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Complete *N*-1 Regiocontrol in the Formation of *N*-Arylimidazoles. Synthesis of the Active Site His-Tyr Side Chain Coupled Dipeptide of Cytochrome *c* Oxidase†

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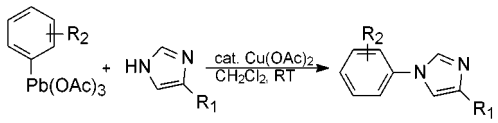
ABSTRACT



Under catalysis by copper(II) acetate, complete regiocontrol (*N*-1 versus *N*-3) was obtained in the arylation of substituted imidazoles with aryllead(IV) reagents. The mildness of the reaction conditions (rt, no added base) allows for the first synthesis of the histidine-tyrosine side chain coupled dipeptide found in the active site of cytochrome *c* oxidase.

N-Arylimidazoles are important compounds in medicinal research.[1] A significant number of these structures are therapeutically useful, and many others are in the process of active study for biomedical applications. Targeted therapeutic areas include thromboxane synthase inhibitors,[2] AMPA receptor antagonists,[3] AMP phosphodiesterase inhibitors,[4] cardiotonic agents,[5] and antiglaucoma agents.[6] Consequently, there is a need for efficient and very mild methods for their construction.

N-Arylimidazoles have been synthesized by nucleophilic aromatic substitution[2b,3,4b,5a,7] and Ullmann-type couplings.[2a,c,d,4,6] Aromatic substitution requires the use of electron-withdrawing substituents, which dampens this methodology. The Ullmann-type couplings are normally done at high temperature, which limits the use of sensitive compounds. Likewise, Buchwald[8] has demonstrated condensation between arylhalides and imidazoles with catalytic amounts of $(CuOTf)_2$·benzene/1,10-phenanthroline/dba/Cs_2CO_3 at temperatures in the range of 110−125 °C. The necessity of such high temperatures and base is expected to limit the utility of this approach with base-sensitive compounds.[9] Collman[10] re-

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ported the room-temperature copper-catalyzed condensation of commercially available arylboronic acids with imidazoles. While this technology is quite mild, it requires 2 equiv of the arylboronic acid and is therefore limited by economics. In addition, both the Collman[10] and Buchwald[8] procedures afford mixtures of regioisomers (<5:1 selectivity) when the reaction is performed on a 4-substituted imidazole.[11]

Our interest in unusual amino acid synthesis[12] directed our attention to the recent discovery of such a target in the active site of cytochrome *c* oxidase. Cytochrome *c* oxidase is a heme-copper oxidase and the terminal respiratory enzyme involved in the reduction of oxygen to water.[13,14] The published amino acid sequence of cytochrome *c* oxidase was recently modified, based upon high resolution X-ray data (Figure 1).[15] It was determined that two individual amino

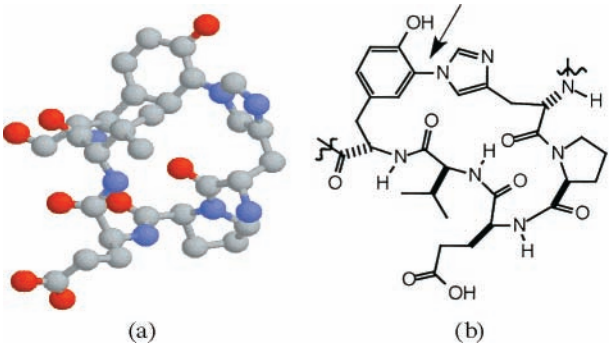


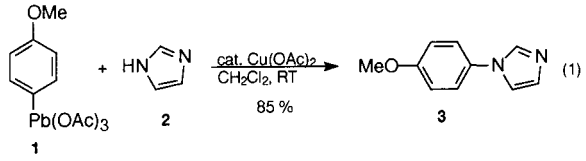
Figure 1. Cyclic pentapeptide from active site of cytochrome *c* oxidase: (a) PDB structure; (b) standard line drawing, arrow indicates unusual side chain linkage.

acid residues [histidine (His[240]) and tyrosine (Tyr[244])[16]] critical to the active site were cross-linked by a covalent C−N bond, thus creating a cyclic pentapeptide.

This unprecedented system is expected to afford the tyrosine-OH unusual physical properties (pK_a, redox potential, etc.) important for the enzymatic event.[17] To date, no detailed information on the spectroscopic or chemical properties of this cross-linked dipeptide is available,[18] and synthesis of the system is imperative.

Our recent research in organolead reagents[19] prompted us to consider their use in the synthesis of this His-Tyr dipeptide. The most common use for organolead reagents[20] is for the formation of sp^2-sp^3 quaternary carbon−carbon bonds.[21] Lead reagents are easily handled, and as previously reported the existence of residual lead is in the background range after workup.[19,22] Organolead reagents also have been shown to *N*-arylate when used in conjunction with a copper catalyst.[23] They are easily prepared from the corresponding tin compound[24] or by direct plumbation.[25] To date, the *N*-arylation of imidazole by a lead reagent has only occurred with *p*-tolyllead triacetate[26] and was performed at 90 °C in a mixture of methylene chloride−DMF. Herein we report the arylation of imidazoles with organolead(IV) reagents. The reaction proceeds with equimolar ratios of the coupling substrates at room temperature in the presence of catalytic amounts of $Cu(OAc)_2$ and results in *exclusive* formation of the 1,4-disubstituted imidazoles in all cases. The reaction is mild enough to afford, for the first time, a suitably protected version of the His-Tyr dipeptide found in the active site of cytochrome *c* oxidase.

