EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202000790

Link to VoR: https://doi.org/10.1002/ejoc.202000790

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COMMUNICATION

Copper-Promoted O-Arylation of the Phenol Side Chain of Tyrosine using Triarylbismuthines

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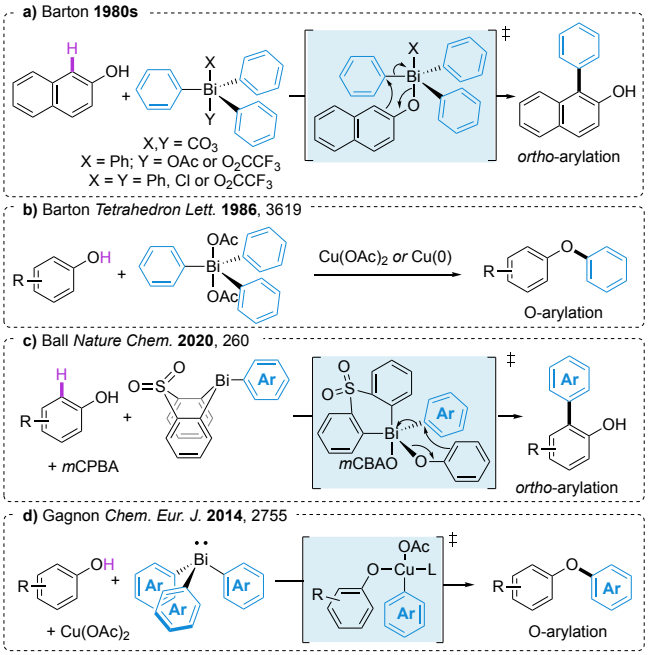
Abstract: A general method for the O-arylation of the side chain of tyrosine using triarylbismuth reagents is reported. The reaction is mediated by copper diacetate, operates at 50 °C under oxygen in dichloromethane in the presence of pyridine, shows excellent functional group compatibility and retains the integrity of the stereogenic center. The protocol was used to arylate the tyrosine residue of dipeptides and tripeptides.

Bismuth occupies the 83rd position of the periodic table. This heavy metal is the last natural member of the group 15 called the pnictogens and the heaviest stable and non-radioactive element of the periodic table.[1] Contrary to its immediate neighbors, bismuth shows relatively low toxicity, thus allowing its incorporation into therapeutic ingredients.[2] Organobismuth compounds are organometallic species that contain one or multiple C–Bi bonds and that can be subdivided into trivalent and pentavalent species in which the bismuth is in the +3 or +5 oxidation state, respectively.[3] Due to unique properties such as the ability to accommodate up to six ligands and to form hypercoordinating interactions,[4] and a wide range of available charge states from anionic to dicationic, organobismuths have been used as catalysts[5] and reagents[3,6] in a wide range of reactions.

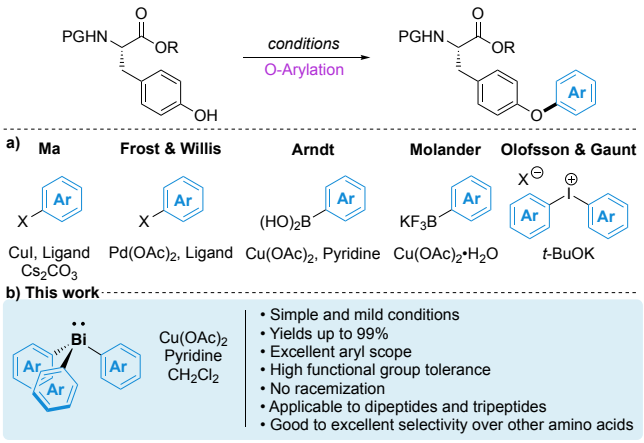
The demonstration that organobismuth compounds can act as arylating agents was made by Barton in 1980 when the oxidation of quinine using triphenylbismuth carbonate unexpectedly provided the corresponding α-phenyl keto derivative.[7a] The *ortho*-phenylation of β-naphthol using various pentavalent bismuth reagents was then reported and proposed to proceed through a concerted mechanism (**Scheme 1a**).[7] In 1986, Barton showed that triphenylbismuth diacetate reacts with phenols in the presence of cupric acetate or metallic copper to give the product of O-phenylation (**Scheme 1b**).[8] While these reports demonstrated the value of organobismuth species in synthesis, they showed limitations such as sensitivity to the reaction conditions, a narrow scope and a reliance on pentavalent bismuth species which require many steps for their preparation.

