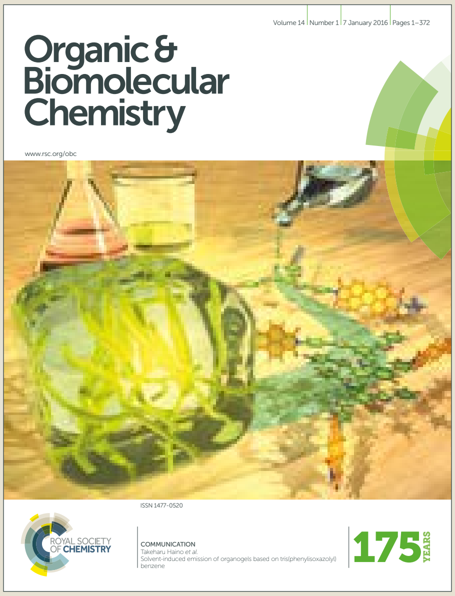
View Article Online
View Journal

Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: Q. Liu, B. He, P. Qian and L. Shao, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C6OB02704K.



Volume 14 | Number 1 | 7 January 2016 | Pages 1–372

Organic & Biomolecular Chemistry

www.rsc.org/obc

ISSN 1477-0520

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION
Takeharu Haino et al.
Solvent-induced emission of organogels based on tris(phenylisoxazolyl)benzene

175 YEARS

View Article Online
DOI: 10.1039/C6OB02704K

N-Heterocyclic carbene-palladium(II)-1-methylimidazole complex catalyzed direct C-H bond arylation of imidazo[1,2-*a*]pyridines with aryl chlorides

Qing-Xian Liu, Bang-Yue He, Peng-Cheng Qian* and Li-Xiong Shao*

Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
First published on the web Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

We herein reported the *N*-heterocyclic carbene-palladium(II)-1-methylimidazole complex catalyzed direct C-H bond arylation of imidazo[1,2-*a*]pyridines with aryl chlorides. Under the suitable conditions, all reactions between various imidazo[1,2-*a*]pyridines and aryl chlorides worked well to give the desired C3-H arylated products in acceptable to high yields, giving a convenient and alternative method for the direct C-H bond arylation of imidazo[1,2-*a*]pyridines, using the economic and easily available aryl chlorides as the arylating reagents.

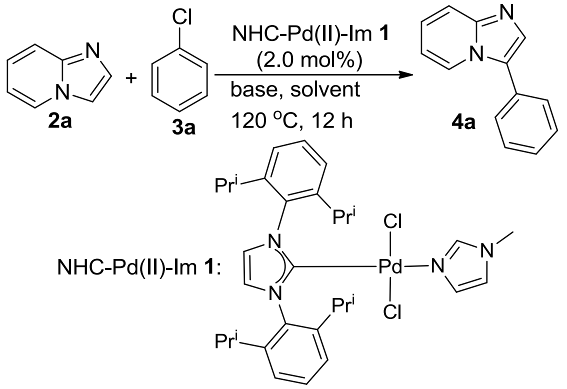
Introduction

During the past years, the transition metal catalyzed direct C-H bond functionalization, which at least can avoid pre-functionalization for one of the substrates, has proven one of the most efficient methods to construct new carbon-carbon and carbon-heteroatom bonds.[1] As a consequence, the direct C-H bond arylation has also been fully developed, and various arylating reagents such as aryl halides, arylmetallic reagents, phenol derivatives, etc., have been used in such transformation.[2] Among them, aryl halides seem to be the most desirable because of their easy availability and economy. However, in most cases, only the more active, while more expensive aryl iodides and bromides were successfully developed, and the economic, stable and easier available aryl chlorides were rarely used, maybe partially due to the lower catalytic activity of the metal catalysts developed during the past years. Therefore, much room still remains in the direct C-H bond arylation, especially using aryl chlorides as the substrates. From 2011, we have developed a well-defined *N*-heterocyclic carbene-palladium(II)-1-methylimidazole [NHC-Pd(II)-Im] complex **1**, and showed it to be a highly efficient catalyst toward not only traditional cross-coupling reactions such as C-C and C-N coupling reactions,[3] but also direct C-H bond arylation reactions using aryl chlorides as the substrates.[4] For instance, recently, we found that NHC-Pd(II)-Im complex **1** was an efficient catalyst for the direct C-H bond arylation of (benzo)oxazoles using aryl chlorides as the arylating reagents, implying that this complex can really activate the less active aryl chlorides toward C-H bond arylation reactions very well.[4b] These results thus prompted us to further investigate its application in the direct C-H bond arylation of other interesting compounds to expand its impact in organic synthesis. In this case, imidazo[1,2-*a*]pyridines were chosen as the substrates, because such compounds are frequently found in kinds of natural products and drugs.[5] Undoubtedly, the direct C-H bond arylation of imidazo[1,2-*a*]pyridines was also developed by several groups during the past years.[6] However, to the best of our knowledge, only the more active aryl bromides, iodides and aryl triflates can be used as the arylating reagents, and aryl chlorides were rarely investigated so far.[7] Therefore, based on our successful experiences on the NHC-Pd(II)-Im complex **1** catalyzed direct C-H bond arylation using aryl chlorides, we then turned our interests to the NHC-Pd(II)-Im complex **1** catalyzed direct C-H bond arylation of imidazo[1,2-*a*]pyridines with aryl chlorides. Herein, we report these results in detail.

