DOI: 10.1002/adsc.201200948

Mild Palladium-Catalyzed Oxidative Direct *ortho*-C–H Acylation of Anilides under Aqueous Conditions

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Received: October 29, 2012; Revised: November 28, 2012; Published online: ■■ ▮▮, 0000

This paper is dedicated to the memory of Professor Árpád Kucsman.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200948.

Abstract: Palladium-catalyzed cross-dehydrogenative coupling between anilides and aromatic aldehydes was achieved under aqueous conditions. A wide variety of the desired benzophenone derivatives was isolated in good to excellent yield. The reaction rate acceleration effect of acid and detergent has been demonstrated. Mechanistic insight has been obtained from quantum chemical calculations.

Keywords: acylation; aldehydes; C–H activation; palladium; surfactants

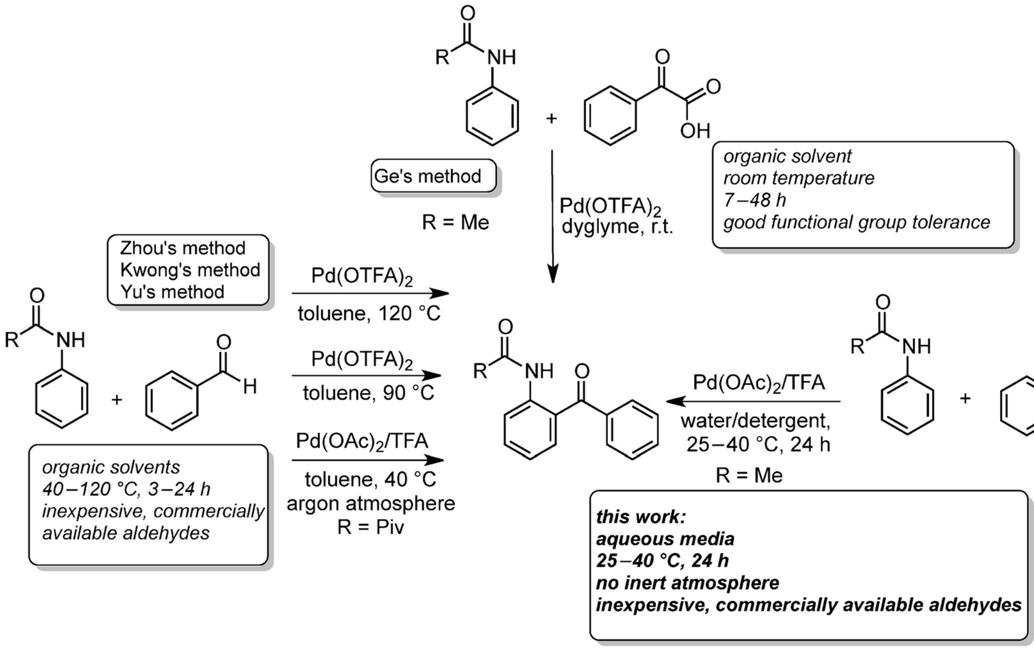
Transition metal-catalyzed direct C–H bond functionalization is one of the most important transformations in recent organic synthetic strategies.[1] Although catalytic transformations based on palladium catalysts are the most frequently utilized oxidative coupling methods in organic syntheses, these reactions usually require harsh conditions (high temperature, long reaction time, necessity of inert atmosphere). Therefore the development of efficient palladium-catalyzed oxidative couplings based on highly active catalyst systems under mild reaction conditions is still highly demanded. Regarding the mechanisms of palladium-catalyzed transformations the presence of monometallic palladium complexes in the catalytic cycle is well accepted.[2] However, very recently the special role and activity of bimetallic palladium species has been discovered and demonstrated in several coupling reactions involving a C–H functionalization step.[3] Besides the assessment of the synthetic potential of bimetallic complexes in organic chemistry, a thorough understanding of their working mechanism is also essential.[4]

There are several applications of palladium-catalyzed oxidative transformations for the formation of new carbon-carbon bonds *via* functional group-directed *ortho*-substitution.[5] Very recently, the synthesis of aromatic ketones from phenylpyridines[6] or acetanilides[7] could be achieved by the palladium-catalyzed oxidative coupling of aldehydes[8] including a C–H activation step.