Recently, there has been a surge of interest for the chemistry of bismuth as demonstrated by the elegant work of Ball where a universal bismacycle was used in conjunction with *meta*-chloro peroxybenzoic acid to *ortho*-arylate an impressive range of phenols via a concerted mechanism (**Scheme 1c**).[9] Over the past decade, our group has reported a repertoire of metal-catalyzed reactions that involve trivalent organobismuth reagents and that result in the transfer of alkyl,[10] cyclopropyl[11] and aryl/heteroaryl[12] groups onto various scaffolds. In 2014, we disclosed a highly efficient protocol for the O-arylation of phenols using triarylbismuth reagents and hypothesized that the reaction proceeds through a copper(III) species where the metal center is simultaneously bound to the phenoxide and the aryl group (**Scheme 1d**).[13] In contrast to Barton's O-phenylation procedure, this reaction operates directly from triarylbismuthines, a class of reagents which can be easily prepared by the addition of Grignard species to bismuth trichloride and where the functional groups can be modified directly on the bismuth species.[14]



Scheme 1. a) *Ortho*-phenylation of β-naphthol using pentavalent bismuth reagents as reported by Barton in the 1980s. **b)** Copper-catalyzed O-phenylation of phenols using triphenylbismuth diacetate as reported by Barton in 1986. **c)** *Ortho*-arylation of phenols using a universal bismacycle as reported by Ball in 2020. **d)** Copper diacetate-promoted O-arylation of phenols using triarylbismuthines as reported by us in 2014. mCPBA = *meta*-chloro peroxybenzoic acid; mCBA = *meta*-chlorobenzoic acid.

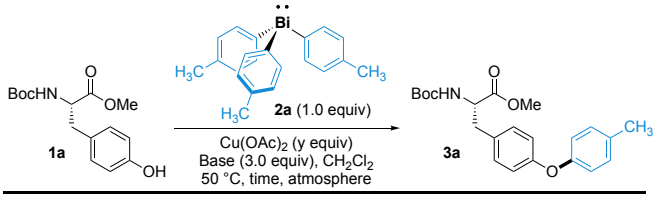
Efficient methods that allow the modification of amino acids are highly desirable, particularly for medicinal chemistry purposes.[15] Tyrosine can be O-arylated using Buchwald-Hartwig[16] and Chan-Evans-Lam protocols,[17] as demonstrated by Ma, Frost, Willis, Arndt and Molander (**Scheme 2a**). Olofsson and Gaunt showed that this reaction can also be performed using diaryliodonium salts.[18] Although multiple methods exist to O-arylate the side chain of tyrosine, many of them show limitations such as low substrate scope, limited functional group tolerance, the need for high temperatures or strong bases, or the necessity of having specific substituents on the aryl moiety. Triphenylbismuth diacetate has been used to arylate the terminal amino function of amino acids.[19] However, to the best of our knowledge, organobismuth reagents have never been used for the arylation of the side chain of amino acids. Recently, we reported a protocol for the N-arylation of the indole side chain of tryptophan that operates directly from triarylbismuth reagents.[20] We now report our results on the copper-promoted O-arylation of the side chain of tyrosine using functionalized triarylbismuthines (**Scheme 2b**).



Scheme 2. a) Existing methods for the O-arylation of the side chain of tyrosine. **b)** O-Arylation of the side chain of tyrosine using triarylbismuths.

Using our conditions for the O-arylation of phenols,[13] N-Boc tyrosine methyl ester **1a** reacted to give the desired product **3a** in 35% yield (**Table 1**, entry 1). Systematic optimization of the reaction parameters (entries 2 to 4) indicated that a quantitative yield could be obtained by using pyridine in the presence of 0.3 equivalents of copper acetate under oxygen at 50 °C for 16 hours in non-anhydrous dichloromethane (entry 5). Reducing the number of equivalents of the base or the bismuth reagent, changing the solvent or running the reaction at room temperature all had a detrimental effect on the yield. Gratifyingly, chiral HPLC analysis indicated that the integrity of the stereogenic center is maintained under our optimal conditions (see supplementary material for details).

