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Selectfluor-mediated mono-C—H activation: The syntheses of mono-*ortho*-substituted anilides

Ranran Zhu [a, b, c], Shaonan Lu [a, b, c], Qing Wang [a, b, c], Jinshan Bai [a, b, c], Yuntao Wang [a, b, c], Qingzhen Yu [a, b, c], Jianhui Huang [a, b, c, *]

[a] *School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China*
[b] *Collaborative Innovation Center of Chemical Science and Engineering, Tianjin/Nankai University, Tianjin 300072, China*
[c] *Tianjin Key Laboratory for Modern Drug Delivery & High-Efficiency, Tianjin University, Tianjin 300072, China*

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ABSTRACT

The C—H activation of aryl amide using readily available $Pd(OAc)_2$ in the presence of selectfluor is reported. The highly mono-selective introduction of sp^2 hybridized functional groups have been realized. A broad range of aryl-, alkenyl- and keto-aryl amides were prepared using unactivated coupling partners under mild conditions.

1. Introduction

Pd catalyzed coupling reactions of aryl halides to form a new Csp2—Csp2 bonds have become one of the most powerful strategies for stitching two arenes together.[1] Arene direct C—H activation as the improvement has attracted much attention for the engineering of the two aromatic systems.[2] The former transformation utilized electron rich Pd(0) catalysts while Pd(II) catalysts are preferred for the latter direct C—H functionalization reactions.[3] However, the reactivities of potential more reactive Pd(IV) species have not been very well explored.[4,5] In this communication, reactions using reactive Pd(IV) intermediates are reported and the new reactivities towards the syntheses of arene anilides, alkenyl anilides as well as keto-anilides have been demonstrated.

During our previous studies, we have proposed that Pd catalysts/intermediates at high oxidation state reacts much faster than the corresponding Pd catalysts/intermediates under mild conditions.[6] Inspired by Vigalok's Pt(IV),[7] Sanford,[8] Ritter's[9] isolation of Pd(IV) species using F-containing oxidants, we were interested in the utilization of Pd catalyst exploring reactions undergoing high oxidative Pd intermediates. Under similar conditions, fluorination or C—H activations have been also studied by Yu and Michael.[10,11]

Inspired by Sanford, Ritter and Yu, we are currently trying to explore the double C—H activation under Pd(IV)/(II) system. Knowing the oxidation of Pd(II) by a common oxidation reagent-selectfluor could provide Pd(IV) adduct, we started the investigation of reactions of common directed arene-acetanilide and *ortho*-xylene.[12,13] As a close reference, similar reactions by You had revealed that the reaction may undergo cationic Pd catalyzed conditions as they have shown that Pd (II) dimer **1a-Pd** can react with *ortho*-xylene **2a** to give the desired **3a** in 92% yield.[14]

2. Results and discussion

Preliminary results suggested that polar less-coordinating solvent hexafluoro isopropanol (HFIP) is a good solvent. When sub-stoichiometric amount of F-containing oxidant selectfluor was used, the desired product **3a** was obtained in a good yield of 62% (SI, Table 1, entry 1). Selectfluor prior to other oxidants has shown the best reactivity towards the anilide synthesis, even other oxidants such as $K_2S_2O_8$, $(NH_4)_2S_2O_8$ are also promising oxidants for the reaction (SI, Table 1, entries 2–5). Other F-containing reagents are

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[*] Corresponding author. School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China.
E-mail address: jhuang@tju.edu.cn (J. Huang).

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also potential good oxidants and the desired product was isolated in 75% and 55% respectively (SI, Table 1, entries 12 and 13). The reactions in the absence of selectfluor did not provide any of our desired products. Further screening on the additives showed that sulfonic acids such as p-TSA, CSA or H_2SO_4 are good additives for the reaction while less strong acids such as HOAc and PivOH are less efficient. (SI Table 2).[15] Very interestingly, reaction using Pd(0) catalyst Pd_2dba_3 also provided the desired product in excellent yield.

The KIE studies for both substrates revealed that the C—H activation processes are rate-determining step rather than the activation of arenes as shown in Scheme 1.

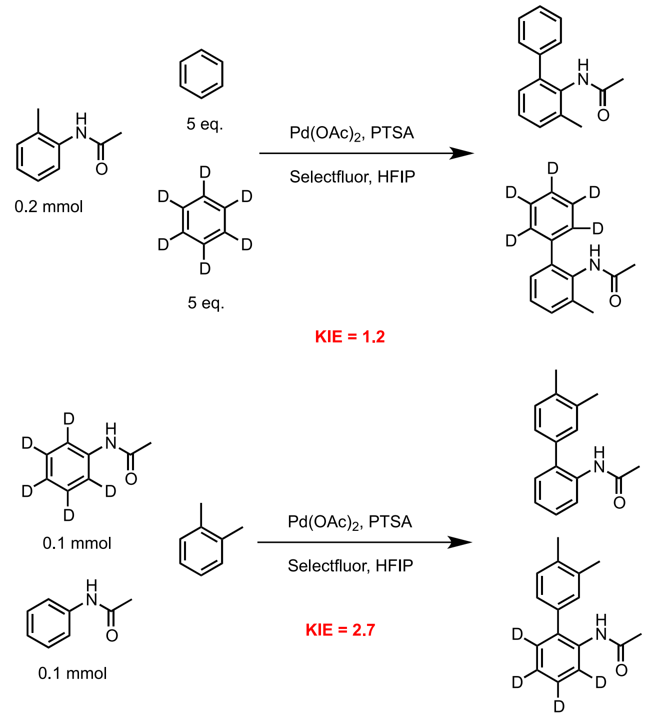
These implied that if the reaction undergoes Friedel-Craft type of arylation forming Pd(IV) with benzene or xylene as one of the substituents then the reaction would be very favored comparing to the corresponding Pd(II) analogue.