The recently described methodologies of Zhou,[7a] Kwong[7b] and Yu[7c] enable the transformation in toluene at 120 °C, 90 °C, and 40 °C, respectively (Scheme 1.). The latter procedure provides the most efficient conditions for the desired coupling due to the relatively short reaction time under the applied conditions (40 °C, 3 h). Utilization of ketocarboxylic acids instead of aldehydes enables the formation of benzophenone derivatives in a similar palladium-catalyzed coupling at room temperature as it was demonstrated by Ge and co-workers.[9] This transformation works efficiently at room temperature and it has excellent functional group tolerance.

It is of note, amongst the previous methodologies depicted on Scheme 1., that only Kwong's procedure[7b] offers possibilities for the transformation of *ortho*-substituted acetanilides.

Palladium-catalyzed oxidative coupling of acetanilides with aromatic aldehydes results in 2-acylacetanilides and 2-aminobenzophenone derivatives after hydrolytic cleavage of the amide bond, which are impor-



Scheme 1. Recently developed couplings.

tant intermediates in the synthesis of many potentially biologically active heterocycles.[10]

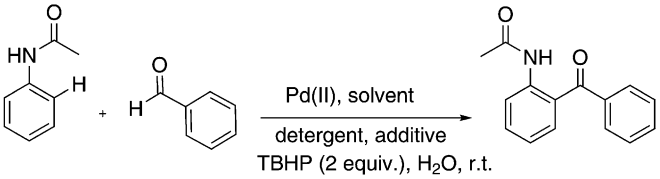
Our goal was to develop a new palladium-catalyzed C–H activation route for the synthesis of aryl ketones from acetanilides and cheap and readily available aldehydes under mild reaction condition in environmentally benign solvent such as water. The utilization of aqueous media and anionic surfactant enables the reaction rate acceleration by the "on water"[11] effect and micellar catalysis.[12] Additionally, we performed quantum chemical calculations to obtain a possible mechanistic picture of the transformation.

Optimization studies were performed with acetanilide and benzaldehyde in the presence of 5 mol% $Pd(OAc)_2$ at room temperature in the presence of trifluoroacetic acid (TFA) and *tert*-butyl hydroperoxide (TBHP, 70 wt% in water) as oxidant. For comparison with literature procedures we examined the applicability of different organic solvents. We found that only chloroform, dichloromethane and toluene[7] are suitable solvent for the coupling and we obtained 22, 30 and 24% conversions, respectively, after 3 h. Coordinating solvents such as DMSO, DMF, MeOH, MeCN gave no reaction and conversion in *t*-BuOH was also negligible (Table 1 entries 1–8).

When the reaction was carried out in water instead of organic media, 60% conversion was obtained (entry 9.). To ensure better solubility of the reactants in water we added 0.5 mol% sodium dodecyl sulfate (SDS) into the reaction, and obtained 67% conversion after 3 h (entry 10).

Further addition of the detergent gave up to 93% conversion (entries 11–13.), showing the importance

