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Copper-Catalyzed O-Arylation of N-Protected 1,2-Aminoalcohols Using Functionalized Trivalent Organobismuth Reagents

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The O-arylation of 1,2-aminoalcohols using functionalized triarylbismuth reagents is reported. The reaction can be performed using substoichiometric amounts of copper acetate and operates under mild conditions. Good functional group tolerance is observed, giving access to a range of β-aryloxyamines. The effect provided by the amino group in the arylation reaction is investigated.

β-Aryloxyamines are frequently found in natural products and in medicinally relevant compounds. For example, this moiety has been identified in shishididemniol A (1) and B (2), two natural products extracted from a tunicate of the family Didemnidae (Figure 1).1 Rosiglitazone (3), an antidiabetic drug, Ulimorelin (TZP-101, 4),2 a ghrelin inhibitor that has advanced into phase-III clinical studies, and Mexiletine (5), an antiarrhythmic drug, also contain a β-aryloxyamine. The importance of 1,2-aryloxyamines in drug discovery can be further exemplified with compounds 6-10 which are inhibitors of various biological targets for which advanced profiling has been performed.3,4,5,6,7

β-Aryloxyamines can be accessed through S$_S$Ar reactions between 1,2-aminoalcohols and electron poor aryl halides.8 Alternatively, these compounds can also be prepared from the same precursors through the addition of phenols using Mitsunobu conditions9 or via S$_S$2 reactions on the corresponding mesylates or tosylates.10 Even though these approaches are widely spread in the pharmaceutical industry, they are not free of limitations as they require the presence of electron withdrawing groups on the aryl unit (S$_S$Ar), necessitate the derivatization of the alcohol (S$_S$2) or lead to the formation of side products that can complicate the isolation of the desired product (i.e. phosphine oxide and urea in the Mitsunobu reaction).

The copper-catalyzed O-arylation of 1,2-aminoalcohols using aryl halides, as illustrated by the pioneering work of Buchwald11 and Evano,12 constitutes a highly efficient strategy for the preparation of β-aryloxyamines.13,14,15 Surprisingly, the O-arylation of 1,2-aminoalcohols using arylmetals has been considerably less studied and to the best of our knowledge, the only example using this approach involved tetraphenylbismuth fluoride as the arylating source.16

We reported over the past few years a portfolio of C–C, C–N, and C–O bond forming reactions involving organobismuth reagents.17 Organobismuthanes are an attractive class of organometallic reagents that can be easily prepared from inexpensive and non-toxic bismuth salts.18 Triarylbismuthanes are air and moisture stable and can be purified by simple silica gel chromatography. In addition, organobismuthanes show remarkable functional group tolerance, making them ideal candidates for the development of methodologies oriented towards medicinal chemistry applications.
We recently disclosed a general copper-catalyzed N-arylation reaction of azoles and diazoles using triarylbumithane reagents.\textsuperscript{15}\textsuperscript{a} In the course of our studies, we found that the arylation of the hydroxypropylinde 11 using tris-meta-((methylphenyl)bismuthane proceeded exclusively on the indole to afford 12, suggesting that an alcohol cannot be arylated under these conditions (Scheme 1). However, when the N-BOC-tryptophane derivative 13 was submitted to the same conditions, the product of bis-arylation 14 was isolated in moderate yield, suggesting that the amino group activates the alcohol towards the arylation. Moreover, the yield of this reaction could be greatly improved by using 2.0 equivalents of the bismuth reagent.

![Scheme 1](image)

**Scheme 1** N- vs O-Arylation of 3-(3-hydroxypropyl)-1H-indole 11 and N-BOC-tryptophanole 13.

David and Thieffry reported in 1983 the effect of neighbouring hydroxylic groups on the arylation reaction of alcohols using triarylbumithane diacetate but never explored the ability of nitrogen moieties in influencing this transformation.\textsuperscript{19} In 1986, Barton briefly studied the arylation of ethanalamine using Ph\textsubscript{3}Bi(OAc)\textsubscript{2} and obtained a complex mixture of N-, N,N-, and N,O-arylation products.\textsuperscript{20} These two reactions relied on pentavalent organobismuth reagents, which are usually less stable and more tedious to prepare than their trivalent counterparts. To our knowledge, the only example of O-arylation of alcohols using a trivalent bismuth reagent was reported in 1999 by Sheppard and required the use of oxone as a stoichiometric oxidizing agent.\textsuperscript{21} We would like to report here our study on the O-arylation of 1,2-aminooalcohols using functionalized triarylbumithanes and our investigation into the accelerating effect provided by the amino group.

