O π-bond insertion, starting from the addition of amide oxygen atom to arynes, proceeded effectively by using the sterically less hindered formamide. The salicylaldehyde derivatives were formed via a route involving the transformation of the formal [2+2] cycloaddition adducts into quinone methide intermediates. Moreover, the sequential transformation of arynes into *ortho*-disubstituted arenes was achieved by one-pot procedure using formamides and dialkylzincs. Interestingly, *o*-aminoalkylphenols and *o*-hydroxyalkylphenols could be selectively prepared by simply changing the one-pot procedure.

3. Experimental

3.1. General

Melting points were taken on a Yanaco MP-J3 and are uncorrected. Infrared spectra were measured on a JASCO FT/IR-4100. ^{1}H NMR spectra were measured on a JEOL ECX-400 PSK (400 MHz) or Varian NMRS 600 (600 MHz). ^{13}C NMR spectra were measured on a JEOL ECX-400 PSK (101 MHz) or Varian NMRS 600 (126 MHz) with $CDCl_3$ as an internal standard (77.0 ppm). ^{19}F NMR spectrum was measured on a JEOL ECX-400 PSK (376 MHz) with C_6F_6 as an internal standard (-162.2 ppm). Mass spectra (EI-MS and ESI-MS) were obtained by use of a Hitachi M-4100 GC/MS spectrometer or Thermo Fisher Scientific Exactive LC/MS spectrometer. Elemental analyses were measured on Yanaco CHN CORDER MT-5. For silica gel column chromatography, SiliCycle Inc. SiliaFlash F60 was used. The anhydrous TBAF was prepared from TBAF·$3H_2O$ by heating the hydrate at 40 °C for 6 h, at 60 °C for 12 h, at 80 °C for 6 h, and then at 120 °C for 12 h under reduced pressure. The anhydrous TBAF was used as a solution in the appropriate solvent, such as DMF, CH_3CN, and so on. Calculation studies were performed on Hartree-Fock 6-311G* by using Spartan'08 Essential Edition (WAVEFUNCTION, INC).

3.2. Experimental procedure for the reaction of aryne precursor 1 with DMF (entries 2 and 4–10 in Table 1)

To a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate **1** (53 μL, 0.20 mmol) and DMF (0.20 mmol, 0.60 mmol or 2.0 mmol) in CH_3CN, THF, CH_2Cl_2, CH_3OH or CH_3CO_2H (1.4 mL) was added TBAF (1.0 M solution in corresponding solvent, 0.60 mL, 0.60 mmol) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/8 with 2% CH_2Cl_2) afforded the product **2**.

*3.2.1. 2-Hydroxy-3-methoxybenzaldehyde (**2**)*[23]. Colorless crystals. Mp 73.5–74.5 °C (AcOEt/hexane). IR (KBr) 3245, 3084, 2893, 1646, 1618, 1465 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 11.97 (1H, s), 10.34 (1H, s), 7.41 (1H, dd, *J*=8.0, 8.5 Hz), 6.52 (1H, d, *J*=8.5 Hz), 6.38 (1H, d, *J*=8.0 Hz), 3.89 (3H, s). ^{13}C NMR ($CDCl_3$) δ 194.5, 163.6, 162.5, 138.4, 110.8, 109.9, 101.0, 55.8. MS (EI$^+$) *m*/*z* 84 (100), 153 (M+H$^+$, 9). HRMS (EI$^+$) calcd for $C_8H_9O_3$ (M+H$^+$) 153.0546, found 153.0553. Anal. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30%. Found: C, 63.14; H, 5.32%.

3.3. Experimental procedure for the reaction of precursor 1 in DMF (entries 1–5 in Table 2)

To a solution of TBAF, CsF, $TBAHF_2$, TBAT or TBAF·$3H_2O$ (0.60 mmol) in DMF (1.2 mL) was added a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate **1** (53 μL, 0.20 mmol) in DMF (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/8 with 2% CH_2Cl_2) afforded the product **2**.

3.4. Experimental procedure for the reaction of precursor 1 in ethyl formate (entry 6 in Table 2)

To a solution of TBAF (157 mg, 0.60 mmol) in ethyl formate (1.2 mL) was added a solution of 3-methoxy-2-(trimethylsilyl) phenyl triflate **1** (53 μL, 0.20 mmol) in ethyl formate (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/8 with 2% CH_2Cl_2) afforded the product **3** (7.5 mg, 25%).

