Received: 26 May 2016 | Revised: 7 July 2016 | Accepted: 8 July 2016

DOI 10.1002/aoc.3581

WILEY Applied Organometallic Chemistry

FULL PAPER

Polystyrene-supported Pd(II) complex-catalysed carboacylation of 2-arylpyridines with alcohols via C—H bond activation under solvent-free conditions

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Polystyrene-supported *N*,*N*-dimethylethylenediamine Pd(II) complex **C** was used as an efficient catalyst for the synthesis of aromatic ketones via *ortho*-acylation of sp^2 C—H bonds of 2-arylpyridines with alcohols as effective coupling partners. The alcohols were oxidized with *tert*-butyl hydroperoxide to their corresponding aldehydes *in situ* and efficiently coupled with 2-arylpyridines to form aryl ketones under solvent-free conditions. Furthermore, catalyst **C** could be easily recovered by simple filtration and reused for five cycles without any significant decrease in its activity.

KEYWORDS

alcohols, C—H activation, carboacylation, palladium(II) complex, solvent-free conditions

1 | INTRODUCTION

Design and development of efficient, eco-economical, green pathway for direct conversion of C—H bonds into C—C bonds via C—H bond activation with reduced number of synthetic operations has become an important target in organic synthesis.[1–3] Directing group-assisted C—H bond functionalization and cross dehydrogenative coupling are commonly employed strategies due to their being atom- and step-economic for achieving selective functionalizations.[4–6] Transition-metal-catalysed C—H activation and subsequent C—H bond functionalization has achieved great progress in modern synthetic chemistry.[7–11] Ru, Rh, Cu and Pd are commonly employed metals for carbon–carbon bond forming processes.[12,13] Palladium complexes are particularly attractive catalysts for ligand-directed C—H functionalization reactions.[14,15] Their versatility is mainly due to the high compatibility of Pd(II) catalysts with oxidants and their exceptional stability towards moisture and air.

Aryl ketones are prominent structural functionalities in the fragrance, dye and pharmaceutical industries.[16] From economic and environmental points of view, direct introduction of carbonyl functional groups onto aromatics through sp^2 C—H bond acylation is highly advantageous over the existing methods for aryl ketone synthesis. To date several research groups have developed transition-metal-catalysed sp^2 C—H bond acylations with aldehydes, toluenes, diketones, carboxylic acids, arylmethylamines and benzylic ethers as acyl sources.[17–22] However, oxidative acylation at aromatic sp^2 C—H bonds with the use of transition metal and employing alcohols as acyl source is extremely rare. Li and co-workers recently reported oxidative *ortho*-acylation of arylpyridines with benzylic and aliphatic alcohols as acyl source through palladium-catalysed C—H bond activation.[23] Yuan *et al.* also reported C—H bond acylation of acetanilides with benzylic alcohols by employing palladium catalyst.[24] Recently, Kim and co-workers demonstrated Pd-catalysed oxidative sp^2 C—H bond acylation of *N*-benzyltriflamides, 2-phenoxypyridines, ketoximes and aldoximes with alcohols as coupling partners.[25–27] Most of the methods for C—H bond acylation are reported under homogeneous conditions. The main advantage of the polymeric Pd(II) complex (**C**) presented here over existing methods is mainly less catalytic loading, better recyclability, broad scope with excellent yields and ease of preparation of the catalyst. From green and industrial perspectives heterogeneous catalysis is advantageous in view of its ease of

handling with high recyclability. Recently polystyrene-supported transition metal complexes have received much attention in the area of heterogeneous catalysis owing to low cost, chemical inertness with facile functionalization.[28–33] Our research mainly focused on developing simple, economic, green pathways for C—C bond formation reactions. In view of the continuing interest in developing simple recyclable polymer-bound metal complexes, we reported polystyrene-supported Pd(II)–*N*,*N*-dimethylethylenediamine complex **C** and its application to the Suzuki–Miyaura cross-coupling reaction in water.[34]

Herein we report the complex **C**-catalysed *ortho*-acylation of 2-phenylpyridines by employing alcohol derivatives as simple coupling partners. As alcohols are naturally abundant and can be readily oxidized *in situ* into aldehydes, we selected alcohols as carbonyl source.[31] The *ortho*-acylation product was obtained in excellent yields using the recyclable, heterogeneous palladium complex under solvent-free conditions with alcohol as an acylating partner (Scheme 1). This protocol is highly desirable due to it being atom- and step-economic for the direct conversion of C—H bonds to C—C bonds for aryl ketone synthesis.

