Copper(II)-Catalyzed O-Arylation of Tertiary Alcohols with Arylbismuth(III) Reagents: A Convenient System for Aryl Transfer

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Abstract: Copper(II)-catalyzed O-arylation of tertiary alcohols with various triarylbismuth reagents was investigated. A convenient and efficient system for aryl ether formation of tertiary alcohols has been developed through the in situ oxidation of stable triarylbismuth(III) to triarylbismuth(V) species using PhI(OAc)₂ as the oxidant in the presence of a catalytic amount of copper(II) acetate.

Key words: O-phenylation, O-arylation, arylbismuth, ether, iodobenzene diacetate, tertiary alcohol

Aryl ethers are ubiquitous structural constituents in pharmacologically important molecules.^{1,2} Arylbismuth(V) reagents are known to transfer aryl groups to phenols and alcohols in the presence of copper catalyst.^{2–7} Copper-catalyzed O-phenylation of tertiary alcohols, 2-hydroxy-2methylpropionate (**2a**) and 2-hydroxy-2-methylbutanoate (**2b**), with triphenylbismuth(V) reagents at room temperature has been extensively examined by Mukaiyama et al.^{6a} We needed an efficient procedure for the transfer of aryl groups containing electron-donating substituents to **2** under mild conditions in our synthetic studies of complex aryl ether natural products.^{1c} We herein describe such a convenient system using a mixture of stable triarylbismuth(III), Cu(OAc)₂, Cy₂NMe, and PhI(OAc)₂ at room temperature.

Copper-catalyzed arylation of a simple primary 1,3-diol with tris(polymethoxyphenyl)bismuth(V) diacetates was reported by Finet and Fedorov.^{5a} However, no examples of the corresponding transfer reactions of aryl groups containing electron-donating substituents to **2** have been described. We first examined the O-arylation of **2** with various triarylbismuth(V) diacetates **1**⁸ using Mukaiyama protocol^{6a} (Table 1).^{9–11} The O-phenylation reactions of **2** were carried out under Mukaiyama's optimum conditions using 1.6 mol equivalents of triphenylbismuth(V) diacetates **(1a)** to give the products **3a** and **4a** in good yields (Table 1, entries 1 and 10) as reported.^{6a}

Since substitution of electron-donating groups hindered the reaction and lowered the yield of the desired product, three mol equivalents of triarylbismuth(V) diacetates 1b-i were used to provide the corresponding products 3b-d, f-h and 4f, h in high yields. An oxygen atmosphere (1)

SYNLETT 2012, 23, 405–408 Advanced online publication: 25.01.2012 DOI: 10.1055/s-0031-1290205; Art ID: U67411ST © Georg Thieme Verlag Stuttgart · New York atm)^{4d,e} was preferred to attain higher yields. Addition of molecular sieves 4 Å (MS4A) was necessary to prevent hydrolytic decomposition of **1**. Without molecular sieves, compound 1 decomposed presumably to phenol due to the presence of water in the solution, which was then arylated by 1 to afford biaryl ether 5 as a byproduct. Substitution of the methyl group at the *ortho* position (1b and 1h) slightly hindered the reaction (Table 1, entries 2, 8, and 12),^{5b} whereas the *o*-methoxymethyloxy (MOM) substituent (1e and 1i) practically inhibited the reaction (Table 1, entries 5 and 9). This lowered transfer reactivity of 1e and 1i may be explained by their chelation effect on the bismuth atom rather than steric hindrance.^{5b} Since O-arylation is slow, bismuth(V) species 1 decomposed, resulting in a considerable amount of aryl acetate 6 and triarylbismuth(III) 7^{5b} as the isolable degradation products (Figure 1). The bismuth(III) species 7 was likely due to the disproportionation^{4d} of diarylbismuth(III) acetate, which was formed as the O-arylation product from 1.

The formation of **7** under Mukaiyama's conditions suggested that O-arylation using a smaller amount of triarylbismuth(III) **7** could be possible through the in situ oxidation^{2b,7} of **7** by PhI(OAc)₂ as the oxidant.¹² In fact, as shown in Table 2, the copper(II)-catalyzed O-phenylation of **2** using 0.7 mol equivalents of Ph₃Bi (**7a**) proceeded satisfactorily in the presence of 1.2 mol equivalents of PhI(OAc)₂, although the reaction was somewhat hindered.