*3.4.1. 3-Ethoxyanisole (**3**)*[24]. Colorless oil. IR (KBr) 2980, 2936, 1601, 1493 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.17 (1H, t, *J*=8.0 Hz), 6.51–6.46 (3H, m), 4.02 (2H, q, *J*=7.0 Hz), 3.79 (3H, s), 1.41 (3H, t, *J*=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 160.8, 160.2, 129.8, 106.6, 106.1, 100.9, 63.3, 55.2, 14.8. HRMS (ESI$^+$) calcd for $C_9H_{13}O_2$ (M+H$^+$) 153.0910, found 153.0905.

3.5. Experimental procedure for the reaction of precursor 1 with amides 4, 6, or 8 (Schemes 4 and 5)

To a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate **1** (53 μL, 0.20 mmol) and 1-formylpiperidine **4**, *N*,*N*-dibenzylformamide **6**, or *N*-methylformamide **8** (2.0 mmol) in CH_3CN (1.4 mL) was added TBAF (1.0 M solution in CH_3CN, 0.60 mL, 0.60 mmol) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/8 with 2% CH_2Cl_2) afforded the products **2**, **5**, **7**, and **9**.

*3.5.1. N-(3-Methoxyphenyl)piperidine (**5**)*[25]. Colorless oil. IR (KBr) 2925, 2853, 1608, 1465 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.14 (1H, br t, *J*=8.0 Hz), 6.55 (1H, br dd, *J*=8.0, 2.5 Hz), 6.47 (1H, br t, *J*=2.5 Hz), 6.37 (1H. br dd, *J*=8.0, 2.5 Hz), 3.78 (3H, s), 3.15 (4H, br t, *J*=5.5 Hz), 1.72–1.67 (4H, m), 1.59 (2H, m). ^{13}C NMR ($CDCl_3$) δ 160.5, 153.6, 129.6, 109.3, 103.9, 102.8, 55.1, 50.6, 25.8, 24.4. MS (EI$^+$) *m*/*z* 190

(100), 191 (M^+, 83). HRMS (EI^+) calcd for $C_{12}H_{17}NO$ (M^+) 191.1305, found 191.1327.

*3.5.2. 3-Methoxy-N,N-dibenzylaniline (**7**)[26].* Colorless oil. IR (KBr) 3027, 2933, 2834, 1610, 1576, 1499, 1452 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.33–7.29 (4H, m), 7.24–7.21 (6H, m), 7.07 (1H, t, J=8.0 Hz), 6.36 (1H, dd, J=8.0, 2.0 Hz), 6.29–6.26 (2H, m), 4.63 (4H, s), 3.69 (3H, s). ^{13}C NMR ($CDCl_3$) δ 160.7, 150.6, 138.5, 129.9, 128.6, 126.8, 126.6, 105.6, 101.5, 99.0, 55.0, 54.2. MS (EI^+) m/z 303 (M^+, 100). HRMS (EI^+) calcd for $C_{21}H_{21}NO$ (M^+) 303.1618, found 303.1624.

*3.5.3. 3-Methoxyphenol (**9**)[27].* Colorless oil. IR (KBr) 3355, 2959, 2839, 1598, 1494, 1464 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.13 (1H, t, J=8.0 Hz), 6.51–6.48 (1H, m), 6.44–6.41 (2H, m), 4.95 (1H, br s), 3.78 (3H, s). ^{13}C NMR ($CDCl_3$) δ 160.9, 156.6, 130.1, 107.7, 106.4, 101.4, 55.3.

3.6. Experimental procedure for the reaction of precursor 1 with DMA (entry 2 in Table 4)

To a solution of TBAF (157 mg, 0.60 mmol) in DMA (1.2 mL) was added a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate **1** (53 μL, 0.20 mmol) in DMA (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/8 with 2% CH_2Cl_2) afforded the products **10** (11.3 mg, 34%), **11** (3.8 mg, 10%), and **12** (1.3 mg, 5%).

