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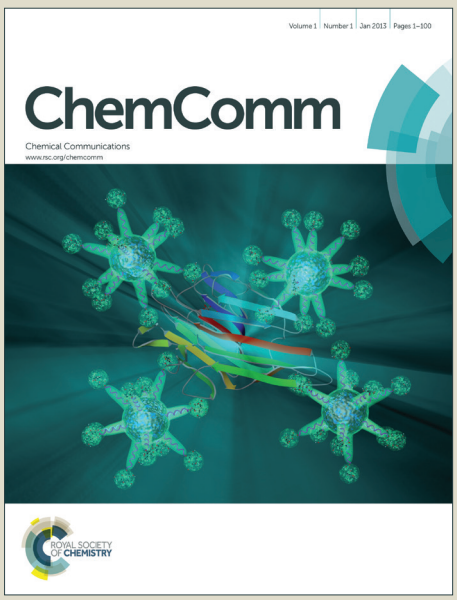

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Palladium-catalyzed oxidative C-H bond acylation of *N*-nitrosoanilines with toluene derivatives: a traceless approach to *N*-alkyl-2-aminobenzophenones

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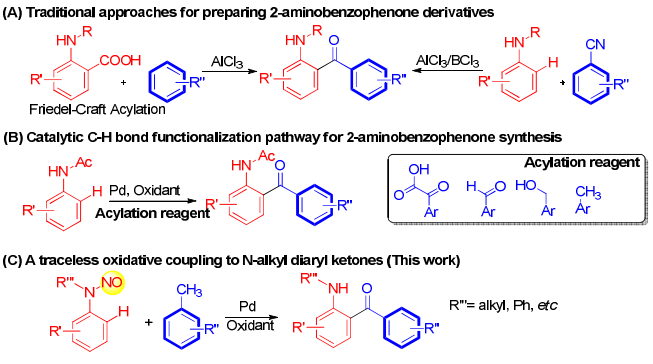
A palladium-catalyzed cascade cross-coupling of *N*-nitroso-anilines and toluene derivatives for the direct synthesis of *N*-alkyl-2-aminobenzophenones is described. *N*-nitroso groups in the anilines can act as the traceless directing group while toluene derivatives can serve as effective acyl precursors under mild reaction conditions.

Transition-metal-catalyzed direct C-H bond functionalization has been successful as a valuable tool for the modular and facile synthesis of structurally similar, yet diversified organic molecules.[1] In general, directing groups are necessary for facilitating the *ortho*-$C_{(sp^2 \text{ or } sp^3)}$-H bond activation 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.[2] However, it may also need additional steps for the directing group to be removed or transformed after the C-H bond functionalization. Recently, traceless directing groups such as *N*-nitroso and *N*-oxide have emerged and been proved to be efficient in the C-H olefination, alkynylation, *etc*.[3] The removal or transformation of this kind groups happened during the C-H bonds coupling, affording the desired product directly, which made them to be attractive alternatives in view of the atom economy.[4]

ortho-Aminobenzophenones are frequently found in pharmaceuticals, natural products, and biologically active molecules.[5] In particular, *N*-alkyl-2-aminobenzophenones are known to be crucial synthetic precursors for a wide range of biologically active compounds including benzodiazepines, acridones, quinazolinones, indoles, and indazoles.[6] The traditional method for the synthesis of 2-aminobenzophenones is the Friedel–Craft acylation of anthranilic acids with arenes in the presence of $AlCl_3$ or the reaction between anilines and benzonitriles promoted by a stoichiometric amount of $BCl_3/AlCl_3$ (Scheme 1A).[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 2010, Ge and co-workers disclosed that the *ortho*-acylation of acetanilides could be done by employing α-oxocarboxylic acid via a Pd-catalyzed decarboxylative pathway (Scheme 1B).[10] In 2011, our group[11] and others[12] independently reported oxidative coupling of aldehydes with acetanilides. In 2012, Yuan showed that benzylalcohols could also act as the acylating agents.[13] Very recently, our group[14] and others[15] independently proved the application of toluene derivatives as the simple coupling partners in the Pd-catalyzed *ortho*-C-H bond acylation of acetanilides. In fact, previous literature reports were mainly focused on the C-H bond acylation of acetanilides, affording *N*-acyl-2-aminobenzophenones as final products. The C-H bond acylation providing *N*-alkyl-2-aminobenzophenones directly has not been reported yet. In continuing our former work on palladium-catalyzed C-H acylation of acetanilides with toluene derivatives,[11,14] herein, we report a new oxidative approach for accessing *N*-alkyl-2-aminobenzophenones by using *N*-nitroso as the traceless directing group and toluene derivatives as acyl sources (Scheme 1C).

