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SHORT COMMUNICATION

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Trideuteriomethoxylation of Aryl and Heteroaryl Halides

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Dedicated to Professor T. K. Chandrashekar[‡]

Keywords: Palladium / Cross-coupling / Ethers / Deuterium / Homogeneous catalysis

Direct access to trideuteriomethoxylated aromatic and heteroaromatic compounds has been developed. Various aryl and heteroaryl halides underwent d_3-methoxylation under mild reaction conditions by using a catalyst system composed of the commercially available monodentate phosphane ligand *t*BuXPhos and $Pd(OAc)_2$. Inexpensive CD_3OD served as an efficient trideuteriomethoxylating agent.

Introduction

Selective incorporation of deuterium in place of hydrogen is a powerful tool in medicinal chemistry.[1] Although they have received less attention, deuterium-containing drugs have the unique ability of altering the therapeutic profile and metabolic fate of the drug thereby retaining its biochemical potency and selectivity.[2] These drugs are increasingly in high demand in pharmaceutical industries[3] and are essential for clinical studies. For example, deuterated analogues[4] of paroxetine (CTP-347; antidepressant drug), [D_9]- and [D_{22}]etacrynic acid *n*-hexylamides (diuretic drug), venlafaxine (SD-254; serotonin-norepinephrine reuptake inhibitor), and Atazanavit (CTP-518; HIV protease inhibitor) have entered in clinical trials, and the results are promising.[1a,5] Especially, [D_3]methoxy incorporated aryl compounds are very important motifs in various drugs such as venlafaxine (SD-254), [D_6]-ψ-DOM, [D_3]Glyburide ([D_3]methoxy), 2-(2-Boc-aminoethoxy)[D_3]anisole, and [D_3]Urapidil ([D_3]methoxy) shown in Figure 1.[6] Therefore, synthesis of deuterium-labeled compounds has a great potential to generate new drugs.

In general, alkyl (hetero)aryl ethers are synthesized through the classical method of O-alkylation by using strong alkylating agents (MeI, Me_2SO_4) that are often carcinogenic.[7] Further, traditional Williamson ether synthesis carried out at higher temperatures (300 °C) leads to low functional group tolerance.[8] Therefore, transition-metal-catalyzed cross-coupling methodologies[9] have become an efficient and versatile tool for the synthesis of alkyl (hetero)aryl ethers. Especially, Pd-catalyzed C–O cross-coupling reactions are well developed with phenol and primary, secondary, and tertiary alcohols under comparably mild conditions.[10] During the last decade, Buchwald,[11] Hartwig,[12] Singer,[13] and Beller[14] have designed a series of phosphane ligands that facilitate the Pd-catalyzed C–O cross-coupling of various (hetero)aryl halides with different types of alcohols. Each of these individual protocols has its own limitations including the cumbersome synthesis of ligands, low selectivity of alcohols, low substrate scope, and unwanted formation of reduced arenes. In addition, simple methanol or its deuterated analogue was very difficult to couple with (hetero)aryl halides because of competing β-hydride elimination.

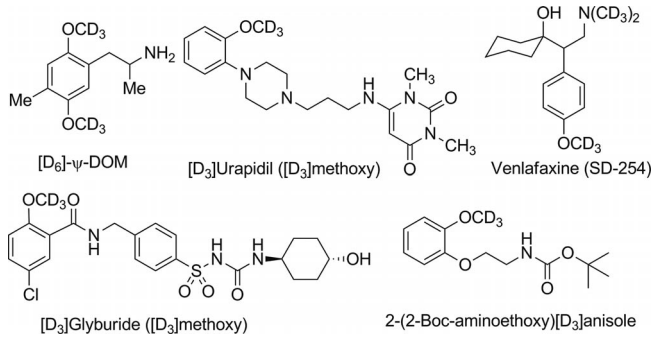

Figure 1. Selected C–OCD_3 bond containing structural motifs.

