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C–H Functionalization

Palladium-Catalyzed Regioselective Acylation of Diazines with Toluenes: A New Approach to the Synthesis of *ortho*-Diacylbenzenes

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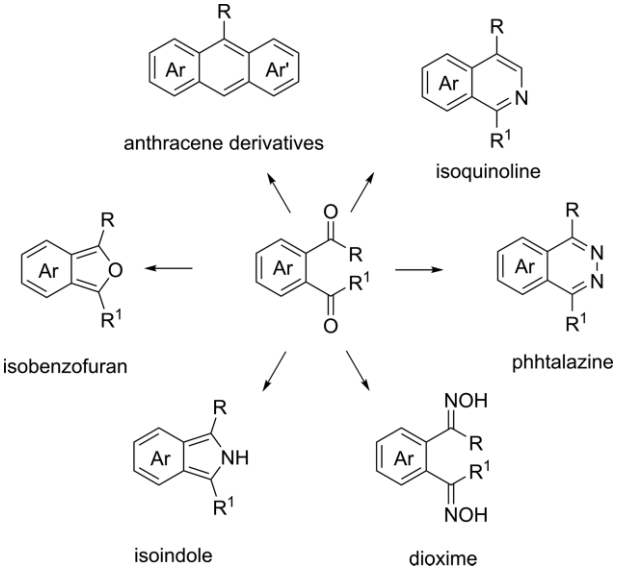
Abstract: A highly efficient and practical procedure for chemo- and regioselective synthesis of *ortho*-diacylbenzenes through Pd-catalyzed oxidative C–H bond activation has been developed. Using this method, a variety of *ortho*-diacylbenzenes were prepared in moderate to good yields, by direct acylation of diazines with toluene derivatives as acylation source. *Ortho*-diacylbenzenes may be used as precursors in synthesis of pharmaceuticals and agrochemicals.

Introduction

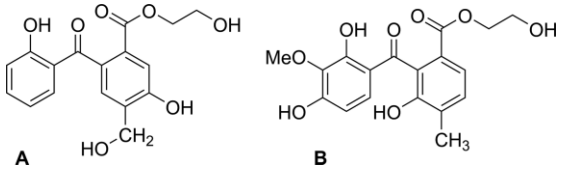
Aryl ketones are crucial precursors for synthesis of many pharmaceuticals and natural products.[1,2] For instance, benzophenone derivatives are proven to be of use in treating immune deficiency disease.[3] Markably, *ortho*-diacylbenzenes are important intermediates for the synthesis of biologically and pharmaceutically active compounds, such as phthalazines,[4] dioximes,[5] isoindoles,[6] isobenzofurans,[7] isoquinolines, anthracene derivatives,[8] indanones and isoindolines[9] (Scheme 1). *Ortho*-diacylbenzenes are also used as fluorescent reagents for amino acids and peptide analysis.[10]

Furthermore, the *ortho*-diacylbenzene structural motif is present at the core of pharmaceuticals e.g. morintrifolin A (**A**) and morintrifolin B (**B**) (Scheme 2). It has been shown that this class of compound exhibits a broad range of useful pharmacological effects, e.g. QR enzyme induction (cancer chemoprevention).[11]

Due to the need for efficient ways to synthesize more elaborate structures possessing biological activity, the development of novel and convenient methods for the preparation of *ortho*-diacylbenzene derivatives is of considerable importance in organic chemistry and numerous synthetic methodologies for the construction of this class of compound have been developed over past decades. The Friedel Crafts reaction is the classic method for the acylation reaction, but it suffers from harsh reaction conditions, low regioselectivity, and limited functional group tolerance. This method is more challenging for the synthesis of *ortho*-diacylbenzenes since the acyl groups are deactivating and *meta*-directing groups. Non-availability and handling difficulty of the reagents are some of the other disadvantages.



Scheme 1. *ortho*-Diacylbenzenes can be used as precursors for the synthesis of various chemicals.



Scheme 2. Bioactive compounds with potential medical applications.

Oxidation of 1,3-diarylisobenzofurans to *ortho*-diacylbenzenes with lead tetra-acetate was reported by Newman in 1961 (Scheme 3, Equ. 1).[12] A Diels-Alder reaction between diacylethylene and butadiene was reported by Goldschmidt in 1961. The reaction leads to the formation of 1,2-diacyl-4-cyclohexene

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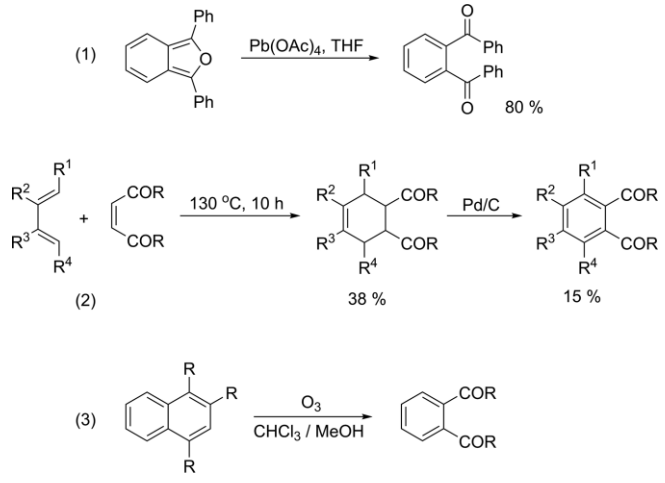
which can afford the desired *ortho*-diacylbenzene derivatives in the presence of Pd/C (Scheme 3, Equ. 2).[13] Another classic method for synthesizing *ortho*-diacylbenzenes is ozonolysis of naphthalenes which was reported by Ito in 1984. The reaction was conducted in various solvents and the best result was obtained in chloroform/methanol (Scheme 3, Equ. 3).[14]



