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Copper-Catalyzed *N*-Arylation of Azoles and Diazoles using Highly Functionalized Trivalent Organobismuth Reagents

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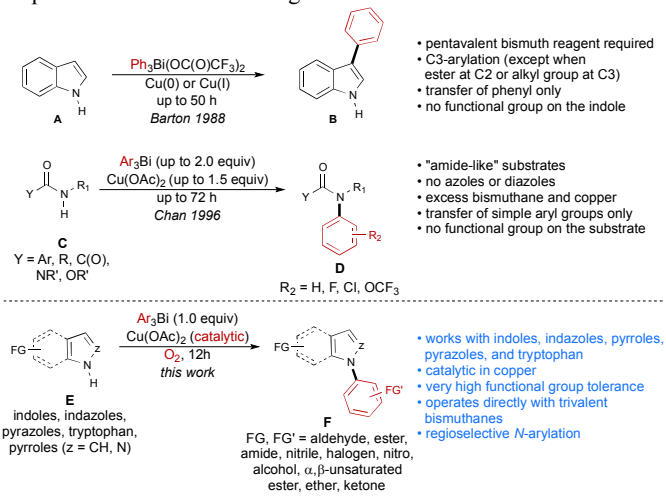
The *N*-arylation of indoles, indazoles, pyrroles, and pyrazoles using highly functionalized trivalent arylbismuth reagents is reported. The reaction is promoted by substoichiometric amount of copper acetate and tolerates a wide diversity of functional groups on the azole as well as on the organobismuth reagent. The method is also applied to the *N*-arylation of tryptophan derivatives.

Azoles and diazoles are privileged scaffolds that are frequently used in medicinal chemistry to project key pharmacophores in different vectors inside the binding pocket of a biological target.[1,2] The *N*-arylation of these nitrogenated compounds allows to screen for new interactions around the inhibitor[3] and to modify its biophysical properties.[4] *N*-Arylazoles have also found numerous applications in material and polymer sciences.[5] *N*-Arylazoles and diazoles are commonly prepared via metal-catalyzed *N*-arylation[6] of N–H heteroarenes using aryl halides[7], arylboronic acids[8], or aryllead[9] reagents. However, while lead reagents are highly toxic, the other methods sometimes require extended reaction times, super-stoichiometric amount of catalyst, or costly ligands to obtain good yields. Consequently, new procedures that lead to the facile installation of densely functionalized aryl groups on azoles and diazoles are still desirable.

We disclosed over the past years a portfolio of reactions for the formation of C–C,[10] C–N,[11] and C–O[12] bonds using organobismuth reagents. Organobismuthanes can be prepared from inexpensive and non toxic bismuth salts and offer a mild reactivity that allows the presence of numerous functional groups on the substrate as well as on the organometallic species.[13] Barton and Finet reported in 1988 the use of triphenylbismuth bis-trifluoroacetate in the arylation of indoles **A** (Scheme 1).[14] However, the method was applied exclusively to the transfer of an unsubstituted phenyl group and required the use of a pentavalent bismuth species which is less stable than the trivalent counterpart. More importantly, C3-arylation was observed in most cases, except when that position was blocked by an alkyl group or when an ester was present at the C2 position of the indole.

In 1996, Chan published a variation of a protocol disclosed by Barton and Finet[15] where trivalent bismuthanes are used to *N*-arylate nitrogenated compounds (Scheme 1).[16] While this method is very useful, it suffers from multiple limitations since it requires up to 2.0 equivalents of the organobismuth reagent, 1.5 equivalent of the copper catalyst and reaction times as long as 72 hours. Additionally, the method was not applied to indoles, indazoles, pyrazoles, nor pyrroles, but rather to compounds of type **C** where the nitrogen atom is connected to a carbonyl function. Finally, the functional group tolerance was not demonstrated as only simple arylbismuthanes were coupled with substrates bearing no functionalities.



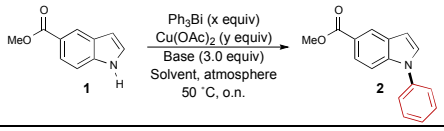
Scheme 1 Comparison of our *N*-arylation reaction with precedents from the literature.