*3.6.1. 2-Hydroxy-6-methoxyacetophenone (**10**)[28].* Colorless crystals. Mp 57–57.5 °C (AcOEt/hexane). IR (KBr) 3110, 3009, 2947, 1623, 1594, 1459 cm^{-1}. ^1H NMR ($CDCl_3$) δ 13.23 (1H, s), 7.33 (1H, t, J=8.0 Hz), 6.56 (1H, dd, J=8.0, 1.0 Hz), 6.39 (1H, dd, J=8.0, 1.0 Hz), 3.90 (3H, s), 2.67 (3H, s). ^{13}C NMR ($CDCl_3$) δ 205.1, 164.6, 161.5, 136.0, 111.3, 110.7, 101.1, 55.6, 33.7. MS (EI^+) m/z 83 (100), 166 (M^+, 3). HRMS (EI^+) calcd for $C_9H_{10}O_3$ (M^+) 166.0624, found 166.0646.

*3.6.2. 2-(N,N-Dimethyl)amino-6-methoxyacetophenone (**11**).* Colorless oil. IR ($CHCl_3$) 2942, 1702, 1577, 1468 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.23 (1H, br t, J=8.0 Hz), 6.67 (1H, br d, J=8.0 Hz), 6.56 (1H, br d, J=8.0 Hz), 3.78 (3H, s), 2.72 (6H, s), 2.50 (3H, s). ^{13}C NMR ($CDCl_3$) δ 205.2, 156.2, 151.8, 130.2, 125.3, 111.0, 104.7, 55.8, 44.8, 31.8. MS (EI^+) m/z 83 (100), 193 (M^+, 0.4). HRMS (EI^+) calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1097, found 193.1121.

*3.6.3. 3-Methoxy-N,N-dimethylaniline (**12**)[29].* Colorless oil. IR (KBr) 2955, 1610, 1493, 1465 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.15 (1H, t, J=8.0 Hz), 6.36 (1H, dd, J=8.0, 2.5 Hz), 6.31–6.27 (2H, m), 3.80 (3H, s), 2.94 (6H, s). ^{13}C NMR ($CDCl_3$) δ 160.6, 151.9, 129.7, 105.7, 101.3, 99.1, 55.1, 40.6. MS (EI^+) m/z 83 (100), 151 (M^+, 0.4). HRMS (EI^+) calcd for $C_9H_{14}NO$ ($M+H^+$) 152.1070, found 152.1055.

3.7. Experimental procedure for the reaction of precursor 1 with thioformamide 13 (Scheme 7)

To a solution of TBAF (157 mg, 0.60 mmol) in CH_3CN (1.2 mL) were added a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate **1** (53 μL, 0.20 mmol) and *N,N*-dimethylthioformamide **13** (51 μL, 0.60 mmol) in CH_3CN (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, Ac_2O (189 μL, 2.0 mmol) was added to the reaction mixture. After being stirred for 12 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/3 with 2% CH_2Cl_2) afforded the product **14** (5.1 mg, 14%) and the recovered triflate **1** (50.5 mg, 77%).

*3.7.1. S-(3-Methoxyphenyl)thioacetate (**14**).* Colorless oil. IR (KBr) 3004, 2938, 1708, 1591, 1479 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.32 (1H, m), 7.02–6.94 (3H, m), 3.81 (3H, s), 2.42 (3H, s). ^{13}C NMR ($CDCl_3$) δ 194.0, 159.8, 130.0, 128.8, 126.6, 119.5, 115.6, 55.3, 30.2. MS (EI^+) m/z 140 (100), 182 (M^+, 40). HRMS (EI^+) calcd for $C_9H_{10}O_2S$ (M^+) 182.0402, found 182.0419.

3.8. General procedure for the reaction of precursors 15–20 in DMF (Table 5)

To a solution of TBAF (157 mg, 0.60 mmol) in DMF (1.2 mL) was added a solution of precursors **15**–**20** (0.20 mmol) in DMF (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/3 with 2% CH_2Cl_2) afforded the products **21**–**27**.

*3.8.1. 2-Hydroxybenzaldehyde (**21**)[30].* Colorless oil. IR (KBr) 3183, 3062, 2845, 1666, 1486 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.02 (1H, s), 9.90 (1H, s), 7.58–7.51 (2H, m), 7.04–6.98 (2H, m). ^{13}C NMR ($CDCl_3$) δ 196.6, 161.6, 136.9, 133.7, 120.6, 119.8, 117.6.