We began by optimizing the reaction conditions for the arylation of \((\cdot)\)N-BOC-D-\(\alpha\)-phenylglycinol 15, a 1,2-aminooalcohol that does not possess an indolic scaffold. When this substrate was submitted to our previously identified conditions,\textsuperscript{17a} the corresponding O-phenyl product 16 was isolated in 73% yield (Table 1, entry 1). Conducting the reaction under air led to a considerable reduction in the yield of the reaction, thus confirming the importance of the oxygen in this process (entry 2). To evaluate the transferability of the second ary group from the triarylbismuthane, we next performed the reaction using 0.7 equivalent of triarylbumithane and observed a substantial drop in the yield of 16, demonstrating that only one ary group can be transferred from the triarylbismuthane (entry 3). This phenomenon is well known in copper-catalyzed reactions involving organobismuth reagents\textsuperscript{17a,b} and efforts to overcome this issue are in progress in our group. A rapid screen of different bases showed that pyridine can be replaced by triethylamine (entry 4) but not potassium carbonate (entry 5). Our studies also demonstrate that 1.2 equivalents of pyridine are sufficient to obtain an optimal yield of the arylated product (entry 6). A survey of different solvents led to the identification of toluene as the most efficient replacement for dichloromethane (entry 7). We next directed our efforts towards lowering the catalyst loading and found a moderate reduction in the yield of the arylation process upon using 0.3 equivalent of copper acetate (entry 8). In addition, reducing the reaction time to 6 hours instead of overnight provided the desired compound in similar yield (entry 9). Finally, a good yield could be obtained under catalytic conditions by conducting the reaction in toluene at 80 °C overnight (entry 10).

**Table 1** Optimization of the conditions for the O-arylation of N-BOC-D-\(\alpha\)-phenylglycinol 15.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Change from &quot;standard conditions&quot;</th>
<th>Yield (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No change</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Ambient air instead of oxygen</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>0.7 equiv Ph\textsubscript{3}Bi instead of 1.0</td>
<td>51</td>
</tr>
<tr>
<td>4</td>
<td>Et\textsubscript{3}N instead of pyridine</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>K\textsubscript{2}CO\textsubscript{3} instead of pyridine</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>1.2 equiv pyridine instead of 3.0</td>
<td>67</td>
</tr>
<tr>
<td>7</td>
<td>Toluene instead of CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>0.3 equiv Cu(OAc)\textsubscript{2} instead of 1.0</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>0.3 equiv Cu(OAc)\textsubscript{2} and 6h instead of o.n.</td>
<td>58</td>
</tr>
<tr>
<td>10</td>
<td>0.3 equiv Cu(OAc)\textsubscript{2} in toluene at 80 °C</td>
<td>71</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield of pure product 16. \textsuperscript{b} 1.2 equiv pyridine.

The ability of other amine protecting groups in enhancing the reactivity of the alcohol towards arylation was then explored (Scheme 2). Performing the reaction directly on the unprotected phenylglycinol afforded the N,O-diaryl product 18a, indicating that the amino group must imperatively be protected to prevent the undesired N-arylation pathway. A survey of different amine protecting groups demonstrated that a benzoxycarbonyl group (18b) and a sulfonyl (18c) give slightly higher yields of the desired O-aryl product than an acetyl (18d).

**Scheme 2** Impact of the protecting group on the arylation of N-protected phenylglycinol derivatives. PG = Protecting Group.