2 | EXPERIMENTAL

2.1 | Materials and instrumentation

Analytical-grade reagents and freshly distilled solvents were used throughout the experiments. The reagents were supplied by Sigma-Aldrich Chemicals Company, USA, and Merck Co. Liquid substrates were redistilled and dried with appropriate molecular sieves. Distillation and purification of the solvents and substrates were done by standard procedures. The starting materials and reagents were purchased from various commercial sources and used without further purification. ACME silica gel (60–120 mesh) was used for column chromatography. Analytical TLC was performed on pre-coated TLC plates with silica gel 60-F_{254} plates and visualized by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded using tetramethylsilane (TMS) in $CDCl_3$ solvent as the internal standard with a 400, 500 MHz spectrometer (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.00 ppm). Chemical shifts were recorded in ppm with respect to TMS as an internal standard and coupling constants are quoted in hertz (Hz). Mass spectra were recorded with a mass spectrometer using the electron spray ionization (ESI) and the data acquired in positive ionization mode. High-resolution MS (HRMS) was conducted with a TOF-type mass analyser. Fourier transform infrared spectra of samples were recorded with a PerkinElmer FTIR 783 spectrophotometer using KBr pellets. An EXSTAR TG/DTA7200 instrument was used for thermogravimetric analysis. The metal content in the catalyst was determined using a Varian AA240 atomic absorption spectrophotometer.

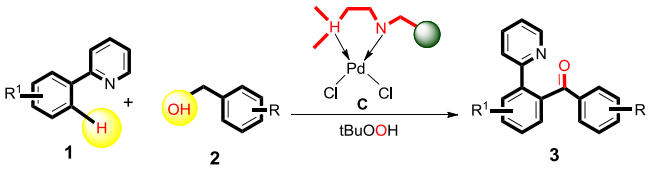
2.2 | General procedure for carbonylation catalysed by polymer-anchored Pd(II) complex (C)

A dried round-bottomed flask equipped with a magnetic stir bar was charged with 25 mg of polymer-anchored Pd(II) catalyst **C**, and 2-phenylpyridine (0.5 mmol), benzyl alcohol (1.0 mmol) and *tert*-butyl hydroperoxide (TBHP; 2.0 mmol) were added to the reaction vessel. The mixture was stirred at 120°C for 12 h, then cooled to room temperature and the catalyst was filtered. The filtrate was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were extracted with water, and dried over anhydrous Na_2SO_4. The organic layers were evaporated under reduced pressure and the resulting crude product was purified by column chromatography using ethyl acetate–hexane (1:4) as eluent to afford the corresponding *ortho*-acylation products. The products were characterized using ^{1}H NMR and ^{13}C NMR spectroscopies and HRMS.

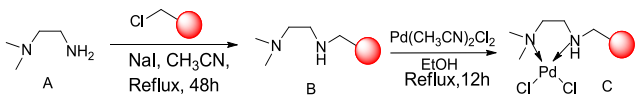
2.3 | Catalytic activity

As polymer-anchored metal complexes exhibit efficient catalytic activity with broad applicability, they have been extensively studied and reported in the literature. In our previous work we studied the complete characterization and their catalytic activity in the field of coupling reactions.[30] Now we decided to investigate the catalytic activity of catalyst **C** in the preparation of benzophenones via the carbonylation reaction with alcohols without using carbon monoxide.

The synthesis of polymer-supported *N*,*N*-dimethylethylenediamine-derived Pd(II) complex **C** is shown in Scheme 2. *N*,*N*-dimethylethylenediamine-functionalized polystyrene resin **B** was formed by heating a mixture of chloromethylated polystyrene and *N*,*N*-dimethylethylenediamine in CH_3CN at 70°C for 48 h. To



SCHEME 1 Acylation of 2-phenylpyridines catalysed by complex C



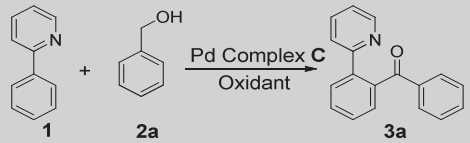
SCHEME 2 Synthesis of *N*,*N*-dimethylethylenediamine-derived Pd(II) complex **C**

B were added EtOH and $Pd(CH_3CN)_2Cl_2$ in 1:1 molar ratio which was then refluxed for 12 h. This resulted in covalent attachment of palladium to give the functionalized polymer complex **C**.

