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Catalysis

Palladium-Catalyzed Rapid Methoxylation and Deuteriomethoxylation of Bromo–chalcones: Uncovering the Catalytic Activity of the Pd/*t*BuXPhos Catalyst System

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We report an unprecedented *t*BuXPhos ligand (**L3**) supported Pd-catalyzed rapid methoxylation and deuteriomethoxylation of bromo-chalcones (5 to 40 min.) with excellent yields. Pd/RockPhos (**L2**) catalytic system also facilitates the coupling reaction, but the reaction time is fairly longer than Pd/*t*BuXPhos (**L3**) catalytic system. The coupling of MeOH/MeOH-d_4 with 4-bromo-chalcones is so rapid than that of 3-bromo-chalcones, which clearly indicates that the former proceeds through a pure electronic pathway of reductive elimination. These catalyst systems facilitate the coupling of 4-bromo-chalcones even with higher alkyl alcohols relatively long reaction time that implies the efficiency and rate of coupling relays on the nucleophilicity of the alcohols. This methodology may be adopted for the ^{11}C-radiolabeling of organic compounds for PET imaging applications.

Introduction

Aryl alkyl ethers are an important class of organic compounds which incessantly kindled chemists interest as their presence in numerous natural products, pharmaceuticals, fragrances, cosmetics, agrochemicals, and organic materials.[1] Substitution by strong electron-donating alkoxy group into conjugated system results a remarkable influence on its electrical and optical properties.[2] Recently, it was demonstrated that the methoxy substitution into p-type semiconducting molecules shows lower ionization potential and higher hole drift mobilities, particularly, *p*-methoxy substitution shows stronger influence on the ionization potential and hole-mobilities.[3] Moreover, the aryl methyl-d_3 ethers have recently been paid considerable attention in pharmaceutical industries due to the fact that the incorporation of deuteriomethoxy groups into drug molecules augments the pharmacokinetics, pharmacodynamics and reduced toxicological properties over their protio versions.[4]

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Much as several traditional methods, such as the Williamson, Mitsunobu, Ullmann reactions and the Bronsted/Lewis acid mediated condensation between methanol and phenols, are available for the synthesis of ethers, still pursuit of an efficient method is of great interest among chemists as it suffers from harsh reaction conditions, strong basic medium, elevated temperature, low functional group tolerance and the use of carcinogenic reagents.[5] Recently, transition-metals catalyzed C–O cross-coupling reaction, particularly Cu[6a] and Pd[6b,c] are appeared to be a promising method of choice and have an edge over the traditional methods due to the good functional group tolerance, mild reaction conditions, moderate temperature, and wide substrate scope.

Although Pd-catalyzed C–O cross-coupling reactions with phenols and alcohols have been known for more than a recent decade, the C–O cross-coupling reaction with methanol has been scarcely explored.[6b,c] In general, the problem associated with the C–O cross-coupling reaction to form aryl ethers is the slow reductive elimination of C–O bond from Pd-alkoxy complex over competing β-hydride elimination. The alkoxides are less neucleophilic and efficient hydride donors for reduction of aryl halides than other nucleophiles such as C, N, etc.[6b,7] The recent advances in the development of various phosphine ligands led to a promising outcomes in the C–O cross-coupling reactions.[6] However, Pd-catalyzed coupling of simple methanol and methanol-d_4 has been paid more attention only in recent years,[4c–e,7b,8c–e] albeit Pd- catalyzed coupling of methanol with aryl bromides (only two examples) has already been reported by Buchwald group.[8a,b]

Until our recent results published,[8e,9] it has been believed that Pd-catalyzed C–O bond-forming reactions are slow since alcohols are weak nucleophiles and strong hydride donor in the Pd-chemistry.[6b,c,7] In our first publication, we demonstrated the clear separation of steric and electronic pathway of reductive elimination by Pd/BrettPhos ligand catalyst system