Recently, an alternative method for the selective incorporation of the D_3CO group into arenes was reported[15] by Jung and Bräse using immobilized triazenes as precursors via deuterio-dediazoniation procedures in the presence of [D_4]methanol and [D_1]TFA (Scheme 1). However, this

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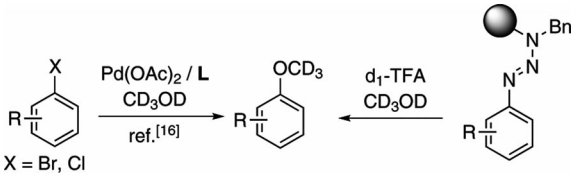
method requires a multistep synthesis of the starting materials, scaling-up of the reaction, and also requires the use of an excess amount of deuterated methanol. Very recently, Beller et al. also synthesized[16] a few deuterated anisoles via the Pd-catalyzed C–O cross-coupling reaction of activated aryl halides with deuterated methanol by using a non-commercial adamantyl-based phosphane ligand.[17] However, commercially available ligands are more attractive than the synthesis of new ligands for this process. Overall, no general methodology is available for the simple cross-coupling reaction of (hetero)aryl halides with CD_3OD in the presence of air-stable, readily available ligands. Herein, we report the Pd-catalyzed cross-coupling of (hetero)aryl halides with inexpensive CD_3OD by using the commercially available *t*BuXPhos ligand[18] to afford the corresponding [D_3]methoxylated compounds in up to 90% yield.

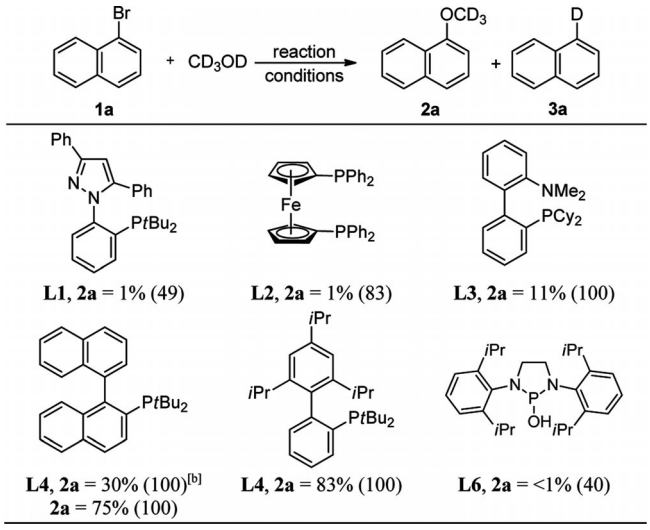


Scheme 1. Synthetic approaches for the preparation of deuterated methyl aryl ethers.

Results and Discussion

Over the last 10 years, commercially available Buchwald diaryl phosphane ligands have drawn interest in the development of palladium-catalyzed cross-coupling reactions thereby meeting both academic and industrial needs.[19] Therefore, we decided to investigate bulky ligands for the Pd-catalyzed C–O cross-coupling reaction of aryl halides with CD_3OD – a difficult coupling partner. Initially, the reaction of 1-bromonaphthalene (**1a**) with CD_3OD was investigated as a model system in the presence of 5 mol-% $Pd(OAc)_2$ and ligands **L1**–**L6** (Table 1). In the absence of ligands **L1**–**L6** only the well-known side product dehalogenated naphthalene **3a** was observed. However, the use of the bulky mono-trippyPhos (**L1**) ligand under similar conditions gave a negligible amount of desired 1-[D_3]methoxynaphthalene (**2a**) along with a considerable amount of reduced product **3a** (Table 1, entry 1). The results were even more disappointing with the commercially available ferrocene-based dppf (**L2**) ligand. On the other hand, experiments performed in the presence of DavePhos (**L3**) provided a better yield than that obtained with ligands **L1** and **L2** but gave only 11% yield of **2a**. On the basis of this result, we started screening the known bisnaphthyl ligand TrixiePhos (**L4**), which afforded expected product **2a** in 75% yield. Unfortunately, the use of this ligand in the absence of a co-solvent resulted in a decrease in the yield by 45%. Gratifyingly, when the experiment was performed in the presence of the commercially available tBuXPhos (**L5**) ligand, the yield improved to 83%. To further improve the yield, we examined different ligands (Table 1, **L6**; see also the Supporting Information); however, bulky monodentate ligand **L5** turned out to be the best for this model reaction. These results once again emphasized the importance of bulky diaryl phosphane ligands for cross-coupling reactions of aryl halides with alcohols.