We report herein the first method for the *N*-arylation of azoles and diazoles **E** using highly functionalized trivalent bismuth reagents and promoted by catalytic amounts of copper acetate. The procedure gives exclusively the product from *N*-arylation and shows exceptional functional group tolerance on both coupling partners. The procedure is also applied to the *N*-arylation of tryptophan derivatives to provide the *N*-arylindolyl products.

We began by optimizing the conditions for the phenylation of methyl indole-5-carboxylate **1** using the Barton-Finet-Chan protocol (Table 1).[15,16] Upon reacting 1.0 equivalent of triphenylbismuth with indole

1 in the presence of 1.5 equivalents of copper acetate and 3.0 equivalents of pyridine under air, we obtained regioselectively the *N*-arylated product **2** in quantitative yield (Entry 1). This result is interesting and important for two reasons. Firstly, to the best of our knowledge, this is the first time that trivalent organobismuth reagents are used directly in the *N*-arylation of indoles, alleviating the need for preparing the less stable bis-trifluoroacetate species. Secondly, it demonstrates that, contrary to triphenylbismuth bis-trifluoroacetate, the process involving triphenylbismuth leads exclusively to *N*-arylation, as opposed to C3-arylation. Using 0.7 equivalent of the organobismuth species led to a 25% drop in the yield of the reaction, suggesting that only one phenyl group can be transferred from the organobismuth species during the process (Entry 2).

Table 1 Optimization of the reaction conditions for the *N*-phenylation of methyl indole-5-carboxylate **1** using triphenylbismuth.



Entry	Ph_3Bi (x equiv)	$Cu(OAc)_2$ (y equiv)	Base	Solvent	Atm.	Yield (%)[a]
1	1.0	1.5	Pyridine	CH_2Cl_2	air	99
2	0.7	1.5	Pyridine	CH_2Cl_2	air	74
3	1.0	1.0	Pyridine	CH_2Cl_2	air	45
4	1.0	1.0	Et_3N	CH_2Cl_2	air	45
5	1.0	1.0	Pyridine	CH_3CN	air	76
6	1.0	1.0	Pyridine	CH_2Cl_2	O_2	96
7	1.0	1.0	Pyridine	CH_2Cl_2	Ar	47
8	**1.0**	**0.1**	**Pyridine**	**CH_2Cl_2**	**O_2**	**99**
9	1.0	0.05	Pyridine	CH_2Cl_2	O_2	45
10[b]	**1.0**	**0.1**	**Pyridine**	**CH_2Cl_2**	**O_2**	**96**
11	1.0	0.1	Pyridine	THF	O_2	82
12	1.0	0.1	Pyridine	DME	O_2	57
13	1.0	0.1	Pyridine	CH_3CN	O_2	54

[a]Isolated yield of pure product **2**. [b]Reaction performed with 1.0 equiv of base.

In order to develop a more efficient protocol, we next sought to reduce the catalyst loading. Unfortunately, the use of stoichiometric amount of copper acetate led to drastic erosion in the yield of the reaction (Entry 3), motivating us to revisit the other parameters of the reaction. Changing the base for triethylamine proved inconsequential (Entry 4), but an improvement in the yield of the reaction was observed upon conducting the reaction in acetonitrile (Entry 5). We reported recently the beneficial effect of oxygen during our studies on the *O*-arylation of phenols using trivalent organobismuthanes.[12] Therefore, we next investigated the use of oxygen as the reaction atmosphere and observed a near quantitative yield for the formation of **2** (Entry 6). To further validate the importance of oxygen, we performed the reaction under argon and observed a yield similar to when the reaction was run under ambient air, thus confirming the positive effect of oxygen on the reaction (Entry 7 vs 3). Encouraged by this observation, we then gradually lowered the amount of catalyst and found that the yield was retained upon using 10 mol% of copper acetate (Entry 8). However, reducing the loading further was not tolerated and gave only a modest yield of the desired *N*-phenyl indole **2** (Entry 9). Although Barton reported a negative impact on the arylation of amines with trivalent organobismuthanes following *exclusion* of oxygen,[15] the possibility of lowering the copper acetate loading upon performing the reaction under pure oxygen was not demonstrated. It is likely that the role of the oxygen is to oxidize the low valent copper species generated during the process to the +2 oxidation state. To minimize the amount of base, we performed the reaction using 1.0 equivalent of pyridine and still obtained a quantitative yield of product **2** (Entry 10). The exploration of non halogenated solvents (entries 11-13) led to the idenfication of THF as the best alternative for dichloromethane.