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	Detergent	Additive	Conv. [%][b]
1	$Pd(OAc)_2$	DMSO		TFA	0
2	$Pd(OAc)_2$	DMF		TFA	0
3	$Pd(OAc)_2$	MeOH		TFA	0
4	$Pd(OAc)_2$	MeCN		TFA	0
5	$Pd(OAc)_2$	*t*-BuOH		TFA	17
6	$Pd(OAc)_2$	$CHCl_3$	–	TFA	22
7	$Pd(OAc)_2$	toluene		TFA	24
8	$Pd(OAc)_2$	DCM	–	TFA	30
9	$Pd(OAc)_2$	H_2O		TFA	60
10	$Pd(OAc)_2$	H_2O	0.5%,SDS	TFA	67
11	$Pd(OAc)_2$	H_2O	2%, SDS	TFA	84
12	$Pd(OAc)_2$	H_2O	5%, SDS	TFA	92
13	$Pd(OAc)_2$	H_2O	7%, SDS	TFA	93
14	$Pd(OAc)_2$	H_2O	5%, SMS	TFA	64
15	$Pd(OAc)_2$	H_2O	5%, SOS	TFA	89
16	$Pd(OAc)_2$	H_2O	5%, SDS	–	16
17	$Pd(OTFA)_2$	H_2O	5%, SDS	–	70

[a] *Reaction conditions:* acetanilide (1.0 mmol), benzaldehyde (2.0 mmol), $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), TBHP (2 mmol), solvent (1 mL) at room temperataure.

[b] Conversion was determined after 3 h with GC.

of an amphiphilic additive. Examining the effect of the chain length of alkyl sulfates we performed the reactions with sodium methyl and octyl sulfates (SMS and SOS, respectively). While the former gave a similar result (64%) to the detergent-free version (compare entries 9 and 14), the latter yielded a similar conversion (89%) to SDS (compare entries 12 and 15). These results prove the positive effect of anionic detergents containing long carbon chains on the coupling.[13]

The presence of TFA was also proved to be essential. In the absence of the acid the $Pd(OAc)_2$-catalyzed reaction becomes significantly slower (16% in 3 h, entry 16.). When the catalyst was replaced with $Pd(OTFA)_2$ without the addition of extra acid the conversion of the reaction was 70%, showing the importance of TFA anion.

With the optimal conditions in hand next we assessed the scope of the developed methodology. We achieved the Pd-catalyzed *ortho*-acylation of differently substituted acetanilides with benzaldehyde (Table 2.) in the presence of $Pd(OAc)_2$ catalyst, TFA and SDS at room temperature. Application of the $Pd(OAc)_2$-TFA system is more economic than $Pd(OTFA)_2$ therefore we choose this composition of catalyst system for the synthesis of benzophenone derivatives.[14]

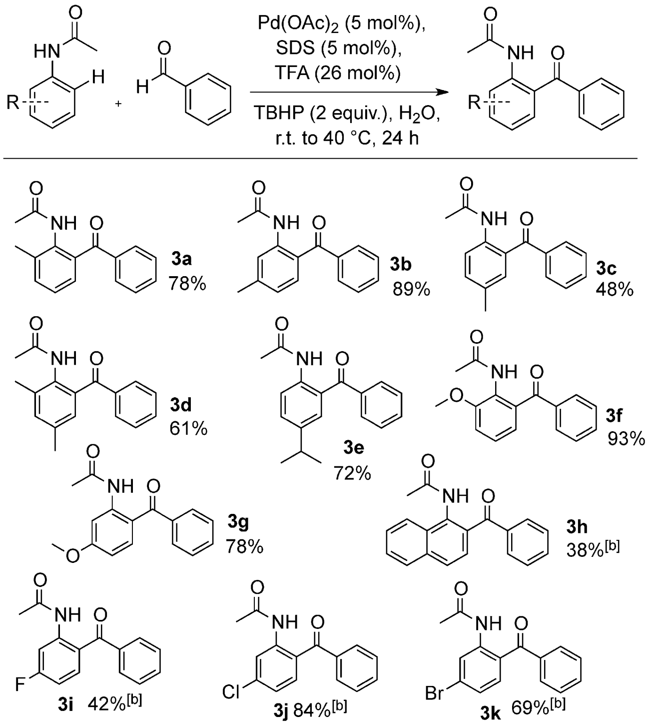
The presence of a methyl group in the anilide slightly affected the yield of the products and **3a-c** were isolated with 48–89%. It is of note that the *ortho*-substituted anilides were also successfully transformed into the appropriate products (**3a**, **3f**) in the C−H activation reaction, in spite of their lower reactivity.

