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Synthesis of Highly Functionalized Triarylbismuthines by Functional Group Manipulation and Use in Palladium- and Copper-Catalyzed Arylation Reactions

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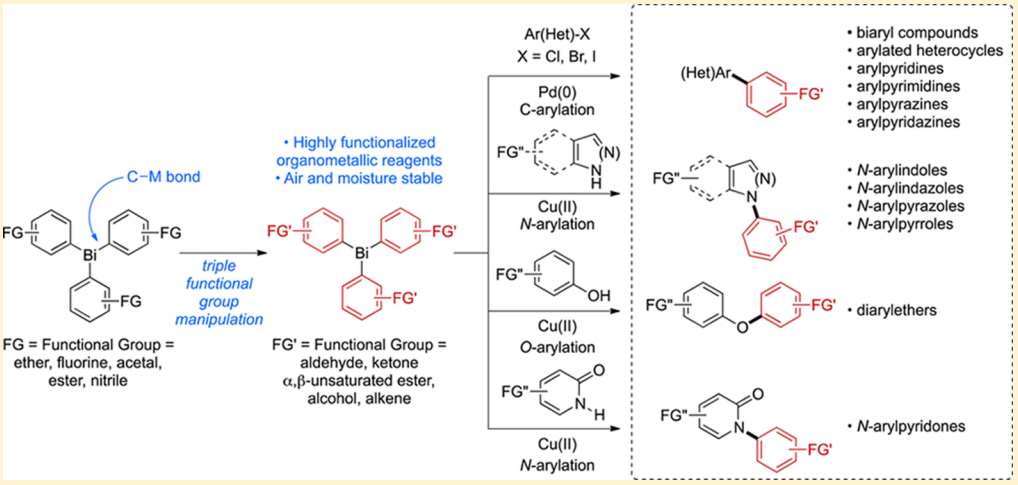
Supporting Information



ABSTRACT: Organobismuthines are an attractive class of organometallic reagents that can be accessed from inexpensive and nontoxic bismuth salts. Triarylbismuthines are particularly interesting due to their air and moisture stability and high functional group tolerance. We report herein a detailed study on the preparation of highly functionalized triarylbismuth reagents by triple functional group manipulation and their use in palladium- and copper-catalyzed *C*-, *N*-, and *O*-arylation reactions.

INTRODUCTION

Triarylbismuthines (also known as triarylbismuthanes) are a class of organometallic reagents that can be prepared from inexpensive and nontoxic bismuth salts.[1,2] These reagents are particularly attractive since they are air and moisture stable and can be purified by simple flash chromatography or crystallization. Moreover, organobismuth reagents are remarkably tolerant to numerous functional groups, making them highly suitable for methodology development.[3] They have also found applications in total synthesis,[4] in the preparation of transition metal complexes,[5] as catalysts for polymerization reactions,[6] and in medicinal chemistry.[7] Organobismuth reagents are divided into two main classes: trivalent and pentavalent organobismuthines, with bismuth in the +3 and +5 oxidation levels, respectively. Both classes have found applications in synthesis. For example, Barton and Finet reported in the 1980s a series of arylation reactions using triphenylbismuth and triphenylbismuth diacetate as arylating agents.[8] More recently, Rao greatly contributed to expanding the use of this class of reagents in organic synthesis and more specifically in palladium-catalyzed reactions.[9]

Our group has reported in recent years a portfolio of methods for the formation of C–C,[10] C–N,[11] and C–O[12] bonds using functionalized trivalent organobismuth reagents. These methods allow the transfer of functionalized aryl groups on scaffolds as diverse as pyridines **2**, pyrimidines **4**, pyrazines **6**, pyridazines **8**, indazoles and pyrazoles **10**, indoles and pyrroles **12**, phenols **14**, pyridones **16**, and 1,2-aminoalcohols **18**, providing access to a range of medicinally relevant compounds (Scheme 1). These methodologies operate under mild conditions and tolerate a wide variety of functional groups on both coupling partners.

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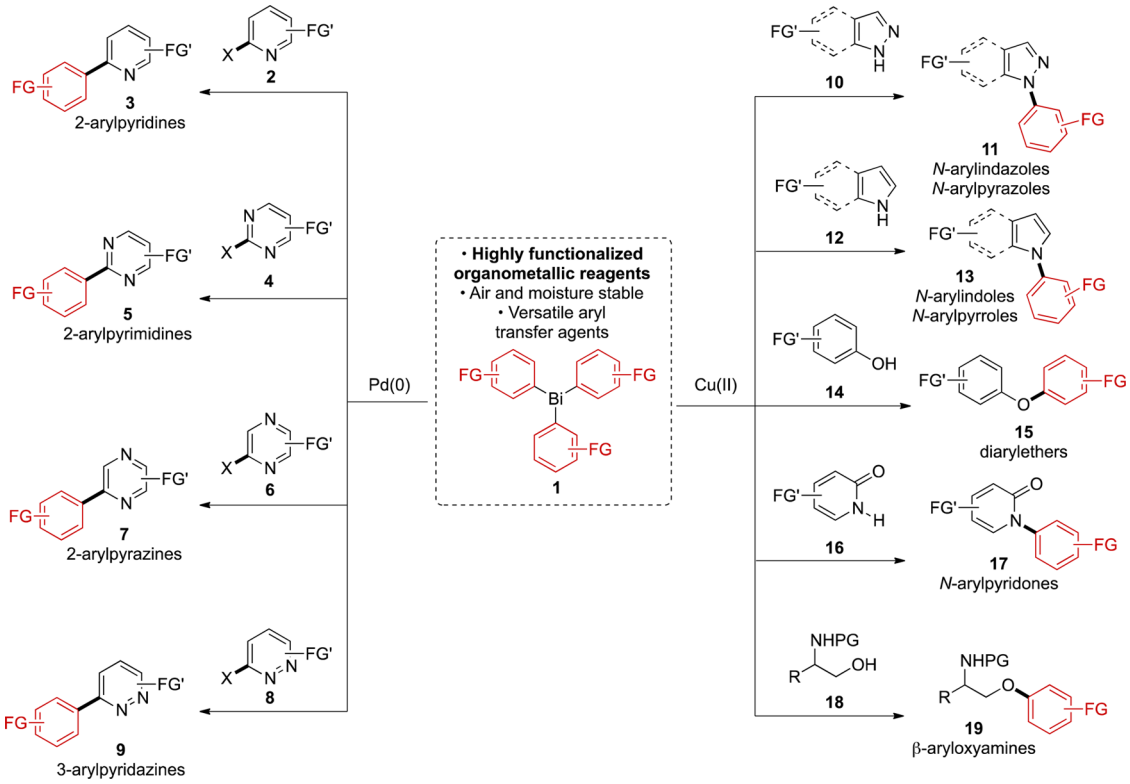
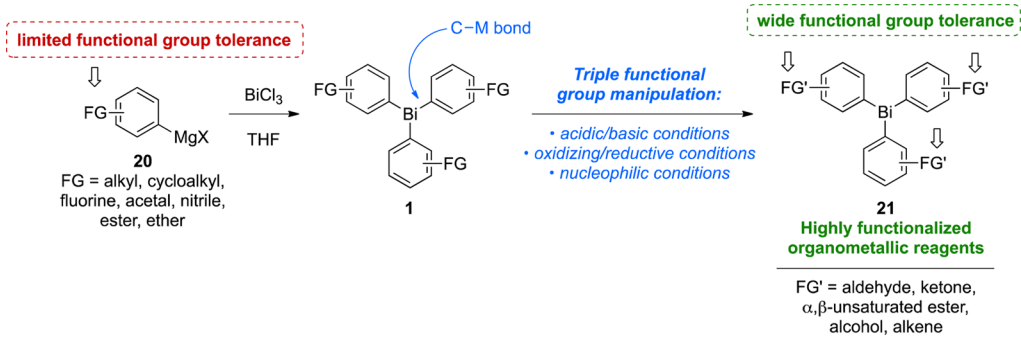
Scheme 1. Triarylbismuthines 1 in Arylation Reactions: Access to Highly Functionalized and Medicinally Relevant Compounds



Scheme 2. Synthesis of Highly Functionalized Organobismuthines 21 by Functional Group Manipulation Directly on Organometallic Species 1 (FG = Functional Group)



Triarylbismuth reagents **1** can be easily accessed via addition of Grignard reagents **20** onto bismuth chloride (Scheme 2). However, due to the high reactivity of organomagnesium reagents, organobismuthines bearing electrophilic or acidic functional groups cannot be synthesized directly using this approach. Condon reported an elegant and powerful method to prepare functionalized organobismuth reagents by the addition of organozinc reagents obtained from a cobalt–zinc metal–halogen exchange reaction on aryl halides.[13] While this method is quite general, groups bearing acidic protons such as alcohols cannot be introduced using this methodology. Therefore, alternative methods are still desirable to access highly functionalized organobismuthines. The strategy that we explored consists of introducing the incompatible functional group by performing a functional group transformation directly on the organobismuth species. In the course of our studies, we found that the C–Bi bond in organobismuthines is remarkably resistant to acidic, reductive, and even oxidative conditions, thus enabling the transformation of the functional group FG in **1** into a more elaborated functional group FG′ in **21** (Scheme 2). This reaction actually corresponds to a triple group manipulation on a single substrate. To be efficient, it therefore requires a high level of control of the reaction conditions since, to a first approximation, the overall yield is given by the cube of the yield-per-function. We report herein an extensive study on the successful preparation of highly functionalized triarylbismuth reagents using this approach and their use in palladium- and copper-catalyzed arylation reactions.

RESULTS AND DISCUSSION

a. Preparation of Triarylbismuthines. We began by synthesizing a set of substituted and unsubstituted organobismuthines **1a–r** bearing simple functional groups by adding organomagnesium reagents **20** to bismuth chloride (Scheme 3). The Grignard reagents **20** were prepared by reacting the corresponding aryl halides **22** with metallic magnesium at reflux of ether or THF. Using this approach, 18 different

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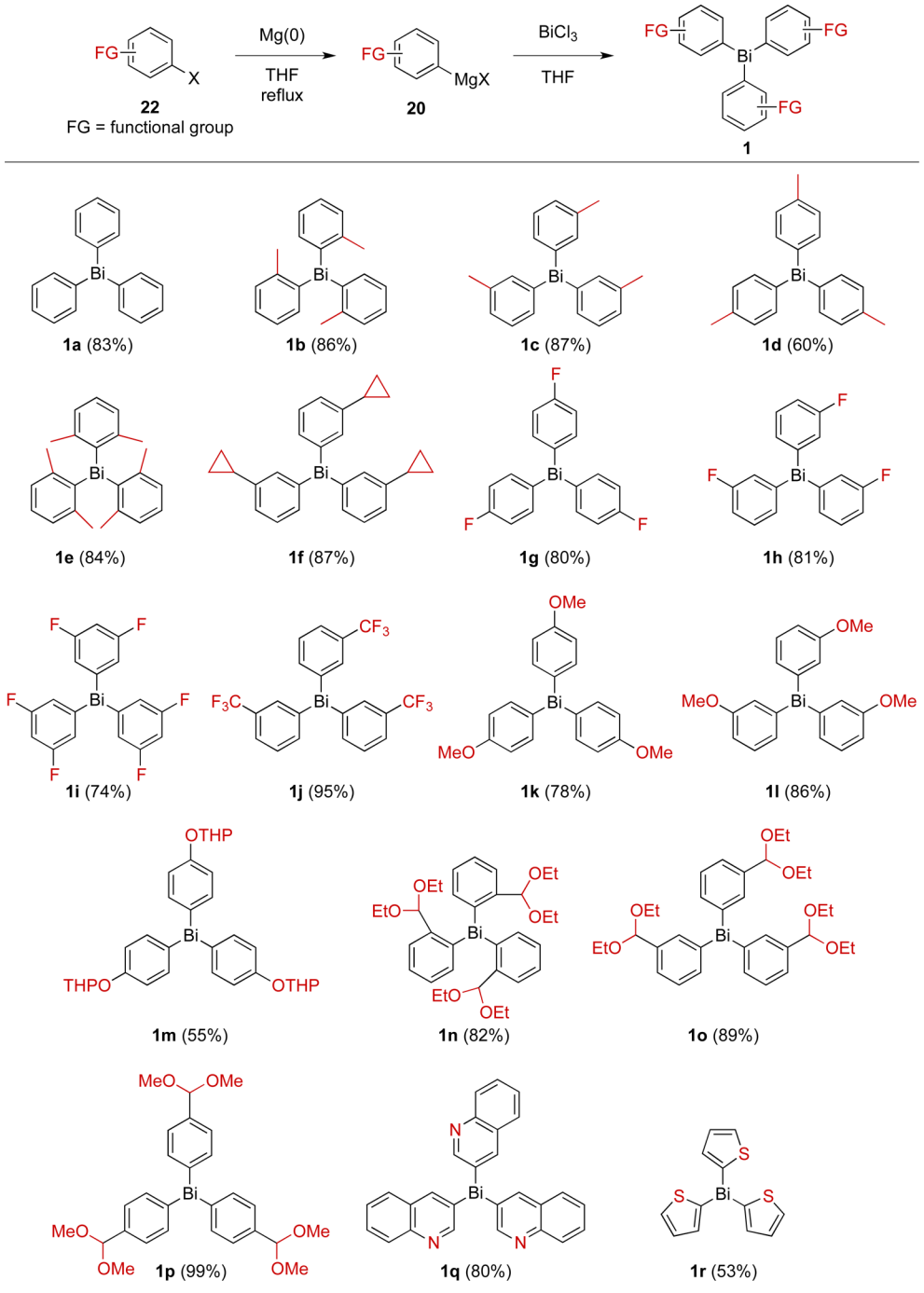
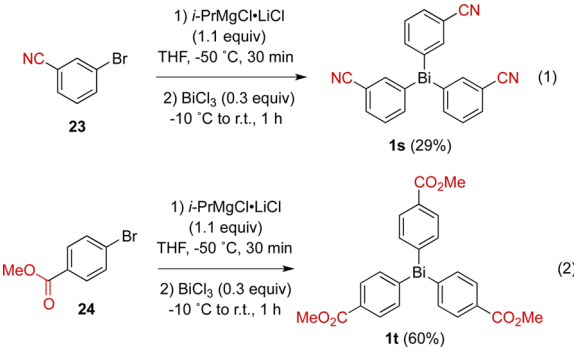
Scheme 3. Direct Preparation of Organobismuthines 1a–r by Addition of Organomagnesium Reagents 20 to Bismuth Chloride



unsubstituted and *ortho*, *meta*, and *para* substituted triaryl- and triheteroarylbismuthines were synthesized in 53% to 99% yields.