We initially probed the temperature requirements of the reaction between *p*-methoxyphenyllead triacetate (**1**) and imidazole (**2**). Gratifyingly, an 85% yield of coupled material (**3**) was obtained within 3 h when the reaction was performed at room temperature with 10 mol % of copper(II) acetate in methylene chloride (eq 1).[27]



We next chose to investigate the regiocontrol of the organolead(IV) protocol. The reaction between 4-methyl-

(9) Recently, researchers at Merck observed the loss of optical integrity in the palladium-catalyzed coupling of vinylogous amides with an aryl halide derived from phenylalanine. The base and temperature conditions of the reaction (Cs_2CO_3, 80 °C) are similar to those employed in the Buchwald procedure. See: Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109−1112.

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(13) Ferguson-Miller, S.; Babcock, G. T. *Chem. Rev.* **1996**, *96*, 2889−2907.

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(16) This numbering scheme is from the bovine sequence.

(17) Proshlyakov, D. A.; Pressler, M. A.; Babcock, G. T. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 8020−8025.

(18) A non-peptide mimic of the His-Tyr system has recently appeared. See: McCauley, K. M.; Vrtis, J. M.; Dupont, J.; van der Donk, W. A. *J. Am. Chem. Soc.* **2000**, *122*, 2403−2404.

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(22) Paquette has recently disclosed the use of $Pb(OAc)_4$ for the removal of colored impurities from olefin metathesis reactions and has presented evidence for very low residual lead in the final product. See: Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Méndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259−1261.

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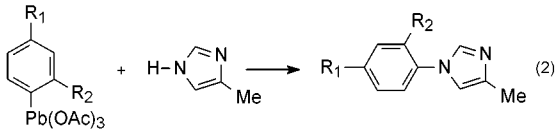
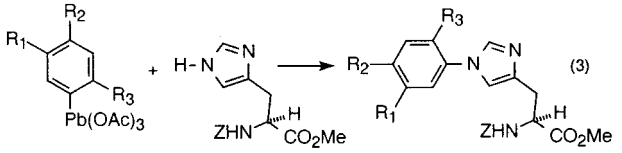
imidazole and phenyllead triacetate **4** could possibly afford both the 1,4- and 1,5-disubstituted imidazoles, and both compounds have been reported in the literature.[28] In the event, exclusive formation of the *N*-1 arylation product was observed with a yield of 80% (eq 2). When the lead reagent



4 $R_1 = R_2 = H$ *80 %*; **1** $R_1 = OMe$; $R_2 = H$ *85 %*; **5** $R_1 = H$; $R_2 = OMe$ *61 %*

was changed to a more electron rich system, such as **1** and **5**, no change in selectivity was observed. The yields of these coupling reactions are 85 and 61% for the isolation of the respective *N*-1 aryl product. At the present time we are uncertain if the lower yield for the *ortho*-substituent lead reagent **5** is due to the bulkiness of the *ortho*-group or to a poor transfer of the aryl group from lead to copper. A single-crystal X-ray structure of **5** shows the oxygen atom of the methoxy group in close proximity to the lead atom with weak donation of electron density.[29] This extra electron density stabilizes the organolead reagent, which could slow the transfer of the aromatic group.

With our reaction conditions developed, we moved to the study of histidine derivatives as the imidazole fragment in the coupling reaction, with the goal of assessing the level of regiocontrol and chiral center integrity attendant in this copper-catalyzed procedure. As the histidine partner we chose Z-His-OMe (**6**), which is commercially available and provides an adequate protection scheme for further elaboration of the desired product. The coupling of **6** with **1** provided the desired product as a single *N*-1 isomer in 68% yield. The desired *ortho* phenol substituent was introduced with the coupling of **6** to **5** and **7** in 46% and 49% yields, respectively. Finally, the target dipeptide was obtained in 48% isolated yield as a single isomer through the reaction of organolead reagent **8**,[21] derived from L-tyrosine, with **6**. To our knowledge, this is the first coupling of amino acids mediated by lead reagents. No racemization is detected by ^1H and ^{13}C NMR for this coupling reaction.



6

1 $R_1 = R_3 = H$; $R_2 = OMe$ *68 %*
5 $R_1 = R_2 = H$; $R_3 = OMe$ *48 %*
7 $R_1 = R_2 = H$; $R_3 = Oallyl$ *49 %*
8 $R_1 = (S)\text{-}CH_2C(H)(NHBoc)CO_2Bn$, $R_2 = H$, $R_3 = OMe$ *48%*

In conclusion, our work constitutes the first examples of an amino acid coupling mediated by organolead reagents. The reaction conditions are quite mild (room temperature, no additional base needed) and no racemization occurs. These reaction conditions provide only *N*-1 regioselectivity, a significant improvement over previous methods. Further studies with the His-Tyr dipeptide reported herein are underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for products of the reactions of **1**, **5**, **7**, and **8** with compound **6** and the reactions of 4-methylimidazole with **1** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) **General procedure**: Substituted imidazole (1 mmol) is stirred in 10 mL of methylene chloride at room temperature. To this solution is added copper(II) acetate (0.1 mmol) along with aryllead tricarboxylate (1.4 mmol). The blue solution, upon completion of time (3−14 h), is quench with 3 mL of a water−sodium sulfide solution. The reaction stirs for an addition 15 min. The black precipitate is passed through Celite. The solution is extracted with methylene chloride (3 × 5 mL). The organic layer is dried over sodium sulfate and concentrated in vacuo. Chromatography provides the substituted arylimidazole.
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