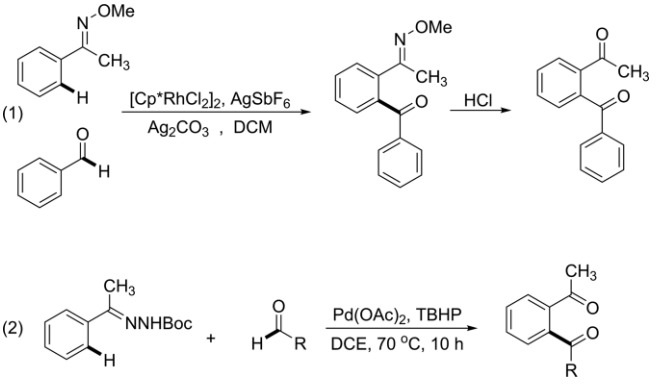
Scheme 3. Classic methods for the synthesis of *ortho*-diacylbenzenes.

For more efficient and greener methods to construct C–C bonds, recent attention has been focused on direct C–H functionalization.[15] This strategy is more appealing when it comes to choosing two un-functionalized materials with two different C–H bonds (CDC reactions) which makes synthetic routes shorter, more efficient, easier and provides a straightforward and economical approach for new C–C bond construction.[16] Synthesis of *ortho*-diacylbenzenes from acylbenzenes via a transition metal-catalyzed C–H bond activation strategy is challenging because the acyl groups are considered to be weak directing groups.

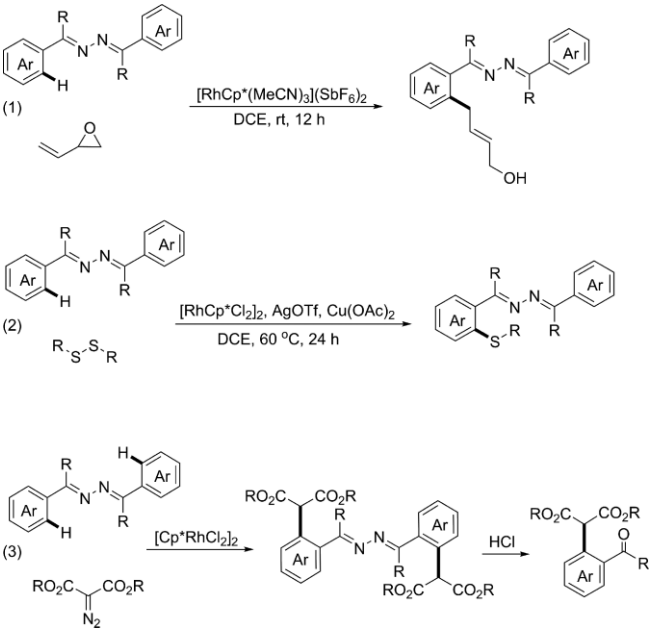
A rhodium-catalyzed cross coupling reaction of aryl ketone *O*-methyl oximes with aldehydes for direct acylation of sp^2 C–H bonds was reported by Zhou in 2012 which can provide a new route to *ortho*-diacylbenzenes after deprotection of the oxime moiety (Scheme 4, Equ. 1).[17] A Pd(II)-catalyzed direct C–H bond acylation of *N*-BoC–Hydrazones with aldehydes was reported by Sharma in 2013 as a one-pot synthesis of 1,2-diacylbenzenes which removes the need for an additional deprotection step (Scheme 4, Equ. 2).[9a]

Recently, a few examples have been appeared in the literature for direct C–H bond functionalization starting with ketazines as the substrates. Namely, a Rhodium(III)-catalyzed coupling of aromatic ketazines with 2-vinyloxirane via C–H activation was reported by Zhu in 2015 (Scheme 5, Equ. 1).[18] Also, a Rhodium(III)-catalyzed directed *ortho*-C–H bond functionalization of aromatic ketazines via C–S and C–C coupling was reported by the same group in 2015 (Scheme 5, Equ. 2).[19] Cui reported a regioselective method for *ortho*-C–H carbenoid insertion to ketazines in 2017 (Scheme 5, Equ. 3).[20]

As part of our ongoing interest to explore C–C bond formations through CDC reactions, herein we report an efficient and highly regioselective procedure for acylation of ketazines with

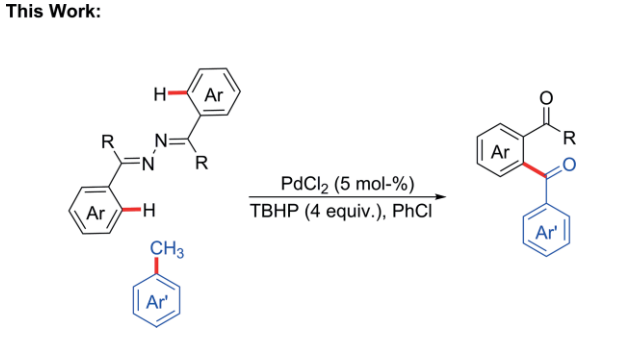


Scheme 4. Cross coupling reactions for synthesis of *ortho*-diacylbenzenes.