For the introduction of nitriles and esters, the required organomagnesium reagents were generated using Knochel's procedure.[14] Thus, addition of the isopropylmagnesium chloride lithium chloride complex onto 3-cyanobromobenzene **23** or methyl 4-bromobenzoate **24** at −50 °C afforded the corresponding Grignard reagents, which were then reacted with bismuth chloride to provide **1s** and **1t** in moderate yields (eqs 1 and 2).



To begin our exploration of functional group manipulation on organobismuthines, we added 6.0 equiv of methylmagne-

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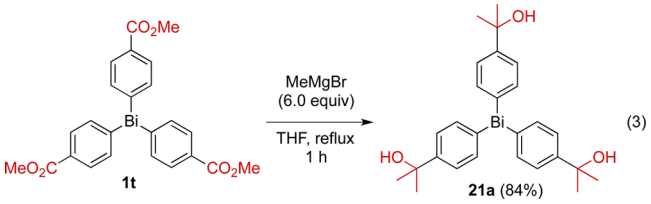
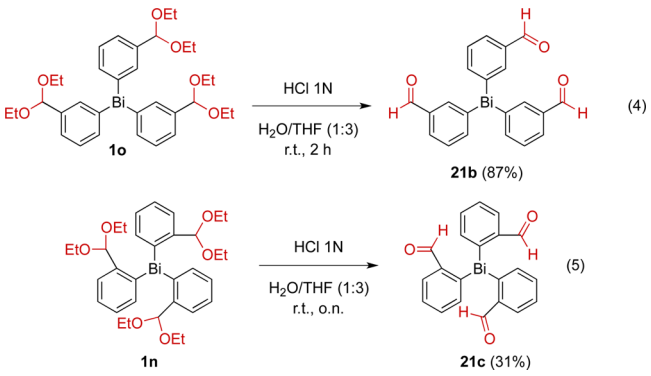
sium bromide on the ester derivative **1t**, affording **21a** in 84% yield (i.e., 94% yield per ester function) (eq 3). This simple



transformation demonstrates that the concept of functional group modification in the presence of a C−Bi bond is viable, giving us an impetus to explore other reactions directly on organobismuthines.

Due to their high electrophilicity, aldehydes cannot be present on organomagnesium reagents. Therefore, the preparation of organometallic reagents bearing aldehydes is only possible with less electropositive metals such as tin,[15] boron,[16] zinc,[17] or indium.[18] However, the toxic nature of tin greatly limits its use in synthesis. Although many organoboronic acids bearing aldehydes are commercially available, their use in metal-catalyzed reactions often requires extensive optimization of the reaction conditions. Conversely, arylzinc reagents possessing aldehydes have proved to be very useful in palladium-catalyzed cross-coupling reactions, but strictly anhydrous conditions are mandatory due to their high sensitivity to moisture. Finally, while organoindiums have generated great interest in the synthetic community over the past decade, the cost of indium greatly limits their application in synthesis. In this context, organobismuthines bearing aldehydes can fill an important need in organic synthesis. Starting from tris((3-diethoxymethyl)phenyl)bismuthine **1o**, we prepared the tris-formyl derivative **21b** in excellent yield by hydrolysis of the acetal function under acidic conditions (eq 4).



Surprisingly, using the same conditions on tris((2-diethoxymethyl)phenyl)bismuthine **1n** led to a much lower yield of the *ortho* analogue **21c** (eq 5). While this overall yield is low, it still corresponds to a 67% yield per acetal function. This example illustrates the need for very efficient conditions to get a satisfactory triple functional group modification.

We then took advantage of the versatility of the aldehyde function in **21b** to introduce other functional groups on the organobismuth species (Scheme 4). For example, addition of methylmagnesium bromide on **21b** provided tris(3-(1-hydroxyethyl)phenyl)bismuthine **21d** in quantitative yield. Reduction of the aldehyde function in **21b** was also accomplished using sodium borohydride, affording tris(3-(hydroxymethyl)phenyl)-bismuthine **21e** in 97% yield. An olefination reaction using Wittig conditions was then performed on **21b**, leading to the corresponding cinnamyl ester and vinyl derivatives **21f** and **21g** in 80% and 82% yield, respectively. These examples show that organobismuthines are resistant to organometallic and reductive reagents in addition to phosphorus ylides.

Next, we sought to introduce a ketone on the organobismuth reagent by oxidizing the secondary alcohol in **21d** (Scheme 5). Since trivalent organobismuthines can be oxidized into their pentavalent counterparts by oxidizing agents[19] and by hypervalent iodonium reagents,[8c,20] it was unclear if the bismuth(III) center would tolerate the oxidizing conditions required to oxidize the alcohol into the corresponding ketone. To our satisfaction, tris(methyl ketone) **21h** was obtained in acceptable yield using Dess-Martin periodinane **25**. Alternatively, compound **21h** could also be prepared in 63% yield via Swern oxidation of all three alcohol functions (86% per function).

b. Structural Characterization of Selected Triarylbismuthines. To further gain insight into the structure of triarylbismuthines,[21] we crystallized and analyzed by X-ray diffraction several derivatives bearing a cyclopropyl group at the *meta* position (**1f**), fluorine atoms at the 3 and 5 position (**1i**), a methoxy group at the *para* position (**1k**), an acetal at the *ortho* position (**1n**), a cyano group at the *meta* position (**1s**), a carbomethoxy function at the *para* position (**1t**), an aldehyde at the *meta* (**21b**) and *ortho* positions (**21c**), and an hydroxymethyl group at the *meta* position (**21e**).[22] The results show that the organobismuthines have a distorted trigonal pyramidal structure with Bi−C bond lengths ranging from 2.24 to 2.27 Å and C−Bi−C angles between 91° and 98° (Figure 1). These Bi−C bond lengths are consistent with known triarylbismuthines crystal structures[23] and with the 2.256 Å value estimated in the gas phase by gas electron diffraction,[24] denoting innocuous crystal packing effects. The small C−Bi−C angles are due to known relativistic effects and fall within the trend observed when going down the pnictogen family ($N > P > As > Sb > Bi$).

Interestingly, the nature and position of the substituent have little impact on the molecular structure of the organobismuthine, except in the case of the *ortho*-(diethylacetal) and *ortho*-formyl derivatives **1n** and **21c**. In these compounds with donor atoms in the *ortho* functional group, secondary intramolecular interactions are observed between the oxygen of the acetals or the carbonyls and the bismuth center (Bi···O from 3.085 to 3.255 Å in **1n** and from 2.911 to 2.991 Å in **21c**; $r_{VdW}(Bi) = 2.07$ Å, $r_{VdW}(O) = 1.52$ Å). This is not unprecedented, as bismuth is capable of acting as a weak acceptor toward other ligands or even metals[25] by accepting electrons in its C−Bi σ^* orbitals.[5a,26]

c. Palladium-Catalyzed Cross-Coupling Reaction between Organobismuthines and Aryl or Heteroaryl Halides. Multiple reports of palladium-catalyzed cross-coupling reactions involving organobismuth compounds have been disclosed in recent years.[27,28] One important aspect of triarylbismuth reagents is their ability to deliver three aryl groups per equivalent of organometallic reagent in cross-coupling reactions, making them more atom-economical than other conventional Ar−M reagents. However, in most cases, a limited array of functional groups were present on the organobismuth partner. We recently reported a palladium-catalyzed reaction to cross-couple triarylbismuthines with halogenated pyridines, pyrimidines, pyrazines, and pyridazines.[10b] Therefore, with our functionalized organobismuthines in hand, we next explored their reactivity in palladium-catalyzed

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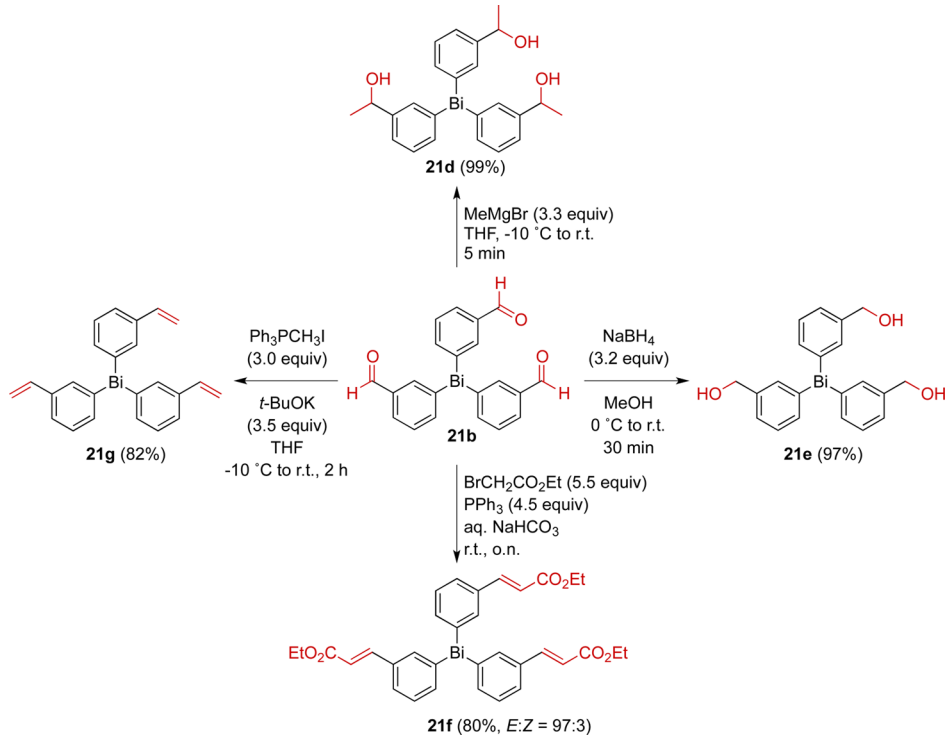
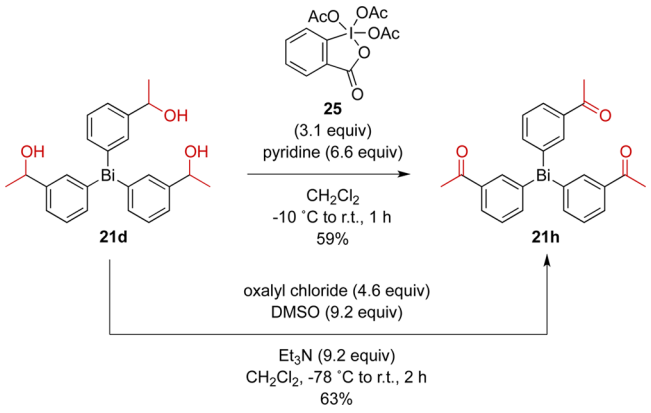
Scheme 4. Synthesis of Highly Functionalized Organobismuthines 21d–g by Derivatization of Tris(3-formylphenyl)bismuthine 21b



Scheme 5. Preparation of Ketone-Bearing Organobismuthine Derivative 21h by Dess-Martin and Swern Oxidation Starting from Tris-alcohol 21d



cross-coupling reactions with other electrophiles in order to further probe the scope and functional group tolerance of this transformation.

First, we optimized the reaction conditions using 1.0 equiv of 4-bromobenzaldehyde **26** and 0.4 equiv of organobismuthine **21d**. Using our previously reported conditions, we obtained the desired cross-coupling product **27** in only 37% yield (Table 1, entry 1). The observed low yield shows that the coupling of highly functionalized organobismuthines represents a substantial challenge and that the reaction conditions had to be reoptimized. Suspecting that the high temperature was possibly responsible for the observed low yield, we performed the reaction at 80 °C but observed no improvement in yield (entry 2). Changing the catalyst for $PdCl_2(PPh_3)_2$ (entry 3), $Pd(OAc)_2$/S-Phos (entry 4), $Pd(OAc)_2/PPh_3$ (entry 5), or PEPPSI-*i*Pr[29] (entry 6) did not improve the yield either.

