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Synthetic Methods

Synthesis of Highly Functionalized Diaryl Ethers by Copper-Mediated O-Arylation of Phenols using Trivalent Arylbismuth Reagents

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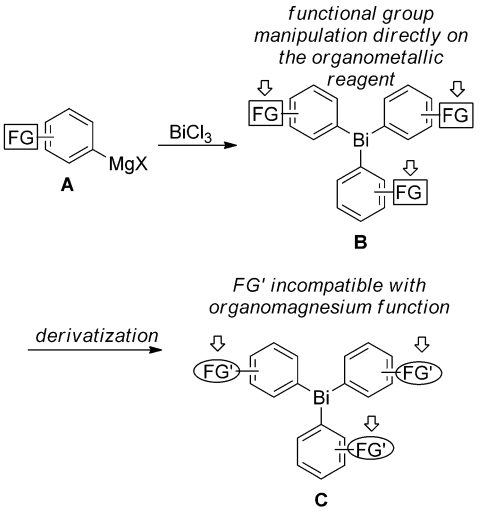
Abstract: Highly functionalized diaryl ethers were prepared by copper(II) acetate mediated O-arylation reaction of phenols using trivalent organobismuthanes. The reaction is performed under simple conditions and tolerates a wide diversity of functional groups on the phenol and on the organobismuth reagent. Substoichiometric amounts of catalyst can be used by performing the reaction under an oxygen atmosphere. The N-arylation of pyridones is also reported.

Diaryl ethers are commonly found in natural products[1] and in medicinally relevant compounds.[2] This motif has also been identified in natural peptides such as vancomycin, complestatin, teicoplanin, and eurypamide.[3] Due to their diversified biological activities, efficient methods that allow the preparation of diaryl ethers is of utmost importance. To be applicable to the context of natural product synthesis, these methods should tolerate a wide range of functional groups. Additionally, to find broad use in medicinal chemistry, these protocols should operate under simple conditions that can be amenable to parallel chemistry and should not require complex or costly ligands or catalysts.[4]

The Ullmann reaction, which consists of the coupling of a phenol with an aryl halide under copper catalysis, was one of the first methods reported to prepare diaryl ethers.[5] However, the necessity of using high temperatures prevented its use in the synthesis of complex molecules. The disclosure by Evans, Chan, and Lam of conditions for the coupling of arylboronic acids with phenols provided a remarkable solution to the problem of diaryl ether synthesis.[6,7] Despite the fact that this reaction is quite general, excess boronic acid is often required to reach good yields. Recently, the introduction of copper complexing ligands by Buchwald allowed catalytic amounts of copper catalyst to be used in the Ullmann reaction.[8] O-Arylation of phenols can also be accomplished using aryliodonium reagents, as reported by Olofsson.[9] However, in this case, a strong base is usually required to promote the reaction.

The O-arylation of phenols using arylmetals remains an attractive strategy to access functionalized diaryl ethers.[10] This approach has been put into practice not only with boronic acids,[6,7] but also with potassium trifluoroborates,[11] organolead[12] and organotin[13] reagents. In the 1980s, Barton reported the use of triphenylbismuth diacetate in the O-arylation of phenols.[14] However, these studies relied on a pre-formed pentavalent organobismuth reagent, did not illustrate the functional group tolerance of the method and involved only the transfer of an unsubstituted phenyl group. Following the publication of this pioneering work, few isolated examples of O-arylation of phenols using trivalent organobismuthanes were reported.[15] To our knowledge, the only comprehensive report of O-arylation reaction using trivalent organobismuthanes involved hydroxy benzyl acetates and required $PhI(OAc)_2$ as a stoichiometric co-oxidant.[16]

Our group has reported a portfolio of methods for the formation of C–C and C–N bonds based on trivalent[17] and pentavalent[18] organobismuthanes. Triarylbismuthanes **B** are particularly attractive organometallic reagents since they show unique reactivity and have low toxicity.[19] These reagents can be easily prepared by the addition of the corresponding Grignard reagent **A** over bismuth chloride (Scheme 1). We demonstrated that functional group manipulation directly on



Scheme 1. Synthesis of highly functionalized organobismuthanes by functional group manipulation. FG = functional group.

