Tetrahedron Letters 56 (2015) 2234–2237

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 18 January 2015
Revised 6 March 2015
Accepted 11 March 2015
Available online 20 March 2015

Keywords:
C–O cross-coupling
Pd/BrettPhos catalyst system
Methoxylation and deuteriomethoxylation
Activated aryl bromides and chalcones
Synthetic methods

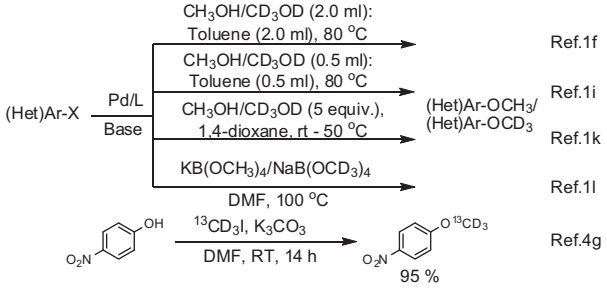
ABSTRACT

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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http://dx.doi.org/10.1016/j.tetlet.2015.03.045
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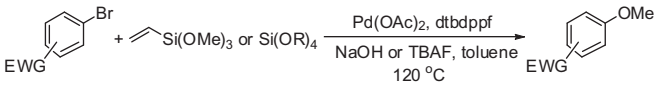


Scheme 2. Pd-catalyzed synthesis of anisoles using alkoxysilanes.

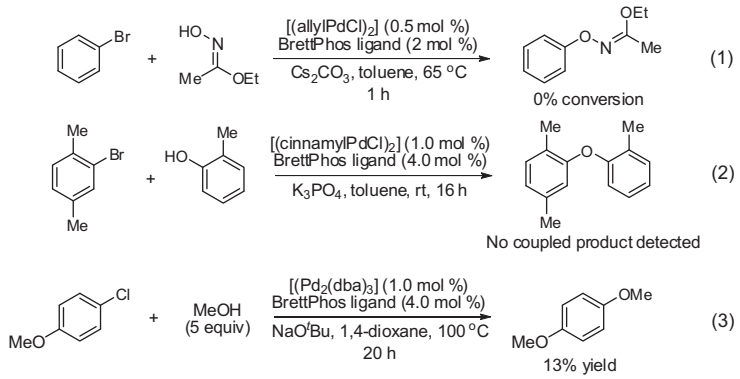
Clarke and co-workers[1n] have reported the Pd-catalyzed methoxylation (alkoxylation) of activated aryl bromides using alkoxysilanes as nucleophiles as shown in the Scheme 2.

Although BrettPhos ligand, one of the promising biaryl phosphine ligands, could effectively couple variety of nucleophiles, such as C–N, C–CF_3, C–C, etc. with aryl halides and aryl tosylate or mesylate, failed to couple aryl halides with oxygen nucleophiles, even without β-hydrogen atoms (Eqs. 1 and 2), as given in the Scheme 3.[1m] This discrepancy in catalyzing the cross-coupling reactions with nucleophile to nucleophile by Pd/BrettPhos ligand system has recently been disentangled in our previous work[1m] in which we described an insight into the phosphine ligand, BrettPhos, that possesses the property of altering the mechanistic pathway of reductive elimination (steric and/or electronic) from nucleophile to nucleophile. This has been demonstrated through C–O and C–C bond-forming reactions under identical reaction conditions as shown in Scheme 4. Thus, the BrettPhos ligand was not known for C–O bond-forming reaction. However, we have reported that all activated aryl halides could effectively couple with monofluoroalcohols to polyfluoroalcohols.[1m] We were then encouraged to explore the Pd/BrettPhos ligand system further to simple alkyl alcohols under our previously optimized reaction conditions.