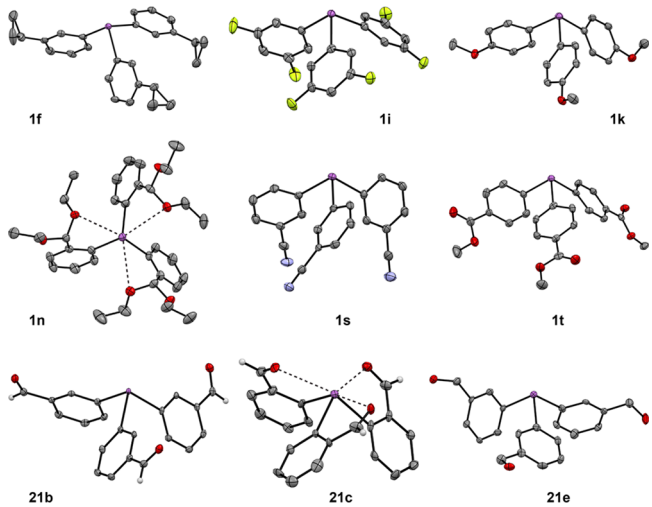


Figure 1. ORTEP view at 50% ellipsoid probability of **1f**, **1i**, **1k**, **1n** (one of three independent molecules), **1s**, **1t**, **21b**,[10b] **21c** and **21e**. Hydrogen atoms are omitted for clarity, except for aldehyde functional groups. Dashed lines indicate weak intramolecular interactions between the bismuth atom and donor oxygen atoms at *ortho* positions.

Knowing the beneficial effect of lithium salts on cross-coupling reactions, as documented by Organ and others,[30] we found a substantial amelioration in yield when 2.0 equiv of lithium chloride were used as an additive (entry 7). Changing the solvent for THF (entry 8), toluene (entry 9), or a mixture of DMF and HMPA (entry 10) was detrimental to the reaction or at best inconsequential. The use of a stronger base such as potassium *tert*-butoxide led to a drastic drop in the yield of the reaction (entry 11). In addition, while potassium carbonate (entry 12) provided a similar yield as cesium carbonate (entry 7), we found that potassium phosphate (entry 13) and

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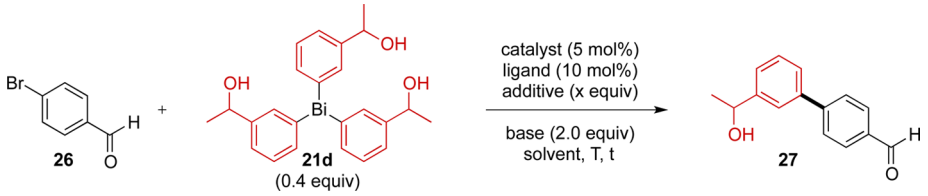
Table 1. Optimization of Reaction Conditions for the Palladium-Catalyzed Cross-Coupling Reaction of 21d with 4-Bromobenzaldehyde 26



Entry	Catalyst	Ligand	Additive (x equiv)	Base	Solvent	T (°C)	t (h)	Yield (%)[a]
1	$Pd(PPh_3)_4$	N.A.	N.A.	Cs_2CO_3	DMF	130	18	37
2	$Pd(PPh_3)_4$	N.A.	N.A.	Cs_2CO_3	DMF	80	6	36
3	$PdCl_2(PPh_3)_2$	N.A.	N.A.	Cs_2CO_3	DMF	80	6	31
4	$Pd(OAc)_2$	S-Phos	N.A.	Cs_2CO_3	DMF	80	6	7
5	$Pd(OAc)_2$	PPh_3	N.A.	Cs_2CO_3	DMF	80	6	31
6	PEPPSI-*i*Pr	N.A.	N.A.	Cs_2CO_3	DMF	80	6	23
7	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	DMF	80	6	64
8	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	THF	80	6	13
9	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	Toluene	80	6	25
10	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	Cs_2CO_3	DMF/HMPA[b]	80	6	59
11	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	*t*-BuOK	DMF	80	6	14
12	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	K_2CO_3	DMF	80	6	69
13	**$Pd(PPh_3)_4$**	**N.A.**	**LiCl (2.0 equiv)**	**K_3PO_4**	**DMF**	**80**	**6**	**82**
14	**$Pd(PPh_3)_4$**	**N.A.**	**LiCl (2.0 equiv)**	**Rb_2CO_3**	**DMF**	**80**	**6**	**75**
15	$Pd(PPh_3)_4$	N.A.	LiCl (1.0 equiv)	K_3PO_4	DMF	80	6	57
16	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	K_3PO_4[c]	DMF	80	6	48
17	$Pd(PPh_3)_4$	N.A.	LiCl (2.0 equiv)	K_3PO_4	DMF/H_2O[d]	80	6	73
18	**$Pd(PPh_3)_4$**	**N.A.**	**CuI (0.4 equiv)**	**Cs_2CO_3**	**DMF**	**80**	**6**	**83**

[a]Isolated yield of pure product. [b]DMF/HMPA (4:1). [c]1.0 equiv of K_3PO_4 was used. [d]DMF/H_2O (5:1).

rubidium carbonate (entry 14) were much more efficient bases in this transformation, providing the desired cross-coupling product **27** in 82% and 75% isolated yield, respectively. Lowering the number of equivalents of lithium chloride (entry 15) or potassium phosphate (entry 16) proved disadvantageous. Interestingly, the yield remained satisfactory when the reaction was run in a 5:1 ratio of DMF/H_2O, showing that strictly anhydrous conditions are not mandatory (entry 17). Rao recently reported the effect of copper salts in cross-coupling reactions involving organobismuthines.[9a] Simultaneously to Rao, we independently explored the effect of cuprous iodide as an additive and obtained a considerable improvement in the yield of the reaction (entry 18). Conditions from entries 13, 14, and 18 represent a substantial improvement over our previous protocol, as they allow the coupling reaction to be performed at a lower temperature, in a shorter time, and with a higher yield.

Having optimized the conditions for the cross-coupling of organobismuthine **21d**, we next investigated the scope of the method using organobismuthines **1a–t** and **21a–h** with selected arylhalides **28**, heteroarylhalides **29**, 2-halopyridines **2**, 2-halopyrimidines **4**, 2-halopyrazines **6**, and 3-halopyridazines **8** (Table 2). The choice of the electrophiles was motivated by the presence of functional groups that could demonstrate the applicability of our protocols in the preparation of highly functionalized compounds. In each case, our best conditions from entries 13, 14, and 18 in Table 1 (named Method A, B, and C, respectively, in Table 2) were tested in order to obtain the highest possible yield of each desired product. Thus, 4-(*N*-BOC-aminoethyl)bromobenzene **28a**, methyl 4-iodobenzoate **28b**, methyl 4-bromobenzoate **28c**, 4-bromobenzaldehyde **28d**, 2-iodo-4-furaldehyde **29a**, 6-chloropyridine-3-carboxaldehyde **2a**, 2-acetyl-6-bromopyridine **2b**, 2-chloro-4-methylpyrimidine **4a**, 2-chloro-6-dimethylaminopyrazine **6a**, and 3-chloro-6-phenylpyridazine **8a** were engaged in cross-coupling reactions with organobismuthines **1a–t** and **21a–h** to afford the corresponding products in acceptable to excellent yields. The results demonstrate that the reaction works with aryl bromides (entries 1, 3, 5), aryl or heteroaryl iodides (entries 2, 4, 6), and 2-chloro and 2-bromo nitrogenated heterocycles (entries 7–12). However, entries 2 and 3 show that iodides are slightly more reactive than bromides. The identity of the optimal set of conditions (whether A, B, or C) depended greatly on the specific combination of Ar(Het)–X and Ar_3Bi. Notwithstanding, these examples demonstrate that our protocols tolerate a wide diversity of functional groups on the electrophile and on the organobismuthine such as BOC-protected amines (**30a**), α,β-unsaturated esters (**30a**), esters (**30b,c**), ethers (**30b**), nitriles (**30c**), aldehydes (**30d**, **31a**, **3a**), dialkylamines (**7a**), and acetals (**3b**, **9b**). More striking is the ability of this method to transfer in acceptable to good yields aryl groups that possess functions that are susceptible to competitive arylation, elimination, or oxidation such as alcohols (**31a**, **7a**), ketones (**9a**), and vinyl groups (**30d**, **5a**).

d. Copper-Catalyzed *N*-Arylation of Indoles, Pyrroles, Pyrazoles, and Pyridones. We recently reported a protocol for the copper-catalyzed *N*-arylation of indoles, pyrroles, pyrazoles,[11a] and pyridones[12b] using organobismuthines with tolerance to a wide variety of functional groups. Other research groups have also reported various copper-catalyzed reactions based on trivalent or pentavalent reagents to *N*-arylate nitrogen-containing compounds.[31] To further expand the functional group diversity of our method, we tested some of the highly functionalized organobismuthines prepared in this

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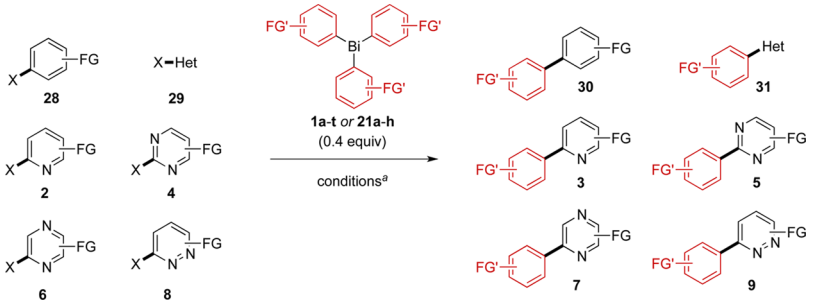
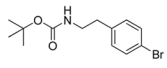
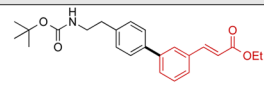
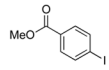
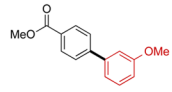
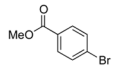
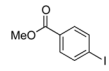
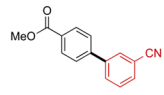
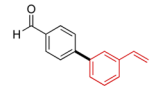
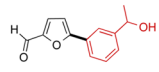
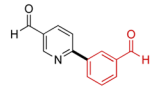
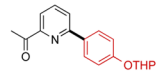
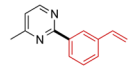
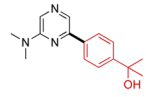
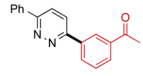
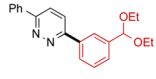
Table 2. Palladium-Catalyzed Cross-Coupling Reaction of Highly Functionalized Organobismuthines 1a−t and 21a−h with Arylhalides (28), Heteroarylhalides (29), 2-Halopyridines (2), 2-Halopyrimidines (4), 2-Halopyrazines (6), and 3-Halopyridazines (8)



Entry	Ar(Het)–X	Ar_3Bi	Product	Yield (%)[b]
1	 **28a**	**21f**	 **30a**	**89 (A)** 10 (B) 80 (C)
2	 **28b**	**1l**	 **30b**	91 (A) 95 (B) **98 (C)**
3	 **28c**	**1l**	**30b**	54 (A) **78 (B)** 66 (C)
4	 **28b**	**1s**	 **30c**	84 (A) **87 (B)** 41 (C)
5	 **28d**	**21g**	 **30d**	58 (A) 46 (B) **76 (C)**
6	 **29a**	**21d**	 **31a**	**82 (A)** 65 (B) 29 (C)
7	 **2a**	**21b**	 **3a**	36 (A) **64 (B)** 33 (C)
8	 **2b**	**1m**	 **3b**	0 (A) **80 (B)** 31 (C)
9	 **4a**	**21g**	 **5a**	**20 (A)** 12 (B) 13 (C)
10	 **6a**	**21a**	 **7a**	**41 (A)** 12 (B) 10 (C)
11	 **8a**	**21h**	 **9a**	**25 (A)** 23 (B) 12 (C)
12		**1o**	 **9b**	0 (A) **45 (B)** 0 (C)

