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Palladium-catalyzed direct oxidative *ortho*-acylation of anilides with toluene derivatives

Jianquan Weng *, Zhiqin Yu, Xinghai Liu, Guofu Zhang *

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China

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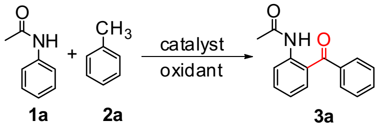
ABSTRACT

Direct oxidative *ortho*-acylation reaction of anilides with toluene derivatives in the presence of palladium acetate using *tert*-butyl hydroperoxide as an oxidant was developed. A broad range of diaryl ketones was obtained in good to excellent yields (up to 95%). The plausible mechanism was also proposed.

Transition-metal-catalyzed C–H functionalization has attracted much attention in recent years.[1] Amongst transition-metal-catalyzed cross-coupling reactions, the direct acylation has emerged as an appealing alternative to the traditional Friedel–Crafts acylation reaction.[2–6] In this content, the aryl C–H bond was coupled efficiently with a series of oxygen-containing acylation reagents, such as aldehydes,[2,4] α-oxocarboxylic acids,[5] and alcohols,[6] to afford aryl ketone compounds which are significant building blocks found in biologically active molecules, pharmaceuticals, and organic functional materials.[7] Recently, much attention has been focused on the oxidation of sp^3 C–H bond. Specially, the oxidation of benzylic C–H bond catalyzed by metallic copper and cobalt catalysts, or organocatalysis could efficiently generate aryl aldehydes, ketones, and aryl carboxylic acids.[8] We thus envisioned that the direct benzoylation of aryl C–H bonds might be realized by using toluene derivatives as acylation reagents, through in situ oxidation and generation of benzaldehydes. Herein, we report a direct benzoylation reaction of anilides to synthesize diaryl ketone compounds by using $Pd(OAc)_2$ as catalyst and *tert*-butyl hydroperoxide (TBHP) as oxidant.

Initially, acetanilide (**1a**) and toluene (**2a**) were selected as model substrates and the reaction was carried out in toluene at 95 °C with 5 mol % $Pd(OAc)_2$ as catalyst and *tert*-butyl hydroperoxide (TBHP, 6 equiv, 70% solution in water) as oxidant (Table 1). To our delight, 37% yield of the desired product *N*-(2-benzoylphenyl)acetamide (**3a**) was isolated in 12 h (entry 1). Different palladium source was then tested and the reaction catalyzed by $Pd(TFA)_2$ gave

Table 1
Reaction optimization[a]



Entry	Cat. (mol %)	Oxidant (equiv)	Solvent	Temp (°C)	Yield (%)
1	$Pd(OAc)_2$ (5)	TBHP (6)	Toluene	95	37
2	$Pd(OAc)_2$ (5)	TBHP (6)	Toluene	75	12
3	$Pd(OAc)_2$ (5)	TBHP (6)	Toluene	115	34
4	$Pd(OAc)_2$ (5)	TBHP (6)	Toluene	135	13
5	$Pd(TFA)_2$ (5)	TBHP (6)	Toluene	95	30
6	$PdCl_2$ (10)	TBHP (6)	Toluene	95	Trace
7	CuBr (10)	TBHP (6)	Toluene	95	0
8	CuI (10)	TBHP (6)	Toluene	95	0
9	$FeCl_2$ (10)	TBHP (6)	Toluene	95	0
10	$Pd(OAc)_2$ (5)	DTBP (6)	Toluene	95	0
11	$Pd(OAc)_2$ (5)	$(NH_4)_2S_2O_8$ (6)	Toluene	95	0
12[b]	$Pd(OAc)_2$ (5)	TBHP (6)	DCE	95	Trace
13[b]	$Pd(OAc)_2$ (5)	TBHP (6)	PhCl	95	Trace
14[b]	$Pd(OAc)_2$ (5)	TBHP (6)	^{t}BuOH	95	Trace
15[b]	$Pd(OAc)_2$ (5)	TBHP (6)	CH_3CN	95	Trace
16	$Pd(OAc)_2$ (10)	TBHP (12)	Toluene	95	68
17	$Pd(OAc)_2$ (15)	TBHP (12)	Toluene	95	82
18	$Pd(OAc)_2$ (20)	TBHP (12)	Toluene	95	94

[a] Reactions and conditions: acetanilide (**1a**, 1.0 mmol), toluene (**2a**, 3 mL), 12 h, isolated yields.
[b] Solvent (3 mL), toluene (5.0 mmol).

