Organic & Biomolecular Chemistry

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

Cite this: DOI: 10.1039/x0xx00000x

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

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Pauline Petiot,[a] Julien Dansereau,[a] Martin Hébert,[a] Imene Khene,[a] Tabinda Ahmad,[a] Samira Samaali,[a] Maxime Leroy,[a] Francis Pinsonneault,[a] Claude Y. Legault*[b] and Alexandre Gagnon*[a]

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 antiarrhytmic 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_NAr 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 conditions[9] or via S_N2 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_NAr), necessitate the derivatization of the alcohol (S_N2) 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 Buchwald[11] 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]

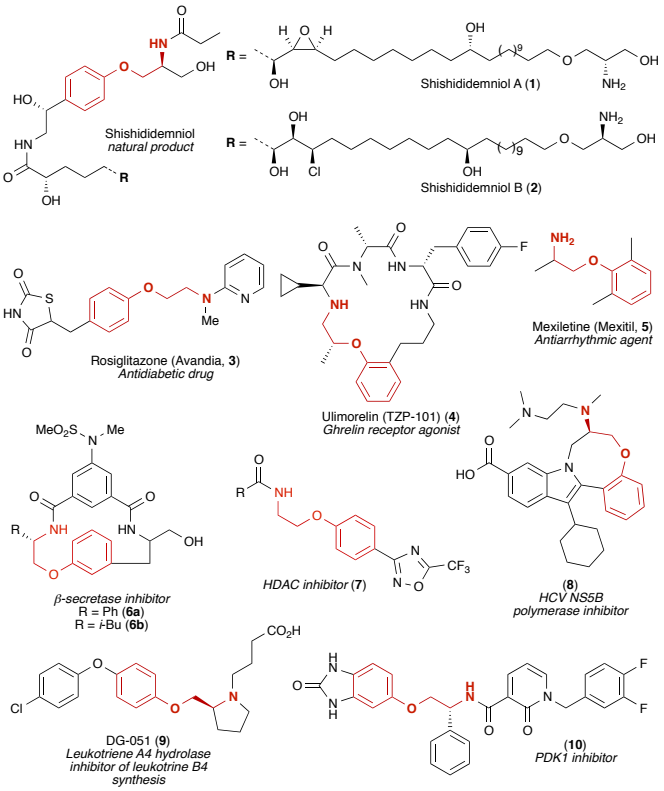
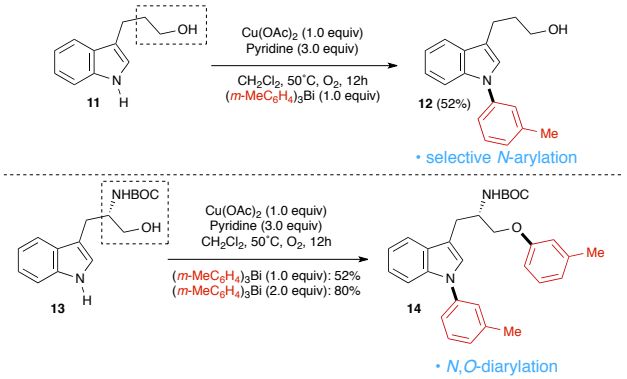


Fig. 1. Selected examples of β-aryloxyamines in natural products, drugs, and medicinal chemistry compounds.

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 triarylbismuth reagents.[17a] In the course of our studies, we found that the arylation of the hydroxypropylindole **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-tryptophanol 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.

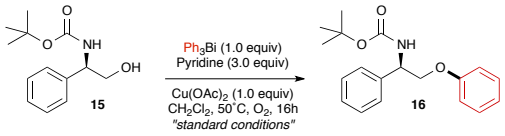


Scheme 1 *N- vs O*-Arylation of 3-(3-hydroxypropyl)-1*H*-indole **11** and *N*-BOC-tryptophanol **13**.

David and Thieffry reported in 1983 the effect of neighbouring hydroxylic groups on the arylation reaction of alcohols using triphenylbismuth diacetate but never explored the ability of nitrogen moieties in influencing this transformation.[19] In 1986, Barton briefly studied the arylation of ethanolamine using $Ph_3Bi(OAc)_2$ and obtained a complex mixture of *N*-, *N*,*N*-, and *N*,*O*-arylation products.[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.[21] We would like to report herein our study on the *O*-arylation of 1,2-aminoalcohols using functionalized triarylbismuthanes and our investigation into the accelerating effect provided by the amino group.