The scope of the reaction was then investigated by coupling different functionalized triarylbumithanes with various 1,2-aminooalcohols (Scheme 3). The tert-butyloxycarbonyl (BOC) or benzoxycarbonyl (Cbz) protecting groups were selected for its ease of installation and removal. The organobismuth reagents were synthesized according to procedures that we reported previously\textsuperscript{17-a,b,d}.
and the protocols involving catalytic (Table 1, entry 10: conditions A) and stoichiometric (Table 1, entry 1: conditions B) amount of copper acetate were utilized. As expected, the introduction of a methyl group at the para position of the triarylbismuthane had little impact on the arylation process and afforded the corresponding O-aryl product 21a in a reasonable yield using either conditions A or B. The transfer of an aryl group bearing an electron-withdrawing group such as a fluorine atom at the para position proceeded equally well, providing compound 21b in 72% yield under conditions B. However, introducing an electron-donating group such as a methoxy at the para position led to a considerable drop in the efficiency of the process, as indicated by compound 21c. The reaction also proved to be very sensitive to steric hindrance, as shown by compound 21d where a methyl group is present at the ortho position of the aryl group being transferred. This phenomenon is not unprecedented and was observed previously in our studies on the copper-catalyzed N-arylation of indoles17a and phenols.17b Unsurprisingly, the effect of the ortho methyl group in the arylation reaction was found to be much higher with alcohols than with azoles and phenols. Next, we investigated the transfer of an aryl fragment possessing a diethylacetal and a trifluoromethyl group at the meta position and obtained the corresponding O-arylated products 21e and 21f in modest yields. Surprisingly, a much lower yield was observed when tris(3-formylphenyl)bismuth was utilized as the arylating agent, as indicated by compound 21g. This is a sharp contrast to the results we obtained with this organobismuthane in the arylation of azoles and phenols.17b where the corresponding arylated products were obtained in excellent yields. The transfer of a phenyl group bearing an \( \alpha,\beta \)-unsaturated ester at the meta position proved more efficient, affording compound 21h in 70% yield under conditions A.

We then turned our attention to substrates where the phenyl group of phenylglycinol is substituted or replaced by an alkyl group. For instance, the para-ethoxy and ortho-methoxy derivatives 21i and 21j were obtained in moderate yields using this protocol. To our surprise, the insertion of a methylene unit between the phenyl group and the aminohalocohol segment led to an unexpected drop in the yield of the reaction (21a→21k). Interestingly, products 21i and 21m where the phenyl group is replaced by a cyclohexyl or an iso-butyl moiety were successfully prepared using this method. Lastly, the arylation could also be performed on a secondary alcohol, as demonstrated by compound 21n.

In order to understand the role of the amino group in the arylation process, we performed a series of control experiments where specific geometric and functional modifications are introduced in the substrate. We first hypothesized that the NHBOC function could be promoting the O-arylation reaction through complexation of the copper species via the carbonyl moiety of the carbamate. To test this hypothesis, we compared the reactivity of the cis- and trans-N-BOC-indanol derivatives cis-22 and trans-22 using conditions B (Scheme 4). In the event, a higher yield was observed for the trans stereoisomer, suggesting that the accelerating effect provided by the amino group is not a result of a complexation of metallic intermediates by the carbonyl group.

Scheme 4 Study of the effect of the conformational effect in the O-arylation of N-BOC-1-amino-2-indanol 22.

To further investigate the hypothesis that the C=O bond of the carbamate could be directing the reaction through complexation of the copper species, we compared the reactivity of the N-benzoyl and N-benzyl derivatives 24a and 24b of phenylglycinol in the arylation reaction (Scheme 5). Should there be a complexation involved, it would be reasonable to expect a much greater yield with the benzoyl compound 24a than with the benzyl analogue 24b. To our surprise, similar yields of the O-aryl products were obtained with both derivatives, thus invalidating our complexation hypothesis.

Scheme 5 Comparison of N-benzoyl 24a and N-benzyl 24b protecting group in the copper-catalyzed arylation of N-protected phenylglycinol.

We then hypothesized that the amide N–H bond could be responsible for the acceleration of the arylation reaction through formation of copper species where the amide acts as a ligand. To test this hypothesis, we performed the arylation reaction using the N-methyl derivatives 26a and 26b and observed a good conversion to the corresponding O-aryl products 27a,b, thus discrediting this second hypothesis (Scheme 6).