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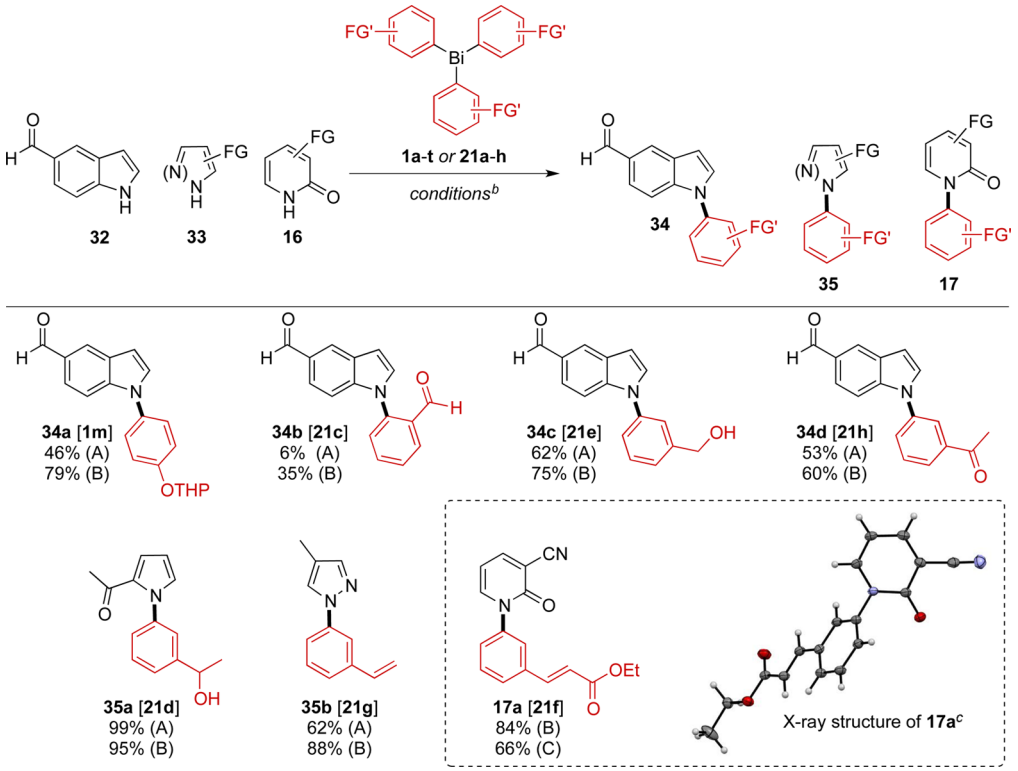
J. Org. Chem. 2016, 81, 5401−5416

Table 2. continued

[a]**Method A**: Ar_3Bi (0.4 equiv), $Pd(PPh_3)_4$ (5 mol %), LiCl (2.0 equiv), K_3PO_4 (2.0 equiv), DMF, 80 °C, 6 h; **Method B**: Ar_3Bi (0.4 equiv), $Pd(PPh_3)_4$ (5 mol %), LiCl (2.0 equiv), Rb_2CO_3 (2.0 equiv), DMF, 80 °C, 6 h; **Method C**: Ar_3Bi (0.4 equiv), $Pd(PPh_3)_4$ (5 mol %), CuI (0.4 equiv), Cs_2CO_3 (2.0 equiv), DMF, 80 °C, 6 h. [b]Isolated yield of pure product.

Scheme 6. *N*-Arylation of Indole 32, Pyrrole and Pyrazole 33, and Pyridone 16 Using Highly Functionalized Organobismuthines 1a−t and 21a−h[a]



[a]The numbers in brackets indicate the organobismuthine used for the synthesis of each compound. [b]Conditions: **Method A**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.1 equiv), pyridine (1.0 equiv), CH_2Cl_2, O_2, 50 °C, o.n.; **Method B**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, o.n.; **Method C**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, air, 50 °C, o.n. [c]ORTEP diagram at 50% ellipsoid probability of compound **17a**.

work in our copper-catalyzed *N*-arylation reaction. The arylations were performed at 50 °C under oxygen using 1.0 equiv of triarylbismuthine, 1.0 equiv of pyridine, and 0.1 equiv of copper acetate (Scheme 6, Method A). Every substrate was also arylated under more "forcing" conditions, that is, using stoichiometric amounts of copper acetate and 3.0 equiv of pyridine (Scheme 6, Method B). Finally, pyridones were arylated using similar conditions, except that the reactions were also performed under air (Scheme 6, Method C). As illustrated in Scheme 6, indole **32**, pyrrole and pyrazole **33**, and pyridone **16** were *N*-arylated in up to 99% yield using these conditions, demonstrating that aryl groups possessing THP-protected phenols (**34a**), aldehydes (**34b**), benzylic alcohols (**34c**), methyl ketones (**34d**), secondary alcohols (**35a**), vinyl groups (**35b**), and α,β-unsaturated esters (**17a**) can be efficiently transferred using our methods. It should be emphasized that groups that are susceptible to elimination (secondary alcohol in **35a**), oxidation (benzylic and secondary alcohols in **34c** and **35a** respectively), enolization (methyl ketone in **34d**), or arylation (alcohols in **34c** and **35a**) are also tolerated using our protocols. The main limitation of this method, as demonstrated previously,[11a] resides in the transfer of an *ortho*-substituted aryl group, as illustrated by compound **34b**.

Mukaiyama reported a copper-free method to *N*-arylate pyridones using pentavalent organobismuth reagents.[32] We demonstrated previously,[12b] based on IR analysis, that the arylation of pyridones using our copper-catalyzed reaction involving trivalent organobismuthines also leads to the *N*-arylated product (as opposed to the *O*-arylated derivative). The analysis of compound **17a** by X-ray diffraction further confirms the chemoselectivity of this arylation reaction toward nitrogen.

e. Copper-Catalyzed *O*-Arylation of Phenols. A few reports on the *O*-arylation of alcohols and phenols using organobismuth reagents have been disclosed in the literature.[33] However, most of these methods rely on pentavalent organobismuth compounds, which must be prepared from their corresponding trivalent analogues. Therefore, the development of *O*-arylation reactions directly from trivalent organobismuthines is of high interest, as it can reduce the number of steps required to obtain the desired *O*-arylated product. We recently reported an efficient and general method to prepare diarylethers via a copper-catalyzed *O*-arylation of phenols using triarylbismuthines.[12b] Using these protocols, we sought to evaluate the applicability of the highly functionalized organobismuthines in the *O*-arylation of methyl 3-hydroxybenzoate **36**. Two sets of conditions were tested: in Method A, the

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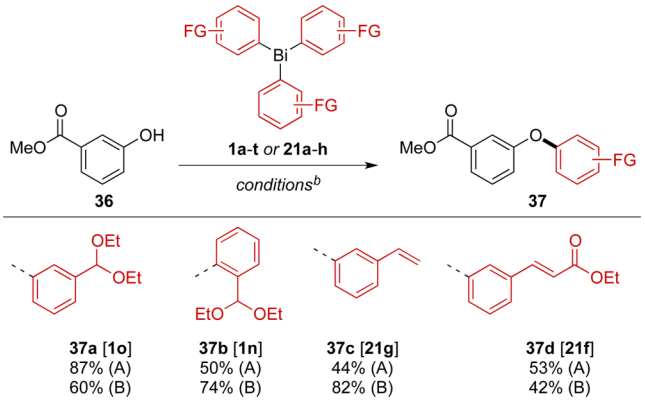
J. Org. Chem. 2016, 81, 5401−5416

reaction was run at 50 °C for 3 h under air using 1.0 equiv of triarylbismuthine, triethylamine as the base, and a stoichiometric amount of copper acetate; in Method B, the catalyst loading was lowered to 0.3 equiv and the reaction was performed under oxygen for 16 h. As shown in Scheme 7, these

Scheme 7. *O*-Arylation of Methyl 3-Hydroxybenzoate 36 Using Highly Functionalized Organobismuthines 1a–t and 21a–h



37a [1o] 87% (A) 60% (B) | **37b [1n]** 50% (A) 74% (B) | **37c [21g]** 44% (A) 82% (B) | **37d [21f]** 53% (A) 42% (B)

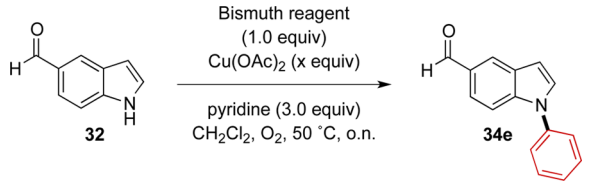
[a]The numbers in brackets indicate the organobismuthine used for the synthesis of each compound. [b]Conditions: **Method A**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 50 °C, air, 3 h; **Method B**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 50 °C, O_2, 16 h.

methods allow the transfer of aryl groups bearing a variety of groups such as acetals (**37a**,**b**), vinyl groups (**37c**), and α,β-unsaturated esters (**37d**). Contrary to the *N*-arylation of indoles, pyrroles, and pyrazoles, the *O*-arylation of phenols even shows high tolerance for substitution in the *ortho* position, as shown by compound **37b**.

f. Mechanistic Investigations on the Copper-Catalyzed Arylation of Indoles and Phenols Using Trivalent and Pentavalent Organobismuth Reagents. Pentavalent organobismuth reagents have been shown to be potent arylating species in copper-catalyzed[8c,d,f,h,i] and even metal-free reactions.[8a] Barton also proposed that, in copper-catalyzed arylation reactions using triphenylbismuth, triphenylbismuth diacetate is formed *in situ* and acts as the effective arylating agent. Therefore, to compare the arylating power of trivalent and pentavalent organobismuth species, we performed the arylation on indole **32** using triphenylbismuth (Ph_3Bi, **1a**) and triphenylbismuth diacetate ($Ph_3Bi(OAc)_2$, **38**) in the presence and absence of copper acetate (Table 3). As expected, in the presence of copper acetate, triphenylbismuth was found to be an excellent arylating agent, providing the *N*-arylindole **34e** in 97% yield (entry 1). By contrast, in the presence of copper acetate, triphenylbismuth diacetate proved to be a much less efficient arylating reagent, affording **34e** in only 20% yield (entry 3). Both species were mostly inactive in the absence of copper acetate, showing that copper is essential for the *N*-arylation reaction (entries 2 and 4).

A comparative reactivity study between triphenylbismuth and triphenylbismuth diacetate was also performed on methyl 3-hydroxybenzoate **36** (Table 4). Contrary to the arylation of indoles, in the presence of copper acetate, triphenylbismuth diacetate was found to be more reactive than triphenylbismuth in the arylation of phenol **36** (entry 3 vs 1). However, similarly

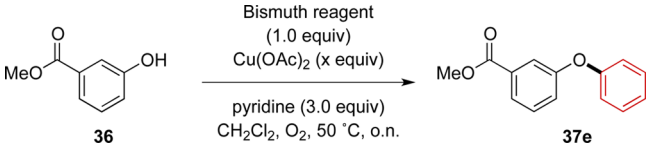
Table 3. Comparison of the Reactivity of Triphenylbismuth 1a and Triphenylbismuth Diacetate 38 in the *N*-Arylation Reaction of Indole 32



Entry	Bismuth reagent	$Cu(OAc)_2$ (*x* equiv)	Yield (%)[a]
1	Ph_3Bi (**1a**)	1.0	97
2	Ph_3Bi (**1a**)	0	2
3	$Ph_3Bi(OAc)_2$ (**38**)	1.0	20
4	$Ph_3Bi(OAc)_2$ (**38**)	0	1

[a]Yields are for isolated pure compound.

Table 4. Comparison of the Reactivity of Triphenylbismuth 1a and Triphenylbismuth Diacetate 38 in the *O*-Arylation Reaction of Phenol 36



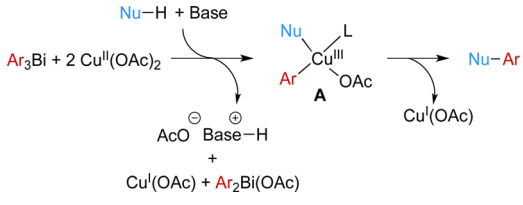
Entry	Bismuth reagent	$Cu(OAc)_2$ (*x* equiv)	Yield (%)[a]
1	Ph_3Bi (**1a**)	1.0	70
2	Ph_3Bi (**1a**)	0	0
3	$Ph_3Bi(OAc)_2$ (**38**)	1.0	92
4	$Ph_3Bi(OAc)_2$ (**38**)	0	4

[a]Yields are for isolated pure compound.

to the arylation of indole **32**, in the absence of the catalyst, both reagents were unable to arylate phenol **36**, showing once again that copper is essential for the *O*-arylation reaction (entries 2 and 4). The results from Table 3 and Table 4 suggest that copper acetate is necessary for both arylation reactions and that trivalent and pentavalent organobismuth species can both act as arylating agents, albeit with different efficiencies depending on the substrate.

