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Toluene derivatives as simple coupling precursors for cascade palladium-catalyzed oxidative C–H bond acylation of acetanilides†

Cite this: *Chem. Commun.*, 2013, **49**, 689

Received 8th October 2012,
Accepted 3rd December 2012

DOI: 10.1039/c2cc37352a

www.rsc.org/chemcomm

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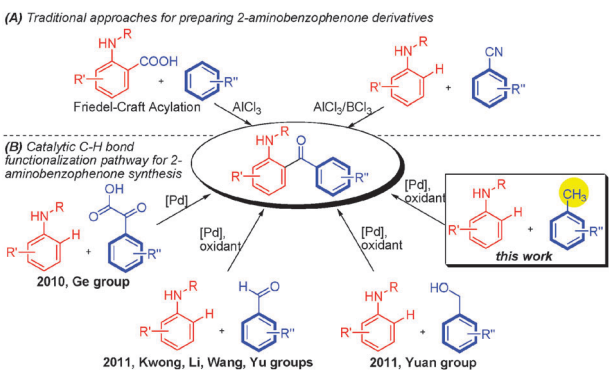
A palladium-catalyzed cascade cross-coupling of acetanilide and toluene for the synthesis of *ortho*-acylacetanilide is described. Toluene derivatives can act as effective acyl precursors (upon sp^3-C–H bond oxidation by a Pd/TBHP system) in the oxidative coupling between two C–H bonds. This dehydrogenative Pd-catalyzed *ortho*-acylation proceeds under mild reaction conditions.

ortho-Acylacetanilides are important structural motifs and resourceful intermediates for preparing natural products and pharmaceutically useful heterocycles,[1] such as fluorenones, cinnoline, acridones, indazoles, indoles, quinolines and benzodiazepines.[2] The traditional method for the synthesis of 2-aminobenzophenones is the Friedel–Craft acylation of anthranilic acids with arenes in the presence of $AlCl_3$ (Scheme 1A).[3] Yet, this reaction suffers from poor regioselectivity when substituted arenes are employed. An alternative synthetic pathway for directly accessing this scaffold is the reaction between anilines and benzonitriles promoted by a stoichiometric amount of $BCl_3/AlCl_3$.[4] With the growing demand for sustainable synthesis of fine chemicals and pharmaceutical intermediates,[5] the direct catalytic C–H functionalization of aniline derivatives by using a relatively non-hazardous acylating agent and under mild reaction conditions becomes more desirable.

Direct C–H bond functionalizations/cross-couplings promoted by transition metal complexes have been successful as a valuable tool for the modular and facile synthesis of structurally similar, yet diversified organic molecules.[6] With the assistance of a directing group, the *ortho*-$C_{(sp^2 \text{ or } sp^3)}$–H bond cleavage (*ortho*-metallation) can be facilitated in the presence of transition metals (*e.g.* Pd, Ir, Rh, Ru, Cu, Fe, *etc.*), leading to a versatile C–H bond functionalization upon trapping with appropriate electrophiles or nucleophiles under basic or oxidative conditions, respectively.[7] In view of minimizing the waste/side product formation in aromatic ketone synthesis,[8] the oxidative coupling between two C–H bonds from two coupling partners is highly attractive.[9] In 2009, research groups of Cheng and Li reported Pd-catalyzed *ortho*-C–H-bond functionalization of 2-arylpyridines using aromatic and aliphatic aldehydes, respectively.[10,11] In 2010, Ge and co-workers disclosed the *ortho*-acylation of acetanilides that could be done by employing α-oxocarboxylic acid *via* a Pd-catalyzed decarboxylative pathway (Scheme 1B).[12] In 2011, our group[13] and others[14] independently reported oxidative coupling of aldehydes with acetanilides. Very recently, Yuan showed that benzylalcohols could act as the acylating agents.[15] With our continuous interest to develop more convenient C–H bond cross-coupling reactions,[16] herein we report a facile synthesis of 2-aminobenzophenone derivatives by Pd-catalyzed *ortho*-C–H bond oxidative coupling/acylation of anilides employing toluene derivatives as the simple coupling partners (Scheme 1B).

We began to investigate the feasibility of *ortho*-C–H bond acylation by using toluene derivatives as the potential acyl source (ESI,† Table S1). In our initial trial, *para*-chlorotoluene was used as the model coupling partner in the cross-coupling of acetanilide. We found that this protocol was viable and the desired product **3al** could be afforded in 15% yield (entry 1). A screening of metal catalysts revealed that $Pd(OAc)_2$ and $Pd(TFA)_2$ were applicable catalysts, while $Ni(acac)_2$ and $Rh(PPh_3)_3Cl$ were found to be inferior (entries 1–6). The effectiveness of the oxidant was also examined (entries 7–10). TBHP was the most suitable oxidant in this reaction. Other oxidants screened were essentially not effective. Increasing the



Scheme 1 Traditional approaches and recent catalytic C–H bond functionalization protocols for the preparation of 2-acylacetanilides.