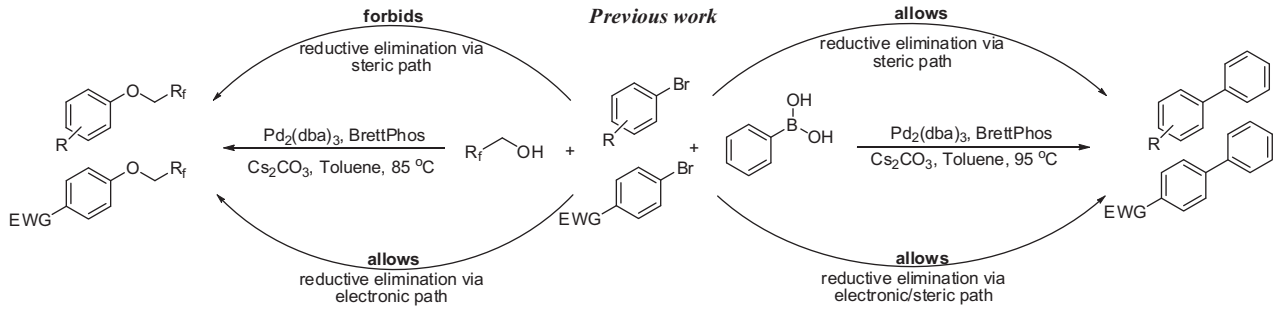
Herein, we report the BrettPhos ligand supported Pd-catalyzed methoxylation and methoxylation-d_3 of activated aryl bromides under mild reaction conditions to afford the desired product up to 98% yield in short reaction times. This methodology has several advantages against other existing methods with respect to activated aryl bromides.[7]

To begin with, we carried out the methoxylation of 4-bromoacetophenone with three equivalents of methanol under our previously optimized reaction conditions at 85 °C, the desired product **1** obtained was only 53% yield in 2.0 h. We then decided to carry out the same reaction at lower temperature, 55 °C, the desired product **1** obtained was in very good yield, 86% in 6.5 h.[8] The results of alkoxylation of activated aryl bromides are given in Table 1.

Buoyed by the results, we were able to couple methanol with all activated aryl bromides such as 4-bromobenzonitrile, methyl-4-bromobenzoate, 1-bromo-4-nitrobenzene, and 4-bromobenzophenone to afford the corresponding methoxylated products, **4**, **6**–**8**, in short reaction times up to 90% yields (Table 1). The bromo-chalcone, (*E*)-3-(furan-2-yl)-1-(4-bromophenyl)prop-2-en-1-one, was also methoxylated smoothly with 1.0 mol % Pd catalyst loading at 85 °C in 3 h, affording the desired chalcone **11** in 74% yield. Subsequently, we carried out the reactions of ethanol with 4-bromoacetophenone and 4-bromobenzonitrile to afford the desired products **2** and **5** in 69% and 75% yields, respectively. With ethanol, activated aryl bromides coupled successfully both at low (55 °C) and high temperature (85 °C). Further, increasing the chain length of the alcohol, *n*-butanol, gave an adverse effect on the yield of **3** (51%) and conversion (96%) of the reaction even at relatively higher Pd catalyst loading (1.0 mol %) and higher temperature (85 °C) over 19 h. Similarly, the reaction of 4-bromobenzophenone with *n*-decanol, no desired product **10** was obtained. This results indicate that the catalytic activity dramatically drops and finally become inactive with increase in the chain length of primary alcohols, whereas the reaction of activated aryl bromides with fluorinated alcohols, 1*H*,1*H*-perfluoroalcohols of up to C-9 carbon chain length,



Scheme 3. Examples of BrettPhos ligand supported Pd-catalyzed C–O cross-coupling reactions.



R_f= CH_2F, -$(CF_2)_nCF_3$; (n = 0,1,2, etc.); R = Electron-releasing groups at *o*-, *m*-, and -*p* positions, -neutral and Electron-withdrawing groups at *o*- and *m*- positions; EWG = Electron withdrawing groups

Scheme 4. Palladium/BrettPhos-catalyzed C–O and C–C bond formation via electronic and steric and/or electronic pathway of reductive elimination, respectively.