Results and discussion

At the outset of this investigation, the reaction of imidazo[1,2-*a*]pyridine **2a** (0.5 mmol) with chlorobenzene **3a** (0.75 mmol) catalyzed by NHC-Pd(II)-Im complex **1** (2.0 mol%) in dioxane (0.5 mL) at 120 ^oC for 12 h was first carried out to test various bases (3.0 equiv) (Table 1, entries 1-8). As can be seen from Table 1, among the bases screened, NaO^{t}Bu gave the best yield of 89% (Table 1, entry 1). In the presence of all other bases, inferior results were found. For example, acceptable yields (49 and 38%) can still be obtained when KO^{t}Bu and KOH were used, respectively (Table 1, entries 2 and 3). In the presence of other bases such as NaOH, Cs_2CO_3, K_3PO_4, LiO^{t}Bu and LiOH, very low yields were observed (Table 1, entries 4-8). Using other bases such as Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, CH_3COOK and Li_2CO_3, no reaction occurred. Subsequently, using NaO^{t}Bu as the base, kinds of solvents were then examined. For example, in these cases, the best yield of 92% was obtained when THF was used as the solvent (Table 1, entry 9). When toluene was chosen as the solvent, good yield can also be obtained (Table 1, entry 10). In polar solvents such as DMAc and DMF, very lower yields were obtained (Table 1, entries 11 and 12), and no desired product was detected in CH_3CN and DMSO, respectively. Finally, it was found that 3.0 equiv NaO^{t}Bu was necessary for such transformation. For instance, when the amount of NaO^{t}Bu decreased to 2.0 equiv for the reaction shown in entry 9, the yield drastically dropped to 41%. Using $Pd(OAc)_2$ or $PdCl_2$ as the catalyst instead of NHC-Pd(II)-Im complex **1**, almost no desired product can be detected. Based on the above tries, the optimized reaction conditions were then established: **2a** (0.5 mmol), **3a** (0.75 mmol), NaO^{t}Bu (3.0 equiv), NHC-Pd(II)-Im complex **1** (2.0 mol%), THF (0.5 mL), 120 ^oC, 12 h.[8]

Table 1. Optimization for the NHC-Pd(II)-Im complex **1** catalyzed reaction of **2a** with **3a**.

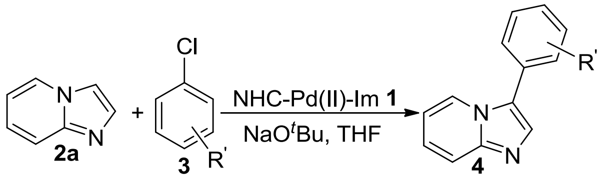


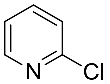
Entry^a	Base	Solvent	Yield (%)^b
1	NaO^{t}Bu	dioxane	89
2	KO^{t}Bu	dioxane	49
3	KOH	dioxane	38
4	NaOH	dioxane	9
5	Cs_2CO_3	dioxane	<5
6	K_3PO_4	dioxane	<5
7	LiO^{t}Bu	dioxane	<5
8	LiOH	dioxane	<5
9	NaO^{t}Bu	THF	92
10	NaO^{t}Bu	toluene	80
11	NaO^{t}Bu	DMAc	37
12	NaO^{t}Bu	DMF	9

^{a}All reactions were carried out using **2a** (0.5 mol), **3a** (0.75 mmol), **1** (2.0 mol%), base (3.0 equiv), solvent (0.5 mL) at 120 °C for 12 h. ^{b}Isolated yields.

