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Synthesis of Diarylated 4-Pyridylmethyl Ethers via Palladium-Catalyzed Cross-Coupling Reactions

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Abstract. The direct arylation of weakly acidic sp^3–hybridized C–H bonds via deprotonated cross–coupling processes (DCCP) is a challenge. Herein, a Pd(NIXANTPHOS)-based catalyst for the mono arylation of 4-pyridylmethyl 2-aryl ethers to generate diarylated 4-pyridyl methyl ethers is introduced. Furthermore, under similar conditions, the diarylation of 4-pyridylmethyl ethers with aryl bromides has been developed. These methods enable the synthesis of new pyridine derivatives, which are common in medicinally active compounds and in application in materials science.

Keywords: aryl bromides; arylation; diarylation; 4-pyridylmethyl ethers; cross-coupling; palladium-catalyzed;

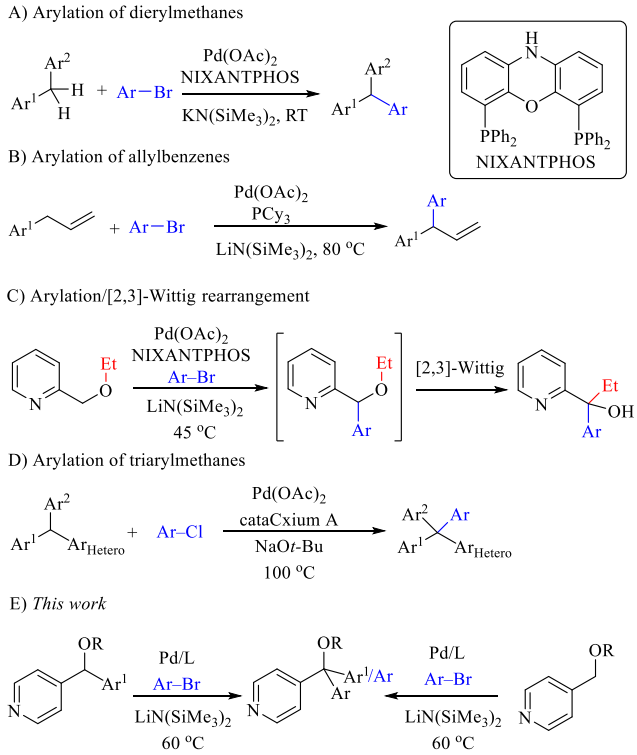
Introduction

Efficient catalytic generation of C–C bonds via the arylation of C(sp^3)–H's has attracted significant recent attention.[1] We,[2] and other research teams,[3] have been interested in the arylation of pronucleophiles bearing weakly acidic C(sp^3)–H bonds. Under basic reaction conditions the pronucleophile C–H is reversibly deprotonated to generate an organometallic species that undergoes transition metal catalyzed coupling with an aryl halide. For example, we have used this approach for the arylation of diarylmethanes to prepare triarylmethanes (Scheme 1A),[4] the arylation of allylbenzenes to prepare 1,1-diaryl prop-2-enes (Scheme 1B),[5] and the arylation of benzylic C–H's situated alpha to heteroatoms,[2b, 6] which can undergo a subsequent [2,3]-Wittig rearrangement (Scheme 1C).[2b] These reactions generally exhibit very high selectivity for mono-arylations, which is usually due to the increased steric shielding of the remaining benzylic C–H relative to those in the starting materials.

A recent analysis of the shapes of a large pool of molecules known to exhibit biological activity indicated that most structures are either linear or disk-shaped.[7] This study found very few examples of bioactive compounds that are better described as sphere-like. We hypothesized that one reason there are few such sphere-like bioactive compounds is that their synthesis is more difficult. To address this challenge, we initiated a program in the exhaustive arylation of benzylic C–H's. In our initial publication, we reported the first general transition metal catalyzed arylation of di- and triarylmethanes to afford sphere-like tetraarylmethanes (Scheme 1D).[8] Herein we expand this approach to the arylation of benzylic ethers to prepare diaryl(4-pyridyl) ether derivatives (Scheme 1E). It is noteworthy that di- and triaryl pyridylmethanol derivatives are active in the treatment for Chagas disease and exhibit in vitro aromatase inhibitory activity.[9]

Under the basic reaction conditions using $MN(SiMe_3)_2$ (M=Li, Na, K), palladium or nickel, and van Leewen's NIXANTPHOS,[10] we found that the NIXANTPHOS N–H (pK_a~21 in DMSO)[11] is deprotonated under the reaction conditions and that the

resulting complex is bimetallic, containing the transition metal and the main group element (M=Li, Na, K).[4b] We have demonstrated that the transition metal and main group metal cooperate to achieve levels of reactivity that are typically much higher than related ligands.[4b, 10, 12] On the basis of these investigations, we initiated our studies on the arylation of 4-pyridyl methyl ether derivatives with the Pd/NIXANTPHOS-based catalyst.