3 | RESULTS AND DISCUSSION

To initiate our study, we examined the carboacylation of 2-phenylpyridines with alcohols in the presence of polymer-supported Pd (II) complex **C** under a variety of reaction conditions. In order to establish the optimum conditions for *ortho*-acylation, we chose 2-phenylpyridine (**1**) and benzyl alcohol (**2a**) as model substrates (Table 1). The effect of various oxidants on the catalytic activity of complex **C** has been studied (entries 1–11). Several oxidants such as $K_2S_2O_8$, O_2, TBHP, H_2O_2 and *tert*-butyl peroxybenzoate (TBPB) were screened at various temperatures (Table 1). However, in the presence of $K_2S_2O_8$, O_2, H_2O_2 and TBPB the desired product was not obtained even at 120°C for 24 h (entries 1–4). To our delight, TBHP proved to be the best oxidant at 120°C for a reaction time of about 12 h and desired product was obtained in 94% yield in the presence of Pd complex **C** (entry 9). But TBHP was ineffective at room temperature with no yield (entry 5) and low yield at 80°C (entry 6). There is a considerable change in yields on increasing the temperature from 100 to 120°C (entries 7 and 8) and reaction time from 6 to 12 h (entries 8 and 9). As expected the desired product was not obtained even in trace amounts in the absence of oxidant, TBHP and catalyst (entries 10 and 11). These optimization studies show that TBHP at 120°C in the presence of Pd complex **C** for 12 h gave the desired product **3a** in 94% yield under solvent-free conditions (Table 1, entry 9).

TABLE 1 Screening of reaction conditions[a]



1 2a 3a

Entry	Oxidant	Temp. (°C)	Time (h)	Yield (%)[b]
1	$K_2S_2O_8$	120	24	—
2	O_2 (1 atm)	120	24	—
3	H_2O_2	120	24	—
4	TBPB	120	24	—
5	TBHP	RT	24	—
6	TBHP	80	24	40
7	TBHP	100	24	73
8	TBHP	120	6	85
9	TBHP	120	12	94
10	—	110	24	—[c]
11	TBHP	110	24	—[d]

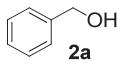
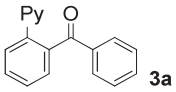
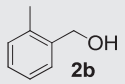
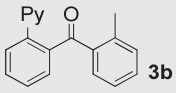
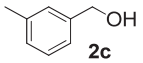
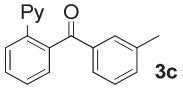
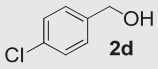
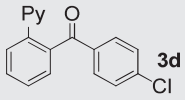
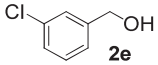
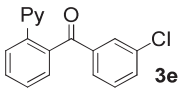
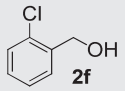
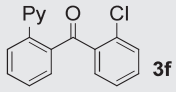
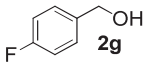
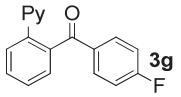
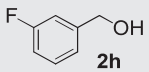
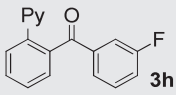
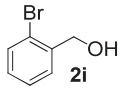
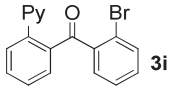
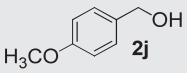
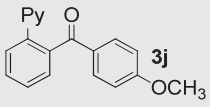
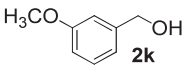
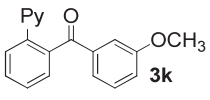
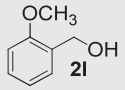
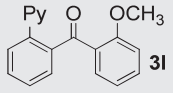
[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), catalyst (25 mg), oxidant (2.0 mmol), solvent-free.

[b]Isolated yield.

[c]No oxidant.

[d]No catalyst.