Under the optimal conditions, the reactions of imidazo[1,2-*a*]pyridine **2a** with a variety of aryl chlorides **3** were first investigated to test the scope and limitation of this methodology. The results are shown in Table 2. It seems that under the suitable conditions, all reactions can perform well to give the desired C3-arylated products **4** in acceptable to good yields. Substituents on the aryl chlorides **3** affected the reactions significantly. That is, aryl chlorides having electron-rich groups were relatively worse substrates under the optimal conditions. For example, using 2- or 3-methoxyphenyl chlorides **3b** and **3c**, and 4-methylphenyl chloride **3g** as the substrates, lower yields were obtained under identical conditions (Table 2, entries 2, 5 and 12). To our pleasure, simply increasing the catalyst loading or prolonging the reaction time, better yields can be still observed (Table 2, entries 4, 6 and 13). It was found that fluoro-substituted aryl chlorides are the most suitable substrates. For instance, the best yields were found when 2-, 3- or 4-fluorophenyl chlorides **3h-j** were used as the substrates under the optimal conditions (Table 2, entries 14-16). In addition, when strongly electron-poor group substituted aryl chlorides such as 4-nitrophenyl chloride, 2-cyanophenyl chloride, 3-cyanophenyl chloride, 4-cyanophenyl chloride, 2-acetylphenyl chloride, were tested in the reactions with imidazo[1,2-*a*]pyridine **2a** under the optimal conditions, no desired product was detected in all cases. Only 45% yield of the corresponding arylated product **4k** was obtained when 4-vinylphenyl chloride **3k** was tested (Table 2, entry 17). Satisfyingly, elevating the temperature to 130 °C, the corresponding yield can drastically increase to 74% (Table 2, entry 18). Acceptable yield was found when heteroaryl chloride such as 2-chloropyridine was used (Table 2, entries 19 and 20).

Table 2. NHC-Pd(II)-Im **1** catalyzed reactions of **2a** with **3**.

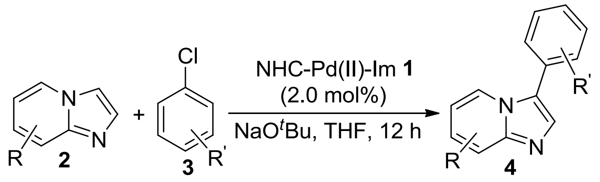


Entry^a	3 (R')	Temp/°C	Time/h	Yield (%)^b
1	**3a** (H)	120	12	**4a**, 92
2	**3b** (2-OMe)	120	12	**4b**, 37
3	**3b**	130	12	**4b**, 42
4^c	**3b**	120	12	**4b**, 71
5	**3c** (3-OMe)	120	12	**4c**, 51
6	**3c**	120	24	**4c**, 69
7	**3d** (4-OMe)	120	12	**4d**, 68
8	**3d**	130	12	**4d**, 67
9	**3e** (2-Me)	120	12	**4e**, 84
10	**3f** (3-Me)	120	12	**4f**, 71
11	**3f**	130	12	**4f**, 79
12	**3g** (4-Me)	120	12	**4g**, 40
13	**3g**	120	24	**4g**, 83
14	**3h** (2-F)	120	12	**4h**, 84
15	**3i** (3-F)	120	12	**4i**, 82
16	**3j** (4-F)	120	12	**4j**, 86
17	**3k** (4-vinyl)	120	12	**4k**, 45
18	**3k**	130	12	**4k**, 74
19	**3l**  N Cl	120	12	**4l**, 33
20	**3l**	130	24	**4l**, 45

^{a}Otherwise specified, all reactions were carried out using **2a** (0.5 mmol), **3** (0.75 mmol), **1** (2.0 mol%), NaO^{t}Bu (3.0 equiv) in THF (0.5 mL). ^{b}Isolated yields. ^{c}**1** (4.0 mol%)