*3.8.2. 2-Hydroxy-5-methoxybenzaldehyde (**22a**)[31] and 2-hydroxy-4-methoxybenzaldehyde (**22b**)[32].* A mixture of **22a** and **22b** (**22a**/**22b**=7/5). Yellow oil. IR (KBr) 3168, 2944, 2840, 1658, 1629, 1486 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.48 (5/12H, s), 10.63 (7/12H, s), 9.86 (7/12H, s), 9.71 (5/12H, s), 7.42 (5/12H, d, J=8.5 Hz), 7.14 (7/12H, dd, J=9.2, 3.2 Hz), 7.00 (7/12H, d, J=3.2 Hz), 6.93 (7/12H, d, J=9.2 Hz), 6.54 (5/12H, dd, J=8.5, 2.5 Hz), 6.43 (5/12H, d, J=2.5 Hz), 3.85 (15/12H, s), 3.81 (21/12H, s). ^{13}C NMR ($CDCl_3$) δ 196.1, 194.4, 166.8, 164.5, 156.1, 152.7, 135.2, 125.2, 120.0, 118.7, 115.2, 108.4, 100.6, 55.9, 55.7. One carbon peak was missing due to overlapping. MS (EI^+) m/z 83 (100), 152 (M^+, 0.2). HRMS (EI^+) calcd for $C_8H_9O_3$ ($M+H^+$) 153.0546, found: 153.0552.

*3.8.3. 2-Hydroxy-1-naphthaldehyde (**23a**)[33].* Pale yellow crystals. Mp 79–80 °C (CH_2Cl_2/hexane). IR (KBr) 3249, 3060, 2895, 2807, 1640, 1584, 1468 cm^{-1}. ^1H NMR ($CDCl_3$) δ 13.16 (1H, s), 10.81 (1H, s), 8.34 (1H, br d, J=8.8 Hz), 7.98 (1H, d, J=9.3 Hz), 7.80 (1H, br d, J=8.3 Hz), 7.62 (1H, dt, J=8.3, 1.5 Hz), 7.44 (1H, dt, J=8.3, 1.0 Hz), 7.14 (1H, d, J=9.3 Hz). ^{13}C NMR ($CDCl_3$) δ 193.3, 164.9, 139.1, 132.9, 129.5, 129.1, 127.8, 124.5, 119.2, 118.6, 111.3. MS (EI^+) m/z 172 (M^+, 100). HRMS (EI^+) calcd for $C_{11}H_8O_2$ (M^+) 172.0519, found 172.0531.

*3.8.4. 1-Hydroxy-2-naphthaldehyde (**23b**)[34].* Pale yellow crystals. Mp 50–51 °C (CH_2Cl_2/hexane). IR (KBr) 3161, 3057, 2836, 1646, 1629 cm^{-1}. ^1H NMR ($CDCl_3$) δ 12.67 (1H, s), 9.97 (1H, s), 8.45 (1H, br d, J=8.3 Hz), 7.79 (1H, d, J=8.3 Hz), 7.67 (1H, dd, J=8.3, 1.5 Hz), 7.56 (1H, dd, J=8.3, 1.5 Hz), 7.49 (1H, d, J=8.3 Hz), 7.38 (1H, d, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 196.3, 161.9, 137.5, 130.6, 127.6, 126.5, 126.1, 124.5, 124.3, 119.4, 114.2. HRMS (ESI^-) calcd for $C_{11}H_7O_2$ ($M-H^-$) 171.0452, found 171.0443.

*3.8.5. 3-Hydroxy-2-naphthaldehyde (**24**)[35].* Pale yellow crystals. Mp 94–95 °C (CH_2Cl_2/hexane). IR (KBr) 3303, 3052, 2873, 1674, 1503, 1459 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.32 (1H, br s), 10.10 (1H, br s), 8.16 (1H, br s), 7.88 (1H, br d, J=8.0 Hz), 7.72 (1H, br d, J=8.0 Hz), 7.57 (1H, dt, J=7.0, 1.5 Hz), 7.38 (1H, dt, J=7.0, 1.5 Hz), 7.29 (1H, s). ^{13}C NMR ($CDCl_3$) δ 197.3, 156.4, 138.8, 138.5, 130.9, 130.0, 128.0, 127.3, 125.0, 122.9, 112.5. MS (EI^+) m/z 83 (100), 172 (M^+, 0.7). HRMS (EI^+) calcd for $C_{11}H_8O_2$ (M^+) 172.0519, found 172.0531.