Table 1. Optimization of the reaction conditions for the copper-promoted O-arylation of N-Boc tyrosine methyl ester **1a** using tri(4-tolyl)bismuth **2a**.[a]

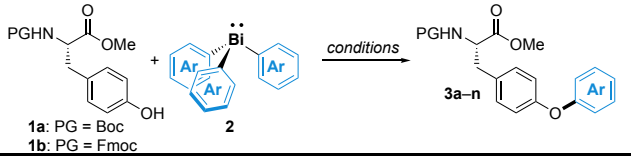


Entry	$Cu(OAc)_2$ (y equiv)	Base	Time (h)	Atmosphere	Yield (%)[b]
1	1.0	Et_3N	3	air	35
2	1.0	Et_3N	16	air	53
3	1.0	Pyridine	16	air	77
4	0.3	Pyridine	16	air	75
5	0.3	Pyridine	16	O_2	99[c]

[a] The reaction was performed in a sealed tube placed in an oil bath at 50 °C. [b] Yields of isolated pure product **3a**. [c] The tube was sparged with pure oxygen for 1 minute prior to the reaction.

Exploration of the scope of the reaction indicated that aryl groups with substituents at any position can be transferred on **1a** using our optimized conditions (**Table 2**, entries 1 to 5). The process showed no sensitivity to electronic effects, demonstrated excellent functional group compatibility, allowed the installation of a 2-naphthyl group and could be performed on Fmoc protected tyrosine methyl ester **1b** (entries 6 to 14).

Table 2. Triarylbismuth scope in the copper diacetate-promoted O-arylation of the side chain of N-protected tyrosine methyl ester.[a]

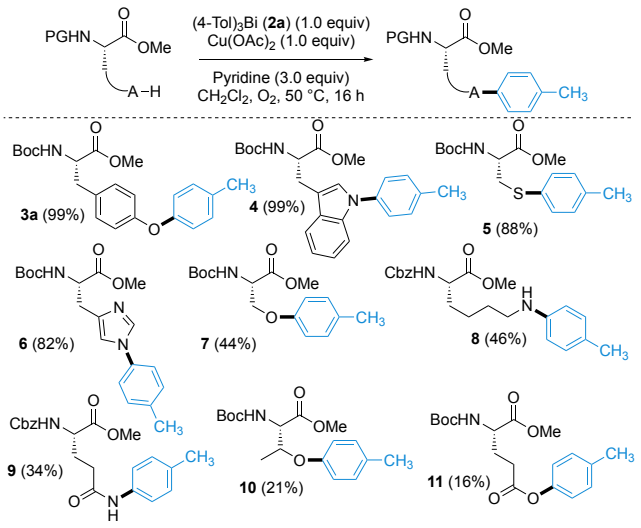


Entry	PG	Ar	Yield (%)[b]
1	Boc (**1a**)	4-Tol	99 (**3a**)
2	Boc (**1a**)	3-Tol	92 (**3b**)
3	Boc (**1a**)	2-Tol	83 (**3c**)
4	Boc (**1a**)	2,6-$Me_2C_6H_3$	75 (**3d**)
5	Boc (**1a**)	Ph	99 (**3e**)
6	Boc (**1a**)	4-(MeO)C_6H_4	99 (**3f**)
7	Boc (**1a**)	4-(CF_3)C_6H_4	99 (**3g**)
8	Boc (**1a**)	4-(THPO)C_6H_4	99 (**3h**)
9	Boc (**1a**)	2-(CHO)C_6H_4	65 (**3i**)
10	Boc (**1a**)	4-($(MeO)_2CH$)C_6H_4	99 (**3j**)
11	Boc (**1a**)	3-(NC)C_6H_4	74 (**3k**)
12	Boc (**1a**)	4-BrC_6H_4	99 (**3l**)
13	Boc (**1a**)	2-Naphthyl	90 (**3m**)

14	Fmoc (**1b**)	4-Tol	99 (**3n**)

[a] Conditions: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, 16 h. The reaction was performed in a sealed tube sparged with pure oxygen and placed in an oil bath set at 50 °C. [b] Yields of isolated pure products **3a**–**n**.

