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Pd-catalyzed oxidative C–H/C–H cross-coupling of pyridines with heteroarenes†

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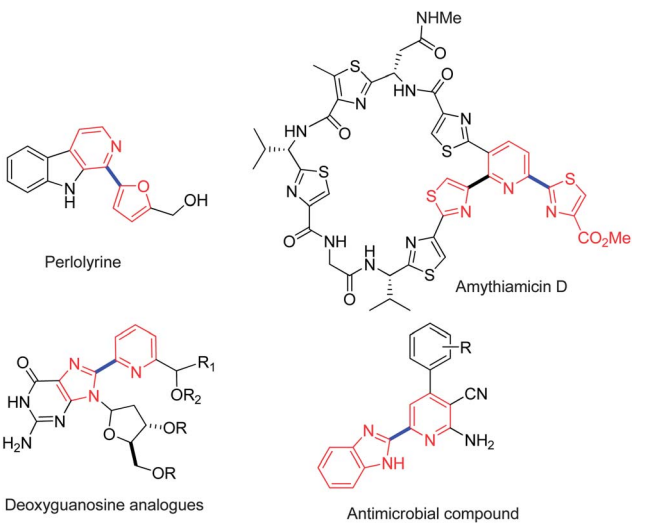
We have developed for the first time a general, concise and highly selective method for the C2-heteroarylation of pyridines and related azines with a broad range of heteroarenes *via* a two-fold C–H activation, which streamlines the previous approaches that require the activated azine *N*-oxide as the coupling partner.

Introduction

Biheteroaryls containing pyridines and related azines (*e.g.*, quinolines, isoquinolines, pyrimidines, pyrazines, pyridazines and quinoxalines) present privileged architectural units frequently found in natural products, pharmaceuticals, bioactive molecules, ligands and other functional synthetic materials (Scheme 1).[1] Catalytic oxidative C–H/C–H cross-coupling between two (hetero)arenes would be one of the most attractive approaches to forge these bi(hetero)aryl units. Since the pioneering work by Fagnou and co-workers on the transition metal-catalyzed oxidative C–H/C–H coupling of indoles with unactivated arenes set up a stage for this field of study,[2] significant progress has been made to assemble various bi(hetero)aryl scaffolds.[3] While a variety of heteroarenes have shown to be adequate coupling substrates,[4] the dehydrogenative (hetero)arylation of pyridine and related azine derivatives still remains particularly challenging, due to the poor electron density of the ring and the strong tendency to bind to a metal center through the nitrogen atom, that may lead to metal sequestration and deactivation.[5,6] More recently, we and others achieved the C2-selective heteroarylations of azine *N*-oxides with π-electron excessive five-membered heterocycles to form unsymmetrical biheteroaryls (Scheme 2).[7] From an academic and step-economic point of view, it would be highly desirable to directly use an unactivated azine instead of the activated azine *N*-oxide as a coupling partner.

The transition metal-catalyzed direct C–H functionalization of pyridines has long been identified as a great challenge by the synthetic organic chemistry community.[8–15] The pioneering works by Bergman, Ellman, Nakao and Hiyama demonstrated selective C2–H alkylation or alkenylation, and selective C4–H alkylation of pyridines by nickel/Lewis acid catalysis.[13] Recently, the Yu group developed a novel Pd-catalyzed arylation and olefination at the pyridine C3 position based on a ligand-assisted strategy.[12,14] The Sames group realized the C3/C4 selective arylation of pyridines containing strong electron-withdrawing groups.[10] Furthermore, other important discoveries in this area, including carboxamide directed arylation and radical arylation were disclosed by Yu[9] and Baran *et al.*[11] In spite of significant progress in C–H/C–X-type arylation of pyridines,[8–12] direct C–H heteroarylation of pyridines surprisingly remains under-represented, which is probably attributed to the general reluctance of heteroaryl halides or pseudohalide to undergo the coupling reactions.[16] Thus, the oxidative C–H/C–H heteroarylation of pyridines with various heteroarenes should be an ideal alternative to afford pyridine-containing



Scheme 1 Selected medicinal and natural molecules containing 2-heteroarylated pyridines.

