DOI 10.5012/bkcs.2011.32.8.2865

Pd-Catalyzed *ortho*-Methylation of Acetanilides *via* Directed C-H Activation†

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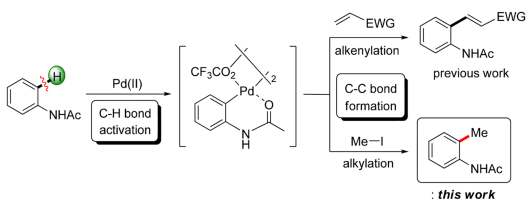
Received February 12, 2011, Accepted February 28, 2011

Key Words : C-H activation, Palladium, Methylation, Acetanilides, C-C bond formation

In view of atom economic and eco-friendly process, direct activation and subsequent functionalization of C-H bond in aromatic compounds have attracted the most attention as an efficient synthetic method with broad applications, providing a powerful alternative to the classical coupling reaction using preformed organometallic reagents.[1] In general, regioselectivity of C-H bond functionalization can be achieved through the introduction of coordinating functionality for synthetic purposes.[2] Recently, we reported a highly effective Pd-catalyzed *ortho*-alkenylation of acetanilides with unprecedented substrate scope (Scheme 1).[3] Our continued interest in Pd-catalyzed C-H bond functionalization prompted us to investigate the possibility of a Pd-catalyzed *ortho*-alkylation of acetanilides. While intensive exploration and significant advances in Pd^{II}-catalyzed regioselective $C(sp^2)$-$C(sp^2)$ bond formation have been made, very few examples of the corresponding $C(sp^2)$-$C(sp^3)$ bond formation have been reported with limited success.[4-6] Since the seminal work on the Pd^{II}-mediated intermolecular alkylation of preformed or in situ generated palladacycle with alkyl halides,[5] the catalytic versions have been recently demonstrated by Yu et al. and Daugulis et al. independently, using the directing group with coordinating heteroatom such as carboxyl and 8-pivaloylaminoquinoline, respectively.[6a-b] Herein, we report a Pd^{II}-catalyzed *ortho*-methylation of acetanilides with MeI via directed C-H activation and C-C bond formation at room temperature.

We focused our initial efforts on establishing optimal conditions for the proposed Pd^{II}-catalyzed *ortho*-methylation of **1a**, which was selected as the first substrate for screening of reaction parameters to promote C-H activation at the *ortho*-position of **1a**. We reasoned that AgOAc would be required to scavenge the iodide from PdI_2, which would be formed in a catalytic cycle, to regenerate the more electrophillic $Pd(OAc)_2$ catalyst.[5a] Gratifyingly, it was found that reaction between **1a** and MeI in TFA/CH_2Cl_2 (4:1) at 100 °C for 12 h in the presence of $Pd(OAc)_2$ (5 mol %), $Cu(OTf)_2$ (1 equiv), and AgOAc (2 equiv) gave the desired mono- (**2a**) and dimethylated (**3a**) products in totally 50% yield.



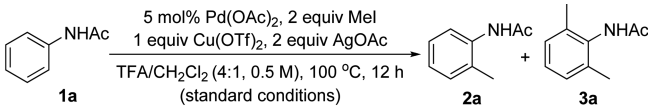
Scheme 1. Pd-catalyzed functionalization of acetanilides *via* C-H activation.

†This paper is dedicated to Professor Eun Lee on the occasion of his retirement and 65th birthday.

Our studies revealed that $Cu(OTf)_2$ is an effective oxidant for this reaction and TFA was superior to other acids examined probably due to its strong acidity which could enhance the electrophilicity of the Pd center, resulting in faster electrophilic metalation of the aromatic C-H bond.[1c, 3] Interestingly, decreasing the reaction temperature to 25 °C led to the improved product yield. Also it has been demonstrated that the use of $Cu(OTf)_2$ along with AgOAc is beneficial although AgOAc can play a dual role both as an oxidant itself and as a scavenger for the iodide. On the other hand, both AgOAc and TFA are essential for the product formation *via* C-H activation–coupling reaction and the amount of AgOAc and TFA did affect the yields to a great extent. $Pd(OAc)_2$ proved to be the most effective palladium catalyst for this reaction, and no reaction was observed in the absence of $Pd(OAc)_2$. Finally, increasing the catalyst amount to 10 mol % led to the optimal result and could reduce the reaction time. Noteworthy is the fact that the reaction efficiency and the ratio of mono- to dimethylation are apparently dependent on the reaction conditions, catalyst loading and the amount of MeI.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this process. As shown in Table 2, a wide range of acetanilides with electron-donating or moderately electron-withdrawing substituents at various positions were found to be good substrates in the reaction, affording the corresponding products in moderate to good yields. Substrates bearing strongly electron-withdrawing group (e.g. NO_2) at the *meta*- or *para*-position could not be applied to this reaction, giving the desired product (**2k**, **2l**) in very low yields. Noteworthy is the fact that this process can tolerate halogen groups (**2h-2j**, **3h**, **3j**), uncomplicated by potential side reaction that could lead to the formation of dehalogenated products. Therefore, the highly functionalized acetanilides from this process might be very useful for further elaboration and structural diversity. The reaction of *meta*-substituted substrates occurred with excellent regioselectivity, leading to only monomethylated products (**2c**, **2f**, **2i**, **2l**) originating from the activation of the less hindered C-H bond. Since palladation and/or cross-coupling reactions of *ortho*-substituted acetanilides are well known to be impeded by the *ortho* substituents,[7] especially noteworthy are the good yields obtained with *ortho*-substituted substrates, such as *o*-methylacetanilide, *o*-methoxyacetanilide, *o*-phenylacetanilide, *N*-Ac-1-naphthylamine, etc. (**2d**, **2g**, **2m**, **2n**).