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the organobismuth species is possible, giving access to highly functionalized organobismuthanes **C** bearing groups that otherwise cannot be present on the organomagnesium species **A**.[17b]

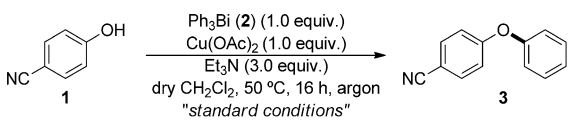
We would like to report herein our results on the copper-catalyzed O-arylation of phenols using highly functionalized organobismuthanes. Since pentavalent organobismuth species are usually prepared from their corresponding trivalent analogues, one of our main goals was to develop conditions that would operate directly with trivalent organobismuthanes. Another objective was to develop a protocol that would allow the use of substoichiometric amounts of catalyst and that would tolerate a wide diversity of functional groups on both coupling partners. With these goals in mind, we began by optimizing the conditions for the O-phenylation of 4-cyanophenol **1** (Table 1). Starting with conditions similar to those that we previously reported for the N-cyclopropylation of azoles,[18] we obtained the desired diaryl ether **3** in 65% yield (entry 1), demonstrating that the reaction can in fact be performed directly with trivalent organobismuthanes. While the addition of molecular sieves did not improve the efficiency of the transformation (entry 2), we found that conducting the reaction in non-anhydrous dichloromethane under ambient air gave a superior yield of product **3** (entry 3), showing that anhydrous and inert conditions are not required to attain good yields. Erosion in the yield of the reaction was observed upon using 0.7 equivalents of triphenylbismuth, indicating that only one phenyl group can be transferred during the process (entry 4). While triethylamine could be replaced by pyridine (entry 5), the use of an inorganic base almost completely shut down the reaction (entry 6). Dichloromethane proved superior to other solvents such as toluene and methanol (entries 7 and 8). Replacing the catalyst with copper bis(trifluoroacetate) or reducing its loading negatively impacted the yield of the reaction (entries 9 and 10). However, the catalyst loading could be reduced to substoichiometric amounts by performing the reaction under oxygen (entries 11 and 12). Reducing the loading further proved detrimental to the reaction.

Using our optimal conditions, we next studied the O-phenylation of diversely substituted phenols and observed that while the reaction is quite tolerant to *para* and *meta* substitution (**5a** and **b**), the introduction of a methyl group at the *ortho* position leads to a modest reduction in the yield of the reaction (**5c**; Scheme 2). This effect was slightly accentuated by flanking the phenol by two methyl groups (**5d**). Good to excellent yields were obtained for the arylation of phenols possessing electron withdrawing (**5e**–**g**) and donating groups (**5h**). A preliminary investigation showed that nitro groups (**5f**), ketones (**5g**), and α,β-unsaturated esters (**5j**) are well tolerated and that the reaction also functions with 3-hydroxypyridines (**5i**). Similar yields were generally obtained using the method involving stoichiometric or substoichiometric amounts of copper acetate (methods A and B, respectively).

Substituted triarylbismuth reagents **6** bearing functional groups were then prepared by adding the corresponding organomagnesium reagent **A** over bismuth chloride as illustrated in Figure 1.

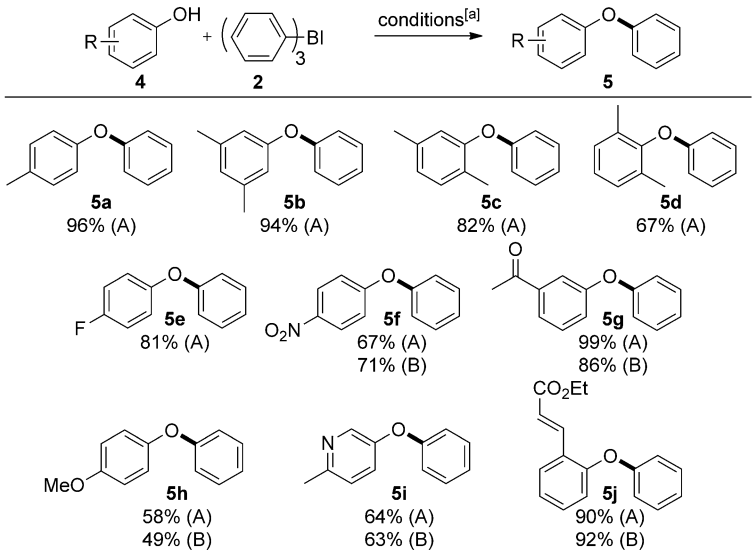
Functionalized organometallic reagents are extremely useful for the transfer of substituted groups on medicinally relevant

Table 1. Optimization of reaction conditions for the O-phenylation of **1**.