TABLE 2 Acylation reaction of 2-phenylpyridine with a variety of benzyl alcohols[a]

Entry	Alcohol	Produt	Yield (%)
1	 2a	 3a	94
2	 2b	 3b	82
3	 2c	 3c	86
4	 2d	 3d	82
5	 2e	 3e	80
6	 2f	 3f	78
7	 2g	 3g	80
8	 2h	 3h	78
9	 2i	 3i	75
10	 2j	 3j	91
11	 2k	 3k	88
12	 2l	 3l	84

[a]Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), catalyst (25 mg), oxidant (2.0 mmol), 120°C for 12 h.

[b]Isolated yield.

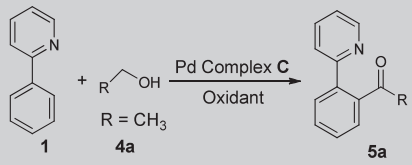
The direct *ortho*-acylation of 2-phenylpyridine with various alcohols was conducted under the optimized reaction conditions, and the results are summarized in Table 2. The reactions with benzylic alcohols bearing electron-donating groups (entries 1–3 and 10–12) and electron-withdrawing substituents at the aromatic ring (entries 4–9) proceeded to give the desired products in good to excellent yields. There is considerable influence on the yields for *ortho*, *para* and *meta* isomers of alcohol derivatives. The *ortho* isomer-containing products had low yields (**3b**, **3f**, **3i** and **3l**) when compared to *para* or *meta* isomers due to steric hindrance (**3d**, **3g**, **3j** and **3c**, **3e**, **3h**, **3k**). However electron-donating group-substituted acylated products (OMe, CH_3) gave better yields than electron-withdrawing substituents (F, Cl and Br). The OMe-substituted *para*, *meta*, *ortho* gave (**3j**) 91%, (**3k**) 88%, (**3l**) 84% yields and Me-substituted *meta*, *ortho* resulted in (**3c**) 86%, (**3b**) 82% yields of the desired products. In the case of chloro-substituted *para*, *meta*, *ortho* the desired product was obtained in (**3d**) 82%, (**3e**) 80%, (**3f**) 78% yields and fluoro-substituted *para*, *meta* in (**3g**) 80%, (**3h**) 78% yields, whereas *meta*-substituted bromo gave (**3i**) 75% yield. The most interesting result is that Ar—Br (**3i**) group is tolerated since Pd species might be expected to cleave C—Br bonds easily.

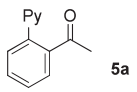
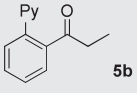
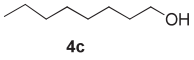
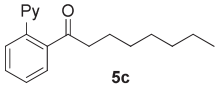
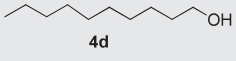
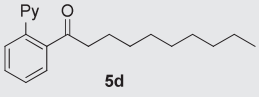
In addition we also tested the reaction with more challenging aliphatic alcohols for direct aroylation of 2-phenylpyridines under the optimized reaction conditions, and the results are summarized in Table 3. It is noted that ethanol and propanol resulted in trace amounts of the desired product (Table 3, entries 1 and 2). However, the reaction gave the monoacylation product selectively with 1-octanol and 1-decanol in (**5c**) 85% and (**5d**) 88% yields, respectively (Table 3, entries 3 and 4).

Further, we extended scope of the reaction with various substituted arylpyridines for the directed aroylation of 2-arylpyridines under the optimized reaction conditions, and the results are presented in Table 4. Functional groups including Me, OMe, OEt, COMe and naphthyl were compatible and the desired products were obtained in excellent yields. For example, arylpyridines substituted with 4-methyl, ethoxy and methoxy (which bears a strong electron-donating group) afforded the desired products **6a**, **6b** and **6c** in 91, 89 and 93%, respectively. Whereas **6d** and **6e** were obtained in 90 and 86% yields and **6g** in 88% yield. In the case of naphthyl-substituted pyridine, the desired product **6f** was also obtained in 85% yield. Thus the aroylation reaction selectively gave the monoacylated products with a variety of 2-phenylpyridines.