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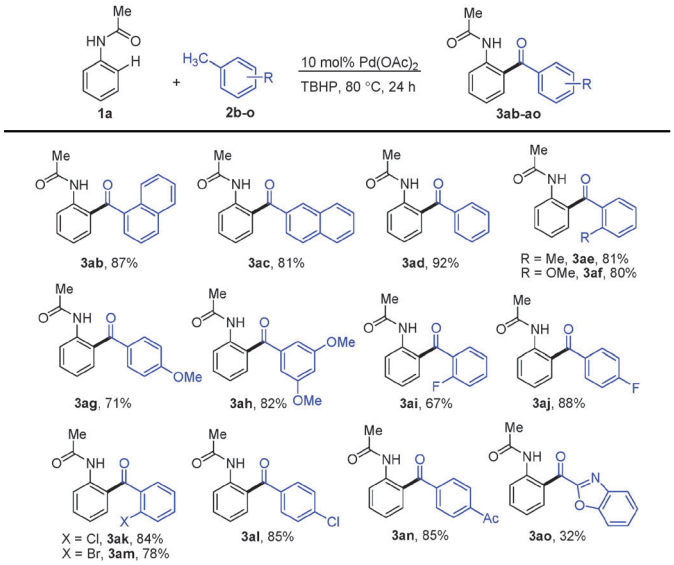
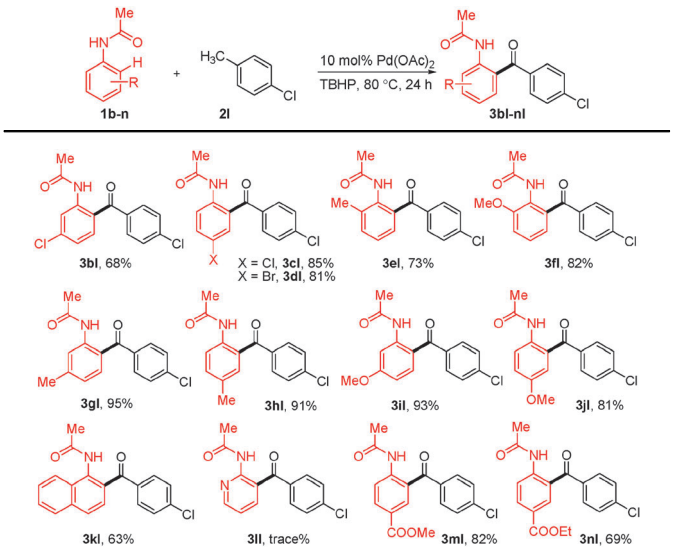
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc37352a

Table 1 Scope of Pd-catalyzed oxidative *ortho*-acylation of acetanilide with different toluene derivatives[a]



[a] Reaction conditions: acetanilide **1a** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (12 mmol), toluene derivatives **2b–o** (2 mL) were stirred at 80 °C for 24 h under air. Isolated yields were reported.

Table 2 Scope of acetanilides in Pd-catalyzed oxidative *ortho*-acylation[a]



[a] Reaction conditions: acetanilide **1b–n** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (12 mmol), 4-chlorotoluene **2l** (2 mL) were stirred at 80 °C for 24 h under air. Isolated yields were reported.

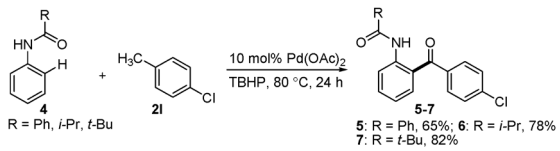
stoichiometry of TBHP significantly increased the yield of the desired product (entries 11–14). Surprisingly, lowering the reaction temperature gave a better yield (entries 14–17). These results were possibly due to the minimization of reagent decomposition. The reaction temperature of 80 °C was found to be optimal (entry 15). Further lowering the reaction temperature decreased the substrate conversion. 1,2-Dichloroethane, dioxane and acetonitrile were not effective solvents for this reaction (entry 18–20).