The coupling also took place straightforwardly in the presence of a methoxy group in the *ortho* position and the desired product (**3f**) was obtained with excellent yield. A methoxy group in a *meta*-position to the amide function afforded the appropriate benzophenone derivative (**3g**) in the catalytic transformation.

We also performed the coupling of anilide derivatives with benzaldehyde-containing a condensed ring system such as naphthalene or halogen substituents. The appropriate products (**3h–k**) were prepared with similar efficiency using 7.5 mol% palladium catalyst at 40 °C.

After studying the effect of acetanilide substituents we examined the effect of functional groups on the aldehyde part (Table 3.). Remarkably, the presence of halogens in any positions of the aromatic ring of the aldehyde afforded similar or better yields for products **3m–t** compared to the unsubstituted derivative **3l**. The products were obtained with good yields when the aldehyde was substituted with electron-donating groups such as methyl or methoxy group (**3u**, **3v**). Larger catalyst loadings and 40 °C were necessary to obtain the target products **3w–z** constructed from 4-nitrobenzaldehyde, heterocyclic, conjugated or aliphatic aldehydes. Finally, demonstrating the applicability of the developed methodology further benzophenone derivatives **3aa–3ee**) bearing functional groups in both aromatic rings were synthesized with 37–60% yields.

Table 2. Scope of *N*-acetanilides for Pd-catalyzed C−H acylation.[a]



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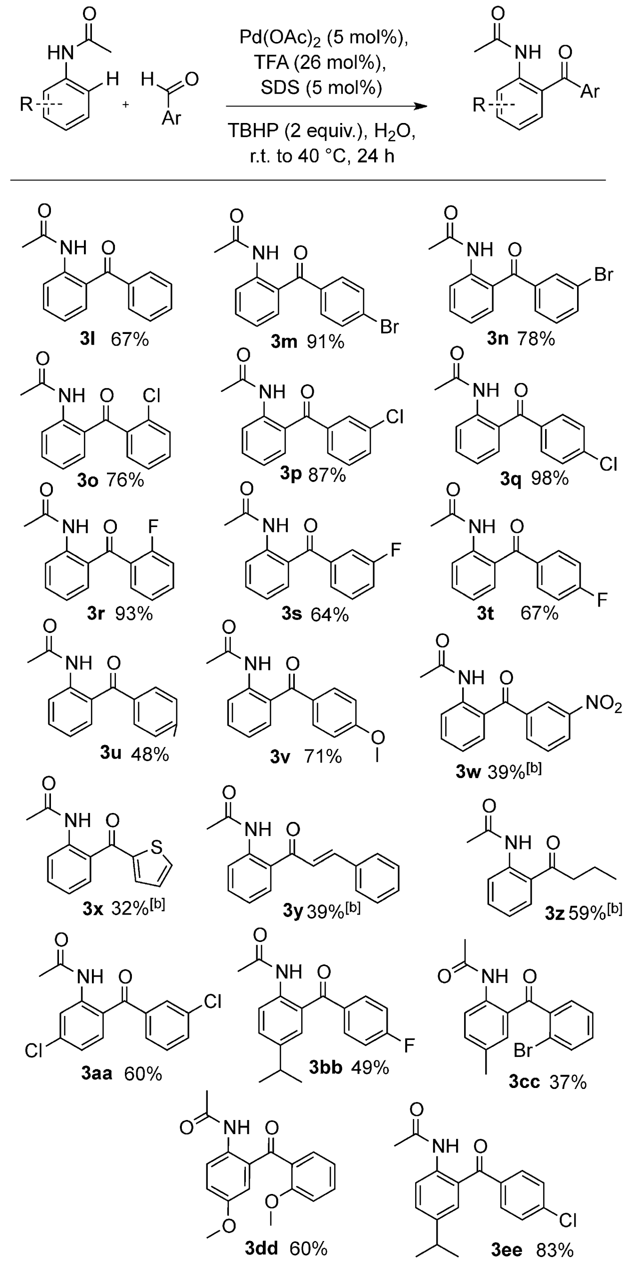
[a] *Reaction conditions:* acetanilide (1.0 mmol), benzaldehyde (2.0 mmol), $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), TBHP (2 mmol, 70 wt% in water), water (1 mL) at room temperature, 24 h. Yields [%] of isolated product.

