DOI: 10.1002/adsc.201100472

Palladium(II)-Catalyzed Direct *ortho*-C–H Acylation of Anilides by Oxidative Cross-Coupling with Aldehydes using *tert*-Butyl Hydroperoxide as Oxidant

Chun-Wo Chan,[a] Zhongyuan Zhou,[a] and Wing-Yiu Yu[a,*]

[a] State Key Laboratory of Chirosciences, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
Fax: (+852)-2364-9932; e-mail: bcwyyu@inet.polyu.edu.hk

Received: June 16, 2011; Revised: July 29, 2011; Published online: November 7, 2011

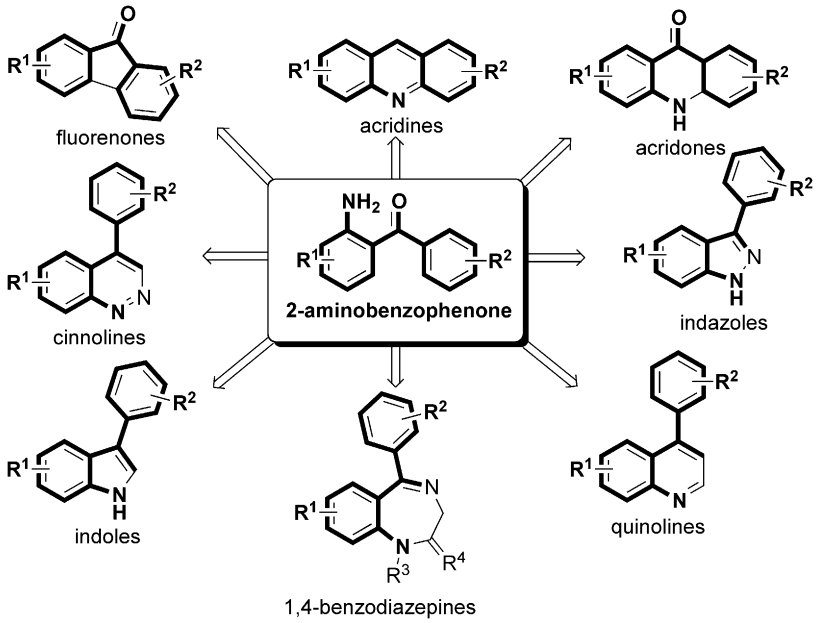
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adcs.201100472.

Abstract: An efficient palladium-catalyzed C–H acylation with aldehydes using *tert*-butyl hydroperoxide (TBHP) transforms various anilides into synthetically useful 2-aminobenzophenone derivatives under mild conditions (40 °C, 3 h). The acylation reaction exhibits excellent regioselectivity and functional group tolerance, and simple aromatic aldehydes, functionalized aliphatic aldehydes and heteroaromatic aldehydes are effective coupling partners. The acylation reaction is probably initiated by a rate-limiting electrophilic C–H cyclopalladation ($k_H/k_D = 3.6$; $\rho^+ = -0.74$) to form an arylpalladium complex, followed by acyl radical functionalization.

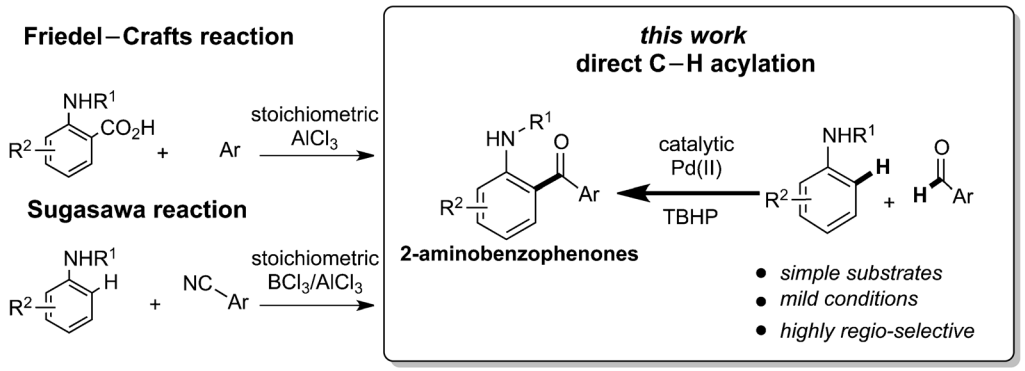
Keywords: acylation; 2-aminobenzophenones; C–H activation; Friedel–Crafts reaction; palladium

Introduction

2-Aminobenzophenones are important precursors to many medicinally useful heterocycles such as fluorenones, cinnolines, acridones, indazoles, indoles, quinolines and benzodiazepines (Scheme 1).[1,2] Conventionally, 2-aminobenzophenones are prepared by Friedel–Crafts acylation reactions of anthranilic acids with



Scheme 1. Some medicinally useful heterocycles derived from 2-aminobenzophenones.