We began by optimizing the reaction conditions for the arylation of (–)-*N*-BOC-D-α-phenylglycinol **15**, a 1,2-aminoalcohol that does not possess an indolic scaffold. When this substrate was submitted to our previously identified conditions,[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 aryl group from the triarylbismuthane, we next performed the reaction using 0.7 equivalent of triphenylbismuth and observed a substantial drop in the yield of **16**, demonstrating that only one aryl group can be transferred from the triarylbismuthane (entry 3). This phenomenon is well known in copper-catalyzed reactions involving organobismuth reagents[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).

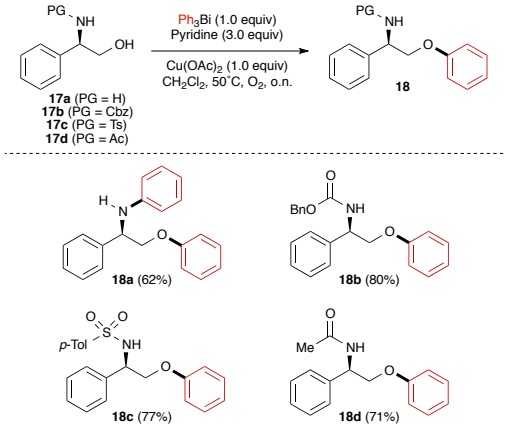
Table 1 Optimization of the conditions for the *O*-arylation of *N*-BOC-D-α-phenylglycinol **15**.



Entry	Change from "standard conditions"	Yield (%)[a]
1	**No change**	**73**
2	Ambient air instead of oxygen	49
3	0.7 equiv Ph_3Bi instead of 1.0	51
4	Et_3N instead of pyridine	73
5	K_2CO_3 instead of pyridine	31
6	1.2 equiv pyridine instead of 3.0	67
7	Toluene instead of CH_2Cl_2	76
8[b]	0.3 equiv $Cu(OAc)_2$ instead of 1.0	62
9[b]	0.3 equiv $Cu(OAc)_2$ and 6h instead of o.n.	58
10[b]	**0.3 equiv $Cu(OAc)_2$ in toluene at 80°C**	**71**

[a] Isolated yield of pure product **16**. [b] 1.2 equiv pyridine.

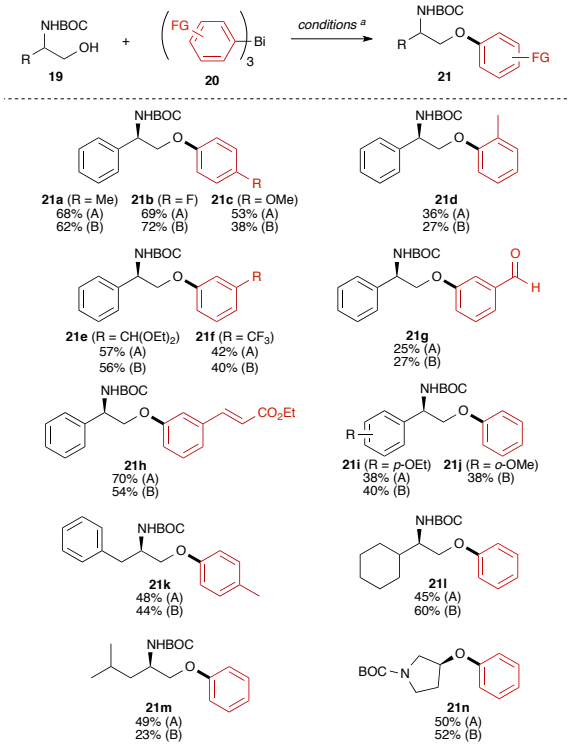
The ability of other amine protecting groups in enhancing the reactivity of the alcohol towards arylation was then explored (**Scheme 2**). Performing the reaction directly on the unprotected phenylglycinol afforded the *N*,*O*-diaryl product **18a**, indicating that the amino group must imperatively be protected to prevent the undesired *N*-arylation pathway. A survey of different amine protecting groups demonstrated that a benzyloxycarbonyl 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 triarylbismuthanes with various 1,2-aminoalcohols (**Scheme 3**). The *tert*-butyloxycarbonyl (BOC) or benzyloxycarbonyl (Cbz) protecting groups were selected for its ease of installation and removal. The organobismuth reagents were synthesized according to procedures that we reported previously[17a,b,d]

