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Mild and efficient palladium/BrettPhos-catalyzed methoxylation and deuteriomethoxylation of activated aryl bromides

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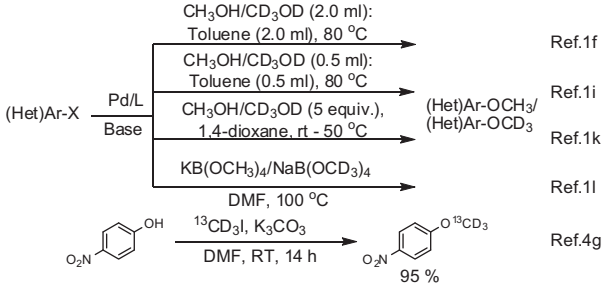
ABSTRACT

A simple and efficient Pd/BrettPhos-catalyzed C–O cross-coupling reaction of activated aryl bromides with methanol and methanol-d_4 has been disclosed. Bromo-chalcones were also found to have coupled effectively with methanol and methanol-d_4. With increasing alkyl chain length of the primary alkyl alcohols, the catalyst system becomes inactive. The catalyst system facilitates the C–O coupling reaction even under mild reaction conditions.

Transition-metals catalyzed C–O cross-coupling reactions, particularly Cu and Pd, are still appealing to organic chemists[1–3] owing to the following two reasons (i) the structural feature of the ether units: (het)aryl ether units, is present in a variety of natural products, biologically active compounds, drugs, etc.[4] and (ii) the palladium-catalyzed C–O cross-coupling reactions are the gateway to several advantages, including high functional group tolerance, a broad range of substrate scope even under mild reaction conditions albeit it suffers from β-hydride elimination side reaction.[1] Thus, these catalyst systems have an edge over the traditional methods, such as Williamson, the Mitsunobu, the Ullmann reactions and alkoxylation of phenols, which require harsh reaction conditions, strong basic medium, elevated temperature, and carcinogenic reagents.[3b,5]

Much as the physicochemical properties of deuterated and non-deuterated molecules are almost identical, the deuterio version of the molecules are more resistant to chemical or enzymatic cleavage due to the fact that the C–D bond is 6 to 10 times stronger than C–H bond because of the deuterium kinetic isotope effects on C–H/D cleavage.[6] Of late, the incorporation of deuterium in drug molecules has become a valuable method for pharmacologists thanks to enhanced pharmacokinetics, pharmacodynamics and reduced toxicological properties over their protio versions.[1f,i,k,l,4g,6b,c] Recently, Sando and co-workers have demonstrated the utility of ^{13}C labeled fully deuterated methoxy group ($^{13}CD_3O$) as a long-lived hyperpolarized ^{13}C nuclear magnetic resonance (NMR) probe which can be used as a chemical probe for sensing HOCl, a biomarker of inflammation. The hyperpolarization lifetime is directly proportional to molecular size, thus $^{13}CD_3O$ unit will serve as a potential hyperpolarized NMR probe of future interest.[4g]

Palladium-catalyzed coupling of (het)aryl halides with methanol and methanol-d_4 and ^{13}C labeled deuteriomethylation of 4-nitrophenol are the available methods for the synthesis of anisoles and deuterated anisoles which are given in Scheme 1.



Scheme 1. Synthesis of anisoles, deuterated and ^{13}C labeled deuterated anisoles.

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