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Palladium catalysed cross-dehydrogenative-coupling of 1,3,5-trialkoxybenzenes with simple arenes†

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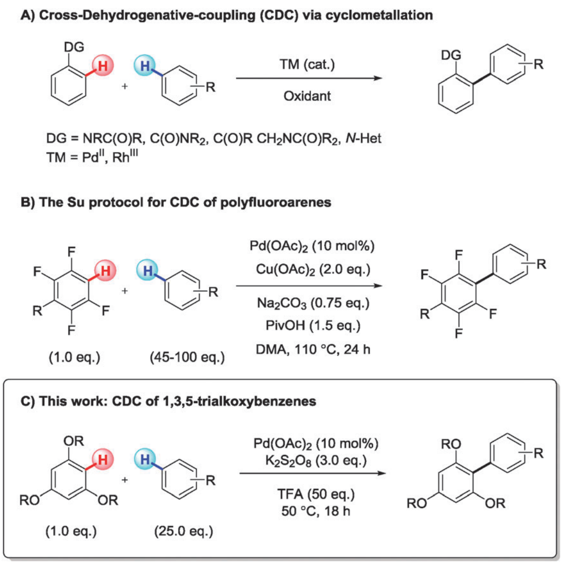
Pd-catalysed cross-dehydrogenative coupling of 1,3,5-trialkoxybenzenes with simple aromatic hydrocarbons is reported. The method enables the coupling of two aromatic C–H positions to generate multi-*ortho*-substituted biaryls.

There is great current interest in the discovery of new C–H cross-coupling reactions with improved atom economy and substrate scope.[1] Cross-dehydrogenative coupling (CDC), where C–C bond formation takes place at two C–H sites on different molecules, represents an ideal transformation in this regard. No pre-functionalisation is required on either coupling partner, creating exciting possibilities for rapid and economic synthesis. The oxidative homo-coupling of arenes is well known, with precedent stretching back to the 19th century for stoichiometric metal couplings,[2] and with many more recent reports describing transition metal catalysed processes in the presence of cheap oxidants.[3] Extending this idea to encompass two distinct C–H coupling partners, however, remains a major challenge.[4] Notable advances in this area include Kita's hypervalent iodine mediated couplings,[5] the CDC of acidic heteroarenes or polyfluorobenzenes[6] with aromatic solvents[7] and other heteroarenes,[8] and the use of directing groups to effect chelation controlled metallation and subsequent coupling.[9] Lu and co-workers have shown that naphthalene[10] can be effectively cross-coupled with simple aromatics using Pd^{II} catalysis. Extension to other substrates, however, gave poor selectivities and low yields. These reports illustrate the potential power of CDC for arene synthesis, encouraging us to investigate the feasibility of metal-catalysed CDC of two electron rich arenes in the absence of chelating groups, a transformation with little precedent (Scheme 1).

Using the Lu conditions as a starting point, we investigated the CDC of 1,3,5-trimethoxybenzene (**1**) (limiting reagent) with *para*-xylene (**2a**) (solvent and super stoichiometric reagent), to form the penta substituted biaryl **3a** (Scheme 2). A comprehensive screen of reaction parameters (see ESI†) established the following reaction



Scheme 1 CDC strategies.

conditions (25.0 eq. simple arene, 10 mol% $Pd(OAc)_2$, 3.0 eq. $K_2S_2O_8$ and 50.0 eq. TFA, at 50 °C for 18 h), producing **3a** in 64% yield. Biaryl **3a** was characterised by single crystal X-ray crystallography,[11] showing the highly congested-tri-*ortho*-substituted biaryl axis to possess an average torsion angle of 83.8(8)° (Scheme 2). In most reactions performed in this study, the concurrent production of homo-coupled **2** (2,2′,5,5′-tetramethyl-1,1′-biphenyl and 1,4-dimethyl-2-(4-methylbenzyl)benzene) was observed along with **3a**, but no homo-coupled or benzylated products of **1** were observed.[3l] Further investigations revealed that the CDC reaction proceeds at lower temperatures, even down to 0 °C, albeit in lower yields. Reproducibility issues were, however, evident at lower temperatures and a reaction temperature of 50 °C was found to provide consistent and reproducible results.

