

Copper(II)-catalyzed O-Phenylation of Alcohols with Organobismuth(V) Reagents: A Convenient Method for the Synthesis of Simple *tert*-Alkyl Phenyl Ethers

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A convenient method for copper(II)-catalyzed O-phenylation of simple alcohols with organobismuth(V) compounds under mild conditions is described. Treatment of tetraphenylbismuth fluoride (Ph₄BiF) with various simple alcohols in the presence of a catalytic amount of Cu^{II} acetate affords the corresponding phenyl ethers in good yields and the present reaction is successfully applied to the preparation of various *tert*-alkyl phenyl ethers.

To date, a C(aryl)–O bond formation was generally carried out by using transition metal-catalyzed (Cu or Pd) coupling reactions between aryl halides and alcohols developed by Buchwald¹ and Hartwig.² The copper-catalyzed reaction (classical Ullmann type) needed harsh reaction conditions and no reaction was demonstrated concerning tertiary alcohols under above-mentioned conditions.³ The Pd-catalyzed reaction was applied to tertiary alcohols, however, it needed to use a strongly basic nucleophile such as alkoxide.⁴ Recently, Batey reported that an alternative C(aryl)–O bond formation by using cross-coupling reaction of potassium organotrifluoroborate salts and alcohols proceeded under mild conditions which is a modified protocol of Chan–Evans's method, whereas etherification of tertiary alcohols did not proceed at all.⁵

Arylations of simple alcohols by using organobismuth reagents were studied intensively by Barton, Finet, and Dodonov.⁶ However, fewer examples were reported in the case of tertiary alcohols and the yields were moderate. Recently, it was reported from our laboratory that Cu^{II}-catalyzed O-phenylation of functionalized tertiary alcohols proceed smoothly by using triphenyl or tetraphenyl bismuth(V) complexes (Ph₃Bi(OAc)₂,⁷ [Ph₄Bi⁺][BF₄[−]],⁸ or Ph₄BiF⁹) as phenyl donor.¹⁰ In the above examples, the participation of a neighboring functional group such as carbonyl group was needed to complete the full conversion to afford the corresponding ethers.^{6a,11} Thus, effective C(aryl)–O bond formation of simple tertiary alcohols such as *t*-butanol under mild conditions has not yet been developed. Now, we would like to describe a convenient and successful method for the phenylation of simple alcohols with Ph₄BiF in the presence of Cu(OAc)₂. Further, we discussed remarkable reactivity differences of organobismuth(V) reagents and effects of copper salts.

In the first place, the effects of Bi reagents were examined by taking 2-methyl-4-phenylbutan-2-ol (**1a**) as a simple substrate. The results of the reaction of various Bi^V reagents with **1a** in the coexistence of a catalytic amount of Cu(OAc)₂ and 2 equiv. of a base, *N,N*-dicyclohexylmethylamine (Cy₂NMe), are summarized in Table 1. When triphenylbismuth complex such as Ph₃Bi(OAc)₂ and cationic tetraphenylbismuthonium complexes such as [Ph₄Bi⁺][BF₄[−]], [Ph₄Bi⁺][OTf[−]],¹² or

Table 1. Effect of organobismuth reagents

Entry	Bi reagent	Cu(OAc) ₂ /mol %	Yield/% ^a
1	Ph ₃ Bi(OAc) ₂	15	ND ^b
2	[Ph ₄ Bi ⁺][BF ₄ [−]]	15	ND
3	[Ph ₄ Bi ⁺][OTf [−]]	15	ND
4	[Ph ₄ Bi ⁺][OTs [−]]	15	ND
5	Ph ₄ BiOCOCF ₃	15	6
6	Ph ₄ BiF	15	54
7	Ph ₄ BiF	5	3

^aIsolated yields. ^bNot Detected.

[Ph₄Bi⁺][OTs[−]]¹³ were employed, the expected phenyl ether was not formed (Entries 1–4). Instead, the desired phenyl ether was obtained in 6 and 54% yields, respectively, when the reaction was carried out in the presence of Ph₄BiOCOCF₃¹³ or Ph₄BiF (Entries 5 and 6) though the reaction was sluggish by using 5 mol % of Cu(OAc)₂ (Entry 7). It was assumed that reactivity of organobismuth(V) reagents correlate with the cationic character of Bi atom (Bi–F bond of Ph₄BiF was 2.218 Å and Bi⁺–O[−] bond of [Ph₄Bi⁺][OTs[−]] was 2.77 Å).^{9,13}


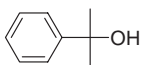
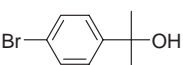