[b] *Reaction conditions:* acetanilide (1.0 mmol), aldehyde (2.0 mmol), $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), TBHP (2 mmol, 70 wt% in water), water (1 mL) at 40 °C, 24 h.

In order to support our hypothesis regarding a probable mechanism of the reaction, we have performed density functional calculations.[15] As a simplified theoretical model we have chosen the coupling of acetanilide and benzaldehyde in the presence of $Pd(OAc)_2$ catalyst in water (Table 1. entry 9.). We have followed two different reaction routes featuring mono- and binuclear active Pd species.[16] The corresponding free energy profiles are displayed on Figure 1. We propose that palladium acetate reacts with acetanilide and forms cationic palladium species S1 which is involved in the carbopalladation step. The profiles are initiated at the predicted resting state of the reactants (Scheme 2). Both routes start with the carbopalladation step which is the rate-limiting step of the overall

Table 3. Scope of aldehydes for Pd-catalyzed C–H acylation.[a]



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[a] *Reaction conditions:* acetanilide (1.0 mmol), aldehyde (2.0 mmol), $Pd(OAc)_2$ (0.05 mmol), TFA (0.26 mmol), TBHP (2 mmol, 70 wt% in water), water (1 mL) at room temperature, 24 h. Yields [%] of isolated product.

[b] *Reaction conditions:* acetanilide (1.0 mmol), aldehyde (2.0 mmol), $Pd(OAc)_2$ (0.075 mmol), TFA (0.39 mmol), TBHP (2 mmol, 70 wt% in water), water (1 mL) at 40 °C, 24 h.

process (Figure 1). During this step the aromatic ring is deprotonated by the acetate ligand.[19]