Scheme 2. Synthesis of 2-aminobenzophenones.

arenes.[1b] However, the Friedel–Crafts acylations suffer from poor regioselectivity using an over-stoichiometric amount of Lewis acid catalyst (Scheme 2). While the direct Friedel–Crafts acylation of anilines with acyl chlorides is problematic, 2-aminobenzophenones can be prepared by directly reacting anilines with benzonitriles promoted by stoichiometric amounts of BCl_3 and $AlCl_3$ (the Sugasawa reaction).[3] Notwithstanding, with the growing demand for sustainable chemical synthesis, the direct catalytic C–H functionalization of anilines by employing non-hazardous acylating reagents under mild conditions is highly desirable.[4]

Catalytic dehydrogenative cross-coupling (CDC) reactions of two simple C–H bonds are an attractive and yet challenging approach for C–C bond formation.[5] In this regard, recent advances have been made in Pd-catalyzed regioselective direct C–H functionalizations.[6,7] With the assistance of a donor group (e.g., pyridyl, imino, amido, carboxylato), highly regioselective C–H bond couplings with arenes (biaryl formation)[8,14e], alkenes (Heck-type vinylation)[9] and alkynes (cycloaddition)[10] have been accomplished. Yet, the analogous direct C–H acylations with aldehydes are far less established. In 2009, Cheng and co-workers described the intermolecular Pd-catalyzed oxidative coupling of 2-arylpyridines with benzaldehydes to aromatic ketones.[11] Recently, the analogous coupling with aliphatic aldehydes was also accomplished by Li and co-workers.[12] Nevertheless, examples of the direct coupling of anilines with aldehydes have limited precedents in the literature. Notably, Li and co-workers reported the Cu-catalyzed cyclization of formyl-*N*-arylformamides for the synthesis of indoline-2,3-diones under an O_2 atmosphere.[13]

With an interest to develop catalytic C–H bond cross-coupling reactions,[14] here we describe a highly versatile 2-aminobenzophenone synthesis[15] by Pd-catalyzed oxidative *ortho*-C–H bond cross-coupling of anilides with aldehydes using TBHP as oxidant.[16] Unlike the Friedel–Crafts reactions, the catalytic anilide coupling reactions proceed at 40 °C and exhibit excellent regiocontrol and functional group tolerance; aliphatic, aromatic and heteroaromatic aldehydes are effective coupling partners to generate structurally diverse 2-aminobenzophenone derivatives.

Results and Discussion

Reaction Optimization

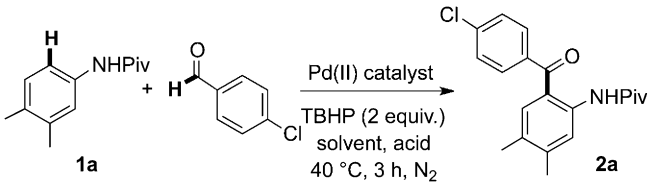
With reference to our earlier work,[14a] we began by examining the reaction of 3,4-dimethyl-*N*-pivalanilide (**1a**, 0.25 mmol) and 4-chlorobenzaldehyde (0.75 mmol) in the presence of TBHP (0.5 mmol), TFA (0.25 mmol) and $Pd(TFA)_2$ (10 mol%) in undegassed DCE (1 mL) at 100 °C for 3 h. We were gratified to find that **2a** was obtained in 50% yield (Table 1, entry 1), and its structure has been established by X-ray crystallography (see Supporting Information). Under our experimental conditions, no *ortho*-arylation of the anilide was observed.

In the absence of $Pd(TFA)_2$ or TFA, **2a** was not obtained with full recovery of the starting materials (entries 2 and 3). Notably, no **2a** formation was observed without TBHP as oxidant (entry 4). Yet, other oxidants such as *tert*-butyl peroxide, benzoyl peroxide, H_2O_2, $K_2S_2O_8$, benzoquinone and $Cu(OAc)_2$ failed to effect any significant product formation (see Supporting Information). With TBHP as oxidant, **2a** was produced in 90% yield when the reaction was performed at 40 °C under an N_2 atmosphere (entry 5). Comparable results were obtained when toluene was employed as solvent (entry 9).

However, donor solvents such as 1,4-dioxane, DME and CH_3CN afforded poor results (*ca.* 40%; entries 6–8). After several trials, **2a** was obtained reproducibly in 86% yield (entry 9) under the optimized reaction conditions: **1a**, 4-chlorobenzaldehyde (3 equiv.), TBHP (2 equiv.), TFA (1 equiv.) and $Pd(OAc)_2$ (5 mol%) in toluene at 40 °C under N_2.