*3.8.6. 3-Trifluoromethanesulfonyl-2-naphthol (**25**)[22].* Yellow crystals. Mp 120–121 °C (benzene/hexane). Sublimation (ca. 102 °C). IR (KBr) 3296, 2873, 1687, 1504, 1459 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.46 (1H,

s), 7.98 (1H, s, offset by D_2O), 7.91 (1H, d, J=8.0 Hz), 7.78 (1H, d, J=8.0 Hz), 7.66 (1H, ddd, J=1.5, 1.5, 7.5 Hz), 7.48 (2H, m). ^{13}C NMR ($CDCl_3$) δ 151.8, 139.5, 135.7, 131.5, 129.6, 127.3, 126.7, 125.8, 119.8 (q, J=327 Hz), 115.1, 114.6. ^{19}F NMR ($CDCl_3$) δ −79.3. MS (EI^+) m/z 115 (100), 276 (M^+, 87). HRMS (EI^+) calcd for $C_{11}H_7F_3O_3S$ (M^+) 276.0063, found 276.0068. Anal. Calcd for $C_{11}H_7F_3O_3S$: C, 47.83; H, 2.55%. Found: C, 48.07; H, 2.78%.

*3.8.7. 2-Hydroxy-3-methylbenzaldehyde (**26a**)*[36]. Colorless oil. IR (KBr) 3413, 2923, 1729, 1464 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.27 (1H, s), 9.88 (1H, s), 7.41–7.39 (2H, m), 6.93 (1H, t, J=7.5 Hz), 2.27 (3H, s). ^{13}C NMR ($CDCl_3$) δ 196.7, 160.0, 137.8, 131.3, 126.8, 120.0, 119.3, 15.0. MS (EI^+) m/z 136 (M^+, 0.1), 83 (100). HRMS (EI^+) calcd for $C_8H_9O_2$ ($M+H^+$) 137.0597, found: 137.0577.

*3.8.8. 2-Hydroxy-6-methylbenzaldehyde (**26b**)*[37]. Colorless oil. IR (KBr) 3240, 3046, 2927, 1642, 1458 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.91 (1H, s), 10.33 (1H, s), 7.38 (1H, t, J=8.0 Hz), 6.82 (1H, t, J=8.0 Hz), 6.72 (1H, d, J=8.0 Hz), 2.61 (3H, s). ^{13}C NMR ($CDCl_3$) δ 195.3, 163.2, 142.1, 137.4, 121.8, 118.5, 116.1, 18.1. HRMS (ESI^-) calcd for $C_8H_7O_2$ ($M-H^-$) 135.0452, found 135.0442.

*3.8.9. 2-Hydroxy-4,5-dimethoxybenzaldehyde (**27**)*[38]. Pale yellow crystals. Mp 104–105 °C (CH_2Cl_2/hexane). IR (KBr) 3249, 2959, 2923, 2842, 1628, 1593, 1507 cm^{-1}. ^1H NMR ($CDCl_3$) δ 11.39 (1H, s), 9.69 (1H, s), 6.89 (1H, s), 6.47 (1H, s), 3.93 (3H, s), 3.87 (3H, s). ^{13}C NMR ($CDCl_3$) δ 194.0, 159.3, 157.2, 142.9, 113.2, 112.8, 100.1, 56.4, 56.3. HRMS (ESI^+) calcd for $C_9H_{11}O_4$ ($M+H^+$) 183.0652, found 183.0650.

3.9. General procedure for the trapping reaction giving *o*-aminoalkylphenols 28–31 (Scheme 8)

To a suspension of CsF (91 mg, 0.60 mmol) in freshly distilled DMF (1.2 mL) was added a solution of aryne precursor **1** or **15** (0.20 mmol) in freshly distilled DMF (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 15 min, Et_2Zn (1.05 M in hexane, 0.95 mL, 1.0 mmol), Me_2Zn (1.0 M in hexane, 1.0 mL, 1.0 mmol), or Ph_2Zn (220 mg, 1.0 mmol) were added to the reaction mixture at room temperature. After being stirred at the same temperature for 12 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/0 with 2% CH_2Cl_2) afforded the products **28**–**31**, accompanied by the products **32**–**34**.

