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A general and efficient Pd-catalyzed rapid 2-fluoroethoxylation of bromo-chalcones

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ABSTRACT

An efficient unprecedented Pd-catalyzed rapid 2-fluoroethoxylation of bromo-chalcones has been unveiled. The oxygen nucleophiles (fluoroalcohols) experience the rapid C—O bond forming reaction for the first time, albeit the alcohols are known to be a weak nucleophile and have greater competing β–hydride elimination in the transition-metal-catalyzed (especially Pd and Cu) C—O cross-coupling reaction. The higher fluoroalcohols have also been effectively coupled with bromo-chalcones with relatively lower rate.

1. Introduction

Incorporation of fluorine or fluorine containing functional groups into organic molecules has recently received a gargantuan growth of interest among chemists, thanks to fabulous physico-chemical properties and even bizarre behavior of fluorine compounds [1–3]. Startling properties of fluoroorganic compounds are clearly evident from their widespread applications in medicinal chemistry [1–3], positron emission tomography (PET) imaging technology [4,5], material sciences [6,7], etc. Latterly, (hetero)aryl fluoroalkyl ethers containing organic molecules are widely used as drugs [8,9] and PET [10–15] tracers in medical sciences (Fig. 1).

After the advent of transition-metal-catalyzed cross-coupling methodologies the growth of fluorine chemistry is tremendous due to the fact that the transition-metal-catalyzed cross-coupling reactions are addressing long-standing challenges for fluoroorganic chemists [16–18]. In general, oxygen nuclophiles are known to be poor nucleophiles in transition-metal-catalyzed cross-coupling reactions (especially Pd and Cu) as (1) alcohols are weak nucleophiles, (2) C—O reductive elimination is significantly slower, and (3) β-hydrogen elimination is rather fast [19–24]. However, novel Pd/L catalytic systems, which have recently been developed to overcome these problems, successfully facilitated the coupling of alcohols with electron-rich, neutral and heteroaryl halides [25]. Thus, alcohols are not believed to be involved in the rapid reductive elimination to form C—O bond even with activated aryl halides. To the best of our knowledge, only one example of room temperature, rapid intramolecular C—O bond forming reaction has been reported by Hartwig et al. [26]. Recently, it has been reported in our previous publication that 2,2,2-trifluoroethanol and methanol could be rapidly coupled with activated aryl bromides for the first time using $[Pd_2(dba)_3]$/*t*BuXPhos catalyst system [27]. With this gleeful result, and the availability of facile protocol for the preparation of 2-[^{18}F] fluoroethanol [28,29], we are further engaged in developing a suitable catalyst system for rapid 2-fluoroethoxylation of activated molecules, bromo-chalcones, of biological interest [10–15]. Rapidness of the methodology can be useful in the 2-[^{18}F]fluoroethoxylation for positron emission tomography (PET) imaging technology with a necessary modification. Herein, we recount an unprecedented efficient Pd-catalysed rapid 2-fluoroethoxylation of bromo-chalcones of biological interest. The methodology is also extended to higher fluoroalcohols.

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