We found that effective coupling of **1a** with 4-chlorobenzaldehyde would also occur even at room

Table 1. Reaction optimization.[a,b]



Entry	Pd (mol%)	Solvent	Acid (equiv.)	Yield [%]
1[c]	$Pd(TFA)_2$ (10)	DCE	TFA (0.5)	50
2[c]	–	DCE	TFA (0.5)	0
3[c]	$Pd(TFA)_2$ (10)	DCE	–	0
4[d]	$Pd(TFA)_2$ (10)	DCE	TFA (0.5)	0
5	$Pd(TFA)_2$ (10)	DCE	TFA (0.5)	90
6	$Pd(TFA)_2$ (10)	dioxane	TFA (0.5)	34
7	$Pd(TFA)_2$ (10)	DME	TFA (0.5)	56
8	$Pd(TFA)_2$ (10)	CH_3CN	TFA (0.5)	31
9	$Pd(TFA)_2$ (10)	toluene	TFA (0.5)	94
10	**$Pd(OAc)_2$ (5)**	**toluene**	**TFA (1)**	**86[e]**
11[f]	$Pd(OAc)_2$ (5)	toluene	TFA (1)	77
12	$Pd(OTs)_2(CH_3CN)_2$ (5)	toluene	TFA (1)	67
13	$PdCl_2(CH_3CN)_2$ (5)	toluene	TFA (1)	<5
14	$PdCl_2(PPh_3)_2$ (5)	toluene	TFA (1)	39
15	$Pd(OAc)_2$ (5)	toluene	AcOH (1)	<5
16	$Pd(OAc)_2$ (5)	toluene	PivOH(1)	0
17	$Pd(OAc)_2$ (5)	toluene	TsOH (1)	48

[a] *General conditions:* **1a** (0.25 mmol), 4-ClC_6H_4CHO (3 equiv.), Pd catalyst, TBHP (2 equiv.), acid (0.5–1 equiv.), solvent (1 mL) at 40 °C under N_2 for 3 h.
[b] Yields determined by NMR using dibromomethane as internal standard.
[c] Temperature is 100 °C, undegassed.
[d] Without TBHP as oxidant.
[e] Isolated yield = 80%.
[f] Room temperature for 12 h.

temperature with **2a** being obtained in 77% yield (entry 11). Among a panel of common Pd catalysts including $Pd(OTs)_2(CH_3CN)_2$, $PdCl_2(CH_3CN)_2$ and $PdCl_2(Ph_3P)_2$, $Pd(OAc)_2$ gave the best result for the coupling reaction (entries 10–14). While TFA is the most effective additive; other carboxylic acids (e.g., AcOH, PivOH and TsOH) failed to afford better product yields (entry 14–16).

Substrate Scope Study

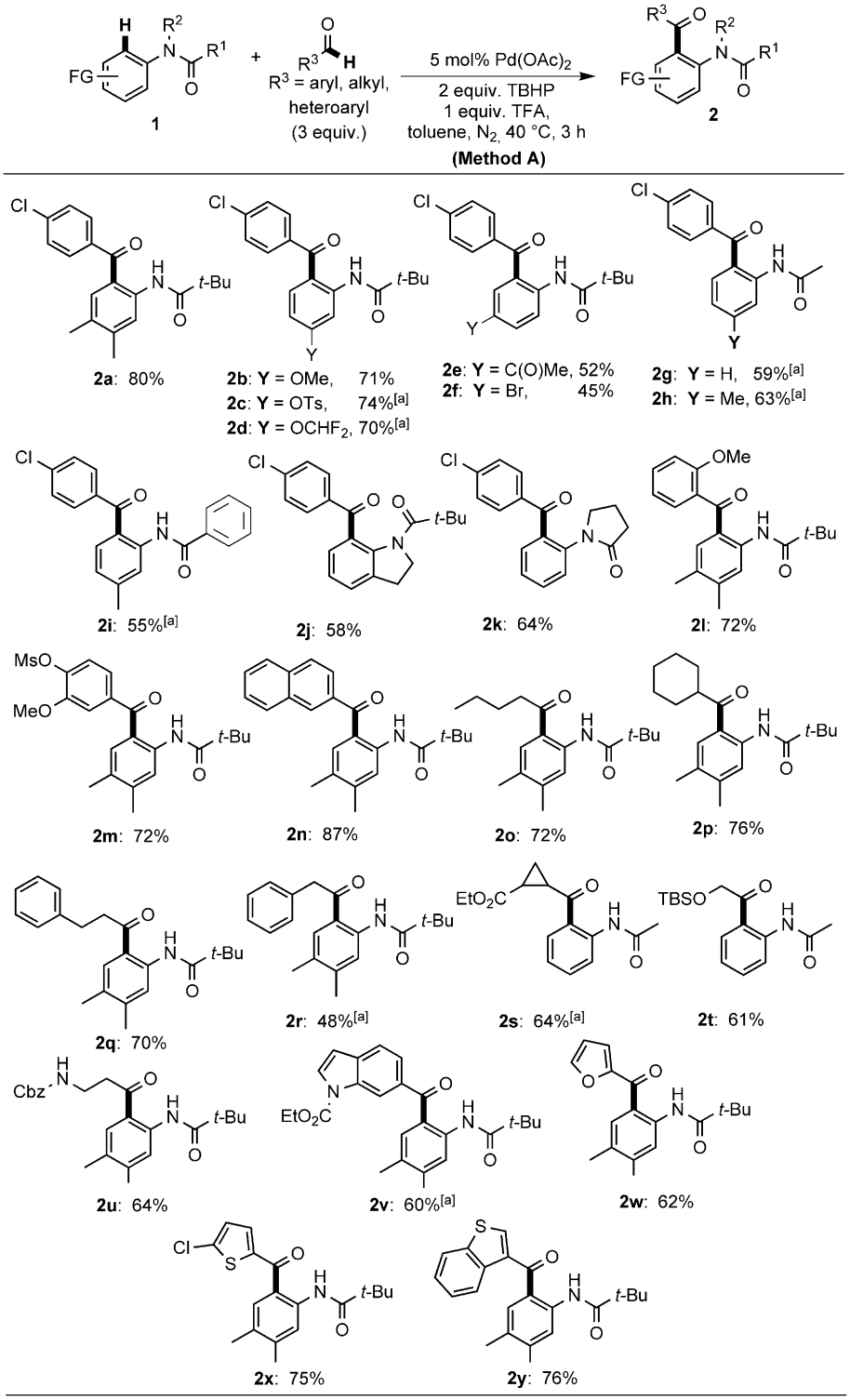
Scheme 3 depicts the substrate scope of the Pd-catalyzed oxidative coupling reaction. Treating 4-chlorobenzaldehyde (3 equiv.) and 3-methoxypivalanilide (**1b**) in the Pd-catalyzed conditions [$Pd(OAc)_2$ (5 mol%), TBHP (2 equiv.), TFA (1 equiv.), N_2, toluene, 40 °C, 3 h (**Method A**)] afforded **2b** in 71% yield. However, Method A was less effective for the analogous reaction of 3-tosyloxypivalanilide (**1c**) with **2c** being formed in 28% yield. After several attempts, effective cross-coupling of **1c** was achieved to furnish **2c** in 74% yield when TBHP was added in a batchwise fashion (**Method B**). Similarly, other substituted pivalanilides [Y = 3-$OCHF_2$, 4-C(O)Me and 4-Br] would undergo facile cross-coupling with Method B: **2d** (70%), **2e** (52%), **2f** (45%). Acetamido, benzamido and tertiary amide groups are capable directing groups for the *ortho*-C–H coupling reactions to give aryl ketones **2g–k** in 64–55% yields.

