

Mild and General Palladium-Catalyzed Synthesis of Methyl Aryl Ethers Enabled by the Use of a Palladacycle Precatalyst

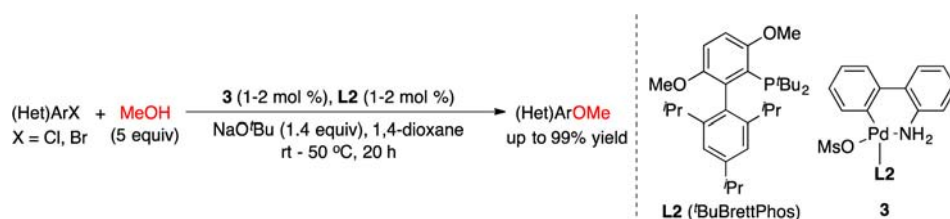
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ABSTRACT



A general method for the Pd-catalyzed coupling of methanol with (hetero)aryl halides is described. The reactions proceed under mild conditions with a wide range of aryl and heteroaryl halides to give methyl aryl ethers in high yield.

Methyl aryl ethers, including anisoles and methoxy-substituted heteroarenes, are structural components of natural products,¹ pharmaceuticals,^{2,3} and agrochemicals.⁴ Figure 1 shows some examples of approved drug molecules containing methyl aryl ethers.² The replacement of methoxy groups with trideuteriomethoxy groups in drug molecules can alter the metabolic activity of drugs and thus enhance their pharmaceutical potency.⁵ Therefore, the development of techniques for the intermolecular construction of C–O bonds to synthesize methyl aryl ethers is of particular importance.

To date, various synthetic methods have been discovered for the preparation of methyl aryl ethers. These include

nucleophilic aromatic substitution of aromatic halides with alkali metal methoxides,⁶ the Williamson⁷ and Mitsunobu⁸ ether syntheses, and the Brønsted/Lewis acid mediated condensation between methanol and phenols.⁹ These traditional methods often require harsh reaction conditions and/or the use of toxic methylating agents (MeI, Me₂SO₄) and sometimes have a limited substrate scope. Recently, the multistep synthesis of methyl aryl ethers via Pd-catalyzed arylation of hydroxide followed by the methylation of the resulting phenols has been reported.¹⁰ Methoxy-substituted silanes [Si(OMe)₃H,¹¹ Si(OMe)₄]¹² are also utilized as the methanol surrogates in Pd-catalyzed cross-coupling with

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aryl halides¹¹ and in copper-catalyzed decarboxylative arylation with aromatic carboxylic acids.¹² However, these methods are limited to electron-deficient and/or *ortho*-substituted (e.g., NO₂, Me, OMe) aryl coupling partners.^{10b,11,12}

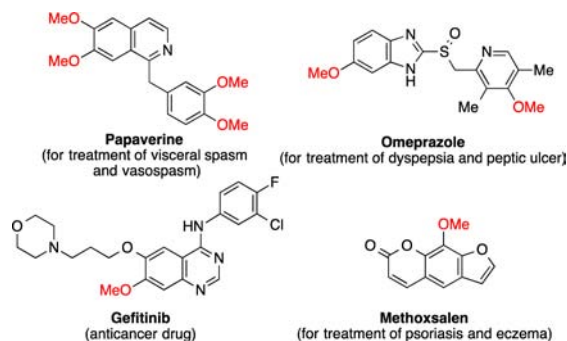


Figure 1. Selected pharmaceutical molecules containing the methyl aryl ether motifs.

The cross-coupling between methanol and aryl halides represents a direct, convenient, and atom-economical approach to synthesize methyl aryl ethers. We have previously reported two examples of Pd-catalyzed coupling of methanol with electron-deficient aryl halides.¹³ In 2012, Beller¹⁴ and Peruncheralathan^{5c} reported a more general Pd-catalyzed coupling of methanol and methanol-*d*₄ with aryl halides to access a broader range of anisoles and methoxypyridines and their trideuteriomethoxy derivatives, by using a sterically demanding BippyPhos-based phosphine ligand and *t*BuXPhos ligand, respectively. In addition, copper-catalyzed coupling of methanol with aryl iodides also serves as a convenient method to prepare anisoles.¹⁵ Despite these advances, the substrate scope is generally limited to aryl halides and halopyridines. Moreover, a relatively high temperature (≥ 70 °C) is usually required. Herein, we report an improved, general method for the synthesis of a broader range of methyl aryl ethers and their trideuteriomethyl derivatives under mild reaction conditions enabled by the use of a bulky biarylphosphine ligand and a palladacycle precatalyst.