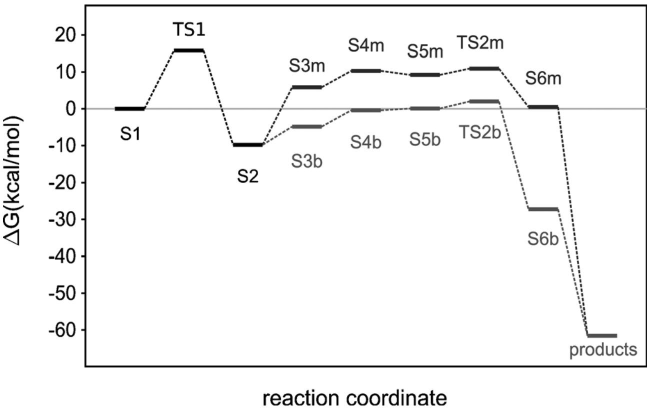


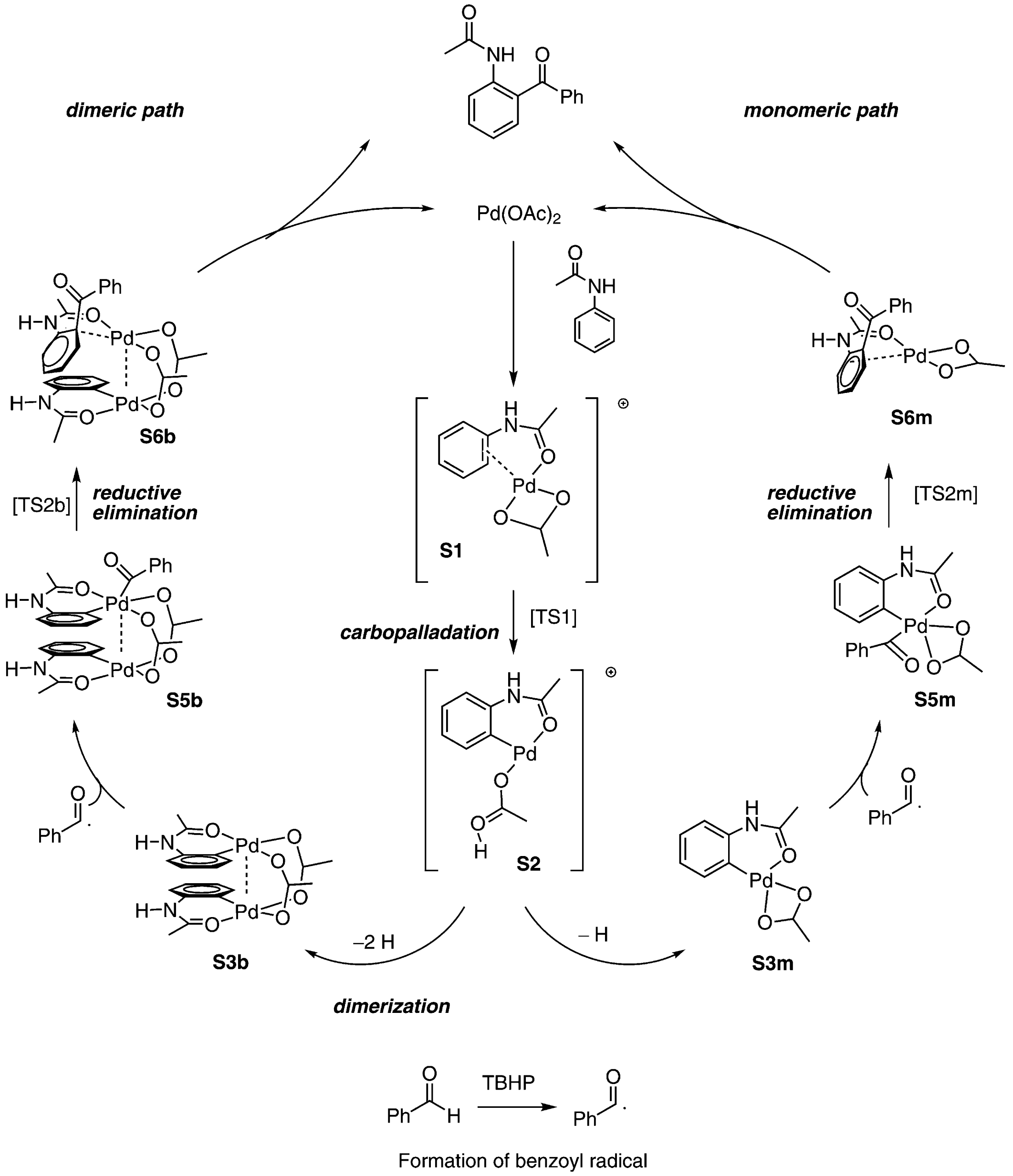
Figure 1. Gibbs free energy diagram for the calculated reaction routes.

After the carbopalladation step the monomeric palladium species S2 can be deprotonated yielding S3m and enter into its cycle or form bimetallic palladium complex S3b in a slightly endergonic dimerization step. In the further calculations the free energy profiles of the catalytic cycles based on mono- and binuclear palladium species were treated separately. Association of the benzoyl radical formed from TBHP and aldehyde[17] and the active Pd species is slightly exergonic for the mono- and endergonic for the binuclear route (S5m and S5b levels, respectively).[18] The next key step in the reaction is the rapid reductive-elimination leading to the S6 intermediates. From the S6 states we have assumed fast reaction steps leading to the products.[19]

Comparison of the two profiles shows that the binuclear pathway is more accessible than the mononuclear one. This can be attributed to the enthalpically favourable formation of the binuclear species with more flexible ligand arrangements which can overcompensate the entropic loss of the association.