Using our optimal conditions, we next explored the impact of varying the steric and electronic properties of the organobismuthane on the yield of the arylation reaction. The functionalized organobismuthanes needed for this study (Fig. 1) were prepared according to procedures that we previously reported.[10b,12]

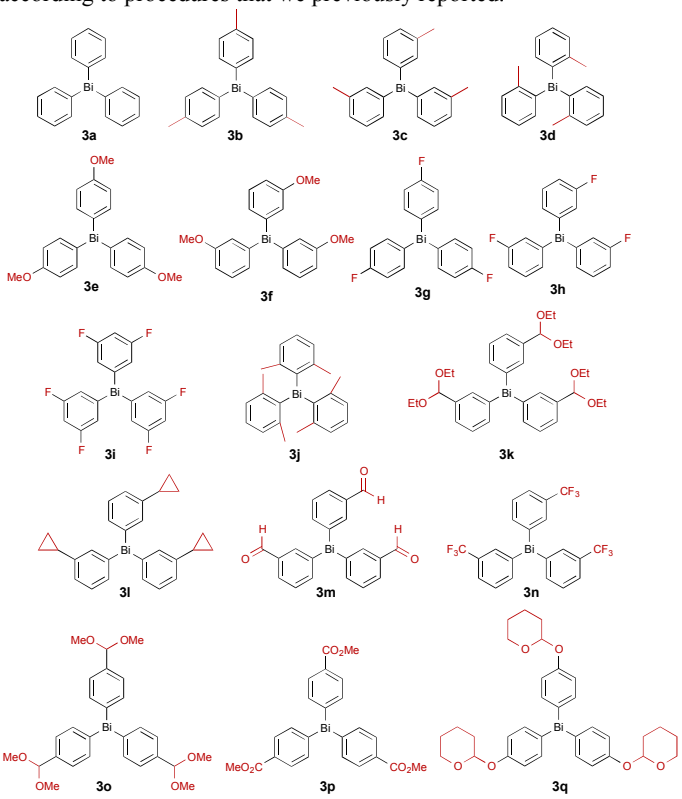
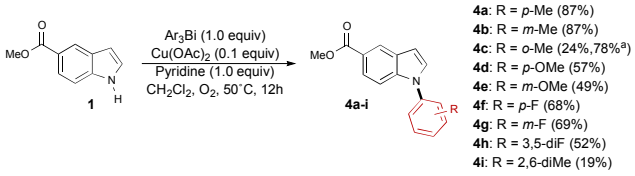


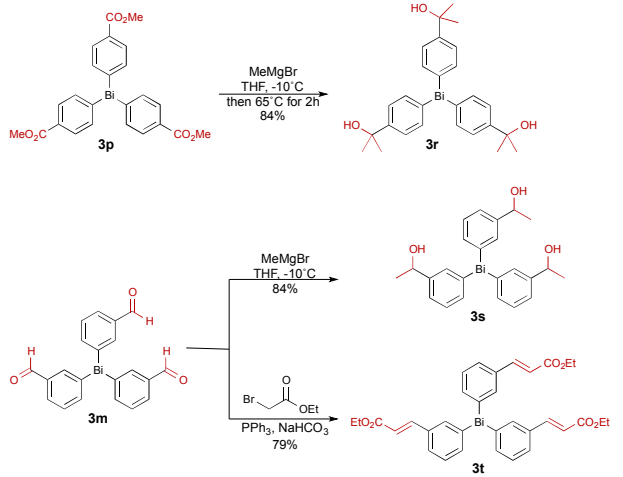
Fig. 1 Functionalized organobismuthanes **3a-q** used in the *N*-arylation of azoles and diazoles.

Our studies show that the transfer of *para* and *meta*-tolyl groups proceeds efficiently, delivering the corresponding products **4a** and **4b** in excellent yield (Scheme 2). The transfer of the more sterically congested *ortho*-tolyl group proved more challenging and required a higher catalyst loading to provide the desired product **4c** in acceptable yield. While it is difficult to establish a clear correlation between the electronic properties of the organobismuthane and the yield of the arylation reaction, the results yet demonstrate that good yields of the *N*-arylated products are obtained upon using triarylbismuthanes substituted with electron donating (**4a,b,d**) and withdrawing (**4e-h**) groups. Interestingly, a 2,6-dimethylphenyl unit was installed on indole **1** using our conditions, albeit in modest yield (compound **4i**). Very few methods exist for the transfer of this highly hindered group.[17]