Following reaction optimisation, an assessment of both arene substrates was performed. The use of *para*- and *meta*-xylene both provided synthetically useful quantities of **3a** and **3b** (64% yield),

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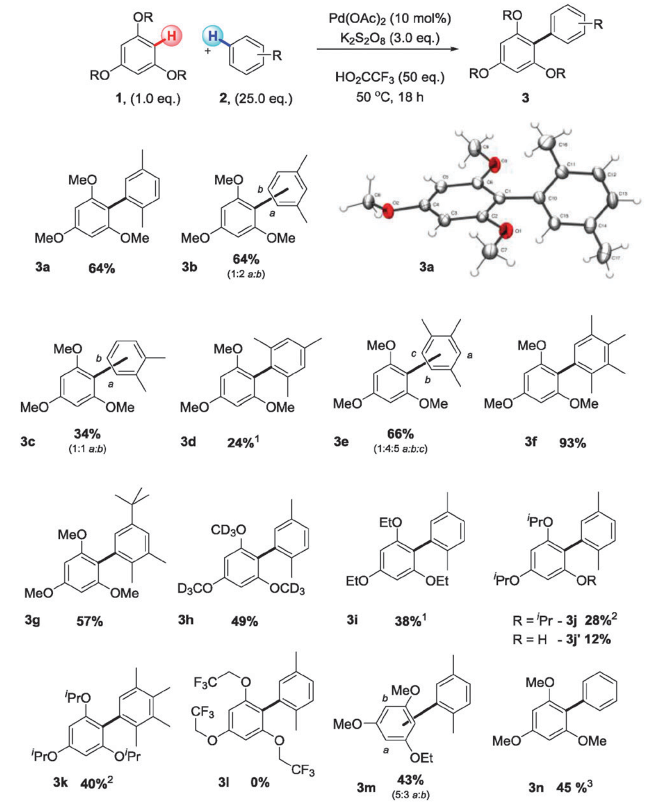


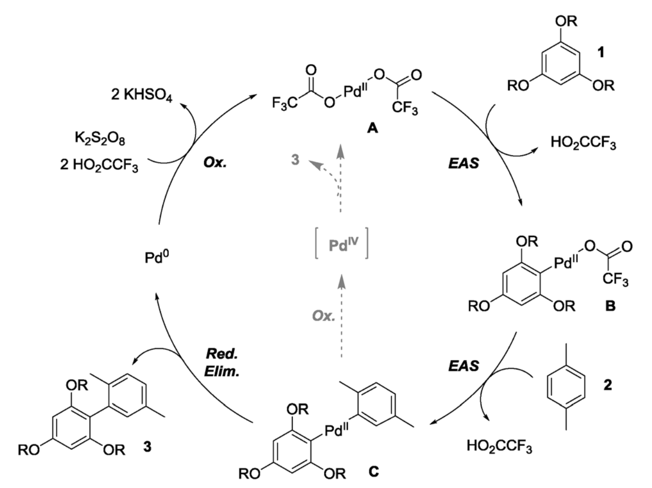
Scheme 2 CDC of trialkoxybenzenes. [1] Residual starting material in product sample. [2] 10 equiv. of TFA used. [3] $Pd(O_2CCF_3)_2$ used as catalyst and 5.0 eq. of TFA used. Thermal ellipsoids shown at 50% for X-ray structure of **3a**.

whereas *ortho*-xylene was less successful yielding only 34% of the desired biaryl product **3c**. Likewise, when moving to more sterically hindered aromatic hydrocarbons significantly reduced yields were observed; with mesitylene as the coupling partner only 24% of **3d** could be obtained. These results are not surprising, as the synthesis of tetra-*ortho*-substituted biaryls is a significant challenge and usually necessitates the use of specialised catalyst–ligand combinations.[12] The reaction of pseudocumene (1,2,4-trimethylbenzene) with **1** proceeded smoothly to supply **3e** in 66% yield as a mixture of isomers. Interestingly, prehenitene (1,2,3,4-tetramethylbenzene) could be employed to great effect yielding **3f** in an excellent yield of 93%. When multiple C–H bonds on the aromatic hydrocarbon solvent are available for arylation multiple isomeric products are observed (**3b**, **3c** and **3e**). Use of 4-*tert*-butyl-*ortho*-xylene, however, gave the sterically least-hindered biaryl **3g** in good yield as a single isomer. Aromatic solvents bearing electron withdrawing groups could not be coupled to **1**.