	Change from "*standard conditions*"	Yield [%][a]
1	No change	65
2	4 Å molecular sieves added	57
3	**Non-anhydrous CH_2Cl_2, ambient air, 3 h**	**73**
4[b]	0.7 equiv of Ph_3Bi instead of 1.0 equiv	40
5[b]	Pyridine instead of Et_3N	57
6[b]	K_2CO_3 instead of Et_3N	2
7[b]	Toluene instead of CH_2Cl_2	26
8[b]	Methanol instead of CH_2Cl_2	11
9[b]	$Cu(OC(O)CF_3)_2$ instead of $Cu(OAc)_2$	0
10[b]	0.7 equiv of $Cu(OAc)_2$ instead of 1.0 equiv	39
11	0.7 equiv of $Cu(OAc)_2$ under O_2	76
12	**0.3 equiv of $Cu(OAc)_2$ under O_2**	**81**

[a] Isolated yield of pure product **3**. [b] Reaction performed under ambient air for 3 h using non-anhydrous dichloromethane.



Scheme 2. O-Phenylation of substituted phenols. [a] Isolated yields. Method in parentheses. Conditions: Method A: Ph_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Et_3N (3 equiv), CH_2Cl_2, 50 °C, air, 3 h; Method B: Ph_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Et_3N (3 equiv), CH_2Cl_2, 50 °C, O_2, 16 h.

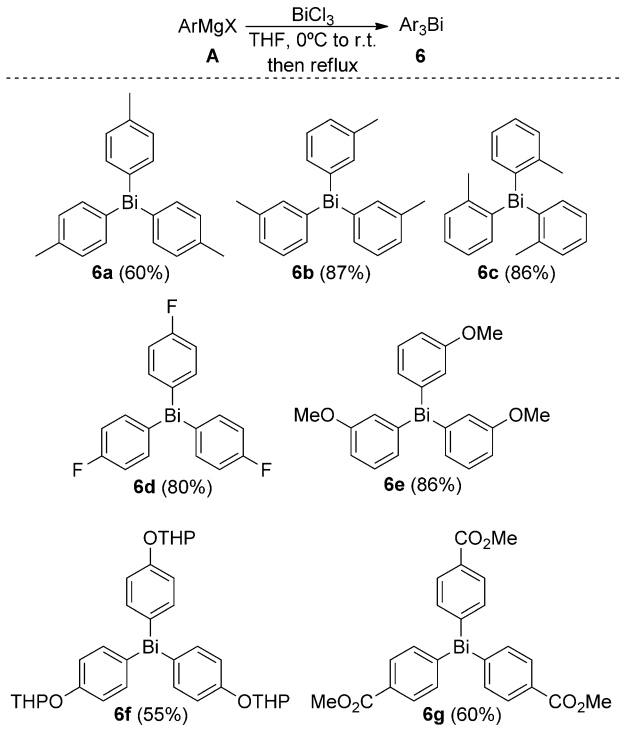
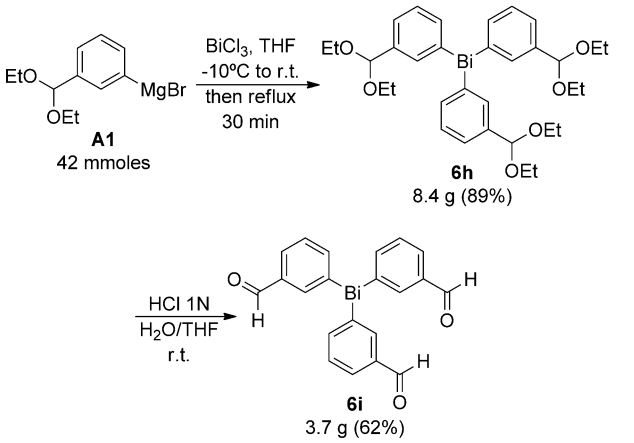


Figure 1. Functionalized organobismuthanes used in the O-arylation reaction of phenols.



Scheme 3. Synthesis of tris(3-formylphenyl)bismuthine **6i**.

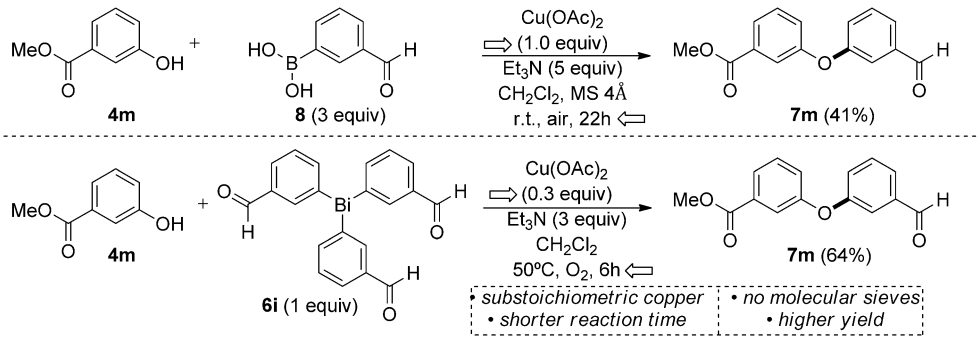
scaffolds.[20] Introduction of functional groups that are not tolerated on the Grignard reagent was accomplished by transforming the functional group directly on the organobismuth reagent. As a representative example, tris(3-formylphenyl)bismuthine **6i** was prepared on a multi-gram scale by hydrolyzing tris(3-(diethoxymethyl)phenyl)bismuthine (**6h**; Scheme 3). The organobismuth reagents **6a–i** are air and moisture stable and can be manipulated in the air without any precaution.