Scheme 1. Transition metal-catalyzed arylation chemistry.

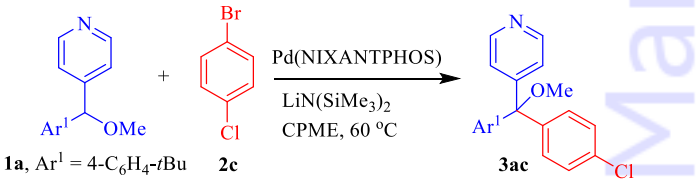
Results and Discussion

Initial studies began with 4-pyridylmethyl 2-(4-*tert*-butyl-phenyl) ether (**1a**), 4-chloro-1-bromobenzene (**2c**), $Pd(OAc)_2$ (5 mol %) and NIXANTPHOS (7.5 mol %) as the ligand. The acidity of the 4-pyridylmethyl methyl ether is likely similar to those of 2- and 4-methylpyridine (pK_a's 32–34 in THF).[11, 13] Solvent and base play an important role in cross-coupling reactions. We therefore employed 4 solvents (THF, DME, 1,4-dioxane and CPME) with 5 strong bases [$LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, NaO^tBu and KO^tBu], and the reactions were conducted for 18 h at 60 °C. The results are displayed in Table 1 (entries 1–9). The cross-coupling between compounds **1a** and **2c** with $LiN(SiMe_3)_2$ afforded poor assay yields (AY) [16–55%, assay yields determined by ^1H NMR] when conducted in THF, DME or dioxane (Table 1, entries 1–3). In contrast, $LiN(SiMe_3)_2$ in CPME resulted in 91% AY (entry 4). The arylated product **3ac** was isolated in 89% yield after column chromatography. Substitution of $NaN(SiMe_3)_2$ for $LiN(SiMe_3)_2$ in CPME or DME under otherwise identical reaction conditions afforded low yields (8–20%, entries 5–6). No product was obtained using $KN(SiMe_3)_2$, NaOtBu or KO^tBu (entries 7–9).

We next examined the impact of reaction times on the yield. Cutting the reaction time from 12 to 6 h resulted in a drop in the AY to 46% (entry 10 vs. 4). No significant change in yield was found when the reaction time was prolonged to 18 h (entry 11). Reducing the equivalents of $LiN(SiMe_3)_2$ from 3.0 to 1.5 equiv under identical conditions resulted in incomplete reaction, with 68% AY (entry 12).

The impact of different Pd and NIXANTPHOS loadings on the coupling reaction was examined. Changing Pd:NIXANTPHOS loading from 5:7.5 to 3:4.5 mol % resulted in similar AY and isolated yield (entry 4 vs. 13). Further reducing the catalyst loading significantly decreases the reaction yield. Next, different reaction temperatures were examined at 3 mol % Pd and 4.5 mol % NIXANTPHOS with a 12 h reaction time. The results indicated that decreased yields were observed when the reactions were conducted at 25, 40 or 80 ℃ (Table 1, entries 14–16).

Table 1. Optimization of arylation of 4-pyridylmethyl methyl aryl ether **1a** with aryl bromide **2c**[a, b]



	base (equiv)	solvent	Pd/L (mol%)	temp (°C)	yield (%)
1	LiHMDS (3)	THF	5/7.5	60	16
2	LiHMDS (3)	DME	5/7.5	60	47
3	LiHMDS (3)	dioxane	5/7.5	60	55
4	LiHMDS (3)	CPME	5/7.5	60	91
5	NaHMDS(3)	DME	5/7.5	60	20
6	NaHMDS(3)	CPME	5/7.5	60	8
7	KHMDS (3)	CPME	5/7.5	60	0
8	NaO^tBu (3)	CPME	5/7.5	60	0
9	KO^tBu (3)	CPME	5/7.5	60	0
10	LiHMDS (3)	CPME	5/7.5	60	46[c]
11	LiHMDS (3)	CPME	5/7.5	60	93[d]
12	LiHMDS (3)	CPME	5/7.5	60	68
13	LiHMDS (3)	CPME	3/4.5	60	89[e]
14	LiHMDS (3)	CPME	3/4.5	25	26
15	LiHMDS (3)	CPME	3/4.5	40	62
16	LiHMDS (3)	CPME	3/4.5	80	53

[a] Reactions conducted on a 0.1 mmol scale using 1 equiv of **1a**, and 1.2 equiv of **2c** for 12 h.