*3.9.1. 2-[1-(Dimethylamino)propyl]-3-methoxyphenol (**28**).* Colorless oil. IR (KBr) 3311, 2937, 1593, 1468 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.06 (1H, t, J=8.0 Hz), 6.44 (1H, dd, J=8.0, 1.0 Hz), 6.35 (1H, dd, J=8.0, 1.0 Hz), 3.76 (3H, s), 3.74 (1H, m), 2.33 (6H, s), 1.88–1.72 (2H, m), 0.76 (3H, t, J=7.5 Hz). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR ($CDCl_3$) δ 158.7, 157.9, 128.1, 113.7, 109.6, 101.1, 64.4, 55.3, 43.3 (br s), 24.9, 9.5. MS (EI^+) m/z 153 (100), 209 (M^+, 13). HRMS (EI^+) calcd for $C_{12}H_{19}NO_2$ (M^+) 209.1416, found 209.1421.

*3.9.2. 2-[1-(Dimethylamino)ethyl]-3-methoxyphenol (**29**).* Colorless oil. IR (KBr) 3428, 2957, 1566, 1461 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.04 (1H, t, J=8.0 Hz), 6.44 (1H, dd, J=8.0, 1.0 Hz), 6.34 (1H, dd, J=8.0, 1.0 Hz), 3.84 (1H, t, J=6.5 Hz), 3.78 (3H, s), 2.33 (6H, br s), 1.33 (3H, d, J=6.5 Hz). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR ($CDCl_3$) δ 158.3, 157.0, 128.0, 116.1, 109.7, 101.2, 59.4, 55.5, 43.4 (br s), 18.7. MS (EI^+) m/z 180 (100), 195 (M^+, 51). HRMS (EI^+) calcd for $C_{11}H_{17}NO_2$ (M^+) 195.1259, found 195.1275.

*3.9.3. 2-[1-(Dimethylamino)phenylmethyl]-3-methoxyphenol (**30**).* Colorless crystals. Mp 150–151 °C (AcOEt/hexane). IR (KBr) 3121, 3060, 2962, 2838, 1609, 1593, 1466 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.48 (2H, br d, J=7.0 Hz), 7.27–7.17 (3H, m), 7.03 (1H, t, J=8.0 Hz), 6.49 (1H, dd, J=8.0, 1.0 Hz), 6.26 (1H, dd, J=8.0, 1.0 Hz), 4.69 (1H, s), 3.70 (3H, s), 2.27 (6H, br s). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR ($CDCl_3$) δ 157.9, 157.4, 141.2, 128.4 (2C), 127.4, 114.8, 109.9, 101.5, 70.2, 55.5, 44.2 (br s). One carbon peak was missing due to overlapping. MS (EI^+) m/z 211 (100), 257 (M^+, 37). HRMS (EI^+) calcd for $C_{16}H_{19}NO_2$ (M^+) 257.1416, found 257.1431; Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44%. Found: C, 74.69; H, 7.46; N, 5.41%.

*3.9.4. 2-[1-(Dimethylamino)propyl]phenol (**31**).* Colorless oil. IR (KBr) 3303, 2975, 1608, 1461 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.18 (1H, dt, J=8.0, 2.0 Hz), 6.96 (1H, dd, J=7.5, 2.0 Hz), 6.87 (1H, dd, J=8.0, 1.0 Hz), 6.81 (1H, dt, J=7.5, 1.0 Hz), 3.43 (1H, br dd, J=9.5, 4.0 Hz), 2.47 (6H, s), 2.09–1.83 (2H, m), 0.79 (3H, t, J=7.5 Hz). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR ($CDCl_3$) δ 156.5, 129.2, 129.1, 123.3, 119.1, 116.7, 71.7, 42.6, 23.5, 10.8. MS (EI^+) m/z 84 (100), 179 (M^+, 0.1). HRMS (EI^+) calcd for $C_{11}H_{17}NO$ (M^+) 179.1310, found 179.1329.

3.10. Experimental procedure for the trapping reaction using amide 4 (entry 3 in Table 6)

To a solution of TBAF (157 mg, 0.60 mmol) and 1-formylpiperidine **4** (222 μL, 2.0 mmol) in CH_3CN (1.2 mL) was added a solution of 3-methoxy-2-(trimethylsilyl)phenyl triflate **1** (53 μL, 0.20 mmol) in CH_3CN (0.8 mL) under argon atmosphere at room temperature. After being stirred at the same temperature for 15 min, Et_2Zn (1.05 M in hexane, 0.95 mL, 1.0 mmol) was added to the reaction mixture. After being stirred at the same temperature for 12 h, H_2O (0.1 mL) was added to the reaction mixture. The reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/0 with 2% CH_2Cl_2) afforded the product **35** (20.1 mg, 40%).