The recyclability of the polymer-anchored Pd(II) complex **C** was tested in the acylation of 2-phenylpyridine and benzyl alcohol. As shown in Figure 1, the catalyst can be reused for five cycles with only 4% decline of activity after the fifth recycle. The leaching of palladium from the polymer-anchored Pd(II) complex **C** was confirmed by carrying out atomic absorption spectroscopic analysis. The analytical data for the used catalyst did not show

TABLE 3 Acylation reaction of 2-phenylpyridines with aliphatic alcohols[a]

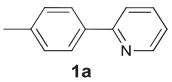
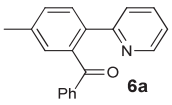
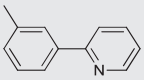
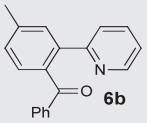
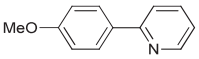
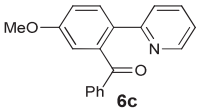
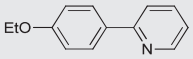
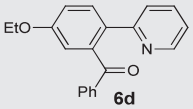
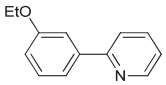
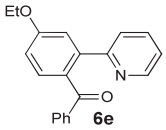
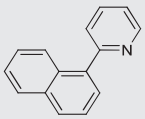
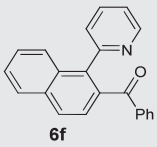
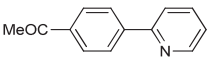
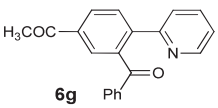


Entry	Alcohol	Product	Yield (%)[b]
1	 4a	 5a	trace
2	 4b	 5b	trace
3	 4c	 5c	85
4	 4d	 5d	88

[a]Reaction conditions: **1** (0.5 mmol), **4** (1.0 mmol), catalyst (25 mg), oxidant (2.0 mmol), 120°C for 12 h.

[b]Isolated yield.

TABLE 4 Acylation reaction of a variety of 2-phenylpyridines with benzyl alcohol[a]

Entry	2-Phenylpyridine	Product	Yield (%)[b]
1	 1a	 6a	91
2	 1b	 6b	89
3	 1c	 6c	93
4	 1d	 6d	90
5	 1e	 6e	86
6	 1f	 6f	85
7	 1g	 6g	88

[a]Reaction conditions: **1a–g** (0.5 mmol), **2a** (1.0 mmol), catalyst (25 mg), oxidant (2.0 mmol), 120°C for 12 h.

[b]Isolated yield.

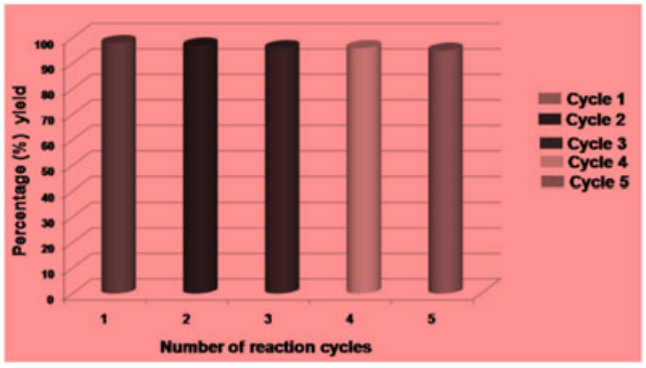


FIGURE 1 Recyclability of polymer-anchored Pd(II) complex C

appreciable loss in palladium content as compared to the fresh catalyst, indicating the heterogeneous nature of this complex.

4 | CONCLUSIONS

In view of minimizing the waste/side product formation for acylation with benzyl alcohol for (hetero)arenes bearing *ortho*-directing group, we have developed a simple recyclable Pd(II) catalyst. This heterogeneous catalyst is versatile, active and stable, and can be reused for five cycles without appreciable loss of activity, indicating effective anchoring of the polymer. It is noteworthy that this heterogeneous palladium complex gave the *ortho*-acylation products in excellent yields under solvent-free conditions with broad substrate scope. Thus this represents an efficient, eco-economical, green pathway for carbonylation/*ortho*-acylation of 2-phenylpyridines.

ACKNOWLEDGMENTS

P.S.P. gratefully acknowledges the financial assistance provided by CSIR-Senior Research Associateship (Scientist's Pool Scheme), New Delhi and P.C.P. (UGC-SRF) is grateful for the fellowship provided by UGC, Government of India. We also acknowledge the director IICT for providing infrastructural facilities.

REFERENCES

[1] J. Q. Yu, Z. J. Shi, *C-H Activation*, Springer, Berlin **2010**.

