Copper(II)-catalyzed O-Phenylation of Tertiary Alcohols with Organobismuth(V) Reagents

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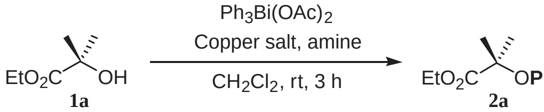
A new method for the $Cu(OAc)_2$-catalyzed phenylation of tertiary alcohols under mild basic conditions is described. Triphenylbismuth(V) diacetate and tetraphenylbismuth reagents undergo cross-coupling reactions with α-hydroxycarbonyl compouds efficiently. For non-chelating tertiary alcohols, tetraphenylbismuth fluoride is found suitable as a phenyl donor.

The copper-mediated formation of C(aryl)–O bonds (Ullmann ether synthesis[1,2]) is an important and frequently employed transformation in organic synthesis. O-Arylation of aliphatic alcohols has been performed by using aryl halides and aryl metalloid reagents such as organo-boron and -bismuth compounds as aryl donors.[2] Recently, Buchwald demonstrated that copper(I) iodide promoted the cross coupling of aryl halides with aliphatic alcohols at elevated temperatures.[3] Batey reported coupling reactions of aliphatic alcohols with aryltrifluoroborate salts in the presence of catalytic amounts of $Cu(OAc)_2$ and 4-(dimethylamino)pyridine (DMAP) at room temperature,[4] which is a modified protocol of Chan–Evans's method for the arylation of phenols using aryl boronic acids.[5] Although these Cu-catalyzed O-arylation reactions proceed effectively with primary and secondary alcohols, the synthesis of *tert*-alkyl aryl ethers from sterically-hindered tertiary alcohols is still difficult.[6] Pd-catalyzed reactions enable the cross coupling of tertiary alcohols with aryl chlorides or bromides,[7] but these etherification reactions need strongly basic alkoxides and proceed at elevated temperatures.

Triarylbismuth reagents such as $Ar_3Bi(OAc)_2$ are also known to transfer their aryl groups to aliphatic alcohols particularly in the presence of a catalytic or stoichiometric amount of copper salts.[2a–2c,8] Moreover, the reactions using these Bi reagents were applied to the selective O-arylation of hydroxyl groups of complex, biologically-active natural products.[9] However, the arylation of tertiary alcohols has not yet been examined thoroughly despite the above successful results. Dodonov reported the Cu-catalyzed reaction of $Ph_3Bi(OAc)_2$ in *t*-butanol used as solvent gave *t*-butyl phenyl ether in a poor yield (based on the Bi reagent).[10] As a part of our study on the organobismuth chemistry,[11] we now report the $Cu(OAc)_2$-catalyzed O-phenylation of tertiary alcohols with tri- or tetraphenylbismuth reagents in the presence of a tertiary amine. The reactions can be carried out under air without exclusion of moisture.

At first, ethyl 2-hydroxy-2-methylpropionate (**1a**) was chosen as a model on considering the chelating effect of the substrate,[12] and then the O-phenylation of **1a** using several copper salts (10 mol %), triethylamine (2.0 equiv.), and $Ph_3Bi(OAc)_2$ (1.1 equiv.) in dichloromethane at room temperature was examined (Table 1, Entries 1–6). The use of $Cu(OAc)_2$ was the best to promote the reaction, providing the desired product **2a** in 64% yield (Entry 6). On the other hand, the use of metallic copper, CuI, $CuCl_2$, $CuBr_2$, or $Cu(acac)_2$ was less effective. Then, the combinations of $Cu(OAc)_2$ and several tertiary amines were screened. The yield of **2a** was slightly improved when bulky aliphatic amines such as dicyclohexylmethylamine (Cy_2NMe) were employed (Entries 7 and 8) although *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and pyridine derivatives did not afford **2a** at all (Entries 9–12). In the absence of amine, the yield of **2a** decreased down to 46% (Entry 13).

Table 1. Effect of copper salts and tertiary amines[a]



Entry	Copper salt	Amine	Yield/%
1	Cu	Et_3N	2
2	CuI	Et_3N	45
3	$CuCl_2$	Et_3N	44
4	$CuBr_2$	Et_3N	45
5	$Cu(acac)_2$	Et_3N	1
6	$Cu(OAc)_2$	Et_3N	64
7	$Cu(OAc)_2$	*i*-Pr_2NEt	66
8	**$Cu(OAc)_2$**	**Cy_2NMe**	**68**
9	$Cu(OAc)_2$	TMEDA	0
10	$Cu(OAc)_2$	Pyridine	0
11	$Cu(OAc)_2$	DMAP	0
12	$Cu(OAc)_2$	1,10-Phenanthroline	0
13	$Cu(OAc)_2$	None	46

[a]The reactions were carried out by using **1a** (1.0 equiv.), $Ph_3Bi(OAc)_2$ (1.1 equiv.), Cu salt (10 mol %), and amine (2.0 equiv.).

Table 2. Effect of organobismuth reagents[a]

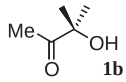
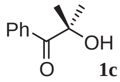
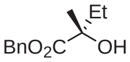
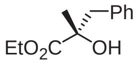
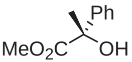
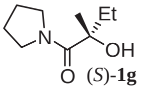
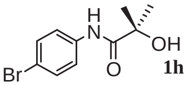
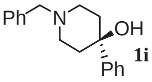
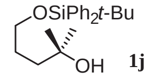
Entry	Bi reagent (equiv.)	Yield/%
1	$Ph_3Bi(OAc)_2$ (1.1)	69
2	**$Ph_3Bi(OAc)_2$ (1.6)**	**89**
3[b]	$Ph_3Bi(OAc)_2$ (1.6)	79
4	**$[Ph_4Bi^+][BF_4^-]$ (1.6)**	**95**
5	**Ph_4BiF (1.6)**	**93**
6	Ph_3Bi (1.6)	0
7	Ph_3BiCl_2 (1.6)	0
8	Ph_3BiCO_3 (1.6)	0

[a]The reactions were carried out by using **1a** (1.0 equiv.), Bi reagent, $Cu(OAc)_2$ (5 mol %), and Cy_2NMe (2.0 equiv.) in CH_2Cl_2 at rt for 3 h. [b]1 mol % of $Cu(OAc)_2$ was used.