Scheme 5. Coupling reactions of aromatic ketazines.

toluenes as a low toxic, stable, and commercially available acylating agent.[21] This method provides a new approach to diacylbenzenes with high atom economy and without the need for an extra step for removing the azine moiety (Scheme 6).



Scheme 6. Acylation of ketazines with toluenes.

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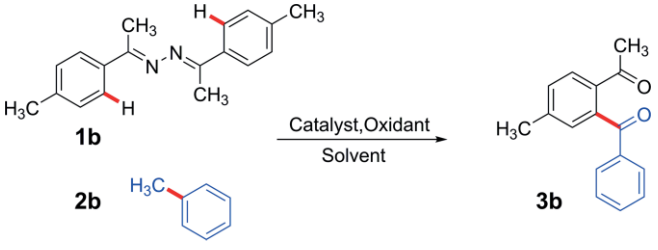
Results and Discussion

Our initial attempt toward this aim was started by an investigation of the reaction between (1*E*,2*E*)-1,2-bis[1-(*p*-tolyl)ethylidene]hydrazine (**1b**) and toluene as the model reaction. To optimize the reaction parameters, the effects of different factors e.g. catalysts, additives, solvents and temperature were examined (Table 1). The initial trial gave desired product **3b** in 83 % yield with 5 mol-% of $PdCl_2$ as the catalyst (Table 1, entry 1). An increase in catalyst loading to 10 mol-% did not improve the reaction efficiency (Table 1, entry 2). Other catalysts such as $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2(COD)$, were employed, but there was no increase in the yield. As shown in Table 1, the use of some other copper and ruthenium catalysts provided unsatisfying results (Table 1, entries 6–10).

Table 1. Optimization of the reaction conditions.



Entry	Catalyst [mol-%]	Oxidant (equiv.)	Solvent	Temp [°C].	Yield[a] [%]
1	**$PdCl_2$ (5)**	**TBHP(4)**	**PhCl**	**140**	**83**
2	$PdCl_2$ (10)	TBHP(4)	PhCl	140	74
3	$Pd(OAc)_2$ (5)	TBHP(4)	PhCl	140	40
4	$Pd_2(dba)_3$ (5)	TBHP(4)	PhCl	140	37
5	$PdCl_2(COD)$ (5)	TBHP(4)	PhCl	140	22
6	CuI (5)	TBHP(4)	PhCl	140	trace
7	CuCl (5)	TBHP(4)	PhCl	140	trace
8	$NiBr_2$ (5)	TBHP(4)	PhCl	140	trace
9	$Ni(OAc)_2$ (5)	TBHP(4)	PhCl	140	trace
10	$[Ru(p\text{-cymene})Cl_2]_2$ (5)	TBHP(4)	PhCl	140	trace
11	–	TBHP(4)	PhCl	140	0
12	$PdCl_2$ (5)	–	PhCl	140	0
13	$PdCl_2$ (5)	TBHP(1)	PhCl	140	trace
14	$PdCl_2$ (5)	TBHP(2)	PhCl	140	42
15	$PdCl_2$ (5)	TBHP(3)	PhCl	140	55
16	$PdCl_2$ (5)	TBHP(4)	CH_3CN	140	74
17	$PdCl_2$ (5)	TBHP(4)	DCE	140	41
18	$PdCl_2$ (5)	TBHP(4)	PhCl	120	62
19	$PdCl_2$ (5)	TBHP(4)	PhCl	100	46
20	$PdCl_2$ (5)	TBHP(4)	PhCl	80	trace
21	$PdCl_2$ (5)	TBHP(4)	PhCl	60	trace

[a] Reaction conditions: **1b** (0.3 mmol), **2b** (0.6 mmol), oxidant [equiv.], catalyst [mol-%], solvent (1.0 mL) at given temperatures for 18 h.