The mechanism that we propose for the copper-catalyzed *N*- and *O*-arylation of indoles, pyrroles, pyrazoles, pyridones, and phenols (summarized by Nu–H) using triarylbismuthines involves the formation of an organocopper(III) species **A** where the deprotonated nucleophile, the aryl group, and one acetate are simultaneously ligated to the metal (Scheme 8).[34] This species would be formed by the reaction of triarylbismuthine Ar_3Bi and copper acetate, concomittantly with the

Scheme 8. Proposed Mechanism for the Copper-Catalyzed *N*- and *O*-Arylation of Indoles, Pyrroles, Pyrazoles, Pyridones, and Phenols Using Triarylbismuthines (Nu–H = Indole, Pyrrole, Pyrazole, Pyridone, or Phenol)



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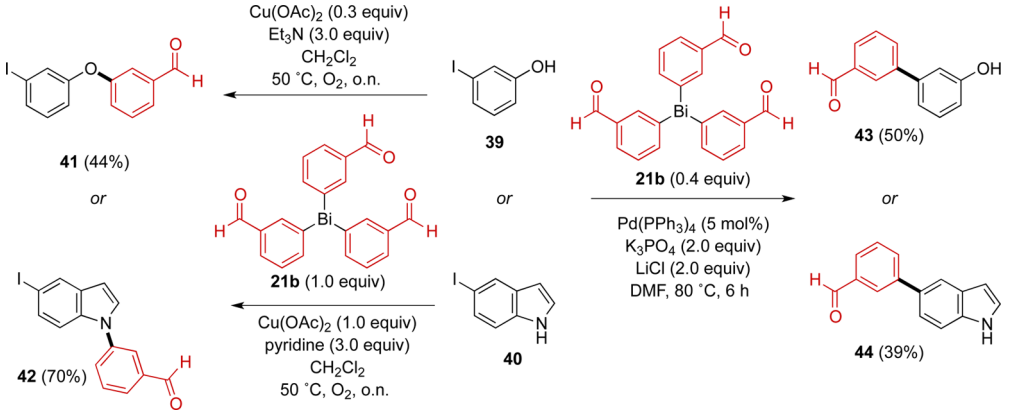
Scheme 9. Orthogonal *C*-, *N*-Arylation and *O*-Arylation of 3-Iodophenol 39 and 5-Iodoindole 40 Using Tris(3-formylphenyl)bismuthine 21b



deprotonation of the nucleophile Nu–H by the base (either triethylamine or pyridine), leading to copper(III) intermediate **A**, copper(I) acetate, and diarylbismuth acetate ($Ar_2Bi(OAc)$). Reductive elimination from species **A** would then provide the arylated nucleophile Nu–Ar. This mechanism is similar to that proposed by Barton and Finet in the copper-catalyzed arylation of amines and indoles using triphenylbismuth diacetate.[8g] Moreover, intermediate **A** was also proposed by Evans in the arylation of phenols using arylboronic acids,[35] in the Ullmann–Goldberg copper-catalyzed *N*-arylation of amines using aryl halides[36] and in detailed mechanistic studies published by Stahl on the Chan–Evans–Lam reaction.[37]

g. Orthogonal *C*-, *N*-, and *O*-Arylation Reactions on Iodo Phenols and Indoles. To further test the scope of our copper- and palladium-catalyzed methods, we explored the orthogonal transfer of aryl groups on the halogenated phenol **39** and indole **40** (Scheme 9). Using copper acetate and organobismuthine **21b**, the arylation could be directed chemoselectively to the oxygen of **39** or the nitrogen of **40**, providing **41** and **42** in 44% and 70% yield, respectively. These products would be difficult to obtain using copper(I) or palladium(0) catalysis since reaction at the aryl–I bond would compete with the desired *O*- or *N*-arylation process.[38] In addition, the palladium-catalyzed cross-coupling reaction between 3-iodophenol **39** and 5-iodoindole **40** with triarylbismuthine **21b** delivered **43** and **44**, respectively, in moderate yields. These cross-coupling reactions represent a substantial challenge since competitive dehalogenation can occur due to the presence of the phenol and N–H indole functions.

CONCLUSION

In summary, we demonstrated that highly functionalized triarylbismuthines can be prepared by triple functional group manipulation using acidic, nucleophilic, and reducing conditions or involving organometallic reagents or ylides. Using this approach, triarylbismuthines bearing primary, secondary, and tertiary alcohols, aldehydes, α,β-unsaturated esters, vinyl groups, and methyl ketones were prepared. These triarylbismuthines represent a class of highly functionalized and versatile organometallic reagents that are in high demand. We then developed improved protocols for the palladium-catalyzed cross-coupling reaction between these highly functionalized reagents and aryl or heteroaryl halides. These modified procedures involve lithium chloride or copper iodide as an additive and potassium phosphate or rubidium carbonate as a base and require shorter reaction times and lower temperatures. Using these protocols, highly functionalized *C*-arylated compounds were obtained in good to excellent yields. The highly functionalized organobismuthines prepared using the functional group manipulation approach were then engaged in a copper-catalyzed *N*-arylation of indoles, pyrroles, pyrazoles, and pyridones and *O*-arylation of phenols to afford highly functionalized arylated products. We then demonstrated that our palladium- and copper-catalyzed processes can be successfully used orthogonally on halogenated indoles and phenols. Preliminary mechanistic studies demonstrate that copper acetate is essential for the reaction to proceed and that the order of reactivity between the trivalent and pentavalent species depends on the nature of the substrate. Our palladium- and copper-catalyzed arylation reactions are simple to operate and show high functional group tolerance. The *C*-, *N*-, and *O*-arylation procedures developed in this work constitute an efficient and general portfolio of methods for the preparation of medicinally relevant scaffolds.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reactions were run under argon in nonflame-dried glassware. For reactions performed under oxygen, 99.6% extra dry oxygen was used. Unless otherwise stated, commercial reagents were used without further purification. Grignard reagents were prepared by conventional methods using metallic magnesium or via Knochel's procedure.[14] Anhydrous bismuth chloride >98% and triphenylbismuth diacetate 98% were purchased from Aldrich. Triarylbismuthines **1b**, **1d**, **1g**, **1l**, **1m**, **1q**, **1r**, **1s**, and **1t** were prepared according to a procedure that we previously reported.[10b] Triarylbismuthines **1c**, **1o**, and **21b** were prepared according to methods previously reported by us.[12b] Triarylbismuthines **1e**, **1f**, **1h**, **1i**, **1j**, **1k**, **1p**, **21a**, **21d**, and **21f** were prepared according to a procedure that we previously reported.[11a] Anhydrous solvents were obtained using an encapsulated solvent purification system and were further dried over 4 Å molecular sieves. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230–400 mesh silica using the indicated solvent system according to standard techniques. For compounds **1n**, **1o**, **1p**, **9b**, **37a**, and **37b**, the silica gel was washed with 3 volumes of 0.5% Et_3N/hexanes prior to performing the flash chromatography to avoid hydrolysis of the acetal. Melting points are uncorrected. Nuclear magnetic resonance spectra (^1H, ^{13}C) were recorded on a 300 or 600 MHz spectrometer. Chemical shifts for ^1H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26

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ppm; methanol, δ 3.31 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qt = quintuplet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet), coupling constant J in Hz, and integration. Chemical shifts for ^{13}C spectra are recorded in parts per million from tetramethylsilane using the central peak of deuterochloroform (δ 77.16 ppm) or the central peak of tetradeuteromethanol (δ 49.00 ppm) as the internal standard. IR spectra were recorded on an FT-IR from thin films and are reported in reciprocal centimeters (cm^{-1}). HRMS was performed on a TOF LCMS analyzer using the electrospray (ESI) mode.

General Procedure for the Synthesis of Triarylbismuthines. In a flask equipped with a magnetic stir bar and a condenser, bismuth chloride (500 mg, 1.6 mmol) was dissolved in anhydrous THF (23 mL) under argon and was cooled to −10 °C (ice/acetone bath). The organomagnesium reagent (5.23 mmol) was slowly added dropwise under argon. The reaction mixture was stirred at room temperature for 1 h and heated at 65 °C for 30 min. After cooling to room temperature, the solution was diluted with sat. aq. $NaHCO_3$ (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 × 100 mL), sat. aq. NaCl (2 × 100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using the indicated solvent system to afford the desired triarylbismuthine.

*Triphenylbismuth (**1a**).* The general procedure was followed on a 2.27 mmol scale starting from bismuth chloride and phenylmagnesium bromide. The crude product was purified on silica gel (2% EtOAc/hexanes) to afford triphenylbismuth **1a** as a white solid (831 mg, 83%): mp 78−79 °C; R_f 0.33 (2% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[39] ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.5 Hz, 6H), 7.42−7.30 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 137.7, 130.6, 127.9; IR (neat) 3133, 3053, 3011, 2582, 1943, 1871, 1810, 1566, 1471, 1422, 1053, 992, 718, 692. Anal. Calcd for $C_{18}H_{15}Bi$: C, 49.10; H, 3.43. Found: C, 49.28; H, 3.39.

*Tris(2-(diethoxymethyl)phenyl)bismuthine (**1n**).* The general procedure was followed on a 5.33 mmol scale starting from bismuth chloride and 2-(benzaldehydediethylacetal)magnesium bromide. The crude product was purified on silica gel (5% EtOAc/hexanes) to afford tris(2-(diethoxymethyl)phenyl)bismuthine **1n** as a white solid (3.3 g, 82%): mp 78−79 °C; R_f 0.81 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, J = 6.5, 1.4 Hz, 3H), 7.60 (dd, J = 7.3, 1.4 Hz, 3H), 7.30 (dt, J = 7.2, 1.4 Hz, 3H), 7.13 (dt, J = 7.3, 1.5 Hz, 3H), 5.53 (s, 3H), 3.55−3.34 (m, 12H), 1.01 (t, J = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 144.5, 140.6, 131.0, 127.5, 126.8, 104.4, 61.4, 15.1; IR (neat) 3049, 2973, 2928, 2871, 1438, 1336, 1204, 1108, 1090, 1050, 757; HRMS (ESI) calcd for $[C_{33}H_{45}BiO_6 + Na]^+$: 769.2912, found 769.2868.

*Tris(2-formylphenyl)bismuthine (**21c**).* H_2O (10 mL) and HCl 12N (0.90 mL) were added at room temperature to a stirred solution of **1n** (1.0 g, 1.3 mmol) in THF (30 mL). The reaction mixture was stirred overnight and then diluted with EtOAc (20 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL mL), sat. aq. NaCl (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(2-formylphenyl)bismuthine **21c** as a yellow solid (213 mg, 31%): mp 179−180 °C; R_f 0.46 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 10.23 (s, 3H), 8.02 (dd, J = 7.5, 1.4 Hz, 3H), 7.59−7.54 (m, 6H), 7.34 (td, J = 7.5, 1.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 196.0, 171.2, 142.3, 140.9, 136.9, 136.4, 127.7; IR (neat) 3042, 2977, 2806, 2724, 1690, 1671, 1571, 1556, 1197, 835, 759; HRMS (ESI) calcd for $[C_{21}H_{15}BiO_3 + H]^+$: 525.0898, found 525.0896.

*Tris(3-(hydroxymethyl)phenyl)bismuthine (**21e**).* A solution of tris(3-formylphenyl)bismuthine **21b** (400 mg, 0.76 mmol) in MeOH (10 mL) was cooled to 0 °C (acetone/ice bath), and $NaBH_4$ (90 mg, 2.4 mmol) was added. After 30 min, the reaction mixture was diluted with sat. aq. $NaHCO_3$ (15 mL) and extracted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and sat. aq. NaCl (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (40% EtOAc/hexanes) to afford tris(3-(hydroxymethyl)phenyl)-bismuthine **21e** as a white solid (392 mg, 97%): mp 107−108 °C; R_f 0.39 (80% EtOAc/hexanes); ^1H NMR (300 MHz, MeOD) δ 7.77 (s, 3H), 7.63 (d, J = 6.9 Hz, 3H), 7.37−7.28 (m, 6H), 4.53 (s, 6H); ^{13}C NMR (75 MHz, MeOD) δ 156.7, 144.3, 137.6, 137.2, 131.4, 127.6, 65.3; IR (neat) 3314 (br), 3038, 2923, 2869, 1563, 1412, 1203, 1012, 776; HRMS (ESI) calcd for $[C_{21}H_{21}BiO_3 + Na]^+$: 553.1187, found 553.1177.

*Tris(3-vinylphenyl)bismuthine (**21g**).* To a solution of Ph_3PCH_3I (1.86 g, 4.58 mmol) in THF (8 mL) at −10 °C, *t*-BuOK was added (606 mg, 5.4 mmol), and the solution was stirred for 30 min. To the yellow solution, tris(3-formylphenyl)bismuthine **21b** (800 mg, 1.53 mmol) was added, and the reaction was warmed up to room temperature and stirred for 2 h. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50 mL), sat. aq. NaCl (3 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford tris(3-vinylphenyl)-bismuthine **21g** as a yellow oil (650 mg, 82%): R_f 0.70 (20% EtOAc/hexanes); ^1H NMR (300 MHz, $CDCl_3$) 7.82 (s, 3H), 7.65−7.62 (m, 3H), 7.40−7.33 (m, 6H), 6.67 (dd, J = 17.6, 11.0 Hz, 3H), 5.66 (d, J = 17.6 Hz, 3H), 5.20 (d, J = 11.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 139.4, 137.2, 137.0, 135.5, 130.7, 125.7, 114.1; IR (neat) 3156, 3084, 3063, 3040, 3006, 2984, 2927, 1939, 1821, 1629, 1580, 1554, 1467, 1401, 1380, 991, 906, 791, 710. Anal. Calcd for $C_{24}H_{21}Bi$: C, 55.60; H, 4.08. Found: C, 55.87; H, 4.01.