Table 1. Screening of ligands for trideuteriomethoxylation.[a]



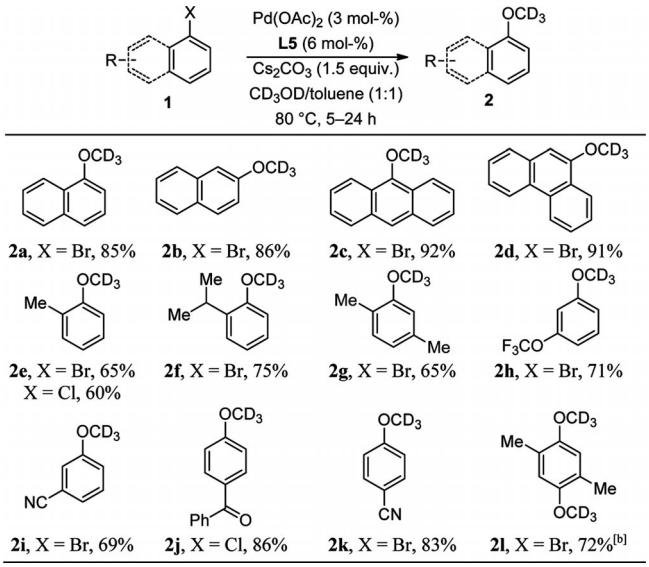
[a] Reaction conditions: 1-bromonaphthalene (0.5 mmol), CD_3OD (0.5 mL), $Pd(OAc)_2$ (5 mol-%), **L1**–**L6** (10 mol-%), Cs_2CO_3 (1.5 mmol), toluene (0.5 mL), 80 °C, 8 h. Conversions are given in parentheses. GC yields are given. [b] Without any co-solvent.

To our delight, the use of *t*BuXPhos gave rise to an 85% yield of desired 1-[D_3]methoxynaphthalene as a benchmark reaction. For further fine-tuning of this process, other palladium precursors such as $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, and $Pd_2(dba)_3$ were screened and found to be less beneficial when compared with $Pd(OAc)_2$.[20] The coupling process was further optimized by varying bases such as KOH, Et_3N, K_2CO_3, and Cs_2CO_3, and the best results were obtained by using Cs_2CO_3.[20] Interestingly, we observed that preactivation of $Pd(OAc)_2$ (3 mol-%) and **L5** (6 mol-%) in toluene at 80 °C followed by subsequent addition of 1-bromonaphthalene in CD_3OD gave an improved yield (90%, GC yield).

With the optimized conditions in our hand, we examined a series of polyaromatic bromides. These bromides were effectively coupled with CD_3OD to furnish the corresponding [D_3]methoxy polyaromatic compounds in excellent yields (Table 2, **2a**–**d**). Next, we performed the coupling of *o*-bromotoluene and the corresponding chloride with CD_3OD and both of them were smoothly converted into the corresponding ether in moderate yield (65 and 60% respectively; Table 2, **2e**). Similarly, the sterically hindered substrate 1-bromo-2-isopropylbenzene gave the corresponding ether in 75% yield (Table 2, **2f**). On the other hand, substrates possessing an electron-withdrawing group at either the *meta* or *para* position (CN, OCF_3, and COPh) were coupled successfully with CD_3OD to afford the products in moderate to very good yields (Table 2, **2h**–**k**). Interestingly, 2,5-dibromo-*p*-xylene was transformed into corresponding ether

product **2l** in 72% yield. The reaction takes place via di-[D_3]methoxylation in [D_4]methanol as described in the reaction conditions.