We recently reported an efficient arylation of primary and secondary alcohols to synthesize a variety of alkyl aryl ethers, using a Pd catalyst based on the bulky

biarylphosphine ligand RockPhos (Table 1, **L1**).^{16,17} **L1** could promote the productive reductive elimination of the proposed (**L1**)Pd(aryl)(alkoxy) intermediate relative to the undesirable, competing β -hydride elimination of the alkoxy group, thus facilitating the formation of alkyl aryl ethers rather than the arene side products.¹⁶ Thus, we began our studies by examining the reaction of 4-chloroanisole with 5 equiv of methanol in 1,4-dioxane at 100 °C, using a strong base, KO^tBu, and a Pd catalyst based on Pd₂dba₃ (2 mol % Pd) and **L1** (4 mol %) (Table 1, entry 1). Under the reaction conditions, the coupling reaction proceeded smoothly to give the desired product, 1,4-dimethoxybenzene (**1**), in excellent yield along with the minimal formation of anisole side product (**2**). Similarly, the use of the structurally related BrettPhos-based ligands, *t*BuBrettPhos (**L2**)¹⁷ and AdBrettPhos (**L3**),¹⁸ also promoted the reaction to give **1** in excellent yields (Table 1, entries 2 and 3). In contrast, when the smaller ligands, BrettPhos (**L4**) and *t*BuXPhos (**L5**), were employed, the ratio of **1** to **2** dropped significantly (Table 1, entries 4 and 5), whereas the use of conformationally more rigid ligand Me₄tBuXPhos (**L6**) resulted in a very low conversion (Table 1, entry 6). As **L2** is available on kilogram scale, we selected it for subsequent studies.

In light of the recent success of the use of aminobiphenyl palladacycle precatalysts to promote cross-coupling reactions under mild conditions,¹⁹ we utilized the precatalyst **3**,^{19b} which contains **L2** preligated to the Pd center, in the

Table 1. Ligand Screen for the Pd-Catalyzed Arylation of MeOH^a

entry	ligand	temp (°C)	conv (%) ^b	yield of 1 (%) ^b	yield of 2 (%) ^b
1	L1	100	100	93	7
2	L2	100	100	92	7
3	L3	100	100	93	7
4	L4	100	53	13	40
5	L5	100	100	73	27
6	L6	100	27	20	7
7	L2	80	100	96	4
8 ^c	L2	80	94	85	7
9 ^d	L2	80	100	93	7
10 ^d	L2	50	100	94	6
11 ^d	L2	rt	50	48	2
12 ^e	L2	rt	100	95	5

^a Reaction conditions: 4-Chloroanisole (0.25 mmol), MeOH (1.25 mmol), NaO^tBu (0.35 mmol), Pd₂dba₃ (1 mol %), ligand (4 mol %), 1,4-dioxane (0.5 mL, 0.50 M), 20 h. ^b Determined by GC. ^c Pd₂dba₃ (0.5 mol %), **L2** (2 mol %), 24 h. ^d **3** (1 mol %), **L2** (1 mol %). ^e **3** (2 mol %), **L2** (2 mol %).

(17) For the synthesis of RockPhos (**L1**) and *t*BuBrettPhos (**L2**), see: Hoshiya, N.; Buchwald, S. L. *Adv. Synth. Catal.* **2012**, *354*, 2031–2037.