*Tris(3-acetylphenyl)bismuthine (**21h**).* *Preparation via Dess-Martin oxidation*: A solution of tris(3-(1-hydroxyethyl)phenyl)bismuthine **21d** (50 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was cooled to −10 °C (acetone/ice bath), and pyridine (46 μL, 0.59 mmol) was added. After 5 min, Dess-Martin Periodinane (123 mg, 0.28 mmol) was added. After 1 h, the reaction mixture was diluted with EtOAc (15 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (15 mL), sat. aq. NaCl (3 × 15 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford tris(3-acetylphenyl)bismuthine **21h** as a white solid (30 mg, 59%). *Preparation via Swern oxidation:* A solution of oxalyl chloride (67 μL, 0.79 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was put under argon and cooled to −78 °C (acetone/ice bath). Anhydrous DMSO (112 μL, 1.57 mmol) was added dropwise to the reaction mixture and stirred for 30 min at −78 °C. Tris(3-(1-hydroxyethyl)phenyl)bismuthine **21d** (100 mg, 0.17 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and added dropwise to the reaction mixture and stirred for 1 h at −78 °C. Et_3N (219 μL, 1.57 mmol) was added, and the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was diluted with sat. aq. $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 × 50 mL), sat. aq. NaCl (2 × 50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford tris(3-acetylphenyl)bismuthine **21h** as a white solid (61 mg, 63%): mp 85−86 °C; R_f 0.17 (20% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[40] ^1H NMR (300 MHz, $CDCl_3$) δ 8.36−8.35 (m, 3H), 7.90−7.88 (m, 6H), 7.49 (t, J = 7.5 Hz, 3H), 2.49 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 156.0, 142.2, 138.8, 137.1, 131.1, 128.3, 26.8; IR (neat) 3344, 3051, 3008, 2923, 1678, 1578, 1559, 1404, 1356, 1255; HRMS (ESI) calcd for $[C_{24}H_{21}BiO_3 + H]^+$: 567.1367, found 567.1400.

General Procedure for the Crystallization of Triarylbismuthines 1f, 1i, 1k, 1n, 1s, 1t, 21b, 21c, 21e and Pyridone 17a. Compounds **1f**, **1i**, **1k**, **1n**, **1s**, **1t**, **21b**, **21c**, **21e**, and **17a** were crystallized by the solvent diffusion technique according to the following procedure: 10 mg of the corresponding compound was dissolved in a minimal amount of dichloromethane in an open vial. The vial was then placed in a bigger vial filled with hexanes with a loosely tightened cap. The vials were kept at room temperature until crystals were obtained.

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General Procedures for the Palladium-Catalyzed Cross-Coupling Reactions. Compounds **3a,b**, **5a**, **7a**, **9a,b**, **27**, **30a−d**, **31a**, **43**, and **44** were prepared according to the following procedures: **Method A** (Table 1, entry 13): In a sealed tube, the aryl or heteroaryl chloride, bromide, or iodide (1.0 equiv) was dissolved in *N,N*-dimethylformamide (4.0 mL). Potassium phosphate (2.0 equiv) was added, followed by tetrakis(triphenylphosphine)palladium (5 mol %), lithium chloride (2.0 equiv), and triarylbismuth reagent (0.4 equiv). Argon was bubbled in the reaction mixture for 1 min. The tube was sealed and heated at 80 °C for 6 h. The reaction mixture was cooled to room temperature, diluted with sat. aq. $NaHCO_3$ (20 mL), and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ (2 × 20 mL), sat. aq. NaCl (2 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using EtOAc/hexanes as the eluent to afford the corresponding product. **Method B** (Table 1, entry 14): Same as conditions **A** except that rubidium carbonate was used instead of potassium phosphate. **Method C** (Table 1, entry 18): Same as conditions **A** except that cesium carbonate was used instead of potassium phosphate and 0.4 equiv of cuprous iodide was used instead of lithium chloride.

*6-(3-Formylphenyl)nicotinaldehyde (**3a**).* Method B was followed on a 0.095 mmol scale starting from 6-chloronicotinaldehyde **2a** and organobismuthine **21b**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **3a** as a white solid (13 mg, 64%): mp 117−118 °C; R_f 0.29 (20% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[41] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1H), 10.12 (s, 1H), 9.15 (d, J = 1.4 Hz, 1H), 8.58 (s, 1H), 8.37 (dt, J = 7.7, 1.2 Hz, 1H), 8.26 (dd, J = 8.2, 2.1 Hz, 1H), 8.01−7.96 (m, 2H), 7.68 (t, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 190.4, 160.6, 152.4, 139.0, 137.2, 137.1, 133.3, 131.3, 130.5, 129.9, 128.9, 120.8; IR (neat) 3053, 2852, 2745, 1689, 1587, 1359, 1212, 1183, 1166, 835, 795, 740; HRMS (ESI) calcd for $[C_{13}H_9NO_2 + H]^+$: 212.0706, found 212.0708.

*1-(6-(4-((Tetrahydro-2H-pyran-2-yl)oxy)phenyl)pyridine-2-yl)-ethanone (**3b**).* Method B was followed on a 0.21 mmol scale starting from 2-acetyl-6-bromopyridine **2b** and organobismuthine **1m**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **3b** as a light pink solid (50 mg, 80%): mp 90−91 °C; R_f 0.47 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07−8.02 (m, 2H), 7.93−7.90 (m, 1H), 7.89−7.84 (m, 2H), 7.21−7.16 (m, 2H), 5.52 (t, J = 3.3 Hz, 1H), 3.97−3.89 (m, 1H), 3.67−3.60 (m, 1H), 2.82 (s, 3H), 2.10−2.00 (m, 1H), 1.93−1.89 (m, 2H), 1.88−1.60 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 158.5, 156.4, 153.4, 137.6, 132.0, 128.3, 122.9, 119.3, 116.8, 96.4, 62.2, 30.4, 25.9, 25.3, 18.8; IR (neat) 3060, 2943, 2872, 2840, 1696, 1606, 1513, 1449, 1355, 1239, 1177, 1036, 960, 919, 845, 806, 739, 613, 593; HRMS (ESI): calcd for $[C_{18}H_{19}NO_3 + H]^+$: 298.1438, found 298.1426.

*4-Methyl-2-(3-vinylphenyl)pyrimidine (**5a**).* Method A was followed on a 0.40 mmol scale starting from 2-chloro-4-methylpyrimidine **4a** and organobismuthine **21g**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **5a** as a yellow oil (16 mg, 20%): R_f 0.60 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (d, J = 5.1 Hz, 1H), 8.48 (t, J = 1.9 Hz, 1H), 8.34 (dt, J = 7.7, 1.5 Hz, 1H), 7.54 (dt, J = 7.7, 1.6 Hz, 1H), 7.45 (t, J = 7.7 Hz, 1H), 7.05 (d, J = 5.0 Hz, 1H), 6.82 (dd, J = 17.6, 10.9 Hz, 1H), 5.87 (dd, J = 17.4, 0.9 Hz, 1H), 5.30 (dd, J = 10.8, 0.9 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 164.3, 156.9, 138.2, 138.0, 136.8, 128.9, 128.3, 127.8, 126.3, 118.8, 114.4, 24.6; IR (neat) 3061, 3038, 2954, 2928, 2867, 1692, 1572, 1555, 1431, 1384, 1364, 912, 789; HRMS (ESI) calcd for $[C_{13}H_{12}N_2 + H]^+$: 197.1073, found 197.1080.

*2-(4-(6-(Dimethylamino)pyrazin-2-yl)phenyl)propan-2-ol (**7a**).* Method A was followed on a 0.32 mmol scale starting from 6-chloro-*N,N*-dimethylpyrazin-2-amine **6a** and organobismuthine **21a**. The crude material was purified on silica gel (40% EtOAc/hexanes) to afford **7a** as a yellow solid (34 mg, 41%): mp 158−159 °C; R_f 0.20 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.99−7.94 (m, 2H), 7.91 (s, 1H), 7.60−7.56 (m, 2H), 3.17 (s, 6H), 2.37 (s(br), 1H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 150.5, 149.2, 136.0, 128.4, 127.9, 126.8, 125.0, 72.6, 37.6, 31.9; IR (neat) 3371 (br), 3059, 2971, 2923, 2869, 1583, 1566, 1527, 1425, 1402, 1372, 1186, 1151, 996, 831; HRMS (ESI) calcd for $[C_{15}H_{19}N_3O + H]^+$: 258.1601, found 258.1603.

*1-(3-(6-Phenylpyridazin-3-yl)phenyl)ethanone (**9a**).* Method A was followed on a 0.26 mmol scale starting from 3-chloro-6-phenylpyridazine **8a** and organobismuthine **21h**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **9a** as a yellow solid (18 mg, 25%): mp 130−131 °C; R_f 0.25 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (t, J = 1.9 Hz, 1H), 8.41 (dt, J = 7.9, 1.4 Hz, 1H), 8.18 (dd, J = 8.1, 1.9 Hz, 2H), 8.11 (dt, J = 6.5, 1.5 Hz, 1H), 8.05−7.97 (m, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.60−7.52 (m, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 158.1, 156.8, 137.9, 136.7, 135.9, 131.4, 130.4, 129.8, 129.5, 129.2, 127.1, 126.9, 124.5, 124.4, 27.0; IR (neat) 3061, 3000, 2932, 1683, 1601, 1585, 1432, 1398, 1358, 1236, 689; HRMS (ESI) calcd for $[C_{18}H_{14}N_2O + H]^+$: 275.1179, found 275.1191.

*3-(3-(Diethoxymethyl)phenyl)-6-phenylpyridazine (**9b**).* Method B was followed on a 0.10 mmol scale starting from 3-chloro-6-phenylpyridazine **8a** and organobismuthine **1o**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **9b** as a beige solid (15 mg, 45%): mp 88−89 °C; R_f 0.36 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (t, J = 1.8 Hz, 1H), 8.19−8.14 (m, 3H), 7.95 (dd, J = 11.3, 9.0 Hz, 2H), 7.63 (dt, J = 7.7, 1.5 Hz, 1H), 7.58−7.51 (m, 4H), 5.61 (s, 1H), 3.73−3.54 (m, 4H), 1.27 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 157.7, 140.3, 136.3, 130.2, 129.2, 129.1, 128.5, 127.1, 125.4, 124.5, 124.3, 101.5, 61.4, 15.4; IR (neat) 3052, 2974, 2917, 2848, 1704, 1450, 1397, 1328, 1095, 1050, 997, 780, 690; HRMS (ESI): calcd for $[C_{21}H_{22}N_2O_2 + H]^+$: 335.1754, found 335.1767.

*3′-(1-Hydroxyethyl)-[1,1′-biphenyl]-4-carbaldehyde (**27**).* Method C was followed on a 0.27 mmol scale starting from 4-bromobenzaldehyde **26** and organobismuthine **21d**. The crude material was purified on silica gel (25% EtOAc/hexanes) to afford **27** as a yellow oil (51 mg, 83%): R_f 0.22 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 7.97−7.93 (m, 2H), 7.78−7.74 (m, 2H), 7.67−7.66 (m, 1H), 7.55 (td, J = 7.1, 1.9 Hz, 1H), 7.49−7.41 (m, 2H) 4.99 (q, J = 6.5 Hz, 1H), 1.82 (s(br), 1H), 1.56 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.1, 147.2, 146.8, 139.9, 135.3, 130.3, 129.2, 127.8, 126.5, 125.6, 124.5, 70.3, 25.4; IR (neat) 3422 (br), 3059, 3032, 2971, 2923, 2836, 2731, 1689, 1603, 1567, 1170, 1077, 794, 703; HRMS (ESI) calcd for $[C_{15}H_{14}O_2 + H]^+$: 227.1067, found 227.1068.

*(E)-Ethyl 3-(4′-(2-((tert-Butoxycarbonyl)amino)ethyl)-[1,1′-biphenyl]-3-yl)acrylate (**30a**).* Method A was followed on a 0.17 mmol scale starting from *tert*-butyl 4-bromophenethylcarbamate **28a** and organobismuthine **21f**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **30a** as a yellow solid (60 mg, 89%): mp 111−112 °C; R_f 0.52 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 16.0 Hz, 1H), 7.73 (s, 1H), 7.61−7.59 (m, 1H), 7.55−7.53 (m, 1H), 7.48 (d, J = 7.5 Hz, 1H), 7.45−7.40 (m, 2H), 7.06 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 16.0 Hz, 1H), 4.53 (s(br), 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.34 (q, J = 6.4 Hz, 2H), 2.75 (t, J = 6.9 Hz, 2H), 1.43 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 155.9, 144.3, 141.3, 138.1, 135.2, 131.7, 130.6, 129.6, 129.0, 127.3, 126.9, 120.3, 119.0, 79.4, 60.7, 41.7, 35.8, 28.5, 14.4; IR (neat) 3437, 3363, 2977, 2931, 2866, 1703, 1637, 1508, 1488, 1365, 1307, 1267, 1248, 1163, 1036, 1011, 789. Anal. Calcd for $C_{24}H_{29}NO_4$: C, 72,89; H, 7.39; N, 3.54. Found: C, 72.90; H, 7.41; N, 3.52.