*3.10.1. 3-Methoxy-2-[1-(1-piperidinyl)propyl]phenol (**35**).* Colorless oil. IR (KBr) 3141, 2934, 1606, 1592, 1466 cm^{-1}. ^1H NMR (CD_3OD) δ 7.02 (1H, t, J=8.0 Hz), 6.40 (1H, br dd, J=8.0, 1.0 Hz), 6.32 (1H, br dd, J=8.0, 1.0 Hz), 3.92 (1H, dd, J=8.0, 4.0 Hz), 3.74 (3H, s), 2.65–2.45 (4H, br m), 1.89–1.52 (8H, m), 0.74 (3H, t, J=7.5 Hz). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR (CD_3OD) δ 160.0, 159.7, 129.4, 114.5, 110.5, 102.4, 64.6, 55.8, 52.8, 27.1, 25.2, 24.9, 9.8. MS (EI^+) m/z 83 (100), 249 (M^+, 0.1). HRMS (EI^+) calcd for $C_{15}H_{23}NO_2$ (M^+) 249.1729, found 249.1738.

3.11. Improved experimental procedure for the trapping reaction (Scheme 10)

To a suspension of CsF (152 mg, 1.0 mmol) in freshly distilled DMF, 1-formylpiperidine **4**, or *N*-allyl-*N*-methylformamide **37** (2.0 mL) was added Et_2Zn (1.05 M in hexane, 0.95 mL, 1.0 mmol) under argon atmosphere at room temperature. After being stirred at the same temperature for 1 min, aryne precursor **1** or **18** (0.20 mmol) was added to the reaction mixture at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was diluted with water and then extracted with CH_2Cl_2. The organic phase was washed with saturated NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/10 to 1/0 with 2% CH_2Cl_2) afforded the products **28**, **35**, **36**, or **38**.

*3.11.1. 3-[1-(Dimethylamino)propyl]-2-naphthalenol (**36**).* Yellow solid. Mp 85–86 °C (CH_2Cl_2/hexane). Sublimation (ca. 80 °C). IR (KBr) 3138, 3052, 2965, 1633, 1462 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.67 (2H,

br d, J=8.5 Hz), 7.39–7.34 (2H, m), 7.26 (1H, m), 7.16 (1H, br s), 3.28 (1H, dd, J=10.0, 4.0 Hz), 2.38 (6H, s), 2.05–1.95 (1H, m), 1.87–1.76 (1H, m), 0.77 (3H, t, J=7.5 Hz). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR ($CDCl_3$) δ 155.4, 134.2, 128.2, 128.0, 127.6, 127.3, 126.0, 125.8, 122.9, 110.5, 73.2, 43.2, 24.3, 11.2. MS (EI^+) m/z 200 (100), 229 (M^+, 21). HRMS (EI^+) calcd for $C_{15}H_{19}NO$ (M^+) 229.1467, found 229.1454.

*3.11.2. 2-[1-(Allylmethylamino)propyl]-3-methoxyphenol (**38**).* Colorless oil. IR (KBr) 3308, 3078, 2971, 1594, 1467 cm^{-1}. ^{1}H NMR (CD_3OD) δ 7.07 (1H, t, J=8.0 Hz), 6.45 (1H, br dd, J=8.0, 1.0 Hz), 6.36 (1H, dd, J=8.0, 1.0 Hz), 5.91–5.81 (1H, m), 5.19–5.14 (2H, m), 3.95 (1H, dd, J=8.5, 4.0 Hz), 3.76 (3H, s), 3.29–2.95 (2H, br m), 2.31 (3H, br s), 1.93–1.72 (2H, m), 0.76 (3H, t, J=7.5 Hz). The exchangeable proton peak of OH group was not clearly detected. ^{13}C NMR (CD_3OD) δ 158.8, 158.1, 134.0, 128.2, 118.7, 113.6, 109.7, 101.2, 62.4, 57.8, 55.3, 38.5, 24.6, 9.7. HRMS (ESI) calcd for $C_{14}H_{22}NO_2$ ($M+H^+$) 236.1651, found 236.1647.