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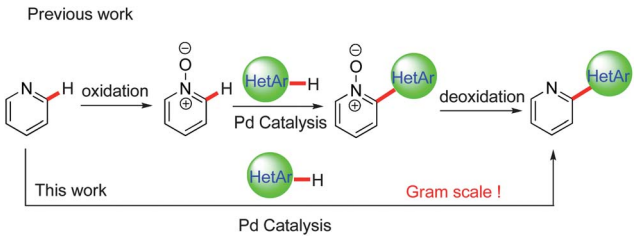


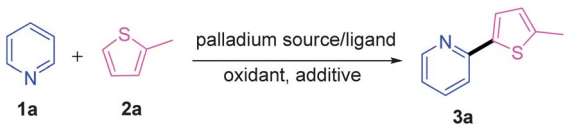
Scheme 2 Evolution of palladium-catalyzed oxidative heteroarylation of pyridines *via* double C–H activation.

biheteroaryls. However, we may face obstacles: (1) the low reactivity at the C-2 and C-6 positions of pyridines; (2) the notorious tendency of heteroarenes to undergo oxidative homocoupling under transition metal-catalyzed conditions in comparison with simple arenes and alkenes;[17–19] (3) the inadequate stability of heteroarenes in the coupling process; (4) the binding of the heteroatom in both the substrate and product to metal complex that may prevent the catalyst from interacting with the reactive C–H bonds; and (5) the regiocontrol of C–H activation of both substrates. Herein, we disclose the discovery, development and solution to meet these substantial challenges.

Results and discussion

We started our investigation by the heterocoupling of pyridine **1a** with 2-methylthiophene **2a** as a model reaction to optimize the reaction conditions (Table 1). As shown in Table 1, several parameters (*e.g.*, oxidant, ligand and additive) were studied. Initial reaction screening led to disappointing results in the absence of either oxidant or Pd(II) salt (Table 1, entries 1 and 2). Among the oxidants investigated, AgOAc was the best choice (Table 1, entries 3–8). After screening various ligands, 1,10-phenanthroline monohydrate (**L1**) gave the best result (Table 1, entries 8–12). Subsequently, we investigated the amount of the ligand used, and found that 0.5 equivalent of 1,10-phenanthroline monohydrate was the most effective (Table 1, entries 8, 14–18). When the reaction was conducted in the presence of 10 mol% of $Pd(OAc)_2$, the product yield was improved to 51% (Table 1, entry 17). Considering that pivalic acid could promote the concerted metalation/deprotonation process (CMD), we added pivalic acid as the additive in the catalytic system. To our delight, the use of PivOH significantly improved the catalytic efficiency (Table 1, entries 19 and 20). Thus, the best results were obtained by using 3.0 equiv. of AgOAc as the oxidant, 0.5 equiv. of 1,10-phenanthroline monohydrate (**L1**) as the ligand,

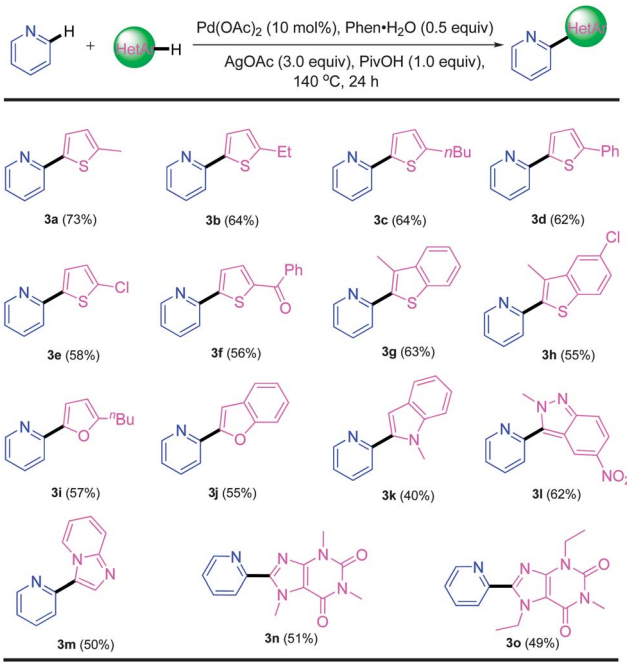
Table 1 Optimization of the reaction conditions[a]