Next, the scope of this protocol was further expanded to the direct C-H bond arylation between various substituted imidazo[1,2-*a*]pyridines **2** and aryl chlorides **3**. As can be seen from Table 3, all reactions performed well to give the desired C-H bond arylated products **4** in good to high yields. It seems that compared to the results involving unsubstituted imidazo[1,2-*a*]pyridine **2a** illustrated in Table 2, better yields can be observed in most cases (Table 3). Substituents on the imidazo[1,2-*a*]pyridines **2** affected the reactions to some extent. For instance, substrate **2e**, having electron-poor 6-fluoro group, gave relatively worse results (Table 3, entries 19-22). Substituents on the aryl chlorides **3** did not affect the reactions significantly. For instance, aryl chlorides **3** having electron-rich, -neutral and -poor groups were all suitable substrates in the reactions investigated. In addition, sterically-hindered 2-fluoroaryl chloride **3h** were also good substrate in such transformation to give the corresponding products **4p**, **4u**, **4z** and **4af** in good to high yields (Table 3, entries 4, 9, 16 and 22).

Table 3. NHC-Pd(II)-Im **1** catalyzed reactions of **2** with **3**.



Entry[a]	**2** (R)	**3** (R')	Yield (%)[b]
1	**2b** (7-Me)	**3a** (H)	**4m**, 94
2	**2b**	**3c** (3-OMe)	**4n**, 88
3	**2b**	**3f** (3-Me)	**4o**, 91
4	**2b**	**3h** (2-F)	**4p**, 84
5	**2b**	**3j** (4-F)	**4q**, 90
6	**2c** (6-Me)	**3a**	**4r**, 94
7	**2c**	**3c**	**4s**, 79
8	**2c**	**3f**	**4t**, 95
9	**2c**	**3h**	**4u**, 92
10	**2c**	**3i** (3-F)	**4v**,92
11	**2c**	**3j**	**4w**, 73
12[c]	**2c**	**3j**	**4w**,87
13	**2d** (7-OMe)	**3a**	**4x**, 76
14[c]	**2d**	**3a**	**4x**, 87
15	**2d**	**3f**	**4y**, 85
16	**2d**	**3h**	**4z**, 84
17	**2d**	**3i**	**4aa**, 73
18	**2d**	**3j**	**4ab**, 81
19	**2e** (6-F)	**3a**	**4ac**, 68
20	**2e**	**3c**	**4ad**, 60
21	**2e**	**3f**	**4ae**, 63
22	**2e**	**3h**	**4af**, 81

[a]Otherwise specified, all reactions were carried out using **2** (0.5 mmol), **3** (0.75 mmol), **1** (2.0 mol%), NaO^{t}Bu (3.0 equiv), THF (0.5 mL) at 120 °C for 12 h. [b]Isolated yields. [c]130 °C.

Conclusions

In conclusion, it was reported that NHC-Pd(II)-Im complex, as an air- and moisture-stable catalyst, can promote the direct C-H bond arylation of imidazo[1,2-*a*]pyridines using the challenging aryl chlorides as the arylating reagents. Under the suitable conditions, most reactions performed well enough to give the desired C3-H bond arylated products in moderate to high yields. The scope and limitation of such transformation was fully investigated with various substrates, displaying that kinds of substituents on both substrates can be tolerated, thus giving an alternative and facile methodology for the direct C-H bond arylation of imidazo[1,2-*a*]pyridines.

Experimental

General Remarks. Melting points are uncorrected. NMR spectra were recorded at 500 MHz (for ^{1}H NMR) and 125 MHz (for ^{13}C NMR), respectively. ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$ solutions were referenced to TMS (0.00 ppm) and the residual solvent peak (77.0 ppm), respectively. *J*-values are in Hz. All solvents were dried by standard methods. The mass analyzer type for the high resolution mass spectra (HRMS) is quadrupole (for ESI). Other commercially obtained reagents were used without further purification. Flash column chromatography was performed on silica gel (300-400 mesh).

General procedure for the NHC-Pd(II)-Im complex 1 catalyzed C-H bond arylation of imidazo[1,2-*a*]pyridines 2 with aryl chlorides 3. Under N_2 atmosphere, NHC-Pd(II)-Im complex **1** (2.0 mol%), NaO^{t}Bu (3.0 equiv), THF (0.5 mL), imidazo[1,2-*a*]pyridines **2** (0.5 mmol), and aryl chlorides **3** (0.75 mmol) were successively added into a sealed tube. The mixture was stirred vigorously under the conditions shown in Tables 1-3. Then the solvent was removed under reduced pressure and the residue was purified by flash column chromatography to give the pure products **4**.