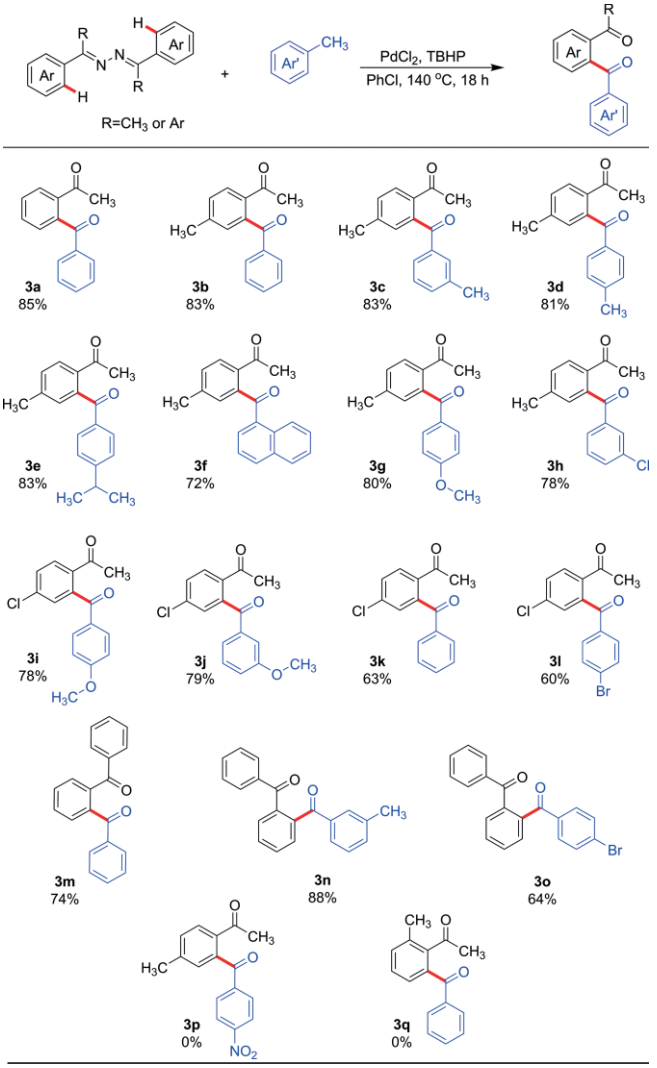
Decreasing the temperature from 140 to 100 °C lowered the reaction yield to 46 %, further decrease in temperature further decreased the yield (Table 1, entries 1, 19–21). A variety of solvents were also examined. As a result, chlorobenzene, which gave the product in 83 % yield, was selected as the best solvent among CH_3CN, 1,2-dichloroethane (DCE), dimethyl sulfoxide (DMSO) dimethylformamide (DMF), toluene and diglyme (Table 1, entries 1, 16, 17).

Subsequent screening of a range of various oxidants revealed that TBHP performed the best in comparison with other oxidants, including DTBP, H_2O_2, $K_2S_2O_8$ and cumene peroxide. The optimum amount of oxidant for the reaction was 4.0 equiv. (Table1, entries 1, 13–15).

We also checked the reaction using acetophenone and toluene in the presence of a catalytic amount of hydrazinium hydroxide to provide a transient directing group in situ but unfortunately the desired product was not obtained.

With the optimized reaction conditions identified, a range of acetophenone diazines were subjected to this protocol (Table 2). Substituted substrates bearing both electron-donating and electron-withdrawing groups were all well tolerated and gave the desired products (**3a**–**3l**) in moderate to good yields. Electron-donating groups such as methyl and methoxy groups on ketazine and toluene substrates were highly effective in this method and gave the desired products in higher yields. Substrates with electron-withdrawing groups such as halogens performed the reaction smoothly to give the desired products in lower yields although the reaction was not successful with

Table 2. Scope of direct acylation of diazines.



[a] Reaction Conditions: Ketazine (0.3 mmol), Toluene (0.6 mmol), $PdCl_2$ (5.0 mol-%), TBHP (1.2 mmol), PhCl (1.0 mL), 140 °C, 18 h.

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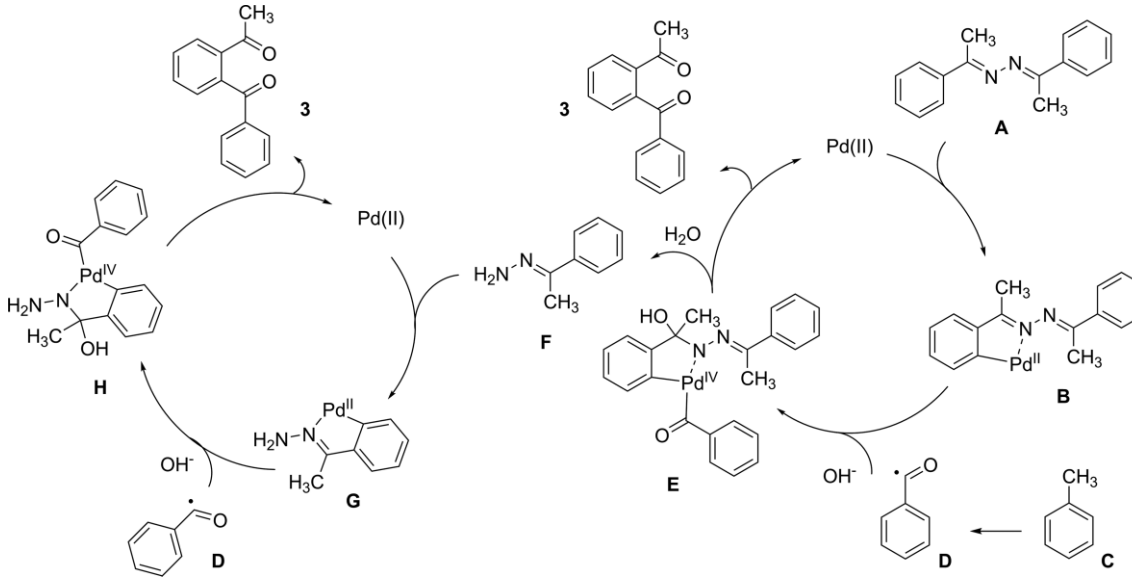
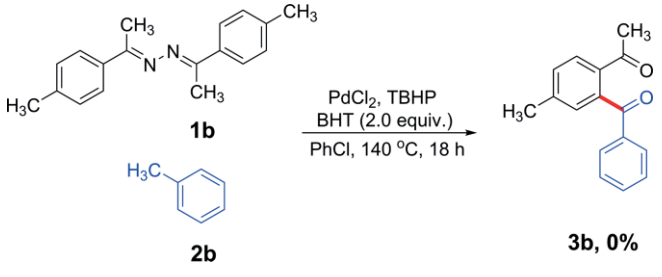


Scheme 7. A plausible mechanism.

the strong electron-withdrawing nitro group on either the ketazine or the toluene substrate (**3p**). Ketazines derived from benzophenone derivatives, successfully reacted under the optimal reaction conditions and gave the desired products in good yields (**3m**–**3o**).