Then, the copper(II)-catalyzed transfer of aryl groups containing electron-donating substituents from triarylbismuth(III) 7b-i to 2 was examined in the presence of PhI(OAc)₂ (Table 3).¹³ The reactions of triarylbismuth(III) with electron-rich aromatic rings 7c,d,f,g (Table 3, entries 2, 3, 5, 6, and 9) worked in high yields, but became rather slow. Therefore, 1.5 mol equivalents of 7, which was half the amount of bismuth reagents required for the previous method as shown in Table 1, as well as 1.9-2.4 mol equivalents of PhI(OAc)₂, were required to obtain the products 3 and 4 in high yields. Under these conditions, substitution of the methyl group at the ortho position (7b and 7h) affected the reaction (Table 3, entries 1 and 7) to some extent, and the *o*-methoxymethyloxy (OMOM) substituent (7e and 7i) inhibited the reaction (Table 3, entries 4 and 8).

In conclusion, convenient and efficient copper(II)-catalyzed O-phenylation and O-arylation of tertiary alcohols **2** at ambient temperature have been developed through the

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$\begin{bmatrix} R^{2} \\ R^{3} \\ R \end{bmatrix}$	Bi(OAc) ₂ +	$HO = OBn - 2a; R^5 = Me$	$\begin{array}{c} Cu(OAc)_2 \ (5 \ mol\%) \\ Cy_2NMe \ (2 \ equiv) \end{array}$ $\begin{array}{c} CH_2Cl_2, \ MS4A \\ O_2 \ (1 \ atm), \ r.t. \end{array}$	R^{2} R^{3} R^{4} R^{4} R^{4} $R^{5} =$	OBn O Me			
Entry	R ¹	$2b: R^3 = Et$ R^2	R ³	4a , f, h: R ⁴	Ar ₃ Bi(C	OAc) ₂ Alcohol	Time	Product, yield (%) ^a
1 ^b	Н	Н	Н	Н	1 a	2a	2.5 h	3a 74
2	Me	Н	Н	Н	1b	2a	3 d	3b 74
3	Н	Me	Н	Н	1c	2a	13 h	3c 98
4	Н	Н	Me	Н	1d	2a	12 h	3d 99
5	OMOM	Н	Н	Н	1e	2a	1 d	3e <10
6	Н	OMOM	Н	Н	1f	2a	1 d	3f 78
7	Н	Н	OMOM	Н	1g	2a	1 d	3g 90
8	Me	Н	Н	OMOM	1h	2a	3 d	3h 77
9	OMOM	Н	Н	CH ₂ OEt	1i	2a	1 d	3i <5
10	Н	Н	Н	Н	1 a	2b	4 h	4a 76
11	Н	OMOM	Н	Н	1f	2b	2 d	4f 90
12	Me	Н	Н	OMOM	1h	2b	3 d	4h 74

 Table 1
 Copper(II)-Catalyzed O-Arylation of 2 Using Various Triarylbismuth(V) Diacetates 1

^a Isolated yield.

^b Conditions: 1.6 mol equiv of Ph₃Bi(OAc)₂.

in situ oxidation of stable triarylbismuth(III) 7 to bismuth(V) species 1 using $PhI(OAc)_2$ as the oxidant in the presence of Cy₂NMe. This procedure requires only 0.7-1.5 mol equivalents of the aryl transfer reagents 7 without the preparation of often unstable bismuth(V) reagents 1 containing electron-donating substituents, prior to the Oarylation reaction. Further studies on the application of

 Table 2
 Copper(II)-Catalyzed O-Phenylation of 2a Using Triphe nylbismuth(III) (7a) in the Presence of PhI(OAc)₂

Ph₂Bi + ⊔O	OBn _	PhI(OAc) ₂ Cu(OAc) ₂ (5 mol%) Cy ₂ NMe (2.0 equiv)	PhO		
7a	С 2а	H ₂ Cl ₂ , MS4A, O ₂ (1 atm) 3 d	3a		
Entry	Ph ₃ Bi (7a) (mol equiv)	PhI(OAc) ₂ (mol equiv)	Product 3a , yield (%) ^a		
1	1.6	1.9	77		
2	1.0	1.2	92		
3	0.7	1.2	87		
4	0.5	1.2	33		

^a Isolated yield.

the present method to the total synthesis are currently under way and will be reported in due course.