*Methyl 3′-Methoxy-[1,1′-biphenyl]-4-carboxylate (**30b**). Starting from methyl 4-iodobenzoate **28b***: Method C was followed on a 0.19 mmol scale starting from methyl 4-iodobenzoate **28b** and organobismuthine **1l**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **30b** as a white solid (45 mg, 98%). *Starting from methyl 4-bromobenzoate **28c**:* Method B was followed on a 0.30 mmol scale starting from methyl 4-bromobenzoate **28c** and organobismuthine **1l**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **30b** as a white solid (57 mg, 78%): mp 55−56 °C; R_f 0.50 (10% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[42] ^{1}H NMR (600 MHz, $CDCl_3$) δ

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J. Org. Chem. 2016, 81, 5401−5416

8.10 (d, J = 4.2 Hz, 2H), 7.65 (d, J = 4.2 Hz, 2H), 7.38 (t, J = 3.9 Hz, 1H), 7.20 (d, J = 3.8 Hz, 1H), 7.16−7.15 (m, 1H), 6.94 (dd, J = 4.1, 1.0 Hz, 1H) 3.94 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 160.1, 145.6, 141.6, 130.2, 130.1, 129.1, 127.2, 119.9, 113.6, 113.1, 55.5, 52.2; IR (neat) 3064, 2999, 2950, 2835, 1932, 1716, 1605, 1434, 1270, 1103, 1017, 849, 764, 694; HRMS (ESI): calcd for $[C_{15}H_{14}O_3 + H]^+$: 243.1016, found 243.1016.

*Methyl 3′-Cyano-[1,1′-biphenyl]-4-carboxylate (**30c**).* Method B was followed on a 0.30 mmol scale starting from methyl 4-iodobenzoate **28b** and organobismuthine **1s**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **30c** as a white solid (62 mg, 87%): mp 137−138 °C; R_f 0.60 (20% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[43] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.88−7.87 (m, 1H), 7.85−7.81 (m, 1H), 7.68−7.54 (m, 4H) 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 143.2, 141.3, 131.7, 131.6, 130.9, 130.5, 130.1, 129.9, 127.2, 118.6, 113.3, 52.4; IR (neat) 3411, 3068, 2954, 2836, 2232, 1608, 1429, 1281, 1186, 1102, 764, 684; HRMS (ESI): calcd for $[C_{15}H_{11}NO_2 + H]^+$: 238.0863, found 238.0870.

*3′-Vinyl-[1,1′-biphenyl]-4-carbaldehyde (**30d**).* Method C was followed on a 0.17 mmol scale starting from 4-bromobenzaldehyde **28d** and organobismuthine **21g**. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **30d** as a colorless oil (27 mg, 76%): R_f 0.30 (5% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.98−7.94 (m, 2H), 7.79−7.74 (m, 2H), 7.66−7.65 (m, 1H), 7.55−7.51 (m, 1H), 7.49−7.42 (m, 2H), 6.80 (dd, J = 17.6, 10.8 Hz, 1H), 5.84 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 10.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 147.2, 140.2, 138.5, 136.6, 135.4, 130.4, 129.3, 127.9, 126.9, 126.3, 125.5, 114.9; IR (neat) 3407 (br), 3057, 2916, 2844, 2734, 1692, 1601, 1384, 1209, 1167, 988, 836, 791, 699; HRMS (ESI): calcd for $[C_{15}H_{12}O + H]^+$: 209.0961, found 209.0965.

*5-(3-(1-Hydroxyethyl)phenyl)furan-2-carbaldehyde (**31a**).* Method A was followed on a 0.23 mmol scale starting from 5-iodofuran-2-carbaldehyde **29a** and organobismuthine **21d**. The crude material was purified on silica gel (30% EtOAc/hexanes) to afford **31a** as a yellow oil (41 mg, 82%): R_f 0.25 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.85 (s, 1H), 7.74−7.71 (m, 1H), 7.43−7.41 (m, 2H), 7.32 (d, J = 3.7 Hz, 1H), 6.86 (d, J = 3.7 Hz, 1H), 4.97 (q, J = 6.5 Hz, 1H), 1.96 (s(br), 1H), 1.53 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 159.5, 151.9, 146.9, 129.2, 129.1, 126.8, 124.4, 123.8, 122.3, 107.9, 70.1, 25.4; IR (neat) 3416 (br), 3103, 2972, 2916, 2871, 2821, 1663, 1516, 1468, 1426, 1265, 1071, 1028, 792; HRMS (ESI) calcd for $[C_{13}H_{12}O_3 + H]^+$: 217.0859, found 217.0867.

*3′-Hydroxy-[1,1′-biphenyl]-3-carbaldehyde (**43**).* Method A was followed on a 0.23 mmol scale starting from 3-iodophenol **39** and organobismuthine **21b**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **43** as a white solid (23 mg, 50%): mp 88−89 °C; R_f 0.38 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.09 (s, 1H), 8.08 (t, J = 1.6 Hz, 1H), 7.86 (dt, J = 7.4, 1.4 Hz, 2H), 7.61 (t, J = 7.7 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.20 (dt, J = 7.6, 1.4 Hz, 1H), 7.11 (t, J = 2.2 Hz, 1H), 6.87 (ddd, J = 8.1, 2.5, 0.8 Hz, 1H), 4.97 (s(br), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 156.3, 141.9, 141.5, 137.0, 133.3, 130.4, 129.7, 129.1, 128.3, 119.8, 115.2, 114.3; IR (neat) 3363 (br), 3062, 2927, 2831, 2734, 1686, 1599, 1588, 1458, 1308, 1212, 1169, 779, 690; HRMS (ESI) calcd for $[C_{13}H_{10}O_2 + H]^+$: 199.0754, found 199.0750.

*3-(1H-Indol-5-yl)benzaldehyde (**44**).* Method A was followed on 0.21 mmol scale starting from 5-iodo-1*H*-indole **40** and organobismuthine **21b**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **44** as a yellow oil (18 mg, 39%): R_f 0.43 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.26 (s(br), 1H), 8.17 (t, J = 1.8 Hz, 1H), 7.95−7.91 (m, 1H), 7.91 (s, 1H), 7.82 (dt, J = 7.6, 1.4 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.49 (s, 2H), 7.28 (t, J = 2.9 Hz, 1H), 6.64 (dd, J = 3.1, 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 143.6, 137.0, 135.8, 133.4, 132.0, 129.5, 128.6, 127.8, 125.3, 121.8, 119.6, 111.6, 103.1; IR (neat) 3414 (br), 3057, 2825, 2738, 1689, 1599, 1578, 1466, 1424, 1316, 1197, 792; HRMS (ESI) calcd for $[C_{15}H_{11}NO + H]^+$: 222.0913, found 222.0924.

General Procedure for the *N*-Arylation of Indoles, Pyrroles, Pyrazoles, and Pyridones. Compounds **17a**, **34a−e**, **35a,b**, and **42** were prepared according to the following procedures: **Method A**: In a sealed tube, the triarylbismuthine (1.0 equiv) was added, followed by copper(II) acetate (0.1 equiv) and the indole, pyrrole, pyrazole, or pyridone (1.0 equiv). The reagents were dissolved in anhydrous dichloromethane (4 mL), and pyridine (1.0 equiv) was added to the mixture. The reaction tube was purged with dry oxygen for 30 s, sealed, and heated at 50 °C overnight. The reaction mixture was cooled to room temperature, transferred, and rinsed with EtOAc in a round-bottom flask. Silica gel was added, and the mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using the indicated solvent system as the eluent to give the corresponding product. **Method B**: Same as method **A** except for copper(II) acetate (1.0 equiv instead of 0.1 equiv) and pyridine (3.0 equiv instead of 1.0 equiv). **Method C**: Same as method **A** except that 1.0 equiv of copper(II) acetate and 3.0 equiv of pyridine were used and the reaction was performed at 50 °C under air in a sealed tube overnight.

*(E)-Ethyl 3-(3-(3-Cyano-2-oxopyridin-1(2H)-yl)phenyl)acrylate (**17a**).* Method B was followed on a 0.21 mmol scale starting from 2-oxo-1,2-dihydropyridine-3-carbonitrile and organobismuthine **21f**. The crude product was purified on silica gel (50% EtOAc/hexanes) to afford **17a** as a white solid (52 mg, 84%): mp 173−174 °C; R_f 0.37 (60% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, J = 7.1, 2.1 Hz, 1H), 7.66 (d, J = 16.1 Hz, 1H), 7.63−7.59 (m, 2H), 7.54 (d, J = 7.7 Hz, 1H), 7.52−7.51 (m, 1H), 7.38 (dt, J = 7.9, 1.6 Hz, 1H), 6.45 (d, J = 16.1 Hz, 1H), 6.38 (t, J = 7.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.3, 148.0, 142.9, 142.6, 140.1, 136.4, 130.3, 129.0, 127.7, 125.6, 120.5, 115.3, 107.0, 105.8, 60.9, 14.4; IR (neat) 3080, 2977, 2924, 2905, 2228, 1707, 1662, 1640, 1542, 1269, 1181; HRMS (ESI) calcd for $[C_{17}H_{14}N_2O_3 + H]^+$: 295.1077, found 295.1099.

*1-(4-((Tetrahydro-2H-pyran-2-yl)oxy)phenyl)-1H-indole-5-carbaldehyde (**34a**).* Method B was followed on a 0.17 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **1m**. The crude product was purified on silica gel (15% EtOAc/hexanes) to afford **34a** as a yellow solid (43 mg, 79%): mp 105−106 °C; R_f 0.52 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.20 (s, 1H), 7.76 (d, J = 8.6 Hz, 1H), 7.53−7.46 (m, 1H), 7.41−7.30 (m, 3H), 7.26−7.20 (m, 2H), 6.80 (d, J = 3.2 Hz, 1H), 5.49 (t, J = 3.3 Hz, 1H), 3.99−3.91 (m, 1H), 3.70−3.63 (m, 1H), 2.08−1.99 (m, 1H), 1.94−1.89 (m, 2H), 1.78−1.62 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 156.5, 139.7, 132.7, 130.5, 130.0, 128.8, 126.5, 126.2, 122.6, 117.6, 111.2, 104.8, 96.7, 62.3, 30.4, 25.3, 18.8; IR (neat) 3101, 3039, 2943, 2873, 2850, 2715, 1683, 1615, 1509, 1330, 1237, 1221, 1201, 1102, 1044, 921, 731; HRMS (ESI) calcd for $[C_{20}H_{19}NO_3 + H]^+$: 322.1438, found 322.1430.

*1-(2-Formylphenyl)-1H-indole-5-carbaldehyde (**34b**).* Method B was followed on a 0.17 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **21c**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **34b** as a yellow oil (15 mg, 35%): R_f 0.44 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.63 (s, 1H), 8.25 (d, J = 0.9 Hz, 1H), 8.13 (dd, J = 7.7, 1.5 Hz, 1H), 7.83−7.77 (m, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.51 (dd, J = 7.9, 0.8 Hz, 1H), 7.39 (d, J = 3.3 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 6.91 (dd, J = 3.3, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 189.1, 141.5, 141.0, 135.4, 132.3, 131.9, 131.7, 130.7, 129.2, 128.7, 128.4, 126.4, 123.6, 110.9, 106.0; IR (neat) 3357, 3106, 3065, 2977, 2920, 2867, 2745, 1687, 1597, 1490, 1331, 1195; HRMS (ESI) calcd for $[C_{16}H_{11}NO_2 + H]^+$: 250.0868, found 250.0873.

*1-(3-(Hydroxymethyl)phenyl)-1H-indole-5-carbaldehyde (**34c**).* Method B was followed on a 0.09 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **21e**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **34c** as a yellow oil (17 mg, 75%): R_f 0.15 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.22 (d, J = 1.1 Hz, 1H), 7.78 (dd, J = 8.7, 1.5 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.55−7.53 (m, 2H), 7.44−7.41 (m, 3H), 6.84 (d, J = 3.3 Hz, 1H), 4.83 (d, J = 4.0 Hz, 2H), 1.84 (t, J = 5.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 143.2,

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J. Org. Chem. 2016, 81, 5401−5416

139.3, 130.2, 130.1, 130.0, 129.2, 126.5, 125.8, 123.8, 123.1, 122.8, 111.2, 105.4, 105.4, 64.8; IR (neat) 3411 (br), 3105, 3055, 2920, 2858, 2815, 2727, 1682, 1601, 1589, 1565, 1493, 1449, 1331, 1223, 1103, 1032, 894, 726, 698; HRMS (ESI) calcd for $[C_{16}H_{13}NO_2 + H]^+$: 252.1019, found 252.1012.

*1-(3-Acetylphenyl)-1H-indole-5-carbaldehyde (**34d**).* Method B was followed on a 0.17 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **21h**. The crude product was purified on silica gel (30% EtOAc/hexanes) to afford **34d** as a yellow oil (27 mg, 60%): R_f 0.34 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.23 (d, J = 1.5 Hz, 1H), 8.09 (t, J = 1.8 Hz, 1H), 8.00 (dt, J = 7.4, 1.6 Hz, 1H), 7.81 (dd, J = 8.7, 1.6 Hz, 1H), 7.73 (dt, J = 8.0, 1.7 Hz, 1H), 7.70−7.65 (m, 1H), 7.57 (d, J = 8.7 Hz, 1H) 7.45 (d, J = 3.3 Hz, 1H), 6.87 (d, J = 3.3 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 192.3, 139.6, 139.2, 139.0, 130.5, 130.4, 129.9, 129.3, 129.1, 127.3, 126.5, 124.3, 123.2, 111.0, 106.0, 26.9; IR (neat) 3357, 3103, 3057, 2924, 2825, 2741, 1682, 1599, 1586, 1491, 1445, 1330, 1236, 1105, 769; HRMS (ESI) calcd for $[C_{17}H_{13}NO_2 + H]^+$: 264.1019, found 264.1012.