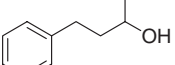
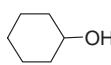
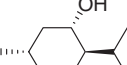
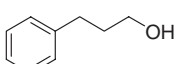
In the next place, the effects of copper salts and of solvents were examined. O-Phenylation of **1a** was examined by the combined use of Ph₄BiF (1.6 equiv.), copper salts (15 mol %) and Cy₂NMe (2 equiv.) in various solvents at room temperature, and the results are summarized in Table 2. It was shown that

Table 2. Effect of solvents and copper salts

Entry	Copper salt	Solvent	Yield/% ^a
1	Cu(OAc) ₂	MEK	59
2	Cu(OAc) ₂	THF	49
3	Cu(OAc) ₂	CH ₃ CN	43
4	Cu(OAc) ₂	DMF	22
5	Cu(OAc) ₂	toluene	84
6 ^b	Cu(OAc) ₂	toluene	quant.
7	CuOAc	toluene	trace
8	Cu(OCOCF ₃) ₂ ·xH ₂ O	toluene	63
9	Cu(OTf) ₂	toluene	ND ^c
10	CuF ₂	toluene	ND

^aIsolated yields. ^b2 equiv. of Ph₄BiF and 20 mol % of Cu(OAc)₂ were used. ^cNot Detected.

Table 3. Phenylation of various alcohols

$\text{R-OH} \xrightarrow[\text{Toluene, rt, 1 h}]{\text{Ph}_4\text{BiF, cat. Cu(OAc)}_2, 2 \text{ equiv. Cy}_2\text{NMe}} \text{R-OPh}$				
Entry	Alcohol	Product	Yield/% ^c	
1 ^a	1b 	2b	87	
2 ^a	1c 	2c	86	
3 ^a	1d 	2d	86	
4 ^a	1e 	2e	87	
5 ^a	1f 	2f	quant.	
6 ^b	1g 	2g	93	
7 ^b	1h 	2h	97	
8 ^b	1i 	2i	91	
9 ^b	1j 	2j	94	

^a2 equiv. of Ph₄BiF and 20 mol % of Cu(OAc)₂ were used. ^b1.5 equiv. of Ph₄BiF and 15 mol % of Cu(OAc)₂ were used. ^cIsolated yield.

the use of non-polar solvent such as toluene gave the best result and **2a** was afforded in 84% yield while it was poor in the case of polar solvents such as MEK, THF, CH₃CN, and DMF (Entries 1–5). When the amounts of Ph₄BiF were increased to 2 equiv. and 20 mol % of Cu(OAc)₂ were used, **2a** was afforded in a quantitative yield (Entry 6). Next, effects of copper salts were examined in toluene and Cu(OCOCF₃)₂·xH₂O was found to give **2a** in 63% yield whereas CuOAc, Cu(OTf)₂, and CuF₂ were not effective (Entries 7–10). Eventually, the condition to use of 2 equiv. of Ph₄BiF, 20 mol % of Cu(OAc)₂, and 2 equiv. of Cy₂NMe in toluene was turned out to be the best for this reaction. It was interestingly noted that reaction proceeded smoothly when Cu^{II}(OAc)₂ was used, but reaction hardly proceeded when Cu^IOAc was used.

The reactions of several substrates (**1b–1j**) under these optimized conditions are shown in Table 3. Reactions of tertiary alcohols such as *t*-BuOH (**1b**) 2-phenylpropan-2-ol (**1c**), 2-(4-bromophenyl)propan-2-ol (**1d**), 1-methylcyclohexanol (**1e**), and adamantan-1-ol (**1f**) gave the corresponding phenyl ethers (**2b–2f**) in more than 85% yields. It is noted that reaction of **1d** having *p*-bromophenyl moiety which was not used for Pd⁰

or Cu catalyzed O-arylation gave **2d** in 86% yield. Additionally, secondary alcohols such as 4-phenylbutan-2-ol (**1g**), cyclohexanol (**1h**), (–)-menthol (**1i**), and primary alcohol such as 4-phenylbutan-1-ol (**1j**) were phenylated efficiently to give the corresponding phenyl ethers in excellent yields without accompanying ketones or aldehydes formed by oxidation of alcohols with Bi^V species.^{6b}

It is noted that the convenient method for the O-phenylation of simple aliphatic alcohols by using a combination of Ph₄BiF and Cu(OAc)₂ under mild conditions was established. This method is applied to the phenylation of alcohols having functional groups unstable to strong bases or at elevated temperature because this reaction proceeds smoothly at room temperature under almost neutral conditions. However, this reaction has some limitations; that is, the preparation of Ph₄BiF needed several steps from Ph₃Bi, and 2 equiv. of Ph₄BiF and 20 mol % of Cu(OAc)₂ were needed for complete conversion. Besides, only one phenyl group of four phenyl groups is used for the phenylation. Further modification of effective C(Aryl)–O bond formation of substituted aryl groups and heterocycles is currently under way in our laboratory.

This study was supported in part by the Grant of the 21st Century COE Program from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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