As expected, other substituted benzaldehydes are effective coupling partners for the Pd-catalyzed acylation of pivalanildes, and the ketones **2l–n** were produced in 87–72% yields. Likewise, the coupling with aliphatic aldehydes such as pentanal, cyclohexanecarboxyaldehyde, 3-phenylpropanal and phenylacetaldehyde furnished ketones **2o** (72%), **2p** (76%), **2q** (70%) and **2r** (48%), respectively. In this work, facile coupling of cyclopropanecarboxyaldehyde with acetanilide afforded exclusively the cyclopropyl aryl ketone **2s** in 64% yield; the ring opened products were not obtained. The lack of ring opened products observed in this work resembles an analogous study on acyl radical addition to fullerenes.[17] Furthermore, the reaction of *α-tert*-butyldimethylsilyloxylacetaldehyde with acetanilde gave **2t** in 61% yield, and the silyloxy group was tolerated. Similarly *N*-Cbz-protected 2-aminopropanal reacted with pivalanilide to afford **2u** in 64% yield. It was reported that amino-functionalized ketones such as **2u** are useful precursors for the *N*-alkylaminoethylcamptothecin analogues.[18] According to the literature, the amino-functionalized aryl ketones were prepared in four steps involving Freidel–Crafts acylation and Michael addition with appropriate alkylamines in 7–44% yields.[19]

Heteroaromatic rings such as indoles are important scaffolds for many pharmaceutically active compounds;[20] 1-aroylindoles can be readily prepared by direct acylation of the N–H free indole precursors. Other regioisomers were prepared from the indolecarboxyaldehydes by Grignard addition, followed by PDC oxidation.[21] In this work, when pivalanilide **1a** was treated with ethyl 5-formyl-1*H*-indole-1-carboxylate under the Pd-catalyzed conditions, ketone **2v** was exclusively isolated in 60% yield. The couplings with furfural, 5-chloro-2-thiophenecarboxyaldehyde and 2-benzothiophenecarboxyaldehyde were also accomplished: **2w** (62%), **2x** (75%) and **2y** (76%). In all cases, no significant oxidation to the heterocycles was observed under our experimental conditions.