Unfortunately, 2-substituted acetophenone azines did not lead to the corresponding products under the standard reaction conditions (**3q**).

On the basis of previous mechanistic reports[9a] a plausible mechanism for the reaction is illustrated in Scheme 7. Initially, a metalation reaction occurs preferentially at the C2-position of the ketazine aryl ring which leads to the formation of palladacycle **B**. Radical intermediate **D** is generated in-situ by hydrogen-atom abstraction from toluene under the reaction conditions. Next, coordination of palladium complex **B** with radical **D** followed by addition of water or hydroxyl anion to imine bond gives Pd(IV) intermediate **E**, which undergoes C–N bond disconnection and reductive elimination at Pd(IV) center to afford the desired product **3** and hydrazone intermediate **F**. This intermediate is involved in a similar acylation cycle to produce the desired product **3**. To prove the radical mechanism, a control reaction that involves the use of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger was performed. When **1b** was treated in the presence of butylated hydroxytoluene (2.0 equiv.), no desired product **3b** was observed (Scheme 8).



Scheme 8. Control experiment.

Conclusion

We have explored an efficient method for the synthesis of *ortho*-diacylbenzenes with toluenes as aroyl surrogates. The reaction is applicable to numerous substrates with good tolerance of various functional groups, and it provides a new approach for *ortho*-acylation of aryl ketones. The reaction products are interesting compounds for research into pharmaceuticals and agrochemicals.

Experimental Section

General

All commercially available chemicals and reagents were purchased from Merck or Sigma or commercial distributors and were used without further purification. Ketone azines were synthesized according to the literature. Analytical thin layer chromatography (TLC) was performed on precoated silica gel60 F254 plates. The products were purified by preparative column chromatography on silica gel (0.063–0.200 mm, Merck). ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on an Inova Varian 500 Advanced instrument in $CDCl_3$ or [D_6]DMSO. Electron ionization (EI) mass spectra were obtained using an Agilent 5975C VL MSD (ion source: EI+, 70 eV, 230 °C).

General Procedure for Synthesis of *ortho*-Diacylbenzene Derivatives: A reaction vessel was charged with the diazine derivative (0.3 mmol, 1.0 equiv.), the toluene derivative (0.6 mmol, 2.0 equiv.), Palladium catalyst (0.015 mmol, 5 mol-%), TBHP (1.2 mmol, 4 equiv.), and PhCl (1 mL) in air. The reaction vessel was then sealed. The reaction mixture was allowed to stir at 140 °C for 18 h. Then, the mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was extracted with ethyl acetate and washed with an aqueous solution of $NaHCO_3$. The organic layer was dried with anhydrous $MgSO_4$, filtered and evaporated. The resulting residue was purified by column chromatography using *n*-hexane/ethyl acetate (5:1) as the mobile phase.

Spectral Data

1-(2-Benzoylphenyl)ethan-1-one (3a):[22] Black oil; yield = 85 %, 114 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 7.89 (dd, J = 7.5, 1.5 Hz, 1H), 7.76–7.72 (m, 2H), 7.65–7.57 (m, 2H), 7.56–7.51 (m, 1H), 7.41 (td, J = 7.8, 1.6 Hz, 3H), 2.52 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 199.1, 197.3, 140.5, 137.2, 137.2, 133.4, 133.1, 130.4, 130.3, 129.1, 129.0, 128.2, 27.8. Ms (EI) m/z (relative intensity) 224 (M$^+$, 8), 105 (66), 91 (16), 77 (83), 43 (100).

1-(2-Benzoyl-4-methylphenyl)ethan-1-one (3b): Brown oil; yield = 83 %, 119 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 8.02 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.6 Hz, 3H), 7.50 (d, J = 8.0 Hz, 1H), 7.48–7.43 (m, 2H), 7.20 (s, 1H), 2.48 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.3, 197.4, 143.9, 141.0, 137.3, 134.3, 133.3, 130.7, 130.6, 129.03, 129.00, 128.5, 27.5, 21.4. Ms (EI) m/z (relative intensity) 238 (M$^+$, 8), 223 (90), 105 (100), 77 (70), 43 (33). $C_{16}H_{14}O_2$ (238.28): calcd. C 80.65, H 5.92; found C 80.92, H 5.89.

1-[4-Methyl-2-(3-methylbenzoyl)phenyl]ethan-1-one (3c): Brown oil; yield = 83 %, 126 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 8.01 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.41 (d, J = 6.2 Hz, 1H), 7.37–7.31 (m, 2H), 7.19 (s, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.32 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.3, 197.4, 143.8, 141.0, 138.4, 137.4, 134.4, 134.0, 130.7, 130.6, 129.2, 128.9, 128.5, 126.5, 27.6, 21.4, 21.3. Ms (EI) m/z (relative intensity) 252 (M$^+$, 40), 237 (100), 209 (20), 161 (30), 119 (32), 91 (35), 84 (60), 66 (70). $C_{17}H_{16}O_2$ (252.31): calcd. C 80.93, H 6.39; found C 80.68, H 6.42.