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

Entry	$Pd(OAc)_2$	Oxidant	Ligand	Additive	Yield[b] (%)
1	—	Ag_2CO_3	**L1** (15 mol%)	—	n.d
2	5 mol%	—	**L1** (15 mol%)	—	n.d
3	5 mol%	BQ	**L1** (15 mol%)	—	n.d
4	5 mol%	O_2	**L1** (15 mol%)	—	n.d
5	5 mol%	$Cu(OAc)_2$	**L1** (15 mol%)	—	n.d
6	5 mol%	Ag_2O	**L1** (15 mol%)	—	Trace
7	5 mol%	Ag_2CO_3	**L1** (15 mol%)	—	Trace
8	5 mol%	AgOAc	**L1** (15 mol%)	—	24
9	5 mol%	AgOAc	**phen** (15 mol%)	—	23
10	5 mol%	AgOAc	**L2** (15 mol%)	—	11
11	5 mol%	AgOAc	**L3** (15 mol%)	—	22
12	5 mol%	AgOAc	**L4** (15 mol%)	—	16
13	5 mol%	AgOAc	—	—	15
14	5 mol%	AgOAc	**L1** (20 mol%)	—	30
15	5 mol%	AgOAc	**L1** (30 mol%)	—	37
16	5 mol%	AgOAc	**L1** (50 mol%)	—	43
17	10 mol%	AgOAc	**L1** (50 mol%)	—	51
18	10 mol%	AgOAc	**L1** (100 mol%)	—	46
19	10 mol%	AgOAc	**L1** (50 mol%)	PivOH (0.5 equiv.)	66
20	10 mol%	AgOAc	**L1** (50 mol%)	PivOH (1.0 equiv.)	73
21[c]	10 mol%	AgOAc	**L1** (50 mol%)	PivOH (1.0 equiv.)	73

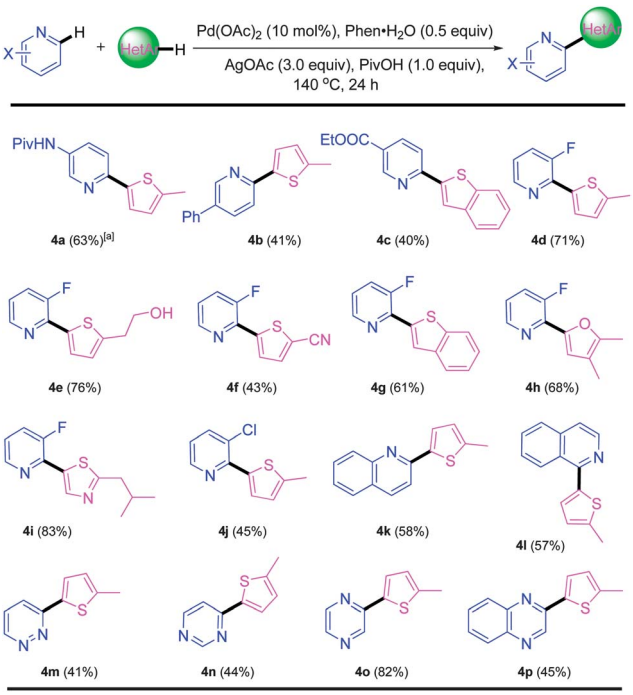
[a] Reactions were carried out using palladium source (5–10 mol%), oxidant (3.0 equiv.), ligand (15–100 mol%), additive (0.5–1.0 equiv.), pyridine **1a** (25.0 equiv.) and 2-methylthiophene **2a** (0.5 mmol) at 140 °C for 24 h. [b] Isolated yield based on **2a**. [c] 2,2,6,6-Tetramethylpiperidinooxy (20 mol%) was added. BQ = benzoquinone, PivOH = pivalic acid, n.d. = not detected, **L1** = 1,10-phenanthroline monohydrate, **L2** = 2,9-dimethyl-1,10-phenanthroline, **L3** = 4,7-diphenyl-1,10-phenanthroline, **L4** = 2,2′-bipyridine.



Scheme 3 Palladium-catalyzed heteroarylation of pyridine with various heteroarenes. For all reactions 0.5 mmol of heteroarene and 25.0 equiv. of pyridine were used under an N_2 atmosphere. Yields of isolated product are based on heteroarene.

and 1.0 equiv. of PivOH as the additive in the presence of $Pd(OAc)_2$ (10 mol%) at 140 °C for 24 h.