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Table 3Copper(II)-Catalyzed O-Arylation of 2 Using Various Triarylbismuth(III) Reagents 7 in the Presence of PhI(OAc)2

R ¹ R ² R ³ R ⁴ (1.5 equiv)	$Bi + HO = 0$ $2a: R^5 = M$ $2b: R^5 = E$	Cu(O Cy ₂ N OBn <u>PhI(OAc</u> CH ₂ Cl ₂ , M fle	Ac) ₂ (5 mol%) IMe (2 equiv)) ₂ (1.9–2.4 equiv) S4A, O ₂ (1 atm), r.t.	$ \begin{array}{c} $	= MeEt			
Entry	R ¹	R ²	R ³	R ⁴	Ar ₃ Bi	Alcohol	Time (d)	Product, yield (%) ^a
1	Me	Н	Н	Н	7b	2a	5	3b 19
2	Н	Me	Н	Н	7c	2a	2	3c 98
3	Н	Н	Me	Н	7d	2a	1	3d 93
4	OMOM	Н	Н	Н	7e	2a	5	3e 0
5	Н	OMOM	Н	Н	7f	2a	4	3f 83
6	Н	Н	OMOM	Н	7g	2a	2	3g 86
7	Me	Н	Н	OMOM	7h	2a	6	3h 30
8	OMOM	Н	Н	CH ₂ OEt	7i	2a	5	3i 0
9	Н	OMOM	Н	Н	7f	2b	3	4f 74

^a Isolated yield.



Figure 1

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- (9) Triphenylbismuth(V) diacetate(1a) is commercially available from Tokyo Kasei Kogyo, Inc. and used without purification. Triarylbismuth(V) diacetates 1b–i were readily prepared from BiCl₃ as described below.^{5a,8a,11,12}
- (10) Synthesis of Triarylbismuth 7b–i: Method A for the Synthesis of Compounds 7e,i

N,N,N',N'-tetramethylethylenediamine (9.7 mmol) was added dropwise to a solution of the methoxymethoxybenzene (9.1 mmol) in anhyd THF (18 mL) at 0 °C. After stirring for 6 h at this temperature, a THF solution (9 mL) of BiCl₃ (2.9 mmol) was added slowly at -35 °C. The reaction mixture was allowed to warm to r.t., quenched with H₂O (30 mL), extracted with EtOAc (2×20 mL), and the combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using hexane-EtOAc or recrystallization from MeOH to give the corresponding triarylbismuth(III). Method B for the Synthesis of Compounds 7b-d,f-h To an anhyd THF solution (17 mL) of arylmagnesium bromide, prepared from Mg (17 mmol) and aryl bromide (17.5 mmol), was added a THF solution (5 mL) of BiCl₃ (5 mmol) at 0 °C. The reaction mixture was allowed to warm to r.t., quenched with H₂O (30 mL), extracted with EtOAc (2 \times 20 mL), and the combined organic layers were washed with brine and dried over Na₂SO₄. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel using hexane-EtOAc or recrystallization from MeOH to give the corresponding triarylbismuth(III).

To a mixture of n-BuLi (9.7 mmol, 1.6 M in hexane) and

(11) Synthesis of Triarylbismuth Diacetate 1b-i Method A for the Synthesis of Compounds 1c-f,i A mixture of NaBO₃·H₂O (4.2 mmol) and Ar₃Bi(III) (1.4 mmol) in AcOH (14 mL) was stirred at r.t. for 30 min. The resulting mixture was poured into H₂O (50 mL) and was extracted with CH₂Cl₂ (2 × 30 mL). The combined organic layers were washed with H₂O (2 × 30 mL) and dried over MgSO₄. The solvent was distilled off, and the crude product was precipitated from a mixture of CH₂Cl₂ (1 mL)-hexane (30 mL) to give the corresponding triarylbismuth(V) diacetate. Method B for the Synthesis of Compounds 1b,g,h A mixture of $Ar_3Bi(III)$ (1.4 mmol) and $PhI(OAc)_2$ (1.5 mmol) in CH_2Cl_2 (14 mL) was stirred under argon atmosphere for 24 h at r.t. The solvent was distilled off, and the crude product was precipitated from a mixture of CH_2Cl_2 (1 mL)–hexane (30 mL) to give the corresponding triarylbismuth(V) diacetate.