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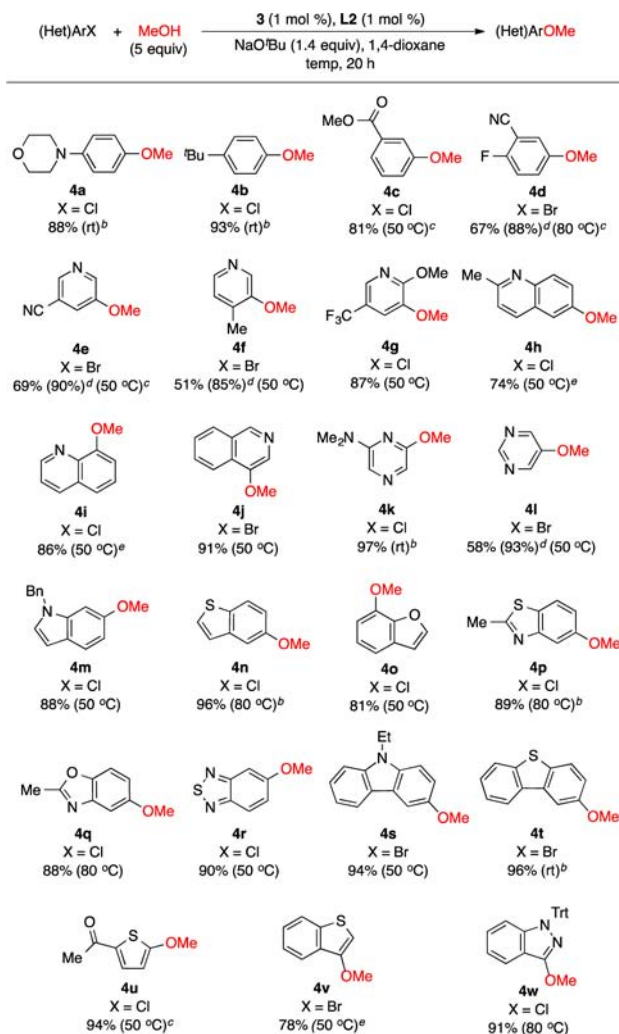
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Scheme 1. Pd-Catalyzed Arylation of Methanol^a

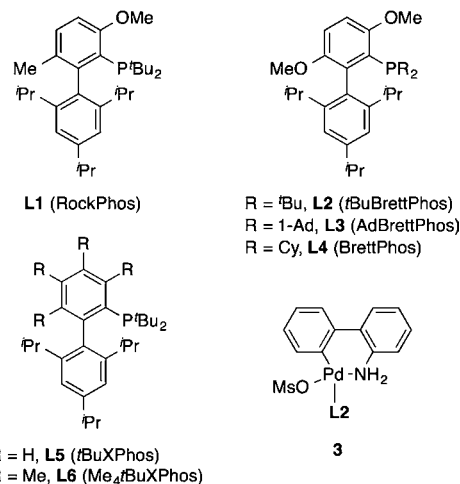


^a Reaction conditions: (Het)ArX (1 mmol), MeOH (5 mmol), NaO^tBu (1.4 mmol), **3** (1 mol %), **L2** (1 mol %), 1,4-dioxane (2 mL, 0.50 M); isolated yields, average of two runs. ^b **3** (2 mol %), **L2** (2 mol %). ^c Cs₂CO₃ (1.5 equiv). ^d ¹H NMR yield of crude product. ^e An inseparable mixture of ether product and heteroarene (HetArH, 2–4%) was isolated.

coupling reaction of methanol. While the Pd catalyst based on Pd₂dba₃/**L2** still efficiently catalyzed the reaction at 80 °C (Table 1, entry 7), incomplete conversion of the substrate was seen when the loading of Pd₂dba₃ was decreased to 0.5 mol % (1 mol % Pd) (Table 1, entry 8). In contrast, 1 mol % precatalyst **3** was sufficient to catalyze efficiently the reaction to afford **1** in excellent yield under otherwise identical conditions and even at 50 °C (Table 1, entries 9 and 10). At a higher loading of **3** (2 mol %), the reaction proceeded smoothly at room temperature (Table 1, entries 11 and 12).

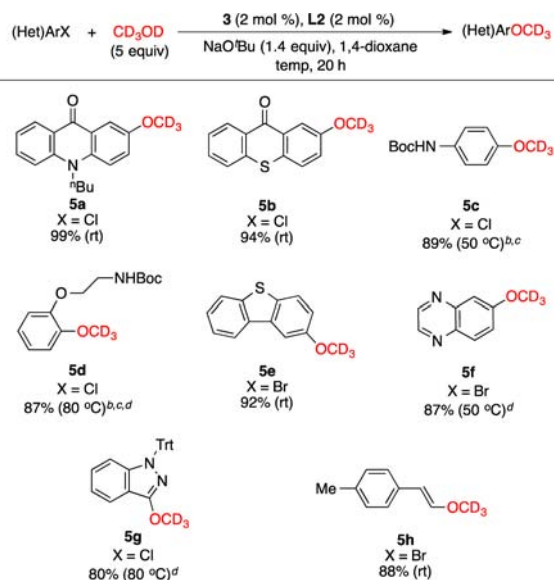
Next, we explored the scope of the Pd-catalyzed synthesis of methyl aryl ethers based on the use of precatalyst **3**