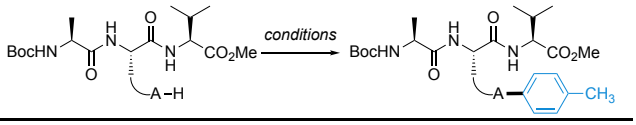
Using stoichiometric amounts of copper diacetate, we next evaluated the intrinsic reactivity of other N-protected amino acid esters that possess a nucleophilic side chain under our conditions (**Scheme 3**). Results show that N-Boc tryptophan methyl ester is as reactive as N-Boc tyrosine methyl ester and that N-Boc cysteine and histidine methyl esters are the third and fourth most reactive amino acids (**3a**, **4**–**6**). The high reactivity of N-protected tryptophan, cysteine and histidine is easily explained by the fact that triarylbismuthines are very efficient at arylating indoles,[12b] thiols[21] and imidazoles.[22] N-Protected serine, lysine and glutamine were much less reactive under these conditions (**7**–**9**). These results are somewhat surprising since 1,2-aminoalcohols,[12c] amines[23] and amides[24] can all be arylated efficiently with triarylbismuthines. Therefore, they suggest that the reactivity of these particular functional groups is impacted by the presence of the proximal ester and carbamate moieties. Because they possess a secondary alcohol and a carboxylic acid, two groups that are difficult to arylate with organobismuth reagents, N-protected threonine and glutamic acid were arylated in low yields (**10** and **11**). No arylation was observed with N-Boc aspartic acid and N-Boc asparagine. Last, N-Boc alanine methyl ester was recovered intact, supporting the conclusion that the arylation of amino acids **3a**–**11** proceeds on the side chain and not the NH-carbamate.



Scheme 3. Evaluation of the reactivity of amino acids containing a nucleophilic side chain in the copper diacetate-promoted arylation using tri(4-tolyl)bismuth. Yields of isolated pure products.

Next, we evaluated the reactivity of the four most reactive amino acids in the context of tripeptides where they are flanked by two inert residues and found that tyrosine and cysteine retain most of their reactivity (**Table 3**, entry 1 and 3). Conversely, our results indicate that tryptophan and histidine are much less reactive when incorporated in a tripeptide (entry 2 and 4).

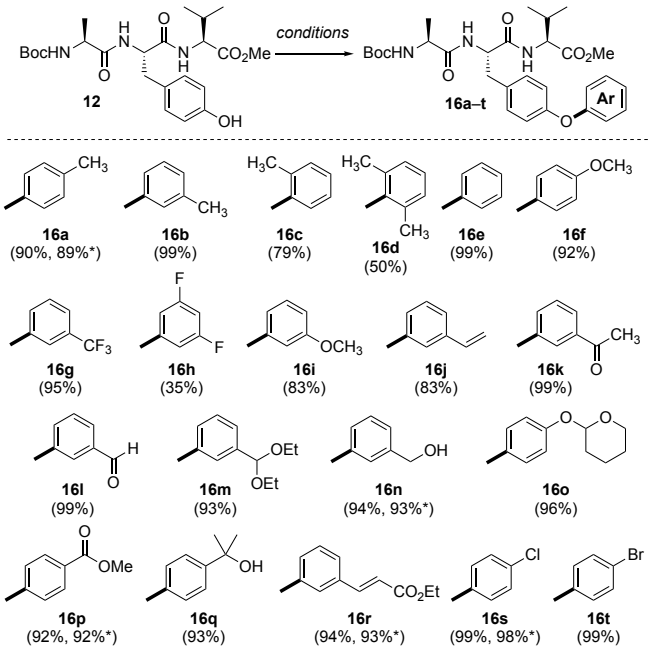
Table 3. Copper diacetate-promoted arylation of tripeptides containing the most reactive amino acids.[a]



Entry	Tripeptide	Yield (%)[b]
1	Boc–Ala–**Tyr**–Val–OMe (**12**)	90 (**16a**)
2	Boc–Ala–**Trp**–Val–OMe (**13**)	63 (**17**)
3	Boc–Ala–**Cys**–Val–OMe (**14**)	81 (**18**)
4	Boc–Ala–**His**–Val–OMe (**15**)	46 (**19**)

[a] Conditions: $(4\text{-Tol})_3Bi$ (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, 16 h. [b] Yields of isolated pure products.

Using conditions from Table 3, we then explored the triarylbismuth scope in the arylation of Boc–Ala–Tyr–Val–OMe **12** (**Scheme 4**). Our results show that the protocol allows the transfer of aryl groups with substituents at any position of the aromatic ring (**16a**–**e**) and substituted by electron withdrawing or donating groups (**16f**–**i**). Excellent functional group compatibility was observed (**16j**–**r**). Groups that would be reactive in arylation methods that require strong bases or copper(I) or palladium(0) catalysts were well tolerated (**16k**,**n**,**q**,**s**,**t**). Some of the examples were performed with 0.3 equivalents of copper(II) acetate with no impact on the yield (yields noted with an asterisk).