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* Corresponding authors. Tel./fax: +86 571 88320147.
E-mail addresses: jqweng@zjut.edu.cn (J. Weng), gfzhang@zjut.edu.cn (G. Zhang).

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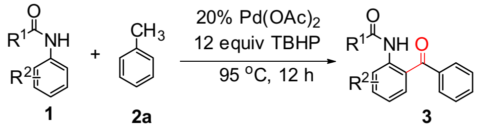
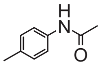
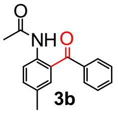
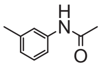
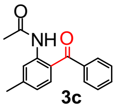
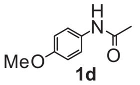
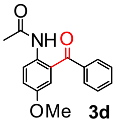
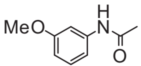
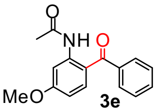
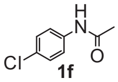
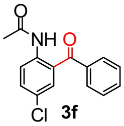
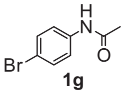
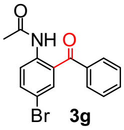
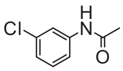
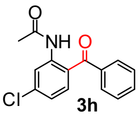
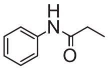
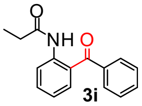
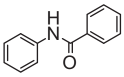
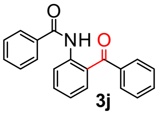
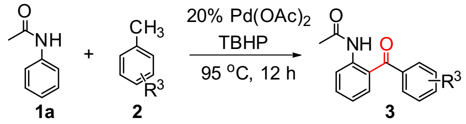
Table 2
Acylation of anilides with toluene[a]

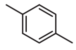
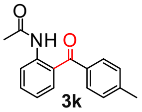
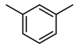
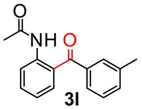
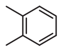
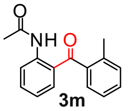
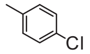
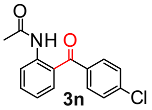
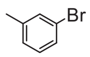
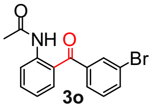


Entry	Anilide	Product	Yield (%)
1	 **1b**	 **3b**	90
2	 **1c**	 **3c**	87
3	 **1d**	 **3d**	86
4	 **1e**	 **3e**	95
5	 **1f**	 **3f**	15
6	 **1g**	 **3g**	24
7	 **1h**	 **3h**	27
8	 **1i**	 **3i**	83
9	 **1j**	 **3j**	78

[a] Reactions and conditions: anilide (**1**, 1.0 mmol), toluene (**2a**, 3.0 mL), Pd(OAc)$_2$ (20 mol %), TBHP (12.0 equiv), 95 °C, 12 h under aerobic condition, isolated yields.

Table 3
Acylation of acetanilide with toluene derivatives[a]



Entry	Tolune	Product	Yield (%)
1	 **2b**	 **3k**	93 (62[b])
2	 **2c**	 **3l**	87
3	 **2d**	 **3m**	83
4	 **2e**	 **3n**	90
5	 **2f**	 **3o**	17

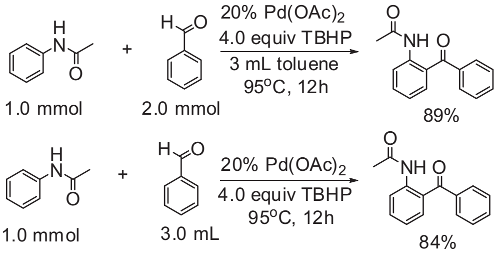
[a] Reactions and conditions: acetanilide (**1a**, 1.0 mmol), toluene (**2**, 3.0 mL), Pd(OAc)$_2$ (20 mol %), TBHP (16.0 equiv), 95 °C, 12 h under aerobic condition, isolated yields.

[b] Oxidant: TBHP (12.0 equiv).