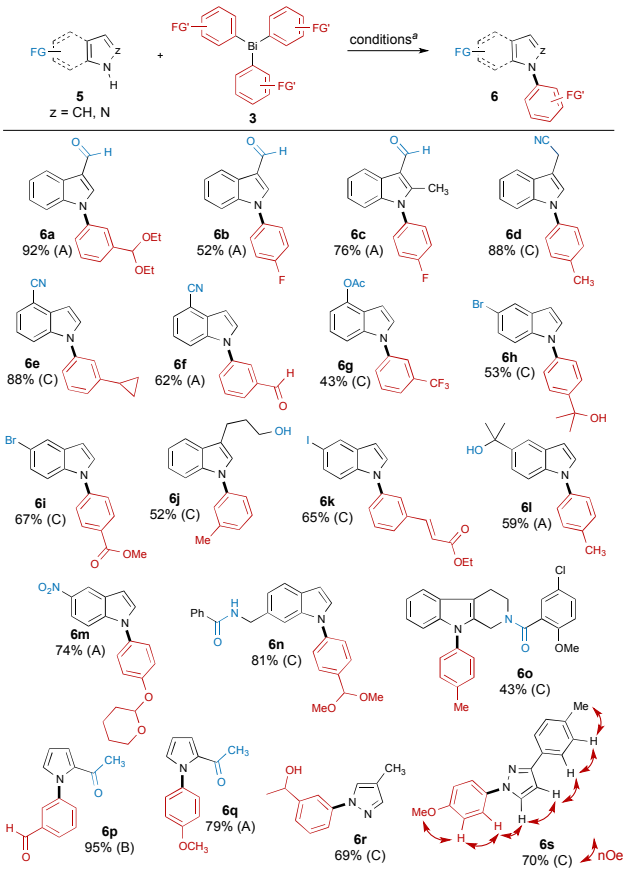
Scheme 2 Study of the steric and electronic effects of the organobismuthane on the *N*-arylation of **1**. [a] Alternative conditions for compound **4c**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 ˚C, 12h.

In order to further expand the functional group tolerance, we prepared three new bismuth reagents by performing functional group manipulation directly on selected organobismuthanes. As illustrated in Scheme 3, triarylbismuthanes **3r** and **3s** bearing alcohol functions were synthesized by Grignard addition on the ester **3p** and on the aldehyde **3m** respectively. These groups are important in medicinal chemistry since the presence of an alcohol allows to control the lipophilicity (log D) of the arylated products that are generated in the next step. A Horner-Emmons-Wadsworth reaction was also performed on **3m** to furnish the cinnamyl ester **3t**. This function is also frequently found in numerous bioactive compounds.



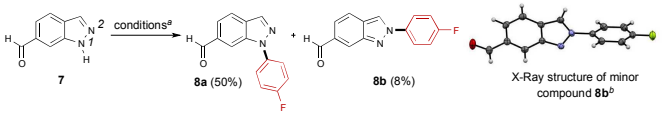
Scheme 3 Preparation of highly functionalized organobismuthanes by functional group manipulation.

The scope of the reaction was then studied by arylating different azoles and diazoles **5** using highly functionalized triarylbismuthanes **3a-t** (Scheme 4). Our investigations reveal that the reaction proceeds smoothly on indoles (**6a-o**), pyrroles (**6p**,**q**), and pyrazoles[18] (**6r**,**s**) to afford the desired *N*-arylated products in good to excellent yield. The results also suggest that the substitution pattern of the indole has little impact on the outcome of the reaction. However, using our conditions, we were not able to arylate 7-methylindole, possibly due to the development of a strong 1,3-allylic-type strain during the formation of the product. In the case of pyrazole **6s**, the product of arylation on the nitrogen distal to the tolyl group was obtained, as shown by NMR studies. Importantly, the procedure tolerates a wide variety of functional groups on the azole such as aldehydes (**6a-c**), nitriles (**6d-f**), *O*-acetates (**6g**), nitro groups (**6m**), amides (**6n**,**o**), and ketones (**6p**,**q**). Bromides (**6h**,**i**), and iodides (**6k**) were also found to be inert under these conditions. These functionalities could be expected to interfere in the direct *N*-arylation of azoles with aryl halides. Numerous functional groups can also be present on the organobismuth reagents, such as acetals (**6a**,**m**,**n**), fluorides (**6b**,**c**), aldehydes (**6f**,**p**), esters (**6i**), ethers (**6q**,**s**) and α,β-unsaturated esters (**6k**). Interestingly, we found that an alcohol can be present on the substrate (**6j**,**l**) or on the arylbismuth reagent (**6r**) without undergoing *O*-arylation. A secondary amide is also not arylated under these conditions (**6n**). Lastly, a cyclopropylphenyl (**6e**) and a trifluoromethylphenyl (**6g**) group were efficiently transferred using this method. These groups are important in medicinal chemistry as they show increased metabolic stability over usual alkyl groups.[19]