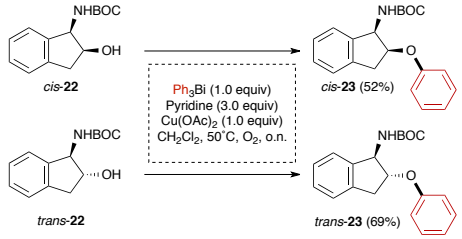
and the protocols involving catalytic (Table 1, entry 10: conditions A) and stoichiometric (Table 1, entry 1: conditions B) amount of copper acetate were utilized. As expected, the introduction of a methyl group at the *para* position of the triarylbismuthane had little impact on the arylation process 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 the context of our studies on the copper-catalyzed *N*-arylation of indoles[17a] and phenols.[17b] Unexpectedly, 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 that we obtained with this organobismuthane in the arylation of azoles[17a] and phenols[17b] where the corresponding arylated products were obtained in excellent yields. The transfer of a phenyl group bearing an α,β-unsaturated ester at the *meta* position proved more efficient, affording compound **21h** in 70% yield under conditions A.



Scheme 3 *O*-Arylation of 1,2-aminoalcohols using functionalized organobismuthanes. [a] **Conditions A**: Ar_3Bi (1.0 equiv), pyridine (1.2 equiv), $Cu(OAc)_2$ (0.3 equiv), toluene, 80˚C, O_2, o.n.; **Conditions B**: Ar_3Bi (1.0 equiv), pyridine (3.0 equiv), $Cu(OAc)_2$ (1.0 equiv), CH_2Cl_2, 50˚C, O_2, o.n.

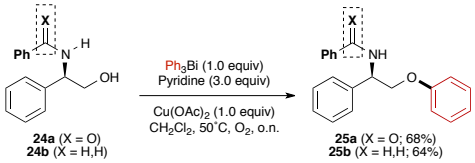
We then turned our attention to substrates where the phenyl group of phenylglycinol is substituted or replaced by an alkyl group. For instance, the *para*-ethoxy and *ortho*-methoxy derivatives **21i** and **21j** were obtained in moderate yields using this protocol. To our surprise, the insertion of a methylene unit between the phenyl group and the aminoalcohol segment led to an unexpected drop in the yield of the reaction (**21a→21k**). Interestingly, products **21l** 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.



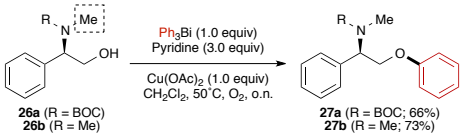
Scheme 4 Study of the effect of the conformational effect in the *O*-arylation of *N*-BOC-1-amino-2-indanol **22**.

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.



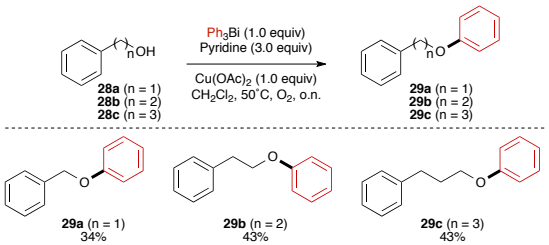
Scheme 5 Comparison of *N*-benzoyl **24a** and *N*-benzyl **24b** protecting group in the copper-catalyzed arylation of *N*-protected phenylglycinol.

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**).



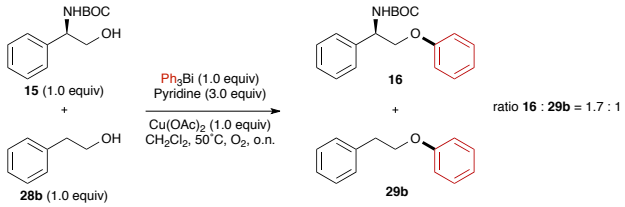
Scheme 6 Arylation of *N*-BOC-*N*-methyl and *N*,*N*-dimethyl phenylglycinol derivatives **26a** and **26b**.