Acknowledgement

Peng-Cheng Qian thanks the Financial support from the Foundation of Department of Education, Zhejiang Province (No. Y201327597) and Natural Science Foundation of Zhejiang Province (No. LY15B020002).

Notes and references

College of Chemistry and Materials Engineering, Wenzhou University, Chashan University Town, Wenzhou, Zhejiang Province 325035, People's Republic of China. Fax: 86 57786689300; Tel: 86 57786689300; E-mail: Shaolix@wzu.edu.cn

† Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C NMR spectra of compounds **4**.]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 For some recent reviews on the direct C-H bond functionalization, please see: (*a*) R. Rossi, F. Bellina, M. Lessi and C. Manzini, *Adv. Synth. Catal.*, 2014, **356**, 17; (*b*) H. Bonin, M. Sauthier and F.-X. Felpin, *Adv. Synth. Catal.*, 2014, **356**, 645; (*c*) O. Daugulis, *Chem. Heterocycl. Compd.*, 2012, **48**, 21; (*d*) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem. Int. Ed.*, 2012, **51**, 10236; (*e*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (*f*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*g*) D.-G. Yu, B.-J. Li and Z.-J. Shi, *Tetrahedron*, 2012, **68**, 5130; (*h*) J. F. Hartwig, *Chem. Soc. Rev.*, 2011, **40**, 1992; (*i*) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976; (*j*) F. Bellina and R. Rossi, *Tetrahedron*, 2009, **65**, 10269.
2 For some recent reviews, please see: (*a*) Y.-X. Su and L.-P. Sun, *Mini-Rev. Org. Chem.*, 2012, **9**, 87; (*b*) G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447; (*c*) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792; (*d*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174.

View Article Online
DOI: 10.1039/C6OB02704K

3 For traditional cross-coupling reactions, please see: (*a*) H.-Y. Yin, M.-Y. Liu and L.-X. Shao, *Org. Lett.*, 2013, **15**, 6042; (*b*) Z.-K. Xiao, H.-Y. Yin and L.-X. Shao, *Org. Lett.*, 2013, **15**, 1254; (*c*) W.-X. Chen and L.-X. Shao, *J. Org. Chem.*, 2012, **77**, 9236; (*d*) T.-T. Gao, A.-P. Jin and L.-X. Shao, *Beilstein J. Org. Chem.*, 2012, **8**, 1916; (*e*) Z.-S. Gu, L.-X. Shao and J.-M. Lu, *J. Organomet. Chem.*, 2012, **700**, 132; (*f*) L. Zhu, T.-T. Gao and L.-X. Shao, *Tetrahedron*, 2011, **67**, 5150; (*g*) Y.-Q. Tang, J.-M. Lu and L.-X. Shao, *J. Organomet. Chem.*, 2011, **696**, 3741.

4 (*a*) S.-C. Yin, Q. Zhou, X.-Y. Zhao and L.-X. Shao, *J. Org. Chem.*, 2015, **80**, 8916; (*b*) X.-B. Shen, Y. Zhang, W.-X. Chen, Z.-K. Xiao, T.-T. Hu and L.-X. Shao, *Org. Lett.*, 2014, **16**, 1984; (*c*) Z.-S. Gu, W.-X. Chen and L.-X. Shao, *J. Org. Chem.*, 2014, ***79***, 5806; (*d*) Y.-Y. Ji, L.-L. Lu, Y.-C. Shi and L.-X. Shao, *Org. Biomol. Chem.*, 2014, **12**, 8488.