With optimized conditions in hand, we explored the scope of this process with respect to heteroarenes summarized in Scheme 3. Our catalytic system accelerated the C2-heteroarylation of pyridine with a wide array of electron-rich heteroarenes (*e.g.*, indole, furan, thiophene, *etc.*) (Scheme 3, **3a–3k**). It was surprising to find that the acidic C–H bonds of various azoles (*e.g.*, indazole, imidazopyridine, xanthines, *etc.*) could also undergo the cross-coupling with pyridine in satisfactory yields (Scheme 3, **3l–3o**). It is of note that the coupling of *N*-methylindole occurred at the indole C2 position rather than the naturally preferential C3 selectivity (Scheme 3, **3k**). In contrast, the previously reported couplings took place at the indole C3 position while pyridyl *N*-oxide was used as the coupling partner.[7] No matter the functional groups of heteroarenes were electron-donating, electron-withdrawing, or sterically hindered, all of them afforded moderate to good yields. The current catalytic system was highly tolerant to a variety of functional groups such as halide, acyl, nitro, amide, ester, nitrile and hydroxyl groups on heteroarenes. These chemoselectivities would enable the cross-coupling products to be used in further transformations. The cross-coupling was regioselective at the C2 position of pyridine, and other regioisomeric products were not observed. X-Ray analysis of single crystals **3f**, **3k**, **3o**, **4c** and **4f** confirmed that the oxidative C–H/C–H cross-coupling occurred at the C2 position on the pyridine ring (Fig. S3, ESI†).[20]

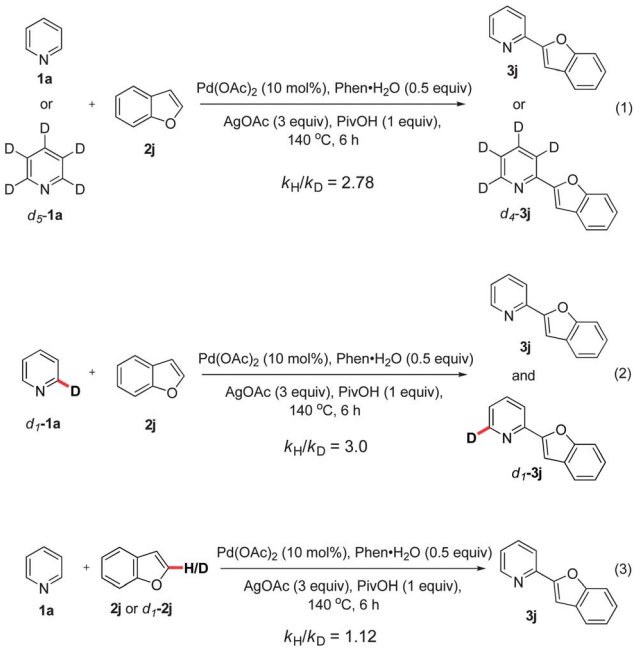


Scheme 4 Heteroarylation of pyridines and related azines with various heteroarenes. For all reactions 0.5 mmol of heteroarene and 1.0 mL of azine were used under an N_2 atmosphere. Yields of isolated product are based on heteroarene; [a] *N*-(pyridin-3-yl)pivalamide (5 mmol) and DMF (0.5 mL).

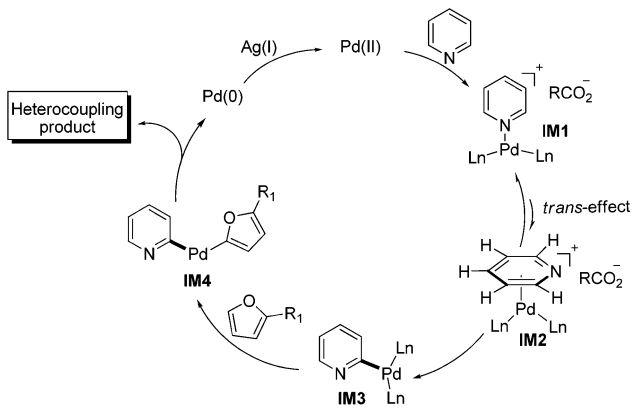
We subsequently applied this protocol to other pyridine derivatives for the synthesis of C2-heteroaryl-substituted pyridines in good yields (Scheme 4, **4a–4j**). To our surprise, pyridines bearing both electron-donating and electron-withdrawing groups could afford the desired products. In addition to these substituted pyridines, this catalytic system also effectively promoted the cross-coupling of a relatively wide range of azines (*e.g.*, pyrimidine, quinoline, quinoxaline, pyrazine, pyridazine, *etc.*) with 2-methylthiophene to give moderate to good yields with excellent regioselectivity (Scheme 4, **4k–4p**). It should be stressed that unreacted starting materials still remained in the lower yielding reactions. The C2 *vs.* C6 selectivity of the C3-substituted pyridines was dependent on the steric and electronic characteristics of the substituents. For example, the C3-pivalamido, phenyl and ester substituted pyridines prefered to give the C6-substituted pyridines probably due to the steric hindrance, and only trace amounts of the C2-substituted products were detected (Scheme 4, **4a–4c**). The C3-fluoro and chloro pyridines predominantly afforded the C2-substituted products, possibly attributed to electronic effects, and only trace amounts of the C6-substituted products were observed (Scheme 4, **4d–4j**). The relatively reactive C1–H position of isoquinoline underwent the cross-coupling process with 2-methylthiophene to afford **4l** as a single product in 57% yield (Scheme 4, **4l**).