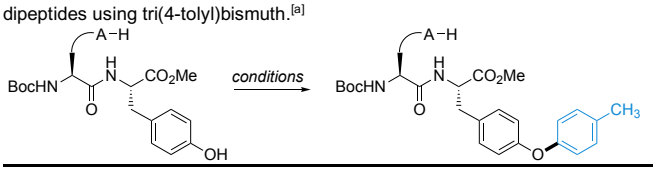


Scheme 4. Triarylbismuth scope in the copper diacetate-promoted O-arylation of the side chain of tyrosine in Boc–Ala–Tyr–Val–OMe **12**. Conditions: Ar_3Bi (1.0 equiv), $Cu(OAc)_2$ (1.0 equiv), Pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, 16 h. Asterisks indicate the yield of the reactions performed with 0.3 equiv $Cu(OAc)_2$. Yields of isolated pure products.

We next explored the applicability of our method to the arylation of various tyrosine-containing dipeptides (**Table 4**). To amplify the inherent differences in reactivity between each amino acid, 0.3

equivalents of copper diacetate were used. In addition, to prevent the formation of diarylation products, some of the entries were also performed at a higher dilution and in a shorter reaction time. Our results indicate that dipeptides where the tyrosine is connected to an inert amino acid such as valine or phenylalanine can be efficiently arylated (entries 1 and 2). To examine the chemoselectivity of the method vis-à-vis amino acids that possess a nucleophilic side chain, we submitted **20c**–**f** to our conditions and obtained the products of O-arylation of tyrosine in yields ranging between 64 and 83% (entries 3 to 6). As predicted by the low reactivity of Boc–Ala–Trp–Val–OMe **13**, the arylation of **20g** occurred regioselectively on the tyrosine residue, giving **21g** in 78% yield (entry 7). The arylation of **20h** proved challenging, providing the product of O-arylation **21h** in only 46% yield (entry 8). No diarylation product was detected for entries 4 to 8, the unreacted starting material being the only other identifiable material in those reactions. As anticipated by the high reactivity of N-Boc cysteine methyl ester **5**, the arylation of **20i** afforded a complex mixture of S and O-arylation products as well as S–S disulfide formation from which **21i** could nevertheless be isolated in 50% yield (entry 9).

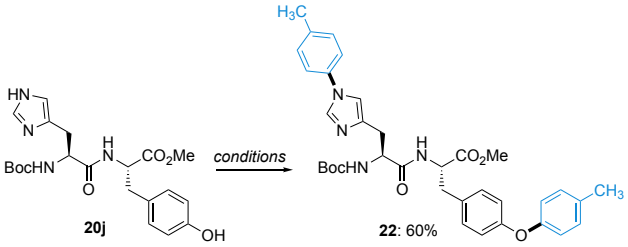
Table 4. Copper diacetate-promoted O-arylation of tyrosine-containing dipeptides using tri(4-tolyl)bismuth.[a]



Entry	Dipeptide	Yield (%)[b]
1	Boc–**Val**–Tyr–OMe (**20a**)	89 (**21a**)
2	Boc–**Phe**–Tyr–OMe (**20b**)	87 (**21b**)
3	Boc–**Met**–Tyr–OMe (**20c**)	83 (**21c**)
4[c]	Boc–**Thr**–Tyr–OMe (**20d**)	73 (**21d**)
5	Fmoc–**Asn**–Tyr–OMe (**20e**)	71 (**21e**)
6[c]	Fmoc–**Asp**–Tyr–OMe (**20f**)	64 (**21f**)
7[c]	Boc–**Trp**–Tyr–OMe (**20g**)	78 (**21g**)
8[c]	Fmoc–**Lys**–Tyr–OMe (**20h**)	46 (**21h**)
9	Boc–**Cys**–Tyr–OMe (**20i**)	50 (**21i**)

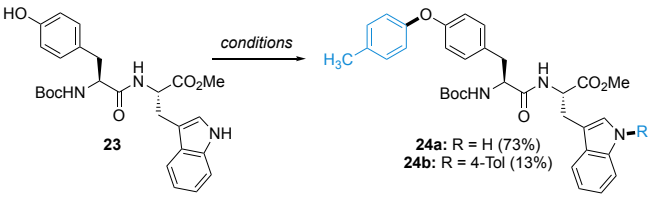
[a] $(4\text{-Tol})_3Bi$ (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, 16 h, 0.1M. [b] Yields of isolated pure products. [c] 6 h, 0.02 M.