5 (*a*) M. Marcinkowska, M. Kołaczkowski, K. Kamiński, A. Bucki, M. Pawłowski, A. Siwek, T. Karcz, B. Mordyl, G. Starowicz, P. Kubowicz, E. Pękala, A. Wesołowska, J. Samochowiec, P. Mierzejewski and P. Bienkowski, *Eur. J. Med. Chem.*, 2016, **124**, 456; (*b*) M. Lwason, J. Rodrigo, B. Baratte, T. Robert, C. Delehouźe, O. Lozach, S. Ruchaud, S. Bach, J.-D. Brion, M. Alami and A. Hamze, *Eur. J. Med. Chem.*, 2016, **123**, 105; (*c*) N. Dahan-Farkas, C. Langley, A. L. Rousseau, D. B. Yadav, H. Davids and C. B. de Koning, *Eur. J. Med. Chem.*, 2011, **46**, 4573; (*d*) M. L. Bode, D. Gravestock, S. S. Moleele, C. W. van der Westhuyzen, S. C. Pelly, P. A. Steenkamp, H. C. Hoppe, T. Khan and L. A. Nkabinde, *Bioorg. Med. Chem.*, 2011, **19**, 4227; (*e*) A. Linton, P. Kang, M. Ornelas, S. Kephart, Q. Hu, M. Pairish, Y. Jiang and C. Guo, *J. Med. Chem.*, 2011, **54**, 7705; (*f*) G. Trapani, M. Franco, A. Latrofa, L. Ricciardi, A. Carotti, M. Serra, E. Sanna, G. Biggio and G. Liso, *J. Med. Chem.*, 1999, **42**, 3934.

6 For aryl halides and triflates as the arylating reagents, please see: (*a*) C.-H. Ke, B.-C. Kuo, D. Nandi and H. M. Lee, *Organometallics*, 2013, **32**, 4775; (*b*) J. Lee, J. Chun, S. M. Byun, B. Moon Kim and C. Lee, *Tetrahedron*, 2013, **69**, 5660; (*c*) S. Kona, R. S. Ravi, M. Chakravarty and V. N. R. Chava, *J. Chem.*, 2013, 305934; (*d*) Y. Liu, L. He, G.-Q. Yin, G.-J. Wu and Y.-D. Cui, *Bull. Korean Chem. Soc.*, 2013, **34**, 2340; (*e*) H.-Y. Fu, L. Chen and H. Doucet, *J. Org. Chem.*, 2012, **77**, 4473; (*f*) H. Yang, L.-P. Yang, Y. Li, F. Zhang, H.-J. Liu and B. Yi, *Catal. Commun.*, 2012, **26**, 11; (*g*) H. Cao, H.-Y. Zhan, Y.-G. Lin, X.-L. Lin, Z.-D. Du and H.-F. Jiang, *Org. Lett.*, 2012, **14**, 1688; for arylmetallic compounds as the arylating reagents, please see: (*h*) L.-M. Zhao, H.-Y. Zhan, J.-Q. Liao, J.-P. Huang, Q.-L. Chen, H.-F. Qiu and H. Cao, *Catal. Commun.*, 2014, **56**, 65; for aryl tosylates and mesylates as the arylating reagents, please see: (*i*) P. Y. Choy, K. C. Luk, Y.-N. Wu, C. M. So, L.-L. Wang and F. Y. Kwong, *J. Org. Chem.*, 2015, **80**, 1457; for arenes as the arylating reagents, please see: (*j*) S.-H. Wang, W.-J. Liu, J.-H. Cen, J.-Q. Liao, J.-P. Huang and H.-Y. Zhan, *Tetrahedron Lett.*, 2014, **55**, 1589.

7 For a pioneering work between 2-substituted imidazo[1,2-*a*]pyridines with aryl chlorides in the presence of palladium salt and phosphine ligand, please see: H. Cao, Y.-G. Lin, H.-Y. Zhan, Z.-D. Du, X.-L. Lin, Q.-M. Liang and H. Zhang, *RSC Adv.*, 2012, **2**, 5972.

8 Other similar NHC-Pd(II) complexes having different *N*-containing ancillary ligands such as morpholine, quinoline, isoquinoline, 3-chloropyridine, have also been tested under the optimal conditions, and slightly lower yields (81%, 80%, 82% and 81%) were observed. Please see: (*a*) Z.-Y. Wang, Q.-N. Ma, R.-H. Li and L.-X. Shao, *Org. Biomol. Chem.*, 2013, **11**, 7899; (*b*) F. Liu, Y.-R. Zhu, L.-G. Song and J.-M. Lu, *Org. Biomol. Chem.*, 2016, **14**, 2563; (*c*) C. J. O'Brien, E. A. B. Kantchev, C. Valente, N. Hadei, G. A. Chass, A. Lough, A. C. Hopkinson and M. G. Organ, *Chem. Eur. J.*, 2006, **12**, 4743.