Turning to the alkoxyarene partner, a necessity for the 1,3,5-substitution pattern was noted, with additional substituents not being tolerated, presumably due to the increased steric congestion. Symmetrical 1,3,5-trialkoxybenzenes gave the CDC product in most cases, but increasing the steric bulk on the alkoxymoiety (Me < Et < ^{i}Pr, **3a**, **3i**, **3j**) led to a steady reduction in reaction yield 64% to 28%. The CDC product of 1,3,5-triisopropoxybenzene and *para*-xylene (**3j**) was accompanied by 12% of the *ortho*-dealkylated product **3j′** (see ESI† for details). This dealkylation is likely to be an acid promoted post-coupling side reaction, given the selectivity and the fact that 3,5-dimethoxyphenol is not a competent substrate. Again, when employing prehenitene as the coupling partner to 1,3,5-triisopropoxybenzene an increased yield of the CDC product, **3k**, was obtained in comparison to using *para*-xylene. The reaction also proved sensitive to the electronic character of the alkoxyarene component, with the trifluoro analogue of 1,3,5-triethoxybenzene failing to react (**3l**). An unsymmetrical 1,3,5-trialkoxybenene substrate was competent in the CDC reaction, affording **3m** in moderate yield as a mixture of isomers. CDC of **1** with benzene was not possible under the established reaction conditions; however, a reduction in the quantity of trifluoroacetic acid in the reaction mixture (5.0 eq.), and using palladium(II) trifluoroacetate as the pre-catalyst proved successful, giving **3n** in 45% yield.

Having a successful CDC protocol in hand, a number of control reactions and mechanistic probes were performed in order to gain a greater insight into the reaction mechanism. The CDC reaction of **1a** with *para*-xylene (**2a**) does not proceed in the absence of the palladium catalyst or TFA. In the absence of the oxidant the reaction only produces trace quantities (<10%, approximately) of the desired product. The intermolecular kinetic isotope effect was determined to be 1.0 using a competition reaction between **2a** and d_{10}-**2a**, which produced **3a** and d_9-**3a** in a 1 : 1 ratio (see ESI† for further details on the KIE determination experiments). Significant incorporation of hydrogen, derived from TFA, was observed at the 4′- and 6′-positions but not the 3′-position of the dimethylphenyl moiety. This D/H exchange is likely to occur post arylation, supported by the fact that H/D exchange almost exclusively occurs at the *ortho* and *para* positions to the electron rich aryl unit. This result is consistent with an electrophilic palladation mechanism whereby the breaking of the C–H bond is not rate limiting and likely happens *via* loss of a proton from a Wheland type arenium intermediate.[13] The KIE of the trimethoxybenzene component could not be ascertained due to facile D/H exchange, indeed, simple stirring of **1** in D_2O generates d_3-**1a**.[14]

With the information gained about the CDC of 1,3,5-trialkoxybenzenes with simple arenes we would like to propose a tentative mechanism for this transformation (Scheme 3). The *in situ* generated



Scheme 3 Mechanistic pathway for CDC.

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palladium(II) trifluoroacetate (**A**) can be nucleophilically attacked by the electron rich arene (**1**). The electrophilic palladation of **1** should be a facile process due to the highly electron rich aromatic ring of **1**.

After loss of a proton from the metallo-Wheland intermediate a palladium(II) arene species (**B**) is generated. **B** can then be intercepted by another aryl-component in a second, likely slower, palladation step to provide a diaryl palladium(II) species (**C**). There are now two possibilities to obtain the desired product from intermediate **C**; (1) reductive elimination to generate the new C–C bond and palladium(0) which can then be rapidly re-oxidised by the peroxydisulfate salt or (2) **C** could be oxidised by the peroxydisulfate anion up to a transient diaryl palladium(IV) species[15] which would swiftly reductively eliminate **3** regenerating the catalytically active species in the process (see ESI†).

It is also feasible that an oxidation of the palladium(II) catalyst up to an intermediate palladium(IV) could occur prior to C–H palladation, these processes have been reported but only in some highly specific examples.[16] Although the possibility of radical mediated processes in action within this reaction system cannot be ruled out without further studies, we believe that this is less likely.[17]

In conclusion, we have developed a new method for the CDC of 1,3,5-trialkoxy benzenes with simple aromatic hydrocarbons, accessing a number of novel highly hindered tri- and tetra-*ortho*-substituted biaryls in a single step. This is the first account of a high yielding protocol for the C–H/C–H cross-coupling of two disparate electron rich benzenes, and further applications are underway in our laboratory.

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