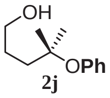
Next, the O-phenylation of **1a** was studied further by using various tri-, or tetraphenylbismuth(V) reagents in the coexis-

Table 3. Phenylation of various tertiary alochols[a]

$$\underset{\mathbf{1}}{\mathrm{ROH}} \xrightarrow[\mathrm{CH_2Cl_2,\ rt,\ 3\ h}]{\mathrm{Bi\ reagent} \atop \mathrm{Cu(OAc)_2,\ Cy_2NMe}} \underset{\mathbf{2}}{\mathrm{ROPh}}$$

Entry	Alcohol	Bi reagent	Yield/ %	Product
1	 **1b**	$Ph_3Bi(OAc)_2$	46	**2b**
2		$[Ph_4Bi^+][BF_4^-]$	85	
3		Ph_4BiF	87	
4	 **1c**	$Ph_3Bi(OAc)_2$	92	**2c**
5		$[Ph_4Bi^+][BF_4^-]$	90	
6		Ph_4BiF	82	
7	 (*S*)-**1d**	$Ph_3Bi(OAc)_2$	88	(*S*)-**2d**
8		$[Ph_4Bi^+][BF_4^-]$	85	
9		Ph_4BiF	85	
10	 (*S*)-**1e**	$Ph_3Bi(OAc)_2$	82	(*S*)-**2e**
11		$[Ph_4Bi^+][BF_4^-]$	89	
12		Ph_4BiF	84	
13	 (*S*)-**1f**	$Ph_3Bi(OAc)_2$	86	(*S*)-**2f**
14		$[Ph_4Bi^+][BF_4^-]$	71	
15		Ph_4BiF	86	
16	 (*S*)-**1g**	$Ph_3Bi(OAc)_2$	80	(*S*)-**2g**
17		$[Ph_4Bi^+][BF_4^-]$	94	
18		Ph_4BiF	85	
19	 **1h**	$Ph_3Bi(OAc)_2$	64	**2h**
20		$[Ph_4Bi^+][BF_4^-]$	73	
21		Ph_4BiF	89	
22	 **1i**	$Ph_3Bi(OAc)_2$	< 22	**2i**
23		$[Ph_4Bi^+][BF_4^-]$	ND[b]	
24		Ph_4BiF	88	
25[c]	 **1j**	$Ph_3Bi(OAc)_2$	3	**2j**
26[c]		$[Ph_4Bi^+][BF_4^-]$	ND[b]	
27[c]		Ph_4BiF	50	

[a]The reactions were carried out by using alcohol (1.0 equiv.), Bi reagent (1.6 equiv.), $Cu(OAc)_2$ (5 mol %), and Cy_2NMe (2.0 equiv.). [b]Not detected. [c]**2j** was obtained after treating the crude product with Bu_4NF.



2j

tence of $Cu(OAc)_2$ (5 mol %) and Cy_2NMe (2.0 equiv.) (Table 2). In the case where 1.6 equiv. of $Ph_3Bi(OAc)_2$ was used under the above conditions, the product **2a** was obtained in 89% yield (Entry 2). Interestingly, tetraphenylbismuth reagents ($Ph_4Bi^+BF_4^-$, Ph_4BiF)[13] were found effective as phenyl donors, which also produced **2a** in high yields (Entries 4 and 5).

With optimal conditions in hand, the scope and limitations of this method were examined (Table 3). As expected, α-hydroxy-ketone, -carboxylic esters and -carboxamides were efficiently phenylated by the use of $Ph_3Bi(OAc)_2$, $Ph_4Bi^+BF_4^-$, and Ph_4BiF at room temperature, and the desired O-phenylated products **2b**–**2h** were obtained in high yields (Entries 1–21). On the other hand, the O-phenylation of the tertiary alcohols **1i** and **1j** was more sluggish probably because they are non-chelating substrates. The desired products **2i** and **2j** were obtained in poor yields when $Ph_3Bi(OAc)_2$ was used because a substantial amount of phenyl acetate was formed by the decomposition of the Bi reagent[12a] (Entries 22 and 25). Also, the use of $Ph_4Bi^+BF_4^-$ did not give the desired products at all (Entires 23 and 26). The results were much better in the reaction with Ph_4BiF, and the O-phenylated products **2i** and **2j**[14,15] were obtained in 88 and 50% yields, respectively (Entries 24 and 27).[16]

Thus, a new protocol for the synthesis of tertiary alkyl–phenyl ethers via the Cu(II)-catalyzed coupling of polyphenylbismuth(V) reagents with tertiary alcohols at room temperature was developed. Both chelating and non-chelating substrates participated in the reactions by using Ph_4BiF as a phenyl donor, and various functionalities including ketone, carboxylic ester, amide, tertiary amine, *t*-butyldiphenylsilyloxy group, and aryl bromide were well-tolerated. It is noted that the present reaction apparently extends the scope of the Ullmann-arylation chemistry. Further investigation on the phenylation of primary and secondary alcohols by this method is currently under way in our laboratory.

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

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16 For experimental procedures and characterization data for the phenylated products **2**, see Supporting Information.