The control experiments of **1a** and **1a-Pd′** were carried out in the presence and absence of selectfluor. As shown in Scheme 2, reactions of **1a** and **1a-Pd′** did not provide any our desired product while reactions in the presence of oxidant gave the corresponding amide **3a** in 35% and 85% yields respectively.

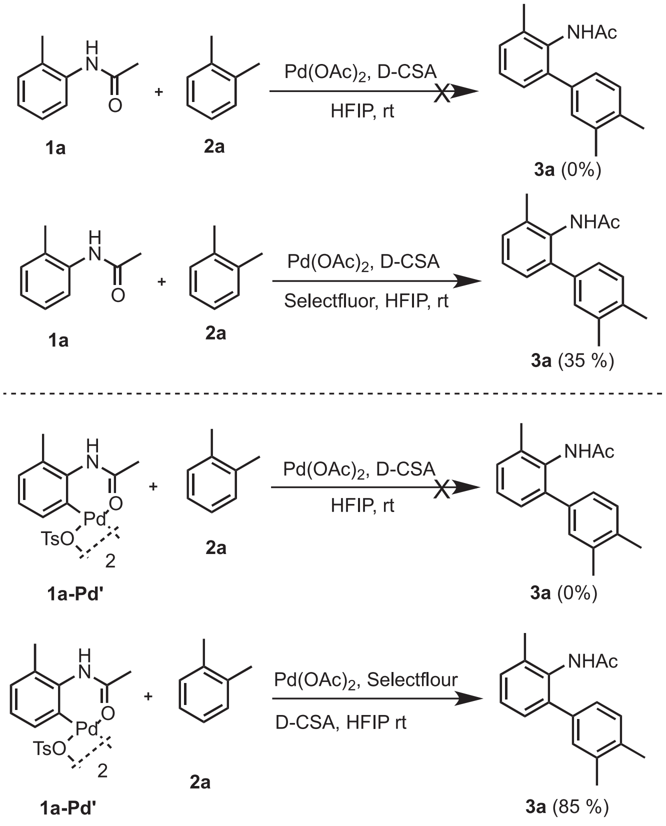
In addition, as shown in Fig. 1 in SI, we have observed the F signal in the ^{19}F NMR when subjecting the reaction mixture for NMR analysis, which may indicate that Pd(IV)-F species were formed in the reaction.

The scope of the Pd-catalyzed reaction with various anilides and unactivated arenes is summarized in Table 1.[16]

The reactions of anilide with arenes such as xylene, toluene and benzene went smoothly the desired products **3b-3f** were isolated in good yields. The substituted anilides were also good substrates for this type of transformation and a number substituted aryl anilides such as **3g-3j** have been prepared. The reactions with anilides other than acetanilide have also been studies and the desired products **3k** and **3l** were isolated in 81% and 62% yields respectively. The reaction of N-Ts aniline is also very successful and the corresponding product **3m** was obtained in 34% yield. The regioselectivity was excellent for this type of reaction due to both steric and electronic reasons. Reactions with xylene and toluene, no other regio-isomers were detected by the 1H NMR of the crude reaction mixtures.



Scheme 1. KIE studies.



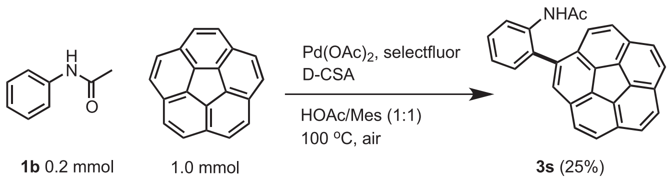
Scheme 2. Control experiments with/without selectfluor.

More interestingly, the reaction with curved aromatic system such as corannuele is also working and the desired corannulene **3s** was isolated in 25% yield after column chromatography(Scheme 3). This approach has provided an excellent way of functionalizing synthetically challenging curved aromatic hydrocarbon like corannulene, even though the reaction gave slight disappointing yield.

Reactions with radical inhibitors such as TEMPO, BHT as well as hydroquinone were used. The reactions seemed to be strongly affected and only a trace amount of product was observed under our standard reaction conditions (Scheme 4).

With the optimal reaction conditions in hand, we have also utilized similar conditions see if coupling reactions with other partners would be possible.

Reactions of anilides with alkenes under similar conditions are fruitful and the results are shown in Table 2.[17] Similar to the reactions with arenes, reactions in the absence of selectfluor did not



Scheme 3. Direct arylation using corannulene **2n**.