Mechanistic Considerations

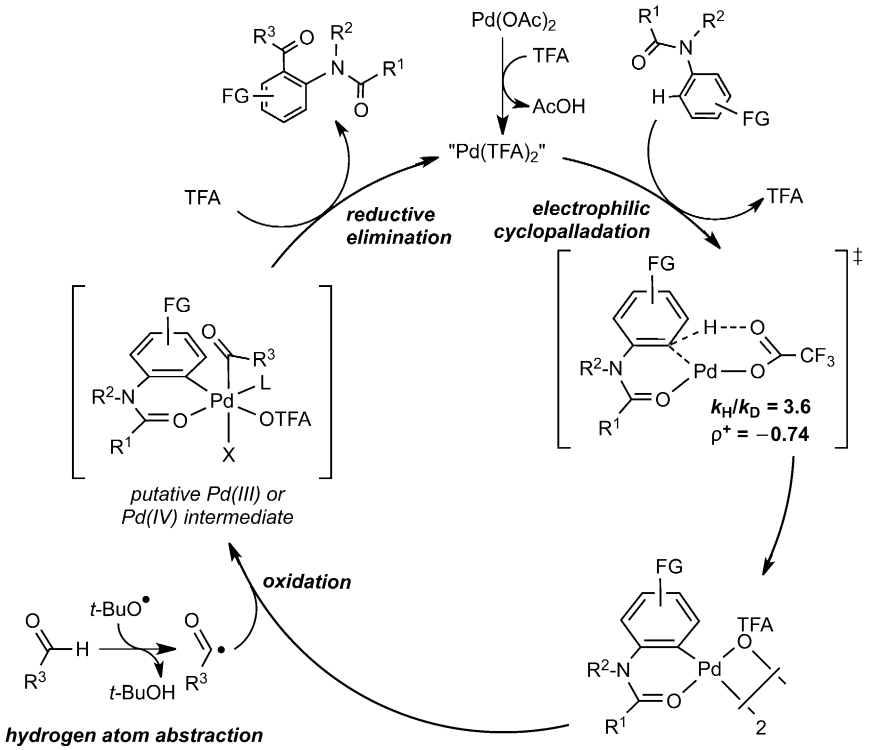
The oxidative acylation of anilides is probably initiated by arene C–H bond palladation to form the cyclopalladated complex (Scheme 4).[16a,b] In this work, we



[a] **Method B**: $Pd(OAc)_2$ (10 mol%), TBHP (2 x 1 equiv.; addition interval 6 h).

Scheme 3. Substrate scope study for the Pd-catalyzed cross coupling reaction of anilides with aldehydes. The reported yields are of isolated product.

prepared the cyclopalladated complex **1g-Pd** by reacting acetanilide **1g** with $Pd(OAc)_2$ in toluene. By competitive experiments with **1g** and **1g-*d*$_5$** as substrates, a primary kinetic isotope effect (k_H/k_D) = 3.6 was observed; this value is compatible with the rate-determining C–H activation step.[22] A Hammett correla-



Scheme 4. Proposed mechanism.

tion study on a series of *meta*-substituted pivalanilides (Y = OMe, Me, Ph, H, Cl and Br) revealed a linear free energy relationship ($R = 0.96$) with the Hammett constant σ_p^+ and the ρ^+ value was found to be −0.74 (Figure 1). It should be noted that this ρ^+ value is too small to support a carbocation intermediate corresponding to an electrophilic aromatic substitution (chlorination of benzene in acetic acid = −9 to −10). Our KIE and Hammett study on the nature of the C–H cleavage steps seems to favour a transition state involving the build-up of partial positive charge (Scheme 4). According to a computational study on the cyclopalladation of *N,N*-dimethylaminobenzene by Davies and Macgregor,[23] the C–H palladation may proceed by the rate-limiting agostic C–H bond interaction with the Pd(II) center with little positive charge development on the arene. The agostic interaction enhances the acidity of the *ortho*-C–H bond, which was subsequently deprotonated by the coordinated carboxylate. Recently, Fagnou and co-workers proposed a concerted metallation deprotonation (CMD) pathway for the Pd-mediated direct C–H arylations.[24] For our Pd-catalyzed C–H acylation reactions, the CMD pathway may not be tenable since this pathway was characterized by a positive Hammett correlation manifesting the building up of negative charge on the arene ring.

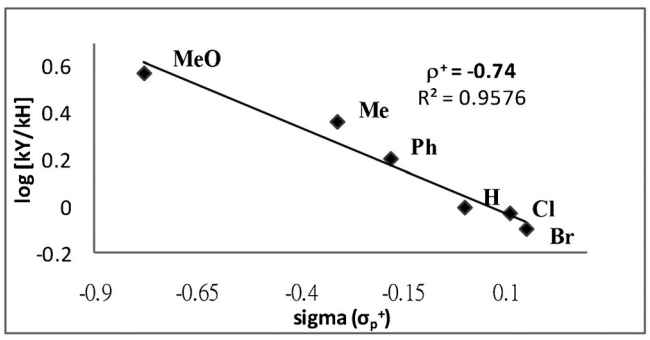


Figure 1. Hammett correlation studies.

Regarding the nature of the anilide-aldehyde coupling reaction, a direct nucleophilic-type reaction of the arylpalladium complex with aldehyde can be ruled out since treatment of **1g-Pd** with aldehyde without TBHP did not produce any coupled ketones. Indeed, significant ketone **2g** formation (59%, comparable to the catalytic results) was only achieved by reacting **1g-Pd** (1 equiv.) with 4-chlorobenzaldehyde (3 equiv.) in the presence of **1g** (1 equiv.), TBHP (2 equiv.), and TFA (1 equiv.) (see Supporting Information).[25] Since decomposition of TBHP is known to generate the reactive *t*-BuO· radical, which would react with aldehyde by hydrogen atom abstraction to give reactive acyl radicals,[26,27] we hypothesize that the acyl radicals[28] would react with the palladacycle to afford the product ketones *via* either Pd(IV)[29] or dimeric Pd(III)[25a,30] intermediates (Scheme 4).