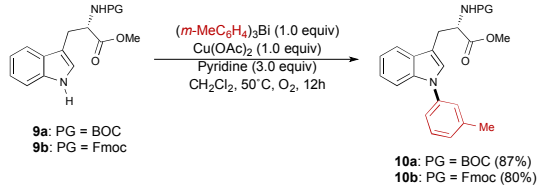
Scheme 4 *N*-Arylation of azoles and diazoles **5** using functionalized triarylbismuthanes **3a-t**. [a] **Conditions A**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.1 equiv), pyridine (1.0 equiv), CH_2Cl_2, O_2, 50 ˚C; **Conditions B**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.1 equiv), pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 ˚C; **Conditions C**: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 ˚C.

The *N*-arylation of indazoles was next evaluated, being aware that a mixture of regioisomers resulting from arylation at N1 and N2 is often obtained with other methods.[18,20] When 1*H*-indazole-6-carbaldehyde **7** was submitted to our conditions, product **8a** generated from arylation at N1 was predominantly formed (Scheme 5). The structure of the minor regioisomer **8b** obtained from arylation at N2 was established by X-ray crystallography.



Scheme 5 *N*-Arylation of 1*H*-indazole-6-carbaldehyde **7**. [a]Conditions: $(p\text{-}FC_6H_4)_3Bi$ (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), pyridine (3.0 equiv), DCM, 50˚C, O_2, o.n.; [b] ORTEP diagram of compound **8b**: thermal ellipsoids are shown at the 50% probability level.

Derivatives of tryptophan are important in medicinal chemistry as these species are involved in numerous biological processes and diseases.[21] The post-synthetic modification of peptides containing tryptophan residues has also found applications in chemical biology.[22] To the best of our knowledge, there are very few methods to *N*-arylate tryptophan derivatives reported in the literature.[23] Gratifyingly, BOC and Fmoc-protected tryptophan derivatives **9a** and **9b** were smoothly *N*-arylated using our protocol to provide selectively the *N*-indolyl derivatives **10a**,**b** in good yield (Scheme 6).[24]



Scheme 6 *N*-Arylation of tryptophan derivatives **9a,b**.

Conclusions

In summary, we have developed an efficient and general method for the *N*-arylation of indoles, indazoles, pyrroles, and pyrazoles that operates directly using highly functionalized trivalent organobismuth reagents. The transformation is promoted by catalytic amounts of copper acetate and tolerates an exceptional diversity of functional groups on both coupling partners, giving access to highly functionalized azoles. The protocol was also applied to the *N*-arylation of tryptophan derivatives. Application of this methodology to other arylation reactions, including amino-acids and tryptophan-containing peptides, is in progress in our laboratory and results will be reported in due course.

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Notes and references

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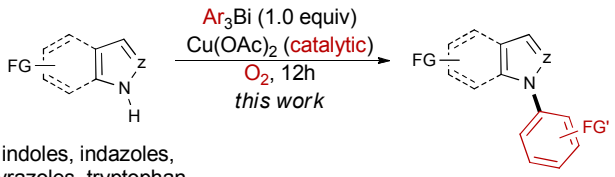
Abstract



indoles, indazoles, pyrazoles, tryptophan, pyrroles (z = CH, N)

FG, FG' = aldehyde, ketones, ester, amide, nitrile, bromides, iodides, fluorides, nitro, alcohol, α,⇓-unsaturated ester, ether

- works with indoles, indazoles, pyrroles, pyrazoles, and tryptophan
- catalytic in copper
- very high functional group tolerance
- operates directly with trivalent bismuthanes
- regioselective *N*-arylation