Table 2. Pd-catalyzed coupling reactions of aryl halides with deuterated methanol.[a]

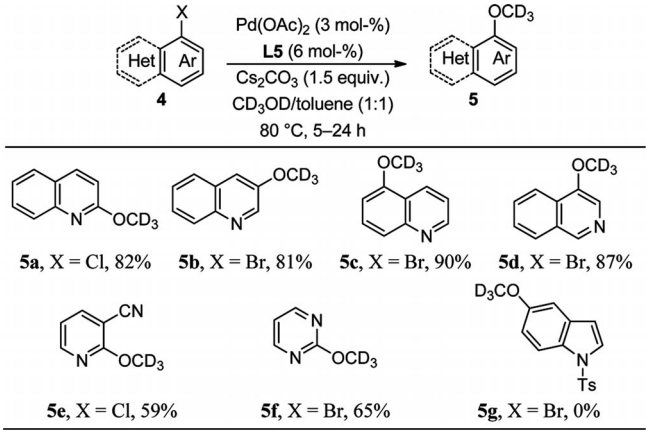


[a] Reaction conditions: 1-bromonaphthalene (0.5 mmol), CD_3OD (0.5 mL), $Pd(OAc)_2$ (3 mol-%), **L5** (6 mol-%), Cs_2CO_3 (1.5 mmol), toluene (0.5 mL), 80 °C, 8 h. Isolated yields are given. Complete consumption of the starting material was monitored by TLC and GC–MS. [b] $Pd(OAc)_2$ (6 mol-%) and **L5** (12 mol-%) were used.

We next turned our attention towards the synthesis of [D_3]methoxylated heterocycles by applying our established synthetic methodology. Unfortunately, this coupling reaction was not explored in substrates such as activated and non-activated quinoline, isoquinoline, pyrimidine, and indole. Thus, 2-chloroquinoline was rapidly coupled with CD_3OD to afford 2-[D_3]methoxyquinoline in very good yield (82%; Table 3, **5a**). In addition, non-activated substrates like 3- and 5-bromoquinolines were smoothly converted into the corresponding coupled products in excellent yields (Table 3, **5b** and **5c**). This process could also be successfully applied to the more challenging substrate 4-bromoisoquinoline to give **5d** in 87% yield. Further, other heteroaryl halides like 2-chloro-3-cyanopyridine and 2-bromopyrimidine proved to be suitable substrates for this process and delivered the products in moderate yields (Table 3, **5e** and **5f**). Unfortunately, 5-bromo-*N*-tosylindole gave only detosylated indole, and desired product **5g** was not detected in the reaction mixture.[21]

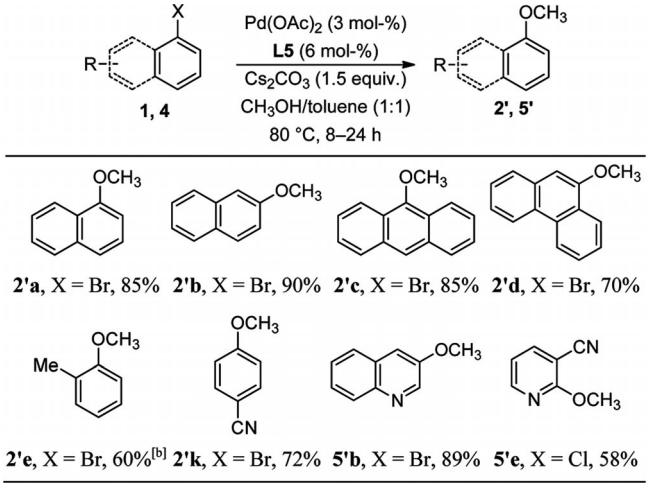
To date, only one general synthetic methodology for the cross-coupling of aryl halides with methanol has been reported.[16,22] Therefore, our present methodology could also be effective for the synthesis of methoxylated (hetero)aryl compounds. As expected, activated and non-activated (hetero)aryl bromides and chlorides were also effectively coupled with methanol to afford the corresponding methoxylated products in moderate to excellent yields (60–90%; Table 4, **2′a**–**e**, **2′k**, **5′b**, and **5′e**), and the yields were comparable to those of the [D_3]methoxylated products. The present protocol adds to the known catalytic systems developed by Buchwald[11] and Beller[14] for the synthesis of alkyl (hetero)aryl ethers, and hence, it has immense applications in organic synthesis.