We next studied the arylation of Boc–His–Tyr–OMe **20j**. Although N-Boc histidine methyl ester **6** is easily N-arylated under our conditions, the reduced reactivity of Boc–Ala–His–Val–OMe **15** gave us hope that the arylation might proceed mainly on the tyrosine residue. However, the reaction afforded exclusively the product of diarylation **22** in 60% yield, suggesting that the reactivity of histidine is considerably influenced by its immediate environment (**Scheme 5**).



Scheme 5. Copper diacetate-promoted arylation of Boc–His–Tyr–OMe **20j** using tri(4-tolyl)bismuth. Conditions: $(4\text{-Tol})_3Bi$ (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, 16 h.

Finally, to determine if the position of the tyrosine has an impact on the chemoselectivity or if the reaction is driven uniquely by the intrinsic reactivity of each amino acid, we submitted Boc–Tyr–Trp–OMe **23** to our conditions and obtained the product of O-arylation **24a** in 73% yield accompanied by 13% of the diarylated product **24b** (**Scheme 6**). Since the complementary dipeptide Boc–Trp–Tyr–OMe **20g** did not provide any diarylation product, these results suggest that the chemoselectivity is influenced by the position of the tyrosine.



Scheme 6. Copper diacetate-promoted arylation of Boc–Tyr–Trp–OMe **23** using tri(4-tolyl)bismuth. Conditions: $(4\text{-Tol})_3Bi$ (1.0 equiv), $Cu(OAc)_2$ (0.3 equiv), Pyridine (3.0 equiv), CH_2Cl_2, O_2, 50 °C, 6 h, 0.02 M.

In conclusion, we developed a mild protocol for the O-arylation of the phenolic side chain of tyrosine using easily accessible triarylbismuthines. The reaction operates in non-anhydrous dichloromethane under oxygen at 50 °C and is catalyzed by copper diacetate. Excellent functional group compatibility was observed and no racemization was detected. N-Protected tryptophan, cysteine and histidine were arylated under these conditions. The arylation of tyrosine-containing dipeptides and tripeptides was achieved. Transposition of this method to solid support peptide chemistry is under investigation in our laboratory and results will be reported in due course.

Acknowledgements

This work was supported by Boehringer Ingelheim Pharmaceuticals Inc. through a Scientific Advancement grant, by the Natural Sciences and Engineering Research Council of Canada (NSERC), and by the Centre in Green Chemistry and Catalysis (CGCC). We would like to thank Pr. Steve Bourgault for useful discussions and advice regarding the synthesis of the peptides. Hwai-Chien Chan is gratefully acknowledged for proofreading the manuscript and the experimental section.

Keywords: Triarylbismuthines • Tyrosine • Copper catalysis • Amino acids • Arylation reaction

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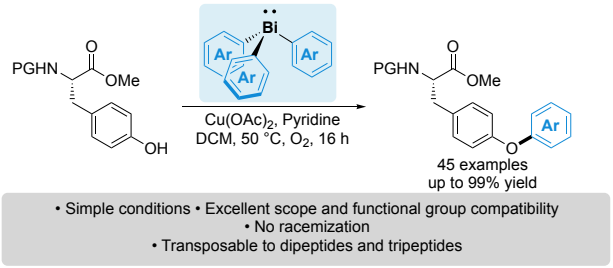
Key Topic: Arylation reaction.

Copper-Promoted O-Arylation of the Phenol Side Chain of Tyrosine using Triarylbismuthines



A procedure for the O-arylation of the side chain of tyrosine using triarylbismuth reagents is reported. The reaction is performed in dichloromethane under oxygen at 50 °C in the presence of pyridine, is promoted by copper diacetate, shows excellent scope and functional group tolerance and retains the integrity of the chiral center. The reactivity of other amino acids possessing a nucleophilic side chain under these conditions is investigated. O-Arylation of tyrosine-containing dipeptides and tripeptides is achieved.