(12) A related one-pot but not in situ copper(II)-catalyzed Narylation of anilines was reported by Combes and Finet.^{5b} Barton et al. found that copper(II)-catalyzed N-phenylation of amines by Ph₃Bi(III) occurs smoothly.^{4d}

(13) Typical Procedure for the O-Arylation of 2 (Table 3, entry 5)

To a suspension mixture of alcohol 2 (0.22 mmol), Cy₂NMe (0.43 mmol), and powdered MS4A (250 mg) in CH₂Cl₂ (1 mL) was added Cu(OAc)₂ (0.01 mmol). After the mixture was stirred for 30 min, Ar₃Bi (0.33 mmol) and PhI(OAc)₂ (0.41 mmol) were added, and the resulting mixture was kept stirring at r.t. under an oxygen atmosphere (1 atm). Upon completion of the reaction (monitored by TLC), 10% aq NH₃ solution (2 mL) was added to the mixture. The precipitates were filtered off, and the filtrate was extracted with CH₂Cl₂ (2 × 10 mL). The combined extracts were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure to give an oily residue. Purification by column chromatography on silica gel using hexane–EtOAc yielded the corresponding aryl ether 3^{14} or 4.

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(14) Spectral Data for the Representative Products 3c,f Benzyl 2-Methyl-2-(3-methylphenoxy)propionate (3c) Yield: 60 mg (98%). Colorless oil. IR (neat): 2936, 1733, 1488, 1280, 1175, 1137, 959, 695 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 1.60$ (6 H, s, Me), 2.22 (3 H, s, tolyl), 5.21 (2 H, s, Bn), 6.57 (1 H, br d, J = 8.0 Hz, H6'), 6.61 (1 H, br s, H2'), 6.78 (1 H, br d, J = 7.6 Hz, H4'), 7.05 (1 H, dd, J = 8.0, 7.6 Hz, H5'), 7.27–7.33 (5 H, m, Bn). ¹³C NMR (100 MHz, CDCl₃): $\delta = 21.5$, 25.6, 67.1, 79.1, 115.9, 120.0, 123.0, 128.4, 128.5, 128.6, 128.9, 135.6, 139.3, 153.4, 174.3. HRMS (ESI-FT): *m/z* calcd for C₁₈H₂₀O₃Na: 307.1310 [M + Na]*; found: 307.1307.

Benzyl 2-[3-(Methoxymethoxy)phenoxy]-2-methylpropanoate (3f)

Yield: 130 mg (83%). Colorless oil. IR (neat): 2938, 1731, 1600, 1486, 1282, 1138, 1017, 851, 696 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.61 (6 H, s, Me), 3.45 (3 H, s, OMe), 5.09 (2 H, s, OCH₂O), 5.20 (2 H, s, Bn), 6.40 (1 H, ddd, *J* = 8.0, 2.3, 0.9 Hz, H6'), 6.57 (1 H, dd, *J* = 2.3, 2.3 Hz, H2'), 6.66 (1 H, ddd, *J* = 8.3, 2.3, 0.9 Hz, H4'), 7.06 (1 H, dd, *J* = 8.3, 8.0 Hz, H5'), 7.27–7.45 (5 H, m, Bn). ¹³C NMR (100 MHz, CDCl₃): δ = 25.5, 56.1, 67.2, 79.3, 94.6, 107.7, 110.1, 112.2, 128.4, 128.6, 129.6, 135.6, 156.6, 158.3, 174.2. HRMS (ESI-FT): *m/z* calcd for C₁₉H₂₂O₅Na: 353.1365 [M + Na]⁺; found: 353.1361.

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