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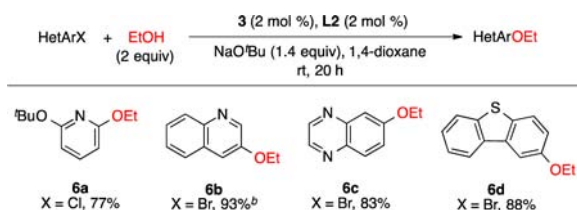
(1–2 mol %) at 50 °C or at ambient temperature (Scheme 1). Both electron-rich and -deficient aryl halides could be coupled with methanol to afford anisoles in high yields (**4a–d**). Additionally, a wide range of heteroaryl halides were shown to be suitable coupling partners, including pyridines (**4e–4g**), (iso)quinolines (**4h–4j**), pyrazines (**4k**), pyrimidines (**4l**), indoles (**4m**), benzothienophenes (**4n**), benzofurans (**4o**), benzothiazoles (**4p**), benzoxazoles (**4q**), benzo-2,1,3-thiadiazoles (**4r**), carbazoles (**4s**), and dibenzothienophenes (**4t**). Significantly, the Pd-catalyzed coupling of methanol with five-membered heteroaryl halides was also demonstrated (**4u–4w**). Sterically hindered substrates were well-tolerated under the reaction conditions (**4f**, **4g**, **4i**, **4j**), while the use of a weaker base, Cs₂CO₃,

Scheme 2. Pd-Catalyzed Arylation of Methanol-d₄^a



^a Reaction conditions: (Het)ArX (1 mmol), CD₃OD (5 mmol), NaO^tBu (1.4 mmol), **3** (2 mol %), **L2** (2 mol %), 1,4-dioxane (2 mL, 0.50 M); isolated yields, average of two runs. ^b Cs₂CO₃ (1.5 equiv). ^c After the reaction, the reaction mixture was further heated with H₂O (100 equiv) for 20 min at the reported temperature to form RNHBoc. ^d **3** (1 mol %) and **L2** (1 mol %).

Scheme 3. Pd-Catalyzed Arylation of Ethanol^a



^a Reaction conditions: (Het)ArX (1 mmol), EtOH (2 mmol), NaO^tBu (1.4 mmol), **3** (2 mol %), **L2** (2 mol %), 1,4-dioxane (2 mL, 0.50 M); isolated yield, average of two runs. ^b EtOH (5 equiv).

in place of NaO^tBu, is necessary when the coupling partners contain base-sensitive functional groups (**4c**, **4d**, **4e**, **4u**). For all substrates, we observed an excellent selectivity for the formation of methyl aryl ethers over the reduced products.²⁰

The reaction protocol based on precatalyst **3** also allowed for the coupling of methanol-*d*₄ with a variety of (hetero)aryl halides under mild conditions, forming the corresponding trideuteriomethyl aryl ethers in good yields (Scheme 2, **5a–5g**). A trideuteriomethyl vinyl ether could be prepared as well (**5h**).

The homologue of methanol, ethanol, has seldom been studied in the Pd-catalyzed C–O coupling reactions.²¹ By utilizing the reaction protocol described above (Scheme 1),

(20) In the coupling reactions with most of the (hetero)aryl halides, no or only a trace of (hetero)arene side-products ((Het)ArH) were detected by GC-MS analysis. See Supporting Information for details.

(21) To our knowledge, there is only one example of the Pd-catalyzed coupling of ethanol with aryl halide.^{13b}

we found that the coupling of ethanol with heteroaryl halides proceeded to afford the ethyl aryl ethers in good yields under ambient conditions (Scheme 3).

In conclusion, we have developed a method for the palladium-catalyzed arylation of methanol and methanol-*d*₄ under mild conditions, with excellent selectivity for the formation of a variety of methyl and deuteriomethyl aryl ethers. We also preliminarily demonstrated the palladium-catalyzed arylation of ethanol at room temperature. We expect these methods to be widely applicable to the synthesis of biologically active molecules containing the methoxy and deuteriomethoxy groups.

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Supporting Information Available. Experimental procedures along with experimental and spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare the following competing financial interest(s): M.I.T. has patents on some of the ligands and precatalysts used in this work from which S.L.B. receives royalty payments.