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Palladium-catalyzed *ortho*-acylation of 2-aryl pyridine derivatives using arylmethyl amines as new acyl sources†

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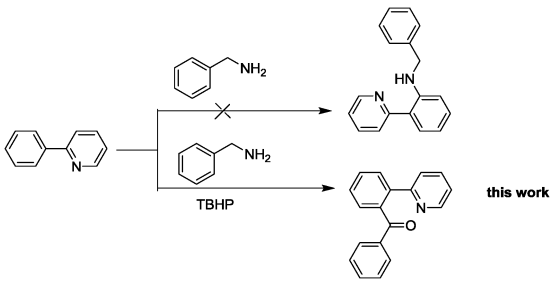
A facile and efficient protocol for palladium-catalyzed *ortho*-acylation of 2-aryl pyridines was developed. Note that this acylation utilized arylmethyl amines as new, cheap and readily available acylation reagents and exhibited high regioselectivity for 2-aryl pyridines bearing a *meta*-substituent in the aryl ring moiety.

Transition metal-catalyzed C–H bond functionalization has become one of the most reliable and facile tools to construct C–C and C–heteroatom bonds in recent years.[1] Among the various efficient C–H activation techniques, the directing group assisted C–H bond activation is one of the most facile and powerful strategies.[2] And this type of *ortho* aromatic C–H bond functionalization has been achieved in several valuable and direct transformations such as olefination, arylation, acylation, alkoxylation, halogenation, and amination with the assistance of pyridines, imines, esters, ketones, oxazolines, amides and nitriles as the directing groups.[3] Inspired by these pioneering reports, we attempted *ortho*-amination of 2-phenylpyridine using benzyl amine as a new amination reagent. However, the amination product was not observed at all, and to our surprise, a large amount of *ortho*-acylation product was obtained instead (Scheme 1).

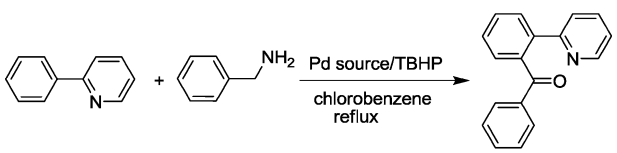
The first successful acylation of *ortho*-C–H bonds was reported by Cheng and coworkers, in 2009, who discovered that *ortho*-C–H bonds of 2-arylpyridines could be directly acylated under palladium catalysis using aldehydes as acylation reagents.[4e] Then, such *ortho*-acylation type reactions were also realized using aldehydes, α-oxocarboxylic acids, alcohols or toluene derivatives as acylation reagents.[4] Compared to these reagents, benzylamine derivatives as new acylation reagents are cheap, stable and easy to handle, and would be an important complement to these reported methods. And herein, we would like to report facile and efficient synthesis of the aromatic ketones *via* palladium-catalyzed regioselective *ortho*-acylation using arylmethyl amines as new acylation reagents.



Scheme 1 Transition metal-catalyzed direct *ortho*-acylation.

The initial optimization process of acylation of 2-phenylpyridine (**1a**) with benzylamine (**2a**) was investigated, and the

Table 1 Optimization of the reaction conditions[a]



1a **2a** **3a**

Entry	Palladium source (mol%)	**1a**/**2a** (mmol/mmol)	Yield[b] (%)
1	$PdCl_2$ (5)	1 : 2	47
2	$PdCl_2$ (10)	1 : 2	56
3	$PdCl_2$ (10)	1 : 1.8	66
4	$PdCl_2$ (10)	1 : 1.6	67
5	$PdCl_2$ (10)	1 : 1.4	69 (57)
6	$PdCl_2$ (10)	1 : 1.2	56 (46)
7[c]	**$PdCl_2$ (10)**	**1 : 1.4**	**81 (68)**
8[d]	$PdCl_2$ (10)	1 : 1.4	35
9[c]	$Pd(OAc)_2$ (10)	1 : 1.4	47
10[c]	$Pd_2(dba)_3$ (5)	1 : 1.4	55
11[c]	$Pd(PPh_3)_2Cl_2$ (10)	1 : 1.4	40

[a] Reaction conditions: 2-phenyl pyridine (**1a**) (0.2 mmol), benzylamine, palladium catalyst, TBHP (0.7 mmol) in 1 mL chlorobenzene at refluxing temperature for 8 h. [b] GC yield (isolated yield) based on the amount of **1a**. [c] Under a nitrogen atmosphere. [d] At 110 °C and under a nitrogen atmosphere.