1-[4-Methyl-2-(4-methylbezoyl)phenyl]ethan-1-one (3d): Reddish brown oil, yield = 81 %, 123 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 7.78 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.3 Hz, 2H), 7.35 (dd, J = 8.2, 1.7 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.17 (s, 1H), 2.47 (s, 3H), 2.43 (s, 3H), 2.38 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.3, 196.9, 143.7, 141.1, 134.9, 134.4, 130.6, 130.5, 130.1, 129.5, 129.2, 128.5, 27.6, 21.6, 21.4. Ms (EI) m/z (relative intensity) 252 (M$^+$, 11), 237 (83), 119 (100), 91 (88), 43 (33). $C_{17}H_{16}O_2$ (252.31): calcd. C 80.93, H 6.39; found C 80.70, H 6.38.

1-[2-(4-Isopropylbenzoyl)-4-methylphenyl]ethan-1-one (3e): Reddish brown oil, Yield = 83 %, 140 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 7.80 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.37 (dd, J = 7.9, 1.9 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.18 (d, J = 1.7 Hz, 1H), 2.95 (p, J = 6.9 Hz, 1H), 2.50 (s, 3H), 2.44 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.3, 196.9, 154.2, 143.7, 141.2, 135.2, 134.3, 130.7, 130.4, 129.9, 129.4, 128.5, 127.0, 126.9, 33.9, 27.6, 24.0, 23.9, 21.4. Ms (EI) m/z (relative intensity) 280 (M$^+$, 6), 265 (53), 223 (50), 161 (51), 147 (56), 118 (41), 103 (62), 91 (80), 77 (67), 43 (100). $C_{19}H_{20}O_2$ (280.36): calcd. C 81.40, H 7.19; found C 81.48, H 7.17.

1-[2-(1-Naphtoyl)-4-methylphenyl]ethan-1-one (3f): Dark red oil, yield = 72 %, 124 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 9.04 (d, J = 8.5 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 7.9 Hz, 1H), 7.69 (ddd, J = 8.5, 6.8, 1.3 Hz, 1H), 7.61–7.54 (m, 1H), 7.42–7.36 (m, 2H), 7.35–7.28 (m, 2H), 2.45 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 199.2, 199.0, 146.0, 143.4, 142.1, 135.1, 134.9, 133.9, 133.4, 131.0, 130.6, 130.5, 129.6, 128.7, 128.3, 126.9, 126.7, 124.8, 27.7, 21.4. Ms (EI) m/z (relative intensity) 288 (M$^+$, 73), 273 (100), 245 (46), 127 (82), 43 (37). $C_{20}H_{16}O_2$ (288.34): calcd. C 83.31, H 5.59; found C 83.49, H 5.63.

1-[2-(4-Methoxybenzoyl)-4-methylphenyl]ethan-1-one (3g): Blood red oil, yield = 80 %, 129 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 7.77 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.9 Hz, 2H), 7.33 (dd, J = 8.1, 2.0 Hz, 1H), 7.14 (s, 1H), 6.87 (d, J = 8.9 Hz, 2H), 3.81 (s, 3H), 2.46 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.3, 196.0, 163.4, 143.6, 141.2, 134.4, 131.4, 130.6, 130.4, 130.3, 128.5, 114.3, 55.9, 27.7, 21.4. Ms (EI) m/z (relative intensity) 268 (M$^+$, 14), 253 (100), 161 (14), 135 (42), 92 (10), 77 (14), 43 (9). $C_{17}H_{16}O_3$ (268.31): calcd. C 76.10, H 6.01; found C 76.28, H 6.03.

1-[2-(3-Chlorobenzoyl)-4-methylphenyl]ethan-1-one (3h): Brownish-red oil, Yield:78 %, 128 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 7.82 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 1.8 Hz, 1H), 7.57 (dt, J = 7.6, 1.1 Hz, 1H), 7.46 (ddd, J = 8.1, 2.1, 1.1 Hz, 1H), 7.42–7.36 (m, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.20–7.12 (m, 1H), 2.49 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.3, 196.1, 140.2, 139.3, 134.0, 133.0, 131.1, 131.0, 130.9, 130.1, 129.2, 128.5, 128.0, 127.7, 27.3, 21.4. Ms (EI) m/z (relative intensity) 274 (M + 2, 5), 272 (M$^+$, 18), 259 (38), 257 (100), 161 (22), 43 (13). $C_{16}H_{13}ClO_2$ (272.73): calcd. C 70.46, H 4.80; found C 70.63, H 4.83.

1-[4-Chloro-2-(4-methoxybenzoyl)phenyl]ethan-1-one (3i): Blood red oil, yield = 78 %, 135 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 7.82 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.8 Hz, 2H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 7.35 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 2.50 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.1, 194.2, 163.6, 142.8, 138.0, 135.6, 132.4, 131.6, 129.9, 129.7, 127.9, 114.4, 56.0, 27.9. Ms (EI) m/z (relative intensity) 290 (M + 2, 6), 288 (M$^+$, 18), 273 (73), 167 (36), 135 (100), 77 (30), 43 (26). $C_{16}H_{13}ClO_3$ (288.73): calcd. C 66.56, H 4.54; found C 66.40, H 4.51.