We then turned our attention to the coupling of these functionalized organobismuth reagents with diversely substituted phenols (Table 2). In the event, the *para* and *meta* tolyl reagents **6a** and **b** reacted smoothly to give the corresponding diaryl ethers in good to excellent yields (entries 1–4). A good yield was also obtained when the triarylbismuthane was substituted at the *ortho* position (**6c**), showing that the reaction is only moderately affected by steric factors (entry 5). The transfer of aryl fragments possessing a fluorine, a methoxy group, an acetal or an aldehyde furnished the corresponding diaryl ethers in good to excellent yields (entries 6–12). When considering the synthesis of diaryl ethers, two different disconnections can be envisaged, leading to two complementary combinations of phenol and organobismuthane. For instance, diaryl ether **7l** was conveniently prepared from phenol **4l** (entry 12) and **4b** (entry 13) by reacting them with organobismuthane **6d** and **g,** respectively.

Contrary to O-arylation reactions involving aryl halides, this protocol allows the presence of a bromide on the phenol **4c**. Also, in contrast to reactions involving pentavalent organobismuthanes, alcohols **4d** and ketones **4i** are not arylated under these conditions.[21,22] Most of the diaryl ethers that were generated using this protocol are highly functionalized and can be further derivatized using a wide range of conditions, including palladium and copper(I)-catalyzed reactions.

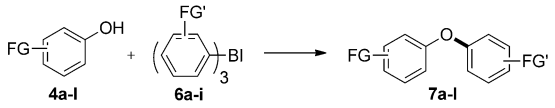
We then compared the ability of boronic acid **8** and bismuthane **6i** to arylate 3-hydroxy methylbenzoate (**4m**; Scheme 4). Using conditions from the literature,[6a] we obtained the diarylether **7m** in 41% yield after 22 h at ambient temperature. The same compound was obtained in 64% yield after 6 h using bismuthane **6i** and 0.3 equivalents of copper acetate. Using our conditions, the coupling of **4m** with **8** provided **7m** in only 14% yield.

Finally, we investigated the arylation of 2(1H)-pyridones using organobismuthanes (Scheme 5). In this particular case, the underlying question was to determine if the arylation would proceed on the oxygen through the hydroxypyridine **9** or on the nitrogen through the pyridone **9′**. Using our optimal conditions, we obtained exclusively the N-arylation product

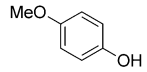
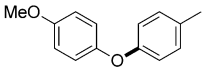
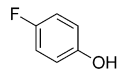
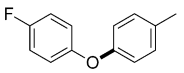
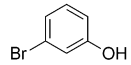
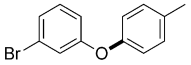
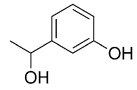
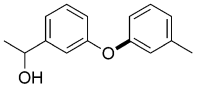
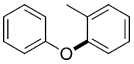
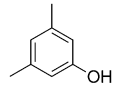
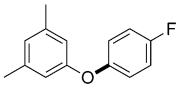
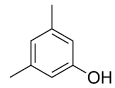
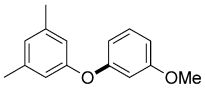
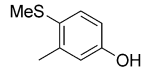
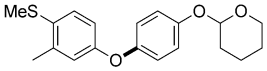
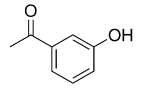
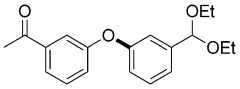
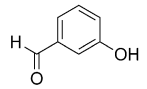
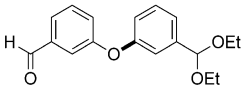
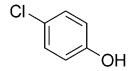
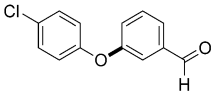
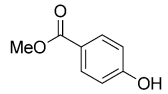
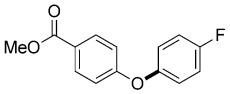
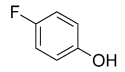
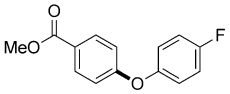


Scheme 4. Comparison of O-arylation of 3-hydroxy methyl benzoate **4m** with organoboronic acid **8** and organobismuthane **6i**.