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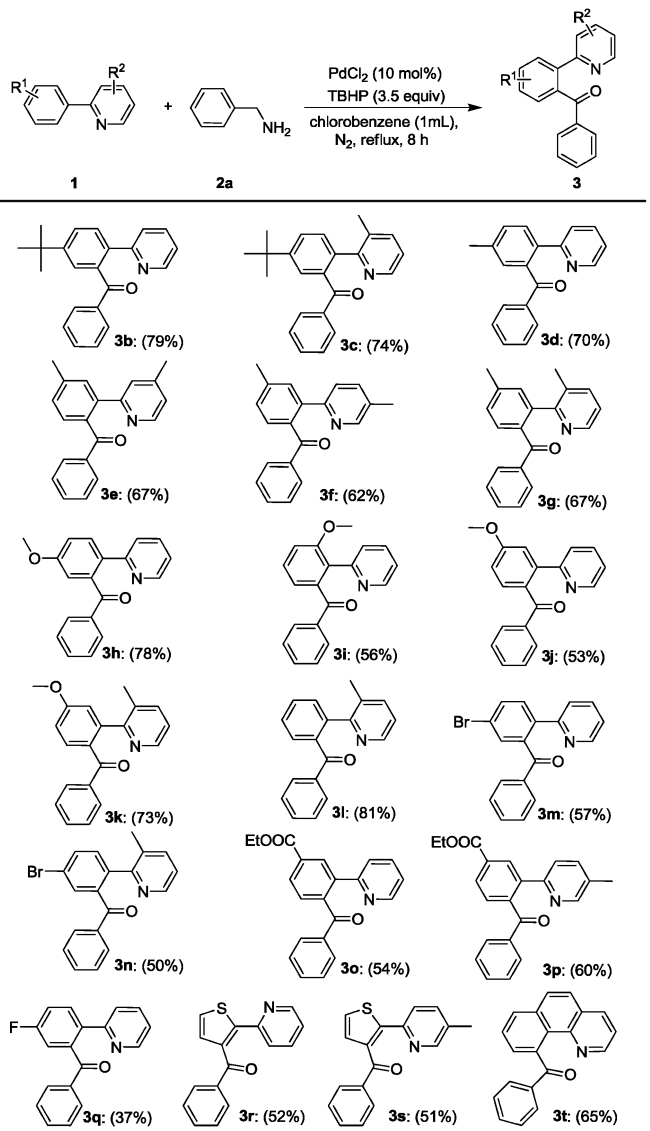
results are displayed in Table 1. After the several effects of ligands, oxidants and the solvents were checked (see ESI†), we found that the acylated product could be obtained in 47% GC yield in the presence of 5 mol% of $PdCl_2$ using TBHP as the oxidant in chlorobenzene (Table 1, entry 1). When the catalyst loading was increased to 10 mol%, the desired product could be obtained in a higher GC yield of 56% (Table 1, entry 2). It should be noted that the ratio of 2-phenyl pyridine (**1a**) to benzylamine (**2a**) played an important role for the successful reaction. For example, when this ratio was changed from 1 : 2 to 1 : 1.8, 1 : 1.6, 1 : 1.4 and 1 : 1.2, the GC yields of the desired products could be obtained from 56% to 66%, 67%, 69% and 56%, respectively (Table 1, entries 2–6). And from these obtained results, it could be found that the ratio of 1 : 1.4 is the best choice (Table 1, entry 5). Notably, when the reaction was performed under a nitrogen atmosphere, the GC yield could be up to 81% (Table 1, entry 7). However, a lower temperature of 110 °C could result in a GC yield of 35% (Table 1, entry 8). Finally, relatively lower yields were observed when other commercially available palladium sources such as $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_2Cl_2$ were used as the catalysts (Table 1, entries 9–11).