3.12. General procedure for the trapping reaction giving *o*-hydroxyalkylphenols 32–34 and 39 (Scheme 11)

To a suspension of CsF (152 mg, 1.0 mmol) in undistilled DMF (2.0 mL) was added aryne precursor **1** or **15** (0.20 mmol) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, Et_2Zn (1.05 M in hexane, 1.9 mL, 2.0 mmol) or Me_2Zn (1.0 M in hexane, 2.0 mL, 2.0 mmol) was added to the reaction mixture at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt/hexane=1/20 to 1/0 with 2% CH_2Cl_2) afforded the products **32**–**34** and **39**.

*3.12.1. α-Ethyl-2-hydroxy-6-methoxybenzenemethanol (**32**).* Colorless oil. IR (KBr) 3292, 2933, 1593, 1469 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.59 (1H, br s), 7.09 (1H, t, J=8.0 Hz), 6.51 (1H, d, J=8.0 Hz), 6.39 (1H, d, J=8.0 Hz), 5.32 (1H, t, J=6.5 Hz), 3.77 (3H, s), 2.49 (1H, br s), 1.92–1.75 (2H, m), 0.99 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 157.1, 156.6, 128.7, 115.4, 110.2, 101.9, 71.8, 55.5, 29.3, 10.0. MS (EI^+) m/z 153 (100), 182 (M^+, 54). HRMS (EI^+) calcd for $C_{10}H_{14}O_3$ (M^+) 182.0943, found 182.0962.

*3.12.2. 2-Hydroxy-6-methoxy-α-methylbenzenemethanol (**33**).* Colorless oil. IR (KBr) 3288, 2965, 1594, 1469 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.65 (1H, br s), 7.08 (1H, t, J=8.0 Hz), 6.50 (1H, d, J=8.0 Hz), 6.38 (1H, br d, J=8.0 Hz), 5.55 (1H, q, J=6.5 Hz), 3.78 (3H, s), 2.55 (1H, br s), 1.52 (3H, t, J=6.5 Hz). ^{13}C NMR ($CDCl_3$) δ 156.8, 156.2, 128.6, 116.4, 110.3, 101.9, 66.9, 55.5, 22.6. MS (EI^+) m/z 83 (100), 168 (M^+, 0.9). HRMS (EI^+) calcd for $C_9H_{12}O_3$ (M^+) 168.0786, found 168.0785.

*3.12.3. α-Ethyl-2-hydroxybenzenemethanol (**34**)[39].* Colorless oil. IR (KBr) 3312, 2927, 1587, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.94 (1H, br s), 7.16 (1H, br dt, J=8.0, 2.0 Hz), 6.94 (1H, br dd, J=7.5, 2.0 Hz), 6.87 (1H, br d, J=8.0 Hz), 6.82 (1H, br dt, J=7.5, 1.5 Hz), 4.76 (1H, t, J=7.0 Hz), 2.56 (1H, br s), 1.99–1.80 (2H, m), 0.97 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 155.6, 128.9, 127.3, 127.0, 119.6, 117.2, 77.8, 30.2, 10.2. MS (EI^+) m/z 83 (100), 152 (M^+, 8.4). HRMS (EI^+) calcd for $C_9H_{12}O_2$ (M^+) 152.0837, found 152.0830.

*3.12.4. α-Deuterium-α-ethyl-2-hydroxy-6-methoxybenzenemethanol (**39**).* Colorless oil. IR (KBr) 3260, 2926, 1593, 1468 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 8.56 (1H, br s), 7.09 (1H, t, J=8.0 Hz), 6.50 (1H, dd, J=8.0, 1.0 Hz), 6.39 (1H, dd, J=8.0, 1.0 Hz), 3.77 (3H, s), 2.45 (1H, br s), 1.92–1.74 (2H, m), 0.99 (3H, t, J=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 157.1, 156.6, 128.7, 115.4, 110.2, 101.9, 71.4 (t, J=91 Hz), 55.5, 29.3, 10.0. MS (EI^+) m/z 84 (100), 183 (M^+, 0.6). HRMS (EI^+) calcd for $C_{10}H_{13}DO_3$ (M^+) 183.1005, found 183.1017.

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