[b] Assay yields determined by ^1H NMR spectroscopy of the crude reaction mixtures.

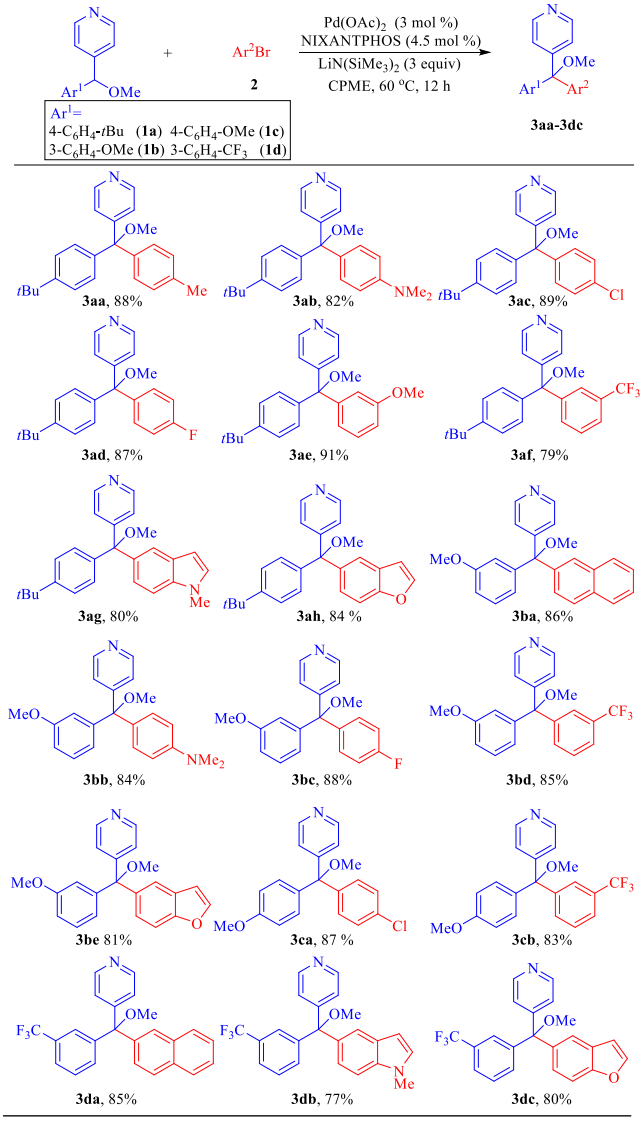
[c] Reaction time 6 h

[d] Reaction time 18 h

[e] Isolated yield after chromatographic purification.

With the optimized conditions (Table 1, entry 13), the scope of the arylation of 4-pyridylmethyl 2-aryl methyl ethers with different aryl bromides was explored (Table 2). Continuing with 4-pyridyl aryl methyl ether **2a**, reactions with aryl bromides bearing electron donating 4-Me and 4-NMe_2 groups gave **3aa** and **3ab** in 88 and 82% yield, respectively. More sterically hindered 2-bromotoluene and 1-bromonaphthylene failed to yield the corresponding arylated products despite the use of higher Pd loading (7.5 mol %). Aryl bromides with 4-Cl and 4-F produced products **3ac** and **3ad** in 89 and 87% yield, respectively. Aryl bromides substituted with electron withdrawing 3-OMe and 3-CF_3 gave **3ae** and **3af** in 91 and 79% yield, respectively. Due to the importance of heterocycles in medicinal chemistry, heterocyclic substrates were examined. Use of *N*-methyl-5-bromoindole and 5-bromobenzofuran furnished the arylated products in 80 and 84% yield.