Conclusions

In summary, we have developed an intermolecular *cross-coupling of simple aldehydes* with anilides *via* C–H bond activation. The cross-coupling reaction exhibits high functional group tolerance and regioselectivity under relatively mild conditions using TBHP as a benign terminal oxidant. It is noteworthy that heteroaromatic aldehydes would effectively couple with anilides to afford structurally diverse 2-aminobenzophenone derivatives. In view of the synthetic utility of 2-aminobezophenones, this reaction would be of broad interest to synthetic chemistry.

Experimental Section

General Procedure for Pd-Catalyzed Acylation of Anilides

A 10-mL Schlenk-type test tube (with a Quick-fit stopper and side arm) equipped with a magnetic stir bar was charged with the anilides substrate (0.25 mmol), $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol), aldehyde (0.75 mmol). The reaction tube was stoppered, then evacuated and charged with N_2 (repeated three times). Subsequently, dry toluene (1 mL), TFA (0.0192 mL, 0.25 mmol), and TBHP (5 M in DCE, 0.1 mL, 0,5 mmol) were added under a flow of N_2. The reaction mixture was stirred at 40 °C for 3 h. The reaction mixture was filtered over a plug of celite and the solvent was removed under vacuum. The resulting residue was purified by silica gel flash column chromatography using hexanes/EtOAc as the eluent.

Procedure for Kinetic Isotope Experiments (KIE)

A 10-mL Schlenk-type test tube (with a Quick-fit stopper and side arm) equipped with a magnetic stir bar was charged with acetanilide (**1g**, 0.1 mmol) and **1g-d_5** (0.1 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), 4-chlorobenzaldehyde (0.084 mg, 0.6 mmol). The reaction tube was stoppered, then evacuated and charged with N_2 (repeated three times). Subsequently, dry toluene (1 mL), TFA (0.0154 mL, 0.2 mmol), and TBHP (5 M in DCE, 0.08 mL, 0.4 mmol) were added under a flow of N_2. The reaction mixture was stirred at 40 °C for 30 min. The reaction mixture was cooled with ice water and quenched by saturated sodium bisulfate solution (2 mL). Then the combined organic solution was dried with Na_2SO_4 and concentrated under vaccum. The resulting residue was purified by a plug of silica gel flash column chromatography using hexanes/EtOAc (1:1) as the eluent. Both the recovered starting materials and the isolated products were analyzed by NMR for determination of conversion and yield with dibromomethane (0.1 mmol, 2 H) as the internal standard.

Procedure for Hammett Correlation Study

A 10-mL Schlenk-type test tube (with a Quick-fit stopper and side arm) equipped with a magnetic stir bar was charged with unsubstituted pivalanilide (0.1 mmol) and *meta*-Y-substituted pivalanilide (Y = MeO; Me; Ph; Cl; Br; 0.1 mmol), $Pd(OAc)_2$ (1.8 mg, 0.008 mmol), 4-chlorobenzaldehyde (0.084 mg, 0.6 mmol). The reaction tube was stoppered, then evacuated and charged with N_2 (repeated three times). Subsequently, dry toluene (1 mL), TFA (0.0154 mL, 0.2 mmol), and TBHP (5 M in DCE, 0.08 mL, 0.4 mmol) were added under a flow of N_2. The reaction mixture was stirred at 40 °C for 4 min. The reaction mixture was cooled with ice/water and quenched by saturated sodium bisulfate solution (2 mL). Then the combined organic solution was dried with Na_2SO_4 and concentrated under vaccum. The resulting residue was analyzed by GC/FID for the determination of conversion using a calibration curve (3 points) with tetradecane (0.1 mmol) as the internal standard. Each result was run in triplicate.

Acknowledgements

We thank the financial support from The Hong Kong Research Grants Council (PolyU 5031/09P, SEG PolyU01).

References

[1] For reviews of 2-aminobenzophenones synthesis, see: a) J. C. E. Simpson, C. M. Atkinson, K. Schofield, O. Stephenson, *J. Chem. Soc.* **1945**, 646; b) D. A. Walsh, *Synthesis* **1980**, 677.

[2] Selected references on the synthesis and bioactivities, for acridine derivatives, see: a) W. A. Denny, *Med. Chem. Rev.* **2004**, 1, 257; b) W. A. Denny, *Curr. Med. Chem.* **2002**, *9*, 1655; c) D. C. Rogness, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 2289; for indazoles, see: d) R. M. Claramunt, C. Lopez, A. Lopez, C. Perez-Medina, M. Perez-Torralba, I. Alkorta, J. Elguero, G. Escames, D. Acuna-Castroviejo, *Eur. J. Med. Chem.* **2011**, *46*, 1439; e) A. Kamal, K. L. Reddy, V. Devaiah, N. Shankaraiah, D. R. Reddy, *Mini-Rev. Med. Chem.* **2006**, *6*, 53; f) C. M. Councekker, C. C. Eichman, B. C. Wray, E. R. Welin, J. P. Stambuli, *Org. Synth.* **2011**, *88*, 33; for quinolines, see: g) M. C. Jose, P. M. Elena, S. Abdeloushid, C. Caria do Carmo, S. Elena, *Chem. Rev.* **2009**, *109*, 2652; h) S. Madapa, Z. Tusi, S. Batra, *Curr. Org. Chem.* **2008**, *12*, 1116; i) S. Atechian, N. Nock, R. D. Norcross, H. Ratni, A. W. Thomas, J. Verron, R. Masciadri, *Tetrahedron* **2007**, *63*, 2811; for benzodiazepines, see: j) B. A. Bunin, M. J. Plunkett, J. A. Ellman *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4708; k) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfieldt *J. Med. Chem.* **1988**, *31*, 2235; l) L. H. Sternbach, *Angew. Chem.* **1971**, *83*, 70; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 34.