Under the optimized reaction conditions, the results of acylation of 2-arylpyridines (**1**) with benzylamine (**2a**) are summarized in Table 2. The acylation could tolerate various functional groups such as OMe, Br, EtOOC, F and thienyl groups, affording the desired products in moderate to good yields. The electronic effect was evident in this type of acylation, and the substrates bearing an electron-donating or electron-neutral group in the benzene ring would give the desired products in higher yields than those bearing an electron-withdrawing group in the benzene ring (Table 2, **3b**–**3q**). And especially, the acylation of 3-methyl-2-phenylpyridine with benzylamine (**2a**) gave a yield of up to 81% (Table 2, **3l**). Remarkably, the acylation also showed high regioselectivity for the substrates containing a *meta*-substituent in the benzene ring, and the reaction could occur at the less sterically hindered *ortho*-C–H bond of the directing group (Table 2, **3e**–**3g**, **3j**, **3k**, **3o**, **3p**). In addition, this acylation could be also applicable to heterocycle-substituted pyridines such as 2-thienylpyridine, 5-methyl-2-thienylpyridine and benzo[*h*]quinoline, and moderate yields of 52%, 51% and 65% were obtained, respectively (Table 2, **3r**–**3t**). The molecular structure of the acylated product (**3e**) was unambiguously determined by the single crystal X-ray diffraction study (Fig. 1).[5]

The scope of palladium-catalyzed acylation of 3-methyl-2-phenylpyridine with various substituted arylmethyl amines was also investigated (Table 3). And the acylation showed good compatibility of substituents on the benzene ring of benzylamines such as OMe, Cl, Br or even strong electron-withdrawing CF_3 groups, affording the corresponding products in moderate to good yields.

Based on the previous reports[4] and our own results, a tentative mechanism for the palladium-catalyzed *ortho*-C–H acylation of 2-phenylpyridine (**1a**) is depicted in Scheme 2. The reaction would be initiated by *ortho*-cyclometalation of 2-phenylpyridine (**1a**) with $PdCl_2$ to form the palladacycle **A**. Meanwhile, benzylamine (**2a**) would undergo oxidation, hydrolysis and the second radical oxidation in a solution of TBHP in water to generate the acyl radical. Then, the intermediate **A** would react with the acyl radical, affording the oxidative

Table 2 The palladium-catalyzed *ortho*-acylation of 2-arylpyridines[a,b]



[a] Reaction conditions: 2-arylpyridine (0.2 mmol), benzylamine (**2a**) (0.28 mmol), $PdCl_2$ (10 mol%) and TBHP (0.7 mmol) in chlorobenzene (1 mL) under a nitrogen atmosphere at refluxing temperature for 8 h. [b] Isolated yield.

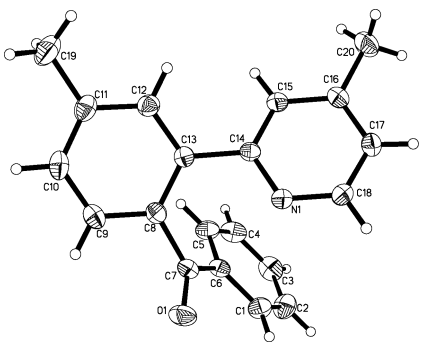
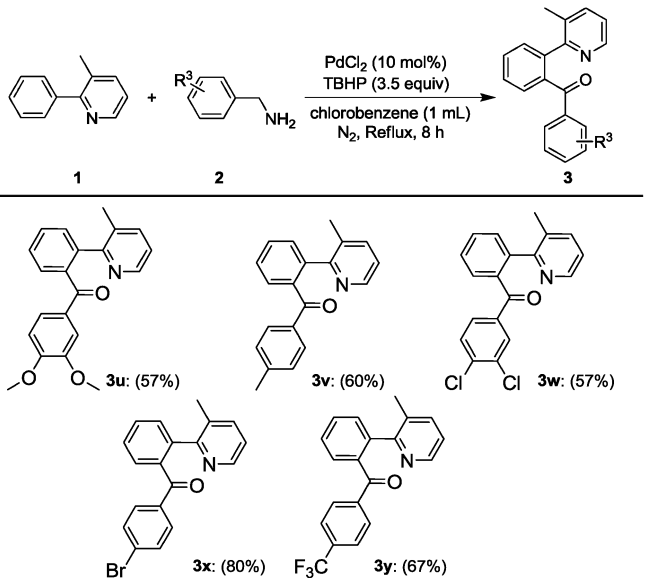
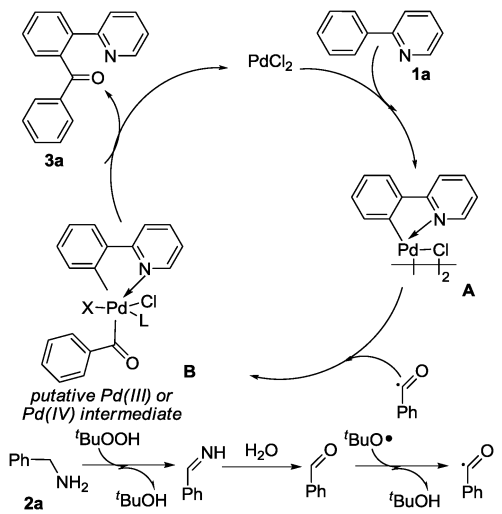