With our optimized reaction conditions in hand, we next tested the scope of the toluene derivative as the simple acyl source (Table 1). Naphthalene with the methyl group at either α or β-position gave good product yields (**3ab** and **3ac**). It is worth noting that *ortho*-hindered substrates were feasible coupling partners in this catalytic system (**3ae** and **3af**).[17] Electron-donating 4-methoxytoluene gave slightly lower yield of the product **3ag**, presumably due to the difficult C–H bond cleavage of the C(O)–H bond.[18] *ortho*- and *para*-Fluoro/chloro substituted toluenes were compatible substrates (**3ai–3al**). In particular, the bromo group remained intact during the course of the reaction (**3ai**). This entry potentially offers further structural fine-tuning using other traditional cross-coupling reactions.[19] Heterocyclic benzoxazole gave lower product yield (**3ao**).

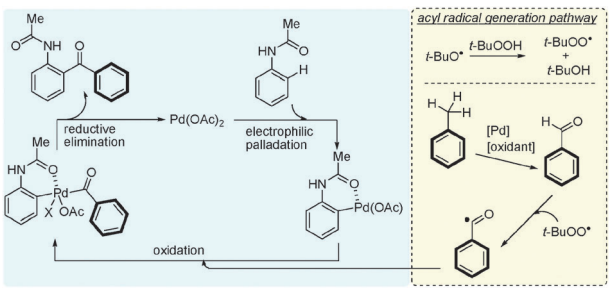
Various substituted acetanilides (**1b–m**) were also examined and the results are compiled in Table 2. No significant electronic effect of *para*-substituted acetanilides was found (**3cl**, **3dl**, **3hl** and **3jl**). Yet, *meta*-substituted acetanilides gave good corresponding product yields when the electron donating group (*e.g.* –Me, –OMe; **3gl**, **3il**, respectively) is at the *para*-position. These results were possibly due to the facilitation of the electrophilic palladation. In contrast, *meta*-chloroacetanilides showed lower yield (**3bl**). Particularly noteworthy is that the *ortho*-substituted acetanilides were also found to be compatible in this catalyst system (**3el** and **3fl**). These results were different from previously reported α-oxocarboxylic acid protocol,[20] in which our route may offer a complementary access to *ortho*-substituted products. Carboxylic ester groups were tolerable under this catalytic system (**3ml** and **3nl**). We also attempted to examine tertiary acetanilides (*e.g.* *N*-acetyl-1,2,3,4-tetrahydroquinoline and *N*-methylacetanilide) in this reaction, yet very low substrate conversion and only a trace amount of desired products were observed from GC-MS analyses.[21]

In addition to the acetamido group, other directing amido moieties were tested in this *ortho*-acylation reaction (Scheme 2). iso-Propyl and *tert*-butyl groups (*e.g.* **6** and **7**) were applicable in this reaction while the phenyl moiety gave slightly lower yield of the desired product **5**.

We suggest that the reaction mechanism begins with aliphatic C–H bond oxidation to aldehyde by the oxidant in the presence of the palladium complex at elevated temperature (Scheme 3).[22] Control experiments revealed that in the presence of only toluene and TBHP (*i.e.* without Pd catalyst), no significant benzaldehyde



Scheme 2 Scope of other amido directing groups.



Scheme 3 A plausible reaction mechanism.

formation was observed as judged by GC-MS analysis.[23] The *t*-BuO$^{\bullet}$ radical reacts with TBHP to generate *t*-BuOO$^{\bullet}$.[24] This species then abstracts an H atom to give reactive acyl radicals.[25,26] Meanwhile, the acetanilide undergoes directed electrophilic palladation and generates a palladacyclic intermediate (Scheme 3).[27] We hypothesize that the acyl radicals would react with the palladacycle to afford the ketone product *via* either a Pd(IV)[28] or a dimeric Pd(III)[29] pathway. The Pd(II) species is regenerated by the reductive elimination process. Moreover, we also attempted to add a radical scavenger (*e.g.* ascorbic acid[30]) to the reaction, the rate of reactions was greatly suppressed and only a trace amount of the product was detected. Thus radical intermediates may involve in this reaction. In order to eliminate the possibility of the carboxylic acid that could also serve as the acyl source, we carried out independent experiments which apply carboxylic acid instead of toluene as a coupling partner. However, no desired product was obtained from these control experiments.

In conclusion, we have reported a cascade cross-coupling of acetanilide and toluene for the synthesis of *ortho*-acylacetanilide. Toluene derivatives can be employed as effective acyl precursors in the oxidative coupling between two C–H bonds. This sequential Pd-catalyzed *ortho*-acylation proceeds under mild reaction conditions. Fluoro, bromo, chloro, methoxy, amide, ester and benzoxazolyl groups are compatible in this catalytic system. We believe that this new synthetic method using simple toluene derivatives as the coupling partners would stimulate chemists to advance other relevant catalytic acylation processes.

We thank the Research Grants Council of Hong Kong (PolyU5010/11P) for financial support. We are grateful to Prof. Albert S. C. Chan (PolyU) for sharing GC instruments.

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