*1-Phenyl-1H-indole-5-carbaldehyde (**34e**).* Method B was followed on a 0.29 mmol scale starting from 1*H*-indole-5-carbaldehyde **32** and organobismuthine **1a**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **34e** as a yellow oil (62 mg, 97%): R_f 0.14 (10% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[44] ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.22 (s, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.61−7.54 (m, 3H), 7.52−7.49 (m, 2H), 7.46−7.41 (m, 2H), 6.84 (d, J = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.4, 139.4, 139.1, 130.3, 130.2, 130.0, 129.2, 127.6, 126.5, 124.9, 122.8, 111.2, 105.4; IR (neat) 3060, 2962, 2921, 2815, 2778, 2709, 1683, 1593, 1498, 1448, 1338, 1222, 1103, 886, 755, 695; HRMS (ESI): calcd for $[C_{15}H_{11}NO + H]^+$: 222.0913, found 222.0919.

*1-(1-(3-(1-Hydroxyethyl)phenyl)-1H-pyrrol-2-yl)ethanone (**35a**).* Method A was followed on a 0.13 mmol scale starting from 1-(1*H*-pyrrol-2-yl)ethanone and organobismuthine **21d**. The crude product was purified on silica gel (35% EtOAc/hexanes) to afford **35a** as a yellow oil (30 mg, 99%): R_f 0.19 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.32 (m, 2H), 7.26 (s, 1H), 7.13−7.08 (m, 2H), 6.94 (dd, J = 2.4, 1.8 Hz, 1H), 6.28 (dd, J = 4.1, 2.6 Hz, 1H), 4.84 (q, J = 6.4 Hz, 1H), 3.51 (s(br), 1H), 2.38 (s, 3H), 1.45 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5, 147.1, 140.8, 131.5, 131.4, 128.6, 124.8, 124.7, 123.4, 120.9, 109.3, 69.6, 27.2, 25.0; IR (neat) 3409 (br), 3114, 3057, 2973, 2920, 2867, 1644, 1489, 1405, 1366, 1348, 1110, 1084, 1050, 940, 793, 738, 654; HRMS (ESI) calcd for $[C_{14}H_{15}NO_2 + H]^+$: 230.1176, found 230.1178.

*4-Methyl-1-(3-vinylphenyl)-1H-pyrazole (**35b**).* Method B was followed on a 0.43 mmol scale starting from 4-methyl-1*H*-pyrazole and organobismuthine **21g**. The crude product was purified on silica gel (20% EtOAc/hexanes) to afford **35b** as a yellow oil (70 mg, 88%): R_f 0.53 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (t, J = 2.0 Hz, 1H), 7.70−7.69 (m, 1H), 7.53 (s, 1H), 7.51−7.48 (m, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.27 (dt, J = 7.7, 1.5 Hz, 1H), 6.73 (dd, J = 17.6, 10.8 Hz, 1H), 5.82 (d, J = 17.6 Hz, 1H), 5.31 (d, J = 10.9 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 140.6, 139.1, 136.3, 129.6, 125.5, 123.9, 118.4, 118.0, 116.6, 115.1, 9.1; IR (neat) 3141, 3118, 3065, 2926, 2863, 1695, 1606, 1585, 1533, 1489, 1454, 1399, 1362, 1047, 791, 755, 697; HRMS (ESI) calcd for $[C_{12}H_{12}N_2 + H]^+$: 185.1073, found 185.1078.

*3-(5-Iodo-1H-indol-1-yl)benzaldehyde (**42**).* Method B was followed on 0.12 mmol scale starting from 5-iodo-1*H*-indole **40** and organobismuthine **21b**. The crude material was purified on silica gel (20% EtOAc/hexanes) to afford **42** as a yellow oil (29 mg, 70%): R_f 0.54 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.03 (d, J = 1.5 Hz, 1H), 7.98−7.97 (m, 1H), 7.87 (dt, J = 7.0, 1.6 Hz, 1H), 7.76−7.68 (m, 2H), 7.49 (dd, J = 8.7, 1.6 Hz, 1H), 7.33 (s, 1H), 7.31 (d, J = 5.2 Hz, 1H), 6.65 (d, J = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4, 140.3, 138.0, 134.9, 132.1, 131.2, 130.7, 130.3, 129.9, 128.5, 128.4, 124.3, 112.3, 103.8, 84.4; IR (neat) 3106, 3068, 2958, 2920, 2829, 2734, 1698, 1588, 1513, 1487, 1459, 1237, 793; HRMS (ESI) calcd for $[C_{15}H_{10}INO + H]^+$: 347.9880, found 347.9896.

General Procedure for the *O*-Arylation of Phenols. Compounds **37a−e** and **41** were prepared according to the following procedures: **Method A**: In a sealed tube, the phenol (1.0 equiv) was dissolved in nonanhydrous solvent grade dichloromethane (3 mL). The organobismuthine (1.0 equiv) was added followed by copper(II) acetate (1.0 equiv) and Et_3N (3.0 equiv). The tube was sealed and heated at 50 °C for 3 h under air. 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 to afford the corresponding product. **Method B**: Same as method **A** except that 0.3 equiv of $Cu(OAc)_2$ was used and the reaction was performed under O_2 for 16 h.

*Methyl 3-(3-(Diethoxymethyl)phenoxy)benzoate (**37a**).* Method A was followed on a 0.26 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **1o**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **37a** as a colorless oil (75 mg, 87%): R_f 0.62 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dt, J = 7.7, 1.3 Hz, 1H), 7.65 (dd, J = 2.6, 1.5 Hz, 1H), 7.42−7.31 (m, 2H), 7.27−7.24 (m, 1H), 7.20 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 7.16 (t, J = 2.1 Hz, 1H), 6.97 (ddd, J = 7.9, 2.6, 1.2 Hz, 1H), 5.48 (s, 1H), 3.88 (s, 3H), 3.67−3.48 (m, 4H), 1.22 (t, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 157.5, 156.8, 141.6, 132.0, 129.9, 129.8, 124.4, 123.4, 122.2, 119.6, 119.0, 117.6, 101.1, 61.2, 52.4, 15.3; IR (neat) 3068, 2973, 2920, 2878, 1726, 1684, 1582, 1483, 1441, 1357, 1270, 1049, 901, 794, 753, 696; HRMS (ESI) calcd for $[C_{19}H_{22}O_5 + Na]^+$: 353.1359, found 353.1369.

*Methyl 3-(2-(Diethoxymethyl)phenoxy)benzoate (**37b**).* Method B was followed on a 0.16 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **1n**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **37b** as a colorless oil (39 mg, 74%): R_f 0.73 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.73 (m, 1H), 7.70 (dd, J = 7.6, 1.8 Hz, 1H), 7.64 (dd, J = 2.6, 1.5 Hz, 1H), 7.37 (t, J = 7.9 Hz, 1H), 7.28 (dt, J = 7.4, 1.8 Hz, 1H), 7.20 (td, J = 7.5, 1.3 Hz, 1H), 7.14 (ddd, J = 8.3, 2.6, 1.1 Hz, 1H), 6.88 (dd, J = 8.2, 1.5 Hz, 1H), 5.73 (s, 1H), 3.89 (s, 3H), 3.70−3.60 (m, 2H), 3.56−3.49 (m, 2H), 1.16 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.2, 153.8, 131.9, 131.2, 129.9, 129.7, 128.0, 124.4, 124.0, 122.6, 119.7, 119.0, 97.6, 62.4, 52.3, 15.2; IR (neat) 3066, 2975, 2877, 1724, 1580, 1482, 1444, 1271, 1230, 1202, 1052, 994, 905, 754; HRMS (ESI) calcd for $[C_{19}H_{22}O_5 + Na]^+$: 353.1359, found 353.1363.

*Methyl 3-(3-Vinylphenoxy)benzoate (**37c**).* Method B was followed on a 0.13 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **21g**. The crude material was purified on silica gel (10% EtOAc/hexanes) to afford **37c** as a yellow oil (27 mg, 82%): R_f 0.74 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (dt, J = 7.7, 1.3 Hz, 1H), 7.66 (dd, J = 2.6, 1.6 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.23−7.17 (m, 2H), 7.07 (t, J = 2.0 Hz, 1H), 6.90 (ddd, J = 8.1, 2.4, 1.0 Hz, 1H), 6.67 (dd, J = 17.6, 10.9 Hz, 1H), 5.70 (dd, J = 17.6, 0.8 Hz, 1H), 5.27 (d, J = 10.9 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 157.5, 157.1, 139.8, 136.3, 132.1, 130.1, 129.9, 124.5, 123.4, 122.0, 119.7, 118.6, 116.8, 115.0, 52.4; IR (neat) 3076, 3008, 2952, 2928, 2844, 1724, 1573, 1485, 1442, 1275, 1250, 1208, 1143, 1098, 991; HRMS (ESI) calcd for $[C_{16}H_{14}O_3 + H]^+$: 255.1016, found 255.1020.

*(E)-Methyl 3-(3-(3-Ethoxy-3-oxoprop-1-en-1-yl)phenoxy)-benzoate (**37d**).* Method A was followed on a 0.25 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **21f**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **37d** as a yellow oil (43 mg, 53%): R_f 0.61 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (td, J = 7.8, 1.3 Hz, 1H), 7.67−7.66 (m, 1H), 7.62 (d, J = 16.0 Hz, 1H), 7.46−7.40 (m, 1H), 7.39−7.34 (m, 1H), 7.30−7.27 (m, 1H), 7.22 (ddd, J = 8.2, 2.6, 1.1 Hz, 1H), 7.14 (t, J = 2.1 Hz, 1H), 7.02 (ddd, J = 8.0, 1.9, 1.2 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 166.5, 157.5, 157.0, 143.8, 136.6, 132.2, 130.5, 130.1, 124.9, 123.7, 123.6, 120.7, 120.0, 119.3, 118.0, 60.7, 52.4, 14.4; IR (neat) 3065,

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J. Org. Chem. 2016, 81, 5401−5416

2980, 2953, 2901, 1709, 1639, 1575, 1484, 1442, 1269, 1230, 1177, 1097, 1036, 983, 756; HRMS (ESI) calcd for $[C_{19}H_{18}O_5 + H]^+$: 327.1227, found 327.1224.

*Methyl 3-Phenoxybenzoate (**37e**).* A modified method B using 1.0 equiv of $Cu(OAc)_2$ instead of 0.3 equiv and pyridine instead of triethylamine was followed on a 0.33 mmol scale starting from methyl 3-hydroxybenzoate **36** and organobismuthine **1a**. The crude material was purified on silica gel (5% EtOAc/hexanes) to afford **37e** as a pale yellow oil (53 mg, 70%): R_f 0.43 (10% EtOAc/hexanes). Spectral data were identical to those of the literature compound:[45] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (td, J = 7.7, 1.3 Hz, 1H), 7.68 (t, J = 2.1 Hz, 1H), 7.43−7.32 (m, 3H), 7.21 (dd, J = 8.2, 2.5 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 8.2 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 157.5, 156.7, 131.9, 129.9, 129.8, 124.3, 123.8, 123.3, 119.6, 119.1, 52.2; IR (neat) 3068, 2947, 2840, 1722, 1582, 1479, 1437, 1266, 1228, 1091, 988, 904, 749, 688; HRMS (ESI): calcd for $[C_{14}H_{12}O_3 + H]^+$: 229.0859, found 229.0863.

*3-(3-Iodophenoxy)benzaldehyde (**41**).* Method B was followed on a 0.23 mmol scale starting from 3-iodophenol **39** and organobismuthine **21b**. The crude material was purified on silica gel (15% EtOAc/hexanes) to afford **41** as a yellow oil (33 mg, 44%): R_f 0.69 (20% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.64 (dt, J = 7.4, 1.1 Hz, 1H), 7.52−7.46 (m, 3H), 7.37 (t, J = 2.0 Hz, 1H), 7.28 (ddd, J = 8.1, 2.5, 1.0 Hz, 1H), 7.09 (t, J = 8.1 Hz, 1H), 6.99 (ddd, J = 8.2, 2.3, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.5, 157.7, 157.1, 138.3, 133.3, 131.4, 130.8, 128.4, 125.5, 125.0, 118.7, 118.6, 94.5; IR (neat) 3059, 2923, 2827, 2734, 1697, 1572, 1465, 1450, 1243, 1208, 846, 781; HRMS (ESI) calcd for $[C_{13}H_9IO_2 + H]^+$: 324.9720, found 324.9714.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00767.

Crystallographic data for **1f**, **1i**, **1k**, **1n**, **1s**, **1t**, **17a**, **21c**, and **21e** (ZIP)

Copies of ^{1}H, ^{13}C, and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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