**Scheme 3** O-Arylation of 1,2-aminoalcohols using functionalized organobismuthanes. *Conditions A*: Ar₂Bi (1.0 equiv), pyridine (1.2 equiv), Cu(OAc)₂ (0.3 equiv), toluene, 80°C, O₂, o.n.; *Conditions B*: Ar₂Bi (1.0 equiv), pyridine (3.0 equiv), Cu(OAc)₂ (1.0 equiv), CH₂Cl₂, 50°C, O₂, o.n.

**Scheme 4** Study of the effect of the conformational effect in the O-arylation of N-BOC-1-amino-2-indanol 22.

**Scheme 5** Comparison of N-benzoyl 24a and N-benzyl 24b protecting group in the copper-catalyzed arylation of N-protected phenylglycinol.
values were calculated to be 15.8 for phenylglycinol that the phenyl effect generated by the aminoalcohol is more reactive than a simple alcohol with no amino group and observed a 30% drop in the yield of the reaction compared to phenylglycinol 15 (Scheme 7). This result clearly indicates that the β-amino group has a dramatic effect on the arylation process. The arylation of benzyl alcohol 28a and 3-phenyl-1-propanol 28c provided the corresponding O-phenyl ethers 29a and 29c in similar yields as 28b.

To evaluate the difference in reactivity between simple alcohols and 1,2-aminoalcohols more accurately, we next performed a competition experiment between N-BOC-phenylglycinol 15 and phenethylalcohol 28b (Scheme 8). After 16 hours, the 1H-NMR analysis of the crude mixture indicated a ratio of O-phenyl-N-BOC phenylglycinol 16 over 29b of 1.7:1.0, suggesting that an aminoalcohol is more reactive than a simple alcohol.

We then postulated that the difference in reactivity between 1,2-aminoalcohols and simple alcohols could derive from an inductive effect generated by the β-amino group, effectively lowering the pKₐ of the alcohol moiety. To test this hypothesis, we performed a second competition experiment between N-BOC-phenylglycinol 15 and pentafluorophenethylalcohol 30 (Scheme 9). After 16 hours, the 1H-NMR analysis of the crude mixture showed a ratio of the O-phenyl-N-BOC phenylglycinol 16 over O-phenylpentafluorophenethyl ether 30 of 1.1:1.0, thus demonstrating that the pentafluorophenethylalcohol 31 has a similar reactivity than N-BOC-phenylglycinol 15 and therefore suggesting that the presence of electron-withdrawing groups increases the reactivity of an alcohol. To furnish further evidence of this effect, the aqueous pKₐ values for alcohols 15, 28b, and 30 using a recent method reported by Pulay et al. The calculations were carried out using ORCA 3.0.1. These values were calculated to be 15.8 for 15, 17.3 for 28b, and 15.6 for 30. These values are in line with the relative reactivities illustrated in Schemes 8 and 9, thus supporting the inductive effect hypothesis.

To further support our hypothesis, we performed the O-arylation of aminoalcohol 32a-c where the distance between the amino group and the alcohol is systematically increased by one methylene unit (Scheme 10). The results indicate that the yield is higher for N-BOC-ethanolamine 32a which has the lowest pKₐ. The yield then decreases as the pKₐ increases, as shown by products 33b and 33c.

The results from Schemes 7 to 10 support our hypothesis that an amino group in β-position relative to an alcohol accelerates the O-arylation reaction mainly via an inductive effect.

Conclusions

In summary, we have developed a copper-catalyzed O-arylation reaction of 1,2-aminoalcohols using functionalized triarylboranes. The reaction is promoted by catalytic amounts of copper acetate and tolerates a variety of substituents on the organobismuthane, giving access to functionalized β-aroylamines. Different protecting groups can be used on the aminoalcohol, such as BOC, Cbz, Ac, and Ts. Finally, we demonstrated that the presence of an amino group in β relative to the alcohol provides an increase in reactivity, probably through inductive effect. The application of this protocol to the arylation of other hydroxy-containing substrates is in progress in our group and results will be reported in due course.

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Notes and references

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3 For compounds 6a,b, see: (a) C. Coburn, S. J. starchel and J. P. Vacca, WO2004/062625 A2; (b) G. G. P. Nantermet, H. A. Rajapakse, H. G. Selnick, K. P. Moore and S. J. Stachel, WO2006/055434 A2.