1-[4-Chloro-2-(3-methyoxybenzoyl)phenyl]ethan-1-one (3j): Blood red oil, yield = 79 %, 137 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 8.15 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 8.4, 2.2 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.42–7.33 (m, 1H), 7.26–7.17 (m, 2H), 7.06 (d, J = 7.7 Hz, 1H), 3.33 (s, 3H), 2.52 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 197.9, 195.3, 159.8, 142.5, 138.25, 138.19, 135.5, 132.5, 130.3, 130.2, 128.0, 122.1, 119.5, 113.3, 55.7, 27.7. Ms (EI) m/z (relative intensity) 290 (M + 2, 21), 288 (M$^+$, 73), 273 (100), 181 (53), 183 (16), 135 (86), 107 (53), 92 (45), 77 (66), 43 (60). $C_{16}H_{13}ClO_3$ (288.73): calcd. C 66.56, H 4.54; found C 66.75, H 4.58.

1-(2-Benzoyl-4-chlorophenyl)ethan-1-one (3k):[9a] Red oil, yield = 63 %, 98 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 8.14 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.4, 2.1 Hz, 1H), 7.63–7.57 (m, 3H), 7.52 (d, J = 2.0 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.0, 195.6, 142.6, 138.3, 136.8, 135.4, 133.6, 132.5, 130.1, 129.13, 129.09, 128.0, 27.6. Ms (EI) m/z (relative intensity) 260 (M + 2, 9), 258 (M$^+$, 21), 243 (28), 153 (34), 105 (100), 77 (73), 43 (35).

1-[2-(4-Bromobenzoyl)-4-chlorophenyl]ethan-1-one (3l): Dark red oil, yield = 60 %, 121 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 8.16 (d, J = 8.4 Hz, 1H), 7.79 (dd, J = 8.4, 2.2 Hz, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 2.1 Hz, 1H), 7.53 (d, J = 8.5 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 198.9, 193.8, 134.6, 132.3, 131.7, 131.0, 130.3, 127.9, 125.9, 125.2, 123.5, 111.1, 27.6. Ms (EI) m/z (relative intensity) 340 (M + 4, 23), 338 (M + 2, 84), 336 (M$^+$, 68), 325 (23), 323 (61), 321(53), 292 (15), 229 (42), 212 (38), 194 (69), 176 (46), 167 (100), 112 (11), 105 (34), 75 (65), 50 (36), 43 (39). $C_{15}H_{10}BrClO_2$ (337.60): calcd. C 53.37, H 2.99; found C 53.51, H 2.96.

1,2-Phenylenebis(phenylmethanone) (3m):[22] Brown oil, yield = 74 %, 127 mg. ^{1}H NMR ([D]Chloroform, 500 MHz): δ (ppm) 7.73–7.69 (m, 4H), 7.64–7.59 (m, 4H), 7.54–7.49 (m, 1H), 7.40–7.34 (m, 4H), 7.26 (s, 1H). ^{13}C NMR ([D]Chloroform, 126 MHz): δ (ppm) 196.6, 140.0, 137.2, 133.0, 130.4, 129.8, 129.7, 128.4. Ms (EI) m/z (relative intensity) 286 (M$^+$, 60), 209 (100), 152 (75), 105 (75), 77 (100), 51 (56).

(2-Benzoylphenyl)(*m*-tolyl)methanone (3n): Dull red oil, yield = 88 %, 159 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 7.75–7.66 (m, 4H), 7.64–7.57 (m, 3H), 7.49–7.43 (m, 4H), 7.38 (d, J = 7.5 Hz, 1H),

7.35–7.29 (m, 1H), 2.26 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 196.4, 196.3, 139.9, 139.7, 138.4, 137.1, 137.0, 134.3, 133.7, 131.3, 131.1, 130.2, 130.0, 129.93, 129.92, 129.0, 128.9, 127.2, 21.2. Ms (EI) *m/z* (relative intensity) 300 (M$^+$, 96), 285 (7), 223 (92), 209 (100), 165 (38), 152 (53), 119 (76), 105 (69), 91 (69), 77 (76), 65 (26), 51 (23), 43 (7). $C_{12}H_{16}O_2$ (300.35): calcd. C 83.98, H 5.37, found C 83.71, H 5.40.

(2-Benzoylphenyl)(4-bromophenyl)methanone (3o): Dull brown oil, yield = 64 %, 140 mg. ^{1}H NMR ([D$_6$]DMSO, 500 MHz): δ (ppm) 7.74 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 3H), 7.64 (dd, *J* = 5.6, 3.1 Hz, 3H), 7.60 (d, *J* = 8.4 Hz, 3H), 7.47 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR ([D$_6$]DMSO, 126 MHz): δ (ppm) 196.3, 195.5, 139.5, 139.4, 136.9, 136.1, 133.8, 132.2, 131.8, 131.4, 130.2, 129.9, 129.1, 127.9. Ms (EI) *m/z* (relative intensity) 366(M + 2, 23), 364 (M$^+$, 23), 289 (42), 287 (42), 230 (20), 223 (60), 209 (100), 152 (57), 119 (28), 105 (85), 91 (28), 77 (85), 43 (8). $C_{20}H_{13}BrO_2$ (365.22): calcd. C 65.77, H 3.59; found C 65.62, H 3.62.