In order to better evaluate the importance of the amino group in the reaction, we then performed the arylation on phenethylalcohol **28b**, 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**.



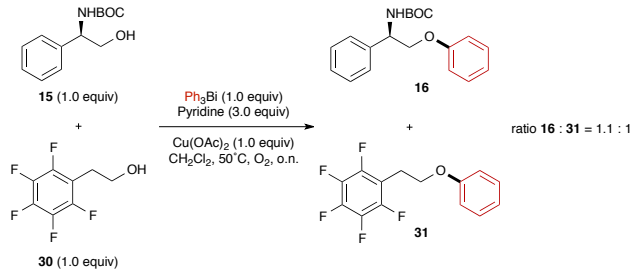
Scheme 7 *O*-Arylation of benzyl alcohol **28a**, phenethyl alcohol **28b**, and 3-phenyl-1-propanol **28c**.

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 ^{1}H-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.



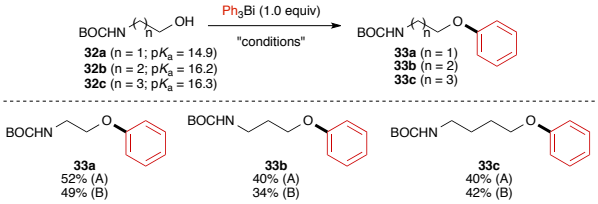
Scheme 8 Competition studies between phenethylalcohol **28b** and *N*-BOC-phenylglycinol **15**.

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 pK_a 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 ^{1}H-NMR analysis of the crude mixture showed a ratio of the *O*-phenyl-*N*-BOC phenylglycinol **16** over *O*-phenylpentafluorophenethylether **30** of 1.1:1.0, thus demonstrating that the pentafluoroalcohol **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 pK_a values for alcohols **15**, **28b**, and **30** using a recent method reported by Pulay *et al.*[22] The calculations were carried out using ORCA 3.0.1.[23] 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.



Scheme 9 Competition studies between 2-(pentafluorophenyl)ethanol **30** and *N*-BOC-phenylglycinol **15**.

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 pK_a. The yield then decreases as the pK_a increases, as shown by products **33b** and **33c**.



Scheme 10 *O*-Arylation of *N*-BOC-ethanolamine **32a**, 3-(*N*-BOC-amino)-1-propanol **32b**, and 4-(*N*-BOC-amino)-1-butanol **32c**. [a] **Conditions A**: Ar_3Bi (1.0 equiv), pyridine (1.2 equiv), $Cu(OAc)_2$ (0.3 equiv), toluene, 80°C, O_2, o.n.; **Conditions B**: Ar_3Bi (1.0 equiv), pyridine (3.0 equiv), $Cu(OAc)_2$ (1.0 equiv), CH_2Cl_2, 50°C, O_2, o.n.

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 triarylbismuthanes. The reaction is promoted by catalytic amounts of copper acetate and tolerates a variety of substituents on the organobismuthane, giving access to functionalized β-aryloxyamines. 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.

Acknowledgements

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Université du Québec à Montréal (UQÀM) and the Centre in Green Chemistry and Catalysis (CGCC). P.P. thanks the faculty

of sciences of UQÀM for a FARE scholarship. J.D. thanks the faculty of sciences of UQÀM for an undergraduate scholarship. S.S. thanks NSERC for a USRA scholarship. F.P. thanks the CGCC for an undergraduate scholarship. We thank Dr. Alexandre Arnold for advanced NMR analyses. Computational resources were provided by Calcul Québec and Compute Canada.

Notes and references

[a] Département de chimie, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, Québec, Canada, H3C 3P8 and Centre in Green Chemistry and Catalysis

[b] Université Sherbrooke, Département de chimie, 2500 boul. de l'Université, Sherbrooke, Québec, Canada, J1K 2R1 and Centre in Green Chemistry and Catalysis

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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