[3] a) K. Prasad, G. L. Lee, A. Chaudhary, M. J. Girgis, J. W. Streemke, O. Repic, *Org. Process Res. Dev.* **2003**, *7*, 723; b) A. W. Douglas, N. L. Abramson, I. N. Houpis, S. Karady, A. Molina, L. C. Xavier, N. Yasuda, *Tetrahedron Lett.* **1994**, *35*, 6807; c) T. Sugasawa, T. Toyoda,

M, Adachi, K. Sasakura, *J. Am. Chem. Soc.* **1978**, *100*, 4842.

[4] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, L. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411.

[5] For reviews, see: a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; c) W. J. Yoo, C. J. Li, *Top. Curr. Chem.* **2010**, *292*, 281; d) C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.

[6] For reviews of Pd-catalyzed C–H functionalization, see: a) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; d) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.

[7] Recent reviews on the rhodium-catalyzed C–H functionalizations: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; for the analogous ruthenium-catalyzed reactions, see: b) R. Vicente, L. Ackermann, *Top. Curr. Chem.* **2010**, *292*, 211; for copper, see: c) M. Zhang *Appl. Organometal. Chem.* **2010**, *24*, 269; for iron, see: d) C.-L. Sun, B.-J. Li, Z.-J Shi, *Chem. Rev.* **2011**, *111*, 1293.

[8] Selected examples of arylation: a) M. J. Tredwell, M. Gulias, B. N. Gaunt Bremeyer, C. C. C. Johansson, B. S. L. Collins, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 1076; b) M. Wasa, B. T. Worrell, J. Q. Yu, *Angew. Chem. Int. Ed.* **2010** *49*, 1275; c) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; d) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904; e) H. A. Chiong, Q. N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879.

[9] Selected examples of vinylation: a) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1064; b) K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2010**, *49*, 6169; c) J. J. Li, T. S. Mei, J. Q. Yu, *Angew. Chem.* **2008**, *120*, 6552; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452; d) C. E. Houlden, C. D. Bailey, J. G. Ford, M. R. Gagne, G. C. Lloyd-Jones, K. I. Booker-Milburn, *J. Am. Chem. Soc.* **2008**, *130*, 10066; e) G. Cai, Y. Fu, Y. Li, X. Wan, Z. Shi, *J. Am. Chem. Soc.* **2007**, *129*, 7666.

[10] Selected examples of cycloaddition: a) F. W. Patureau, T. Besset, N. Kuhl, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2154; b) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; c) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565; d) Z. Shi, S. Ding, Y. Cui, N. Jiao, *Angew. Chem.* **2009**, *121*, 8035; *Angew. Chem. Int. Ed.* **2009**, *48*, 7895.

[11] X. Jia, S. Zhang, W. Wang, F. Luo, J. Cheng, *Org. Lett.* **2009**, *11*, 3120.

[12] O. Basle, J. Bidange, Q. Shuai, C. J. Li, *Adv. Synth. Catal.* **2010**, *352*, 1145.

[13] a) B. X. Tang, R. J. Song, C. Y. Wu, Y. Liu, M. B. Zhou, W. T. Wei, G. B. Deng, D. L. Yin, J. H. Li, *J. Am. Chem. Soc.* **2010**, *132*, 8900. See also: b) P. Alvarez-Bercedo, A. Flores-Gaspar, A. Correa, R. Martin, *J. Am. Chem. Soc.* **2010**, *132*, 466; c) S. Ko, B. Kang, S. Chang, *Angew. Chem.* **2005**, *117*, 459; *Angew. Chem. Int. Ed.* **2005**, *44*, 455.

[14] a) C.-W. Chan, Z. Zhou, A. S.-C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 3926; b) Y.-T. Tsoi, Z. Zhou, A. S.-C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 4506; c) K.-H. Ng, A. S.-C. Chan, W.-Y. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 12862; d) W.-W. Chan, S. H. Yeung, Z. Zhou, A. S.-C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 604; e) W.-Y. Yu, W. N. Sit, Z. Zhou, A. S. C. Chan, *Org. Lett.* **2009**, *11*, 3174; f) W.-Y. Yu, Y.-T. Tsoi, Z. Zhou, A. S.-C. Chan, *Org. Lett.* **2009**, *11*, 469; g) W.-Y. Yu, W. N. Sit, K.-M. Lai, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2008**, *130*, 3304.