Fig. 1 Molecular structure of **3e**.

Table 3 The palladium-catalyzed acylation of 2-phenyl-3-methylpyridine with arylmethyl amines[a,b]



[a] Reaction conditions: 2-phenyl-3-methylpyridine (0.2 mmol), arylmethyl amine (0.28 mmol), $PdCl_2$ (10 mol%) and TBHP (0.7 mmol) in chlorobenzene (1 mL) under a nitrogen atmosphere at refluxing temperature for 8 h. [b] Isolated yield.



Scheme 2 Proposed mechanism for acylation of 2-phenylpyridine.

addition product as intermediate **B**. Finally, the reductive elimination of Pd(III) or Pd(IV) intermediate **B**[4e] would result in the desired product (**3a**) and the regeneration of active palladium species to fulfill the catalytic cycle.

In summary, we have developed convenient and efficient synthesis of aromatic ketones *via* palladium-catalyzed *ortho*-C–H acylation of 2-arylpyridines using arylmethyl amines as cheap and readily available acylation reagents. This protocol showed high regioselectivity for the substrates containing a *meta*-substituent in the benzene ring. Further application of this synthetic methodology is currently underway in our laboratory.

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Notes and references

1 (*a*) P. Müller and C. Fruit, *Chem. Rev.*, 2003, **103**, 2905; (*b*) J. L. Liang, J. S. Huang, X. Q. Yu, N. Y. Zhu and C. M. Che, *Chem.–Eur. J.*, 2002, **8**, 1563; (*c*) L. Ackermann, *Chem. Commun.*, 2010, **46**, 4866; (*d*) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013; (*e*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; (*f*) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem.–Eur. J.*, 2010, **16**, 2654; (*g*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*h*) T. Naota, H. Takaya and S. I. Murahashi, *Chem. Rev.*, 1998, **98**, 2599; (*i*) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (*j*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*k*) M. M. Diaz-Requejo and P. J. Pérez, *Chem. Rev.*, 2008, **108**, 3379; (*l*) G. Dyker, *Handbook of C–H Transformations*, Wiley-VCH, Weinheim, 2005.

2 (*a*) C. J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*b*) O. Daugulis, H. Q. Do and D. Shabashov, *Acc. Chem. Res.*, 2009, **42**, 1074; (*c*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624.

3 (*a*) T. Nishikata and B. H. Lipshutz, *Org. Lett.*, 2010, **12**, 1972; (*b*) K. Dipannita, N. R. Deprez, L. V. Deprez and M. S. Sanford, *J. Am. Chem. Soc.*, 2005, **127**, 7330; (*c*) G. J. Deng, L. Zhao and C. J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 6278; (*d*) A. S. Tsai, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 6316; (*e*) B. Tang, R. Song, C. Wu, Y. Liu, M. Zhou, W. Wei, G. Deng, D. Yin and J. H. Li, *J. Am. Chem. Soc.*, 2010, **132**, 8900; (*f*) X. Chen, X. S. Hao, C. E. Goodhue and J. Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790; (*g*) L. V. Desai, K. J. Stowers and M. S. Sanford, *J. Am. Chem. Soc.*, 2008, **130**, 13285; (*h*) X. B. Wan, Z. X. Ma, B. J. Li, K. Y. Zhang, S. K. Cao, S. W. Zhang and Z. J. Shi, *J. Am. Chem. Soc.*, 2006, **128**, 7416; (*i*) H. Y. Thu, W. Y. Yu and C. M. Che, *J. Am. Chem. Soc.*, 2006, **128**, 9048; (*j*) Y. H. Zhang, J. Q. Feng and C. J. Li, *J. Am. Chem. Soc.*, 2008, **130**, 2900; (*k*) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*l*) J. Wen, S. Qin, L. F. Ma, L. Dong, J. Zhang, S. S. Liu, Y. S. Duan, S. Y. Chen, C. W. Hu and X. Q. Yu, *Org. Lett.*, 2010, **12**, 2694; (*m*) F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9982; (*n*) P. Gandeepan, K. Parthasarathy and C. H. Cheng, *J. Am. Chem. Soc.*, 2010, **132**, 8569; (*o*) T. Nishikata, A. R. Abela, S. L. Huang and B. H. Lipshutz, *J. Am. Chem. Soc.*, 2010, **132**, 4978; (*p*) G. W. Wang, T. T. Yuan and X. L. Wu, *J. Org. Chem.*, 2008, **73**, 4717.