Table 3. Pd-catalyzed coupling reactions of heteroaryl halides with deuterated methanol.[a]



[a] Reaction conditions: 1-bromonaphthalene (0.5 mmol), CD_3OD (0.5 mL), $Pd(OAc)_2$ (3 mol-%), **L5** (6 mol-%), Cs_2CO_3 (1.5 mmol), toluene (0.5 mL), 80 °C, 8 h. Isolated yields are given. Complete consumption of starting material was monitored by TLC and GC–MS.

Table 4. Pd-catalyzed coupling reactions of (hetero)aryl halides with methanol.[a]



[a] Reaction conditions: 1-bromonaphthalene (0.5 mmol), CD_3OD (0.5 mL), $Pd(OAc)_2$ (3 mol-%), **L5** (6 mol-%), Cs_2CO_3 (1.5 mmol), toluene (0.5 mL), 80 °C, 8 h. Isolated yields are given. Complete consumption of the starting material was monitored by TLC and GC–MS. [b] GC yield.

Conclusions

In summary, we have demonstrated the first general and efficient method for the trideuteriomethoxylation of (hetero)aryl halides with CD_3OD by using the commercially available *t*BuXPhos ligand; the yields are moderate to excel-

lent. The synthesis adopted here is simple and straightforward and does not require the addition of additives or an argon atmosphere. The present methodology is also complementary for the synthesis of respective methoxylated compounds. In addition, we found that *t*BuXPhos is highly effective at suppressing β-hydride elimination occurring in C–O coupling reactions involving alcohols like CD_3OD and methanol.[23] Our protocol for the synthesis of deuterium-labeled (hetero)aryl alkyl ethers allows for interesting applications in the pharmaceutical industry. Selective incorporation of the D_3CO moiety in existing drugs is currently underway in our laboratory.

Experimental Section

General Procedure for Trideuteriomethoxylation: An oven-dried, 8-mL reaction vial was charged with $Pd(OAc)_2$ (3 mol-%), ligand **L5** (6 mol-%), Cs_2CO_3 (0.75 mmol), and toluene (0.5 mL), and the mixture was stirred at 80 °C for 5 min. Then, it was cooled and the aryl halide (0.5 mmol) in [D_4]methanol (0.5 mL) was added. The reaction mixture was stirred at 80 °C and was monitored by TLC or GC–MS. After the starting material had been completely consumed, the reaction mixture was cooled to room temperature and purified by flash chromatography.

Supporting Information (see footnote on the first page of this article): Screening of the reaction conditions, general experimental procedures, characterization data, and NMR spectra of the isolated products.

Acknowledgments

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[23] The use of the *t*BuXPhos ligand led to reduced arene. See ref.[11b]

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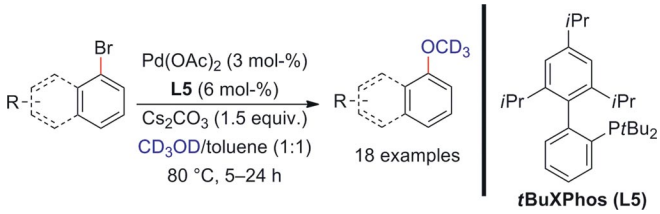
C–O Cross Coupling



The simple and straightforward synthesis of labeled methyl (hetero)aryl ethers via palladium-catalyzed C–O cross-coupling reaction of (hetero)aryl halides with CD_3OD was developed. The *t*BuXPhos ligand is used for the first time in ether synthesis.

Keywords: Palladium / Cross-coupling / Ethers / Deuterium / Homogeneous catalysis