It is of note that the current Pd-catalyzed oxidative C–H/C–H cross-coupling reactions exhibited several advantages, including: (1) the homocoupling products of each coupling partner were almost not detected; (2) the process showed an exclusive C2-regioselectivity of pyridine; (3) the mono-heteroarylated adducts of pyridines and related azines were obtained only; and (4) the reaction was performed without problems on gram scale, delivering 71% yield of the desired product **3a.**

To get some insights into the mechanism of this novel Pd-catalyzed oxidative C–H/C–H functionalization of pyridines, the



Scheme 5 Kinetic isotope effect.



Scheme 6 Plausible catalytic cycle of oxidative C–H/C–H cross-coupling of pyridine with heteroarene.

following experiments were carried out. Addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 20 mol%) as a radical scavenger had a negligible effect on the coupling reaction between pyridine **1a** and 2-methylthiophene **2a**, which ruled out a radical pathway (Table 1, entry 21). Subsequently, both inter- and intra-kinetic isotope effects (KIE) were investigated with regard to the C–H/D bonds for both coupling partners. A primary KIE of 2.78 was observed between pyridine **1a** and its deuterated derivative d_5-**1a** (Scheme 5, eqn (1)), which was in accordance with the Pd-mediated C–H cleavage mechanism. A significant kinetic isotope effect ($k_H/k_D = 3.0$) was observed in an intramolecular competition reaction of pyridine-d_1 (Scheme 5, eqn (2)). These observations indicated that the C2–H bond breaking of **1a** might be related with the rate-limiting step. In addition, no significant KIE value ($k_H/k_D = 1.12$) was observed in an intermolecular competition reaction between benzofuran **2j** and its deuterated derivative d_1-**2j** (Scheme 5, eqn (3)), thereby indicating that the C–H bond cleavage of **2j** was not involved in a rate determining step.

On the basis of the above observations, we assumed the plausible catalytic cycle illustrated in Scheme 6, including: (1) initial coordination of pyridine with Pd *via* the nitrogen atom to form the complex **IM1**, which subsequently encountered a "*trans*-effect" into the π-acceptor **IM2**; (2) C2–H cleavage of **IM2** to give the 2-pyridylpalladium(II) intermediate **IM3** *via* a carboxylate-assisted concerted metalation/deprotonation (CMD) pathway; (3) a regioselective C–H substitution of furan with **IM3** to yield the key heterocoupling intermediate **IM4**, followed by reductive elimination to produce the desired product; and (4) regeneration of the Pd(II) species from Pd(0) by the oxidation of AgOAc (Scheme 6). It is of note that whether in the presence or absence of phenanthroline monohydrate, the reaction occurred preferentially at the C2 site of pyridine (Table 1). Thus, we rationalized that phenanthroline monohydrate described herein served as the ligand to increase the catalytic efficiency. In contrast, the role of phenanthroline ligand postulated by Yu was correlated to the C3-selective functionalization of pyridine derivatives through the "*trans* effect".[12,14]

Conclusions

In conclusion, we have advanced for the first time a general and highly selective methodology for the direct C2-heteroarylation of pyridine and related azine rings with a wide range of heteroarenes. In comparison with previous approaches of azine *N*-oxides, the current method is advantageous for the rapid synthesis of a library of pyridine-containing biheteroaryls without detours because of its concise operation and wide availability of starting materials. Studies on further applications of this direct oxidative C–H/C–H heteroarylation is ongoing in our laboratory.