[15] During the course of our investigation, Ge and co-workers reported the Pd-catalyzed decarboxylative *ortho*-C–H acylation with α-oxocarboxylic acids, see a) P. Fang, M. Li, H. Ge, *J. Am. Chem. Soc.* **2010**, *132*, 11898; b) M. Li. H. Ge, *Org. Lett.* **2010**, *12*, 3464. Very recently, Kwong and co-workers reported the Pd-catalyzed acylation of acetanilides with aromatic aldehydes, see c) Y. Wu, B. Li, F. Mao, X. Li, F. Y. Kwong, *Org. Lett.* **2011**, *13*, 3258.

[16] For selected examples of Pd-catalyzed *ortho*-C–H bond functionalizations of anilides, see a) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 1694; b) C. S. Yeung, X. Zhao, N. Borduas, V. M. Dong, *Chem. Sci.* **2010**, *1*, 331; c) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965; d) R, Giri, J. K. Lam, J. Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 686; e) W. Rauf, A. L. Thompson, J. H. Brown, *Dalton Trans.* **2010**, *39*, 10414; f) B. J. Li, S. L. Tian, Z. Fang, Z. Shi, *Angew. Chem.* **2008**, *120*, 1131; *Angew. Chem. Int. Ed.* **2008**, 47, 1115; g) M. D. K. Boele, G. P. F. van Strijdonck, A. H. M. de Vries, P. C. J. Kamer, J. G. de Vries, P. W. N. M. van Leeuwen, *J. Am. Chem. Soc.* **2002**, *124*, 1586.

[17] M. D. Tzirakis, M. Orfanopoulos, *J. Am. Chem. Soc.* **2009**, *131*, 4063.

[18] W. D. Kingbury, J. C. Boehm, D. R. Jakas, K. G. Holden, S. M. Hecht, G. Gallagher, M. J. Caranfa, F. L. McCabe, L. F. Faucette, R. K. Johnson, R. P. Hertzberg, *J. Med. Chem.* **1991**, *34*, 98.

[19] S.-S. Jew, H.-J Kim, M. G. Kim, E.-Y. Roh, C. L. Hong, J.-K. Kim, J.-H. Lee, H. Lee, H.-G. Park, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3203.

[20] a) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**; b) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, **1970**.

[21] J. P. Liou, C.-W. Wu, H.-P. Hsieh, C.-Y. Chang, C.-M. Chen, C.-C. Kuo, J.-Y. Chang, *J. Med. Chem.* **2007**, *50*, 4548.

[22] Intermolecular primary KIE (k_H/k_D) values of 2–5 have been reported for Pd-catalyzed *ortho*-C–H activation of arenes. For selected examples, see: a) K. J. Stowers, M. S. Sanford, *Org. Lett.* **2009**, *11*, 4584; b) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285.

[23] a) D. L. Davies, S. M. A. Donald, S. A. Macgregor, *J. Am. Chem. Soc.* **2005**, *127*, 13754. For a review on carboxylate-assisted transition metal-catalyzed C–H functionalizations, see b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315.

[24] a) H. Y. Sun, S. I. Gorelsky, D. R. Stuart, L. C. Campeau, K. Fagnou, *J. Org. Chem.* **2010**, *75*, 8180; b) M. Lafrance, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 16496.
[25] Sanford and Ritter also observed a similar dependence on the exogenous free ligand for the stoichiometric C–H functionalizations; see: a) D. C. Powers, M. A. L. Geibel, J. E. M. N. Klein, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 17050; b) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330.
[26] For a review of acyl radicals, see a) C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev.* **1999**, *99*, 1991; for selected example of the Pd-catalyzed radical carbonylation reactions involving acyl radicals, see: b) I. Ryu, S. Kreimerman, F. Araki, S. Nishitani, S. Oderaotoshi, S. Minakata, M. Komatsu, *J. Am. Chem. Soc.* **2002**, *124*, 3812.
[27] For the genaration of acyl radicals by oxygen radicals, see: a) C. Chatgilialoglu, L. Lunazzi, D. Macciantelli, G. Placucci, *J. Am. Chem. Soc.* **1984**, *106*, 5252; b) C. Walling, M. J. Mintz, *J. Am. Chem. Soc.* **1967**, *89*, 1515.
[28] In support of the acyl radical intermediates, we observed the dimethyl-2-hexanoylbutanedioate by reacting hexanal and dimethyl maleate with TBHP at 100 °C in toluene. Formation of ketone can be rationalized by radical addition to the C=C bond (for reference, see: V. Chudasama, R. J. Fitzmaurice, S. Caddick, *Nat. Chem.* **2010**, *2*, 592). Moreover, we found that pivaldehhyde is ineffective for the oxidative anilide coupling reaction, and the coupled ketone was obtained in $<10\%$ yield. Probably, the putative *tert*-butylacyl radical would decarbonylate spontaneously under the experimental conditions (see also ref.[26a]).
[29] a) S. R. Whitfield, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 15142; b) A. R. Dick, J. W. Kampf, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 12790.
[30] D. C. Powers, T. Ritter, *Nat. Chem.* **2009**, *1*, 302