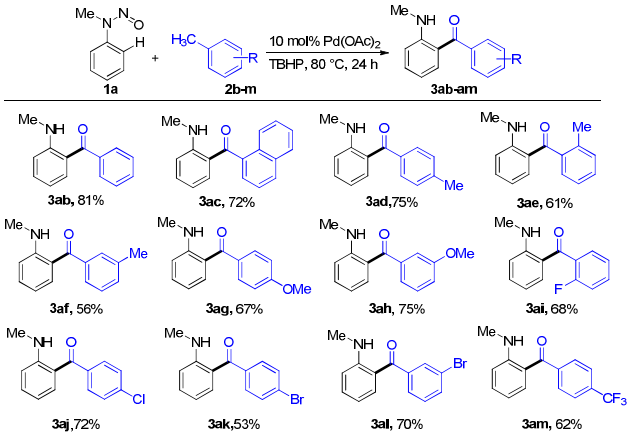


Scheme 1: Protocols for the preparation of *ortho*-aminobenzophenones

In our initial trial, toluene was used as the model coupling partner in the cross-coupling of *N*-methyl-*N*-nitrosoaniline

(ESI, Table 1). The *N*-alkyl-*N*-nitrosoanilines were prepared from commercial available anilines and sodium azide in quantitative yield at room temperature. We found that this protocol was viable and the desired product **3ab** could be afforded in 58% 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 oxidants was also examined (entries 7-10). Our results demonstrated that TBHP was the most suitable oxidant in this reaction. Other oxidants screened were essentially not effective. Increasing the stoichiometry of TBHP significantly increased the yield of the desired product (entries 11-14). Interestingly, lowering the reaction temperature gave a better yield (entries 14-17) 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. In addition, our results showed that 1, 2-dichloroethane, 1,4-dioxane, and trifluoromethylbenzene were not effective solvents for this reaction (entries 18-20).

Table 1: Scope of Pd-catalyzed oxidative *ortho*-acylation of *N*-Methyl-*N*-nitrosoaniline with different toluene derivatives[a]

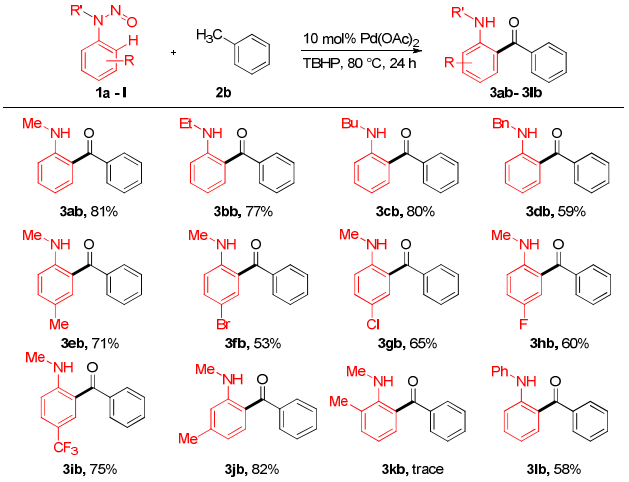


[a] Reaction conditions: *N*-nitrosoaniline **1a** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (12.0 mmol), toluene derivatives **2b-m** (2.0 mL or 30 equiv.) were stirred at 80 °C for 24 h under air. Isolated yields were reported.