We stress that a complete mechanistic view requires the consideration of other possibilities. Further experimental and computational studies are now underway in our laboratories. In particular, we will address the potential role of different Pd oxidation states in the mechanism.

In summary, a new and efficient method has been developed for direct *ortho*-acylation of anilides with aromatic aldehydes *via* C–H bond activation. This palladium-catalyzed oxidative coupling reaction was accomplished between 25-40 °C in water with the aid of an anionic surfactant, using TBHP as oxidant. We demonstrated the rate accelerating effect of long-chain anionic detergent and trifluoroacetic acid under aqueous conditions. With the support of quantum chemical calculations we compared two possible pathways and the preference of bimetallic catalysis over the monomeric route was indicated. However, our assumption regarding the mechanism needs experimental evidence, and consideration of other possible mechanistic pathways is also necessary in the future.



Scheme 2. Mechanistic alternatives proposed for the oxidative coupling of acetanilides and aldehydes.

The developed synthetic procedure has high functional group tolerance and ensures easy access to protected 2-aminobenzophenone derivatives from inexpensive and readily available starting materials. Additionally, the unique behaviour of bimetallic palladium complexes and the mild reaction conditions enable the development of other valuable synthetic tools for the functionalization of aromatic compounds through C–H activation.

Experimental Section

General Procedure

A screw-capped vial with stir bar was charged with the 5 mol% $Pd(OAc)_2$, 5 mol% SDS, acetanilide (1 mmol, 1 equiv.), and water (1 mL). TFA (20 μL, 0.26 mmol, 26 mol%) was added followed by the aldehyde (2 mmol, 2 equiv., and TBHP (250 μL, 2 mmol, 2 equiv., 70 % in H_2O). The reaction vessel was closed, and the reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was washed with EtOAc. The organic phase was washed with water, dried over magnesium sulfate, and concentrated. The crude product was purified with column chromatography (hexane/EtOAc).

Acknowledgements

This project was supported by the "Lendület" Research Scholarship of the Hungarian Academy of Sciences and by OTKA-NKTH (CK 80763), OTKA K-101115 and TÉT 10-1-2011-0245. The help of Prof. K. Torkos and Dr Zs. Eke for providing the necessary analytical background is gratefully acknowledged.

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[13] For time-conversion graphs, see Supporting Information.

[14] Based on the prices of a chemical supplier Pd(OTFA)$_2$ costs 3 times more than Pd(OAc)$_2$ calculating with 1 mol of palladium.

[15] Calculations have been carried out with the G09 package, applying M06/6-31+G* method (LanL2DZ with additional diffuse and polarization functions on Pd) and the SMD water solvent model. Optimizations were done in the gas phase, the solvent model was applied in perturbative manner. Further details and the XYZ coordinates of the calculated species are listed in the Supporting Information.

[16] Due to the presence of benzoyl radical and the supposed SET mechanism we have taken into consideration both monometallic and bimetallic pathways.

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[18] Due to the endergonic step from S3b to S5b we suppose the addition of only one benzoyl radical to the bimetallic complex. Addition of second radical would be entropically less favourable.

[19] Calculated structures of TS1, TS2m and TS2b can be found in the Supporting Information.

8 Mild Palladium-Catalyzed Oxidative Direct *ortho*-C–H Acylation of Anilides under Aqueous Conditions

Adv. Synth. Catal. **2013**, *355*, 1 – 8

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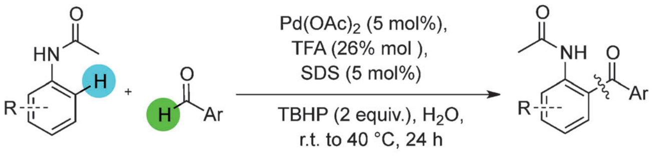

- coupling at r.t. to 40°C
- aqueous medium
- under air
- rate acceleration by detergent
- quantum chemical studies
- 31 examples
- up to 98% yield