4 (*a*) X. F. Jia, S. H. Zhang, W. H. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (*b*) O. Basle, J. Bidange, Q. Shuai and C. J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145; (*c*) C. L. Li, L. Wang, P. H. Li and W. Zhou, *Chem.–Eur. J.*, 2011, **17**, 10208; (*d*) Y. X. Yang, B. Zhou and Y. C. Li, *Adv. Synth. Catal.*, 2012, **354**, 2916; (*e*) C. W. Chan, Z. Y. Zhou and W. Y. Yu, *Adv. Synth. Catal.*, 2011, **353**, 2999; (*f*) C. W. Chan, Z. Y. Zhou, A. S. C. Chan and W. Y. Yu, *Org. Lett.*, 2010, **12**, 3926; (*g*) Y. N. Wu, B. Z. Li, F. Mao, X. S. Li and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 3258; (*h*) P. Fang, M. Z. Li and H. B. Ge, *J. Am. Chem. Soc.*, 2010, **132**, 11898; (*i*) Z. Y. Yang, X. Chen, J. D. Liu, Q. W. Gui, K. Xie, M. M. Li and Z. Tan, *Chem. Commun.*, 2013, **49**, 1560; (*j*) M. Kim, J. Park, S. Sharma, A. Kim, E. Park, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 925; (*k*) J. Park, M. Kim, S. Sharma, E. Park, A. Kim, S. H. Lee, J. H. Kwak, Y. H. Jung and I. S. Kim, *Chem. Commun.*, 2013, **49**, 1654; (*l*) F. H. Xiao, Q. Shuai, F. Zhao, O. Baslè, G. J. Deng and C. J. Li, *Org. Lett.*, 2011, **13**, 1614; (*m*) Y. Yu, D. T. Chen and X. W. Wang, *Adv. Synth. Catal.*, 2011, **353**, 3373; (*n*) S. Guin, S. K. Rout, A. Banerjee, S. Nandi and B. K. Patel, *Org. Lett.*, 2012, **14**, 5294; (*o*) Z. W. Yin and P. P. Sun, *J. Org. Chem.*, 2012, **77**, 11339; (*p*) Y. Wu, P. Y. Choy, F. Mao and F. Y. Kwong, *Chem. Commun.*, 2013, **49**, 689; (*q*) S. Ko, B. Kang and S. Chang, *Angew. Chem., Int. Ed.*, 2005, **44**, 455; (*r*) A. B. Paula, F. G. Areli, C. Arkaitz and M. Ruben, *J. Am. Chem. Soc.*, 2010, **132**, 466; (*s*) B. X. Tang, R. J. Song, C. Y. Wu, Y. Liu, M. B. Zhou, W. T. Wei, G. B. Deng, D. L. Yin and J. H. Li, *J. Am. Chem. Soc.*, 2010, **132**, 8900.

5 CCDC 883839 (**3e**).† Crystal data for compound **3e**: $C_{20}H_{17}NO$, M = 287.35, triclinic, a = 7.9268(9) Å, α = 115.014(13)°, b = 10.2717(13) Å, β = 108.424(12)°, c = 11.4612(16) Å, γ = 93.149(10)°, V = 782.78(18) Å^3, T = 291.15 K, space group = $P\bar{1}$, Z = 2, number of reflections = 6950, independent reflections = 3178, [R_{int} = 0.0205], final R indices [$I > 2\sigma(I)$] R_1 = 0.0450, wR_2 = 0.1098, R indices (all data) R_1 = 0.0625, wR_2 = 0.1209.