Table 2. Scope of aryl bromides in C-H arylation of 4-pyridylmethyl 2-aryl ethers 1a–1d [a, b]



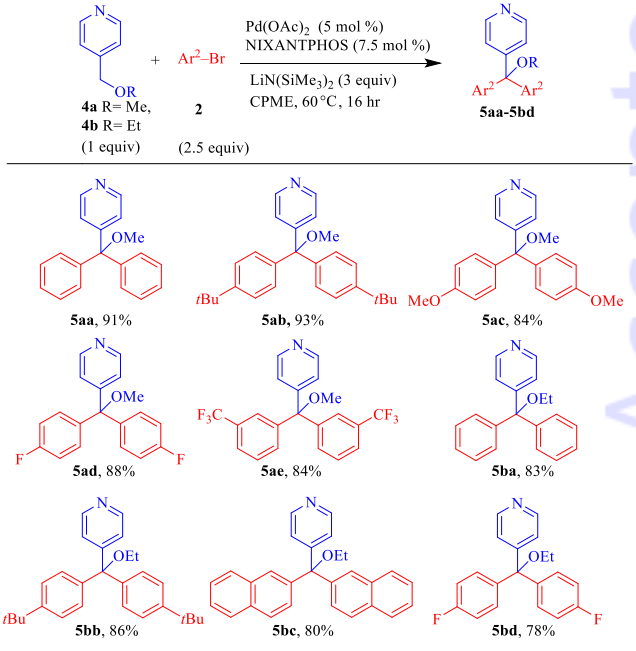
[a] Reactions conducted on 0.2 mmol scale using 1 equiv of **1**, and 1.2 equiv of aryl bromides **2**.

[b] Isolated yields after chromatographic purification.

Using 4-pyridylmethyl aryl ethers where the aryl bears a 3-methoxy group (**1b**), coupling with 2-bromonaphthylene and 4-*N,N*-dimethylamino bromobenzene proceeded in 86 and 84% yield, respectively. 4-Fluoro bromobenzene, 3-trifluoro bromobenzene and 5-bromobenzofuran resulted in coupling products in 81–88% yields. The 4-pyridyl aryl ethers with the aryl 4-methoxy readily coupled with 3-trifluoro bromobenzene (87% yield) and 4-chloro bromobenzene (83% yield). The 4-pyridylmethyl aryl methyl ether with a 3-trifluorophenyl substituent coupled with 2-naphthyl bromide, *N*-methyl-5-bromoindole, and 5-bromobenzofuran in 77–85% yield.

After demonstrating the broad scope of arylation of 4-pyridylmethyl aryl ethers, we next investigated the diarylation of 4-pyridylmethyl ethers (Table 3). For the diarylation of 4-pyridylmethyl ethers with aryl bromides we increased the catalyst loading (5 mol % Pd and 7.5 mol % NIXANTPHOS) and reaction time (16 h) at the same temperature (60 °C). Overall, the diarylated compounds **5aa–5bd** were obtained in 78–94% yield with methyl ethers giving slightly better yields than ethyl ethers. The 4-pyridylmethyl methyl ethers coupled with electron neutral and rich aryl bromides in 84–91% yields, while electron withdrawing analogues generated products in 84–88% yield. For the ethyl ethers, yields ranged from 78–86%.

Table 3. Scope of 4-pyridylmethyl ethers in diarylation with aryl bromides [a, b]



[a] Reactions conducted on a 0.2 mmol scale using 1 equiv of 4-pyridylmethyl ethers **4** and 2.5 equiv of aryl bromides **2**.

[b] Isolated yields after chromatographic purification.

Under similar conditions to those outlined above, 3-pyridylmethyl ethers were unreactive, most likely due to the higher pK_a's of the benzylic hydrogens. Attempts to diarylate the 2-pyridylmethyl ethers resulted in monoarylation followed by [2,3]-Wittig rearrangement (Scheme 1C) under all conditions explored.[2b] Coupling with the heterocyclic aryl bromides 3-bromopyridine and 3-bromofuran resulted in the formation of multiple products and no desired material could be isolated.

Conclusions

In summary, an efficient and versatile approach for the arylation of 4-pyridylmethyl aryl ether derivatives has been developed. This study indicates that a Pd(NIXANTPHOS)-based catalyst in CPME solvent exhibited high yields. Under the optimized reaction conditions, a range of 4-pyridylmethyl 2-aryl ethers underwent coupling with various aryl and heteroaryl bromides in good to excellent yields. Furthermore, diarylated products were furnished in high yields by cross-coupling of 4-pyridylmethyl methyl ethers with 2.5 equivalents of aryl bromides.