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Keywords: Cross-coupling reactions · C–H activation · Acylation · Palladium · *ortho*-Diacylbenzenes

[1] K. R. Romines, G. A. Freeman, L. T. Schaller, J. R. Cowan, S. S. Gonzales, J. H. Tidwell, C. W. Andrews, D. K. Stammers, R. J. Hazen, R. G. Ferris, *J. Med. Chem.* **2006**, *49*, 727–739.
[2] H. Surburg, J. Panten, *Common fragrance and flavor materials: preparation, properties and uses*, John Wiley & Sons, **2016**.
[3] P. G. Wyatt, R. C. Bethell, N. Cammack, D. Charon, N. Dodic, B. Dumaitre, D. N. Evans, D. V. S. Green, P. L. Hopewell, *J. Med. Chem.* **1995**, *38*, 1657–1665.
[4] S. Nan'ya, H. Ishida, K. Kanie, N. Ito, Y. Butsugan, *J. Heterocycl. Chem.* **1995**, *32*, 1299–1302.
[5] A. Kotali, *Org. Mass Spectrom.* **1991**, *26*, 889–891.
[6] S. Nan'ya, T. Fujii, Y. Butsugan, *J. Heterocycl. Chem.* **1990**, *27*, 1407–1408.
[7] J. Jacq, C. Einhorn, J. Einhorn, *Org. Lett.* **2008**, *10*, 3757–3760.
[8] R. Sivasakthikumaran, M. Nandakumar, A. K. Mohanakrishnan, *J. Org. Chem.* **2012**, *77*, 9053–9071.
[9] a) S. Sharma, A. Kim, J. Park, M. Kim, J. H. Kwak, Y. H. Jung, J. S. Park, I. S. Kim, *Org. Biomol. Chem.* **2013**, *11*, 7869–7876; b) A. Kotali, P. A. Harris, *Org. Prep. Proced. Int.* **2003**, *35*, 583–601.
[10] a) M. Roth, *Anal. Chem.* **1971**, *43*, 880–882; b) L. A. Sternson, J. F. Stobaugh, A. J. Repta, *Anal. Biochem.* **1985**, *144*, 233–246; c) H. Ebrahim, K. Dakshinamurti, *Anal. Biochem.* **1986**, *154*, 282–286; d) S. C. Beale, J. C. Savage, D. Wiesler, S. M. Wietstock, M. Novotny, *Anal. Chem.* **1988**, *60*, 1765–1769.
[11] Y. Deng, Y.-W. Chin, H. Chai, W. J. Keller, A. D. Kinghorn, *J. Nat. Prod.* **2007**, *70*, 2049–2052.
[12] M. S. Newman, *J. Org. Chem.* **1961**, *26*, 2630–2633.
[13] S. Goldschmidt, A. Zoebelein, *Chem. Ber.* **1961**, *94*, 169–173.
[14] Y. Ito, A. Matsuura, T. Matsuura, *J. Org. Chem.* **1984**, *49*, 4300–4302.
[15] J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761.
[16] a) S. A. Girard, T. Knauber, C. J. Li, *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; *Angew. Chem.* **2014**, *126*, 76; b) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344.
[17] Y. Yang, B. Zhou, Y. Li, *Adv. Synth. Catal.* **2012**, *354*, 2916–2920.
[18] J. Wen, A. Wu, Y. Miao, J. Zhu, *Tetrahedron Lett.* **2015**, *56*, 5512–5516.
[19] J. Wen, A. Wu, M. Wang, J. Zhu, *J. Org. Chem.* **2015**, *80*, 10457–10463.
[20] Y. Yu, C. Kuai, R. Chauvin, N. Tian, S. Ma, X. Cui, *J. Org. Chem.* **2017**, *82*, 8611–8616.
[21] a) Z. Yin, P. Sun, *J. Org. Chem.* **2012**, *77*, 11339–11344; b) Y. Wu, P. Y. Choy, F. Mao, F. Y. Kwong, *Chem. Commun.* **2013**, *49*, 689–691; c) F. Xiong, C. Qian, D. Lin, W. Zeng, X. Lu, *Org. Lett.* **2013**, *15*, 5444–5447; d) Z. Xu, B. Xiang, P. Sun, *RSC Adv.* **2013**, *3*, 1679–1682; e) H. Song, D. Chen, C. Pi, X. Cui, Y. Wu, *J. Org. Chem.* **2014**, *79*, 2955–2962; f) Y. Wu, L.-J. Feng, X. Lu, F. Y. Kwong, H.-B. Luo, *Chem. Commun.* **2014**, *50*, 15352–15354; g) Y.-F. Liang, X. Li, X. Wang, Y. Yan, P. Feng, N. Jiao, *ACS Catal.* **2015**, *5*, 1956–1963.
[22] P.-Y. Lee, P. Liang, W.-Y. Yu, *Org. Lett.* **2017**, *19*, 2082–2085.

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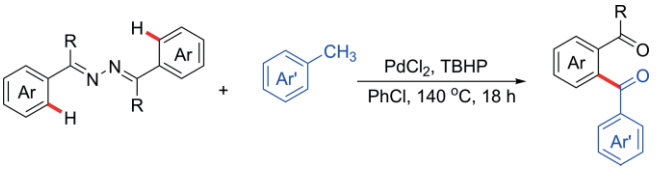
C–H Functionalization



A practical, versatile, and efficient method for the palladium catalyzed regioselective acylation of ketazines with toluene has been developed which provides a new approach for *ortho*-acylation of aryl ketones.

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