With our optimized reaction conditions in hand, we next tested the scope of the toluene derivatives as the simple acyl source (Table 1). 1-methylnaphthalene gave good yields of the corresponding products (**3ac**). It is worth noting that *ortho*-hindered substrates were feasible coupling partners in this catalytic system (**3ae**, **3ai**). Strongly electron-donating *para*-/*meta*- methoxytoluene gave a slightly lower yield of the product presumably due to the difficult C-H bond cleavage of C(O)-H bond (**3ag**, **3ah**).[16] *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 (**3ak, 3al**). This entry potentially offers further structural fine-tuning using other traditional cross-coupling reactions.[17] The electron-withdrawing *para*-trifluoromethyl toluene gave moderate product yield (**3am**).

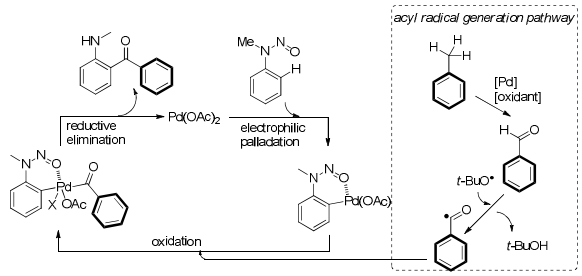
Various substituted *N*-nitrosoanilines (**1b–l**) were also examined and the results are compiled in Table 2. *N*-nitrosoanilines *with* different alkyl groups (*e.g.* Me, Et, Bu, and Bn) reacted well with toluene and generated the corresponding products in 69-81% yields (**3ab-3db**). A variety of functional groups, including F, Br, Cl, CF_3, were tolerated under these reaction conditions and no significant electronic effect was found(**3eb-3jb**). Trifluoromethyl group is tolerable under this catalytic system (**3jb**). *meta*-Methyl-*N*-nitrosoanilines gave good corresponding product yields (**3gb**) while *ortho*-Methyl-*N*-nitrosoanilines gave trace product possible due to the high steric hinder (**3kb**). We also attempted to examine *N*-phenyl-*N*-nitrosoaniline in this reaction, desired product was obtained in moderate yield (**3lb**).

Table 2: Scope of *N*-nitrosoaniline in Pd-catalyzed oxidative *ortho*-acylation[a]



[a] Reaction conditions: *N*-nitrosoaniline **1a-l** (1.0 mmol), $Pd(OAc)_2$ (10 mol%), TBHP (12.0 mmol), toluene (2.0 mL) were stirred at 80 °C for 24 h under air. Isolated yields were reported.

Although the exact reaction mechanism is not clear to date, we suggest that the reaction mechanism began with aliphatic C–H bond oxidation to aldehyde by the oxidant in the presence of the palladium complex at elevated temperature (Scheme 2).[18] Control experiments revealed that in the presence of only toluene and TBHP (*i.e.* without Pd catalyst), no significant benzaldehyde formation was observed as judged by GC-MS analysis.[19] The *t*-BuO• radical reacts with TBHP to generate *t*-BuOO•.[20] This species then abstracts an H atom to give reactive acyl radicals.[21,22] Meanwhile, the *N*-nitroso group undergoes directed electrophilic palladation and generates a palladacyclic intermediate (Scheme 2).[3a] We hypothesize that the acylradicals react with the palladacycle to afford the ketone products *via* either a Pd(IV)[23] or a dimeric Pd(III)[24] pathway. After the reductive elimination along with the N-N(O) bond cleavage, the desired product was released and the Pd(II) species is regenerated to complete the catalytic cycle. Moreover, we also attempted to add a radical scavenger (*e.g.* ascorbic acid [25]) to the reaction, the rate of reactions was greatly suppressed and only a trace amount of the product was detected. Thus radical intermediates may be involved in this reaction.



Scheme 2: A plausible reaction mechanism

In conclusion, we have developed a cascade cross-coupling of *N*-nitrosoanilines and toluene derivatives for the directly accessing to *N*-alkyl-2-aminobenzophenones. The nitroso group could act as a traceless directing group while toluene derivatives served as effective acyl precursors in the oxidative coupling between two C–H bonds under mild reaction conditions. Fluoro, bromo, chloro, methoxy, and trifluoromethyl groups at different positions are compatible in this catalytic system. An array of *N*-alkyl-2-aminoanilines were obtained in moderate to high yields. We believe this synthetic approach will be useful for generating versatile *ortho*-amino diaryl ketone motifs.

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