Recent analyses of medicinally active compounds[7] and databases of known organic structures[14] indicate that the most bioactive compounds are linear or disk shaped[7] and that the majority of organic structures prepared to date contain very limited structural diversity. [14] A goal of this work was to develop straightforward methods to rapidly prepare molecules with less common shapes and structural frameworks. The compounds produced herein are more sphere-like, yet several contain heterocycles that are commonly found in bioactive compounds, like pyridines and indoles.[15] Thus, we expect that this method will be of use to medicinal chemists exploring less conventional molecular space.

Experimental Section

General Methods

All reactions were conducted under an inert atmosphere of dry nitrogen. Anhydrous dioxane and cyclopentyl methyl ether (CPME) were purchased from Sigma-Aldrich and used without further purification. Dimethoxyiethane (DME) and tetrahydrofuran (THF) were dried through activated alumina columns under nitrogen. Unless otherwise stated, Silica gel (Silicaflash, P60, 40-63 µm, Silicycle) was used for air-flashed chromatography. Solvents were commercially available and used as received without further purification. Chemicals were purchased from Sigma-Aldrich, Acros, Fisher Scientific or Matrix Scientific and solvents were obtained from Fisher Scientific. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light. Flash chromatography was performed with Silica gel (Silicaflash, P60, 40-63 µm, Silicycle). NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer at the University of Pennsylvania NMR facility. 1H and 13C chemical shifts in parts per million (δ) were referenced to internal tetramethylsilane (TMS). The infrared spectra were obtained with KBr plates using a Perkin-Elmer Spectrum 1600 Series spectrometer. High-resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte. 4-(Chloromethyl)pyridine hydrochloride (98%) was purchased from Matrix Scientific and used as received.

General procedure for the preparation of Pd-catalyzed monoarylation of 4-pyridylmethyl 2-aryl ethers

An oven-dried 10 mL reaction vial equipped with a stir bar was charged with 4-pyridylmethyl 2-aryl ether (**1**, 0.2 mmol, 1.0 equiv) and aryl bromide (**2**, 0.30 mmol, 1.5 equiv) in dry CPME (1 mL) in a glove box under a nitrogen atmosphere at room temperature. A solution (from a stock solution) of $Pd(OAc)_2$ (1.34 mg, 0.006 mmol, 3 mol %) and NIXANTPHOS (4.97 mg, 0.009 mmol, 4.5 mol %) in 1 mL of dry CPME was taken up by syringe and added to the reaction vial under nitrogen. Then, $LiN(SiMe_3)_2$ (110 mg, 0.6 mmol, 3.0 equiv) was added to the reaction mixture. The vial was capped, removed from the glove box, and stirred for 12 h at 60 °C until TLC showed complete consumption of 4-pyridylmethyl 2-aryl ether. The reaction mixture was quenched with three drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of silica and anhydrous $MgSO_4$. The pad was rinsed with additional ethyl acetate (3 X 2 mL), and the combined solution was concentrated in vacuo. The crude product was loaded onto a silica gel column and purified by flash chromatography using 4:1–2:1 hexanes/ethyl acetate as eluent to afford desired products.

General procedure for the preparation of Pd-catalyzed diarylation of 4-pyridylmethyl ethers

An oven-dried 10 mL reaction vial equipped with a stir bar was charged with 4-pyridylmethyl ether (**4**, 0.2 mmol, 1.0 equiv), aryl bromide (**2**, 0.5 mmol, 2.5 equiv) and dry CPME (1 mL) in a glove box under a nitrogen atmosphere at room temperature. A solution (from a stock solution) of $Pd(OAc)_2$ (2.23 mg, 0.01 mmol, 5 mol %) and NIXANTPHOS (8.27 mg, 0.015 mmol, 7.5 mol %) in 1 mL of dry CPME was taken up by syringe and added to the reaction vial under nitrogen. Then, $LiN(SiMe_3)_2$ (110 mg, 0.6 mmol, 3.0 equiv) was added to the reaction mixture. The vial was capped, removed from the glove box, and stirred for 16 h at 60 °C until TLC showed complete consumption of 4-pyridylmethyl ether. The reaction mixture was quenched with three drops of H_2O, diluted with 3 mL of ethyl acetate, and filtered over a pad of silica and anhydrous $MgSO_4$. The pad was rinsed with additional ethyl acetate (3 X 2 mL) and the combined solution was concentrated in vacuo. The crude product was loaded onto a silica gel column and purified by flash chromatography using 4:1- 2:1 hexanes/ethyl acetate as eluent to afford desired products.

Acknowledgements

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FULL PAPER

The Synthesis of Diarylated 4-Pyridylmethyl Ethers via Palladium-Catalyzed Cross-Coupling Reactions

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