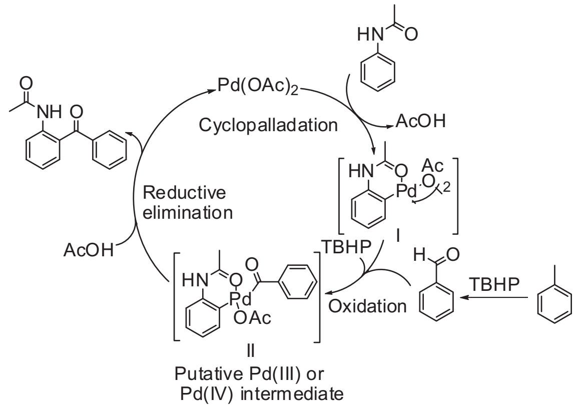
a comparable yield (entry 5), while PdCl$_2$ was completely inefficient (entry 6). No product was detected when CuBr, CuI, and FeCl$_2$ were used as catalysts (entries 7–9) and di-*tert*-butyl peroxide (DTBP), $(NH_4)_2S_2O_8$ were used as oxidants instead of TBHP (entries 10–11). The reaction was fully suppressed when using 5 equiv of toluene in 1,2-dichloroethane (DCE), chlorobenzene (PhCl), ^{t}BuOH, and CH_3CN solvent (entries 12–15). Finally, it was found that the yield could be remarkably improved by increasing both the catalyst loading and the amount of oxidant (entries 16–18), and 94% isolated yield of the product was obtained in the presence of 12 equiv of TBHP and 20 mol % Pd(OAc)$_2$.

With the optimized conditions in hand, the scope of anilides was explored. As shown in Table 2, the substrates bearing electron-donating groups in the *para*- or *meta*-position of phenyl rings of anilides reacted smoothly to give diaryl ketones in good to excellent yields (**3b**–**e**), while significant lower yields were observed for the substrates possessing halides (**3f**–**h**). Unfortunately, when anilides with *ortho*-substituent (such as methyl-, methoxyl-, and chloro-) were employed as substrates, no corresponding compounds were detected owing to the steric effect. Besides the acetyl group, propionyl and benzoyl are suitable protecting groups and the reactions of **1i** and **1j** gave considerable yields of the corresponding products. In addition, other groups substituted anilides (such as *N*-(naphthalen-1-yl)acetamide, *N*-(biphenyl-4-yl)acetamide, *N*-(4-fluorophenyl)acetamide, *N*-(3,5-dichlorophenyl)acetamide, and *N*-(4-nitrophenyl)acetamide) were also investigated, but no corresponding compounds were detected.

Toluene derivatives were then investigated and the results were shown in Table 3. When *para*-xylene was used, the desired product (**3k**) was obtained in 62% yield under the optimal conditions. By increasing the amount of oxidant to 16.0 equiv, the yield was improved to 93%. Under the modified conditions, only mono-acylated



Scheme 1. Palladium catalyzed *ortho*-acylation of anilide with benzaldehyde.



Scheme 2. Plausible mechanism of acylation between acetanilide and toluene.

products were isolated in good to excellent yields when employing *para*-, *meta*-, and *ortho*-xylenes as substrates. Good yield was also observed for the reaction of 4-chlorotoluene, but low yield was for 3-bromotoluene. Noteworthy, the reactions of methylated heteroaromatic compounds (2-methylfuran, 2-methylthiophene, 2-methylpyridine, 3-methylpyridine, and 4-methylpyridine) failed to give the corresponding products.

To probe the mechanism of this reaction, benzaldehyde was employed as acylating reagent to react with acetanilide in the presence of 20% palladium acetate by using 4.0 equiv of TBHP as oxidant. When toluene was used as solvent, the corresponding diaryl ketone was obtained in 89% yield. If benzaldehyde was used as solvent instead of toluene, the desired product was also obtained in 84% yield (Scheme 1). The phenomenon was consistent with the reports by Li and others.[4]

On the basis of the above results and the earlier references reported,[4] a tentative mechanism of this transformation was depicted in Scheme 2. The oxidation of toluene produced benzaldehyde, which was detected in the reaction system and was consistent with the observation by Dismukes.[8d] So the sp^3 C–H bonds of toluene could be oxidized in situ to give benzaldehyde by *tert*-butyl hydroperoxide as oxidizing reagent and subsequently reacted with palladacycle intermediate I[9] (formed through C–H functionalization of anilide) to generate intermediate II.[10] Followed by reductive elimination of II, the desired product was obtained. After regeneration of the catalyst Pd(OAc)$_2$, catalytic cycle was fulfilled.

In conclusion, we have developed a novel approach in the synthesis of diaryl ketone via palladium-catalyzed direct oxidative *o*-acylation of anilides by using commercially available toluenes as acylation reagents. Good to excellent yields were observed in the reactions. Further extension of this methodology to other acylation reaction is ongoing in the lab.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.059.

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