Table 1. Optimization studies for the *ortho*-methylation of **1a**

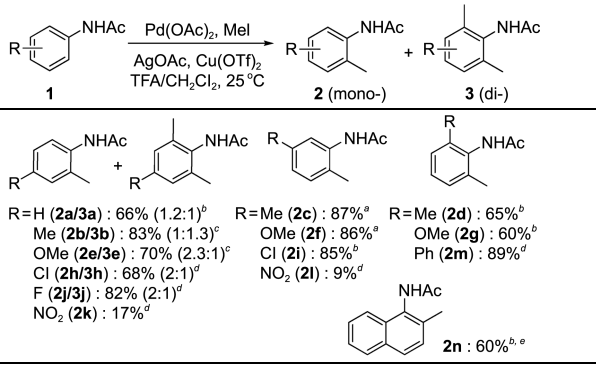


1a **2a** **3a**

Entry	Variation from the standard conditions	Yield (%)[a]
1	none	50 (45+5)
2	other oxidants[b] instead of $Cu(OTf)_2$	0-34
3	other acids[c] instead of TFA	0-3
4	other solvent[d] instead of CH_2Cl_2	0-43
5	at 25 °C	62 (50+12)
6	using 0-1 or 3 equiv of AgOAc at 25 °C	3-43
7	using 0-0.5 or 2 equiv of $Cu(OTf)_2$ at 25 °C	40-56
8	TFA (7 equiv) in CH_2Cl_2 (0.5 M) at 25 °C	54 (44+10)
9	without TFA in CH_2Cl_2 (0.5 M) at 25 °C	0
10	other Pd catalyst[e] under entry 8's conditions	0-49
11	10 mol % $Pd(OAc)_2$ at 25 °C	75 (41+34)
12	**10 mol % $Pd(OAc)_2$ at 25 °C for 4 h**	**78 (66)[f] (36+30)**
13	10 mol % $Pd(OAc)_2$ + 1 equiv MeI at 25 °C	49 (44+5)
14	10 mol % $Pd(OAc)_2$ + 5 equiv MeI at 25 °C	44 (40+4)

[a]Yields and the ratios of **2a** and **3a** were determined by ^{1}H NMR using trichloroethylene as an internal standard. [b]Oxidant: $Phl(OAc)_2$, $K_2S_2O_8$, Oxone, benzoquinone, $CuCl_2$, $Cu(OAc)_2$, Ag_2O, Ag_2CO_3. [c]Acid: AcOH, $CH_3CH_2CO_2H$, PivOH, MsOH, *p*-TsOH, TfOH, HCl, H_2SO_4. [d]Solvent: THF, dioxane, MeCN, DMF, MeOH, acetone toluene. [e]Pd catalyst: $PdCl_2$, $Pd(O_2CCF_3)_2$, $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(dppf)_2$. [f]Isolated yeld.

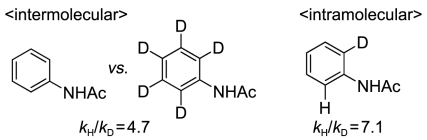
Table 2. Pd-catalyzed methylation of a variety of acetanilides



Reaction conditions: **1** (1 equiv), MeI (2 equiv), $Pd(OAc)_2$ (5-20 mol %), AgOAc (2 equiv), and $Cu(OTf)_2$ (1 equiv) in TFA/CH_2Cl_2 (4:1, 0.5 M) at 25 °C for 3-11 h. Isolated yields are provided and the ratios of **2** and **3** were determined by ^{1}H NMR. [a]5 mol % $Pd(OAc)_2$. [b]10 mol % $Pd(OAc)_2$. [c]15 mol % $Pd(OAc)_2$. [d]20 mol % $Pd(OAc)_2$. [e]Determined by ^{1}H NMR using trichloroethylene as an internal standard.

To gain insight into this reaction, we proceeded to conduct competition experiments of a series of *meta*-substituted acetanilides. This protocol exhibited electronic dependence, showing that the electron-rich substrates reacted considerably faster than the electron-deficient counterparts (rate: **1f** > **1a** > **1i** >> **1l**). This observation indicates the features of the electrophilic attack pathway during the cyclopalladation. In addition, kinetic isotope experiments demonstrate that cleavage of the C-H bond at the *ortho* position is involved in the rate-determining step. [k_H/k_D (intermolecular) = 4.7; k_H/k_D (intramolecular) = 7.1]

Although the reaction mechanism is not clear at this stage, by analogy with the mechanisms reported for the related reactions[5, 6a-b] and on the basis of the preliminary studies, it is plausible that this transformation would be initiated by *ortho*-cyclopalladation of the acetanilide. Subsequent oxidative addition of MeI to the palladacycle affords a Pd^{IV} species, which then undergoes reductive elimination to give the desired methylation product. An alternative mechanistic pathway involving Pd^{II}/Pd^{III} catalytic cycle[8] cannot be completely excluded.



Scheme 2. Kinetic isotope effects.

In summary, we have developed a Pd^{II}-catalyzed *ortho*-methylation of acetanilides with MeI. In comparison with other related works reported previously which required very high reaction temperature and/or basic conditions,[4-6] noteworthy is the fact that this protocol proceeds smoothly even at room temperature *via* sequential directed C-H activation and $C(sp^2)$-$C(sp^3)$ bond formation and may prove complementary to the earlier work[4, 6] in the case of base-sensitive substrates.

Acknowledgments. This work was supported by the research fund of Hanyang University (HY-2010-N).

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