[2] G. Dyker, *Handbook of C-H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim **2005**.

[3] J. F. Hartwig, *Nature* **2008**, *455*, 314.

[4] O. Daugulis, H. Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074.

[5] D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624.

[6] C. J. Li, *Acc. Chem. Res.* **2009**, *42*, 335.

[7] C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Rev.* **2011**, *111*, 1293.

[8] D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174.

[9] R. Giri, B. Shi, K. Engle, N. Maugel, J. Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242.

[10] M. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 2243.

[11] X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094.

[12] P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879.

[13] C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138.

[14] T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147.

[15] G. Dyker, *Handbook of C–H Transformations: Applications in Organic Synthesis*, Wiley-VCH, Weinheim **2005**.

[16] H. Surburg, J. Panten, *Common Fragrance and Flavor Materials*, 5th ed., Wiley-VCH, Weinheim **2006**.

[17] Y. Shin, S. Sharma, N. K. Mishra, S. Han, J. Paek, H. Oh, J. Ha, H. Yoo, Y. H. Jung, I. S. Kim, *Adv. Synth. Catal.* **2015**, *357*, 594.

[18] S. Guin, S. K. Rout, A. Banerjee, S. Nandi, B. K. Patel, *Org. Lett.* **2012**, *14*, 5294.

[19] W. Zhou, H. Li, L. Wang, *Org. Lett.* **2012**, *14*, 4594.

[20] J. Lu, H. Zhang, X. Chen, H. Liu, Y. Jiang, H. Fu, *Adv. Synth. Catal.* **2013**, *355*, 529.

[21] Q. Zhang, F. Yang, Y. Wu, *Chem. Commun.* **2013**, *49*, 6837.

[22] S. Han, S. Sharma, J. Park, M. Kim, Y. Shin, N. K. Mishra, J. J. Bae, J. H. Kwak, Y. H. Jung, I. S. Kim, *J. Org. Chem.* **2014**, *79*, 275.

[23] F. Xiao, Q. Shuai, F. Zhao, O. Baslé, G. Deng, C.-J. Li, *Org. Lett.* **2011**, *13*, 1614.

[24] Y. Yuan, D. Chen, X. Wang, *Adv. Synth. Catal.* **2011**, *353*, 3373.

[25] J. Park, A. Kim, S. Sharma, M. Kim, E. Park, Y. Jeon, Y. Lee, J. H. Kwak, Y. H. Jung, I. S. Kim, *Org. Biomol. Chem.* **2013**, *11*, 2766.

[26] M. Kim, S. Sharma, J. Park, M. Kim, Y. Choi, Y. Jeon, J. H. Kwak, I. S. Kim, *Tetrahedron* **2013**, *69*, 6552.

[27] S. Sharma, M. Kim, J. Park, M. Kim, J. H. Kwak, Y. H. Jung, J. S. Oh, Y. Lee, I. S. Kim, *Eur. J. Org. Chem.* **2013**, 6656.

[28] T. Kang, Q. Feng, M. Luo, *Synlett* **2005**, *15*, 2305.

[29] S. M. Islam, S. Mondal, P. Mondal, A. S. Roy, K. Tuhina, M. Mobarok, S. Paul, N. Salam, D. Hossain, *Catal. Lett.* **2011**, *141*, 1171.

[30] M. Bakherad, S. Jajarmi, *J. Mol. Catal. A* **2013**, *370*, 152.

[31] K. Srinivas, P. Sai Prathima, D. Govardhan, M. Mohan Rao, *J. Organomet. Chem.* **2014**, *765*, 31.

[32] K. Srinivas, P. Sai Prathima, M. Mohan Rao, *Appl. Catal. A* **2015**, *496*, 58.

[33] K. Balaswamy, P. C. Pullaiah, K. Srinivas, M. M. Rao, *Inorg. Chim. Acta* **2014**, *423*, 95.

[34] G. Dobereiner, R. Crabtree, *Chem. Rev.* **2010**, *110*, 681.

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How to cite this article: Perumgani, P. C., Parvathaneni, S. P., Keesara, S., and Mandapati, M. R. (2016), Polystyrene-supported Pd(II) complex-catalysed carboacylation of 2-arylpyridines with alcohols via C─H bond activation under solvent-free conditions, *Appl. Organometal. Chem.*, doi: 10.1002/aoc.3581