Table 2. O-Arylation of highly functionalized phenols using substituted triarylbismuthanes.



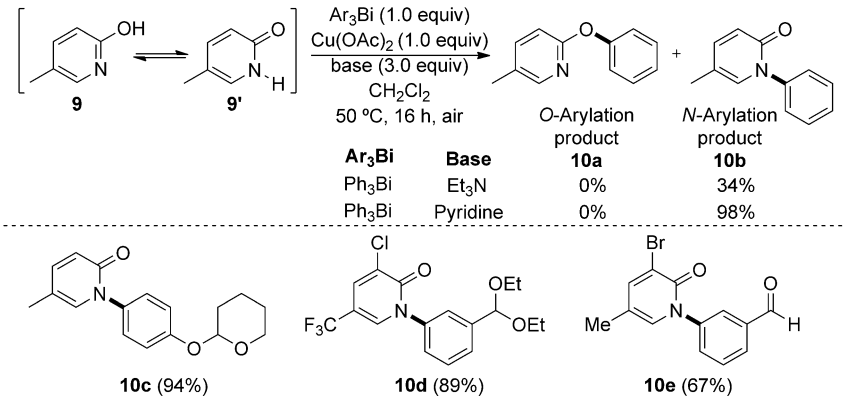
4a-l 6a-i 7a-l

	ArOH		Ar_3Bi	Product		Yield[a] [%]	Method[b]
1		**4a**	**6a**		**7a**	66	(A)
2		**4b**	**6a**		**7b**	85	(A)
3		**4c**	**6a**		**7c**	87	(A)
4		**4d**	**6b**		**7d**	94 82	(A) (B)
5		**4e**	**6c**		**7e**	75	(A)
6		**4f**	**6d**		**7f**	79	(A)
7		**4f**	**6e**		**7g**	75 61	(A) (B)
8		**4h**	**6f**		**7h**	55	(A)
9		**4i**	**6h**		**7i**	82	(B)
10		**4j**	**6h**		**7j**	80	(B)
11		**4k**	**6i**		**7k**	71 87	(A) (B)
12		**4l**	**6d**		**7l**	98	(B)
13		**4b**	**6g**		**7l**	52	(A)

[a] Isolated yield. [b] Conditions: Method A: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Et_3N (3 equiv), CH_2Cl_2, 50 °C, air, 3 h; Method B: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Et_3N (3 equiv), CH_2Cl_2, 50 °C, O_2, 16 h.

10b, albeit in modest yield. Fortunately, the yield could be considerably improved by using pyridine as the base, providing **10b** in 98% yield. The O-arylation product **10a** was not detected under our reaction conditions.[23] In order to demonstrate the applicability of this method in the arylation of other pyridones, compounds **10c**–**e**, which are all densely functionalized, were prepared in good to excellent yields.

In summary, we developed an efficient O-arylation reaction of phenols using functionalized trivalent organobismuth reagents. This reaction operates under simple conditions and tolerates numerous functional groups on both coupling partners, giving access to highly functionalized diaryl ethers. Substoichiometric amounts of catalyst can be used when the reaction is performed under oxygen. The arylation reaction of pyridones provided exclusively the corresponding N-arylated products. Applications to other arylation reactions and to parallel chemistry are in progress in our laboratory and results will be reported in due course.



Scheme 5. Regioselective N-arylation of 2(1 H)-pyridones.

Experimental Section

Typical procedure for the O-arylation of phenols using organobismuthanes:

Method A:

In a sealed tube, the phenol (0.28 mmol) was dissolved in non-anhydrous solvent grade dichloromethane (3 mL). The organobismuthane (1.0 equiv) was added followed by copper (II) acetate (1.0 equiv) and triethylamine (3.0 equiv). The tube was sealed and heated at 50 °C until completion as indicated by TLC analysis. The reaction mixture was cooled to room temperature and silica gel was added. The mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography using the indicated solvent system. The pure fractions were concentrated under reduced pressure to afford the desired pure product.

Method B:

Same as method A, except that 0.3 equivalent of copper (II) acetate was used. The reaction tube was purged with 99.6% extra dry oxygen for 1 min, sealed and heated at 50 °C until completion as indicated by TLC analysis. The reaction mixture was treated as in method A.

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