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Notes and references

1 For selected reviews, see: (*a*) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043–6061; (*b*) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 627–646; (*c*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347; (*d*) M. Schlosser and F. Mongin, *Chem. Soc. Rev.*, 2007, **36**, 1161–1172; (*e*) C. G. Arena and G. Aricò, *Curr. Org. Chem.*, 2010, **14**, 546–580; (*f*) D. Zhao, J. You and C. Hu, *Chem.–Eur. J.*, 2011, **17**, 5466–5492.

2 (*a*) D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172–1175; (*b*) D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072–12073.

3 For recent reviews and highlights on oxidative C–H/C–H cross-couplings, see: (*a*) S.-L. You and J.-B. Xia, *Top. Curr. Chem.*, 2010, **292**, 165–194; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147–1169; (*c*) T. Newhouse and P. S. Baran, *Angew. Chem., Int. Ed.*, 2011, **50**, 3362–3374; (*d*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (*e*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885–1898; (*f*) W. Han and A. R. Ofial, *Synlett*, 2011, 1951–1955; (*g*) X. Bugaut and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 7479–7481.

4 For selected examples of oxidative C–H/C–H cross-couplings between two heteroarenes, see: (*a*) W. Han, P. Mayer and A. R. Ofial, *Angew. Chem., Int. Ed.*, 2011, **50**, 2178–2182; (*b*) M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2012, **51**, 6993–6997; (*c*) S. Fan, Z. Chen and X. Zhang, *Org. Lett.*, 2012, **14**, 4950–4953; (*d*) Z. Mao, Z. Wang, Z. Xu, F. Huang, Z. Yu and R. Wang, *Org. Lett.*, 2012, **14**, 3854–3857; (*e*) X. Qin, B. Feng, J. Dong, X. Li, Y. Xue, J. Lan and J. You, *J. Org. Chem.*, 2012, **77**, 7677–7683; (*f*) J. Dong, Y. Huang, X. Qin, Y. Cheng, J. Hao, D. Wan, W. Li, X. Liu and J. You, *Chem.–Eur. J.*, 2012, **18**, 6158–6162; (*g*) N. Kuhl, M. N. Hopkinson and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 8230–8234.

5 For a review, see: Y. Nakao, *Synthesis*, 2011, 3209–3219.

6 For two sporadic examples of direct C–H (hetero)arylation of specific 2,3,5,6-tetrafluoropyridine with 1-(thiophen-2-yl) ethanone as well as benzene through dehydrogenative coupling processes, see: (*a*) Y. Wei and W. Su, *J. Am. Chem. Soc.*, 2010, **132**, 16377–16379; (*b*) C.-Y. He, S. Fan and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 12850–12852.

7 (*a*) P. Xi, F. Yang, S. Qin, D. Zhao, J. Lan, G. Gao, C. Hu and J. You, *J. Am. Chem. Soc.*, 2010, **132**, 1822–1824; (*b*) Z. Wang, K. Li, D. Zhao, J. Lan and J. You, *Angew. Chem., Int. Ed.*, 2011, **50**, 5365–5369; (*c*) X. Gong, G. Song, H. Zhang and X. Li, *Org. Lett.*, 2011, **13**, 1766–1769; (*d*) A. D. Yamaguchi, D. Mandal, J. Yamaguchi and K. Itami, *Chem. Lett.*, 2011, **40**, 555–557; (*e*) D. Mandal, A. D. Yamaguchi, J. Yamaguchi and K. Itami, *J. Am. Chem. Soc.*, 2011, **133**, 19660–19663; (*f*) Z. Wang, F. Song, Y. Zhao, Y. Huang, L. Yang, D. Zhao, J. Lan and J. You, *Chem.–Eur. J.*, 2012, **18**, 16616–16620; (*g*) X. Qin, H. Liu, D. Qin, Q. Wu, J. You, D. Zhao, Q. Guo, X. Huang and J. Lan, *Chem. Sci.*, 2013, DOI: 10.1039/c3sc22241a.

8 For selected examples of C2-selective Rh or Ni catalytic arylation with aryl halides or arylzinc reagents, see: (*a*) A. M. Berman, J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 14926–14927; (*b*) M. Tobisu, I. Hyodo and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 12070–12071; (*c*) A. M. Berman, R. G. Bergman and J. A. Ellman, *J. Org. Chem.*, 2010, **75**, 7863–7868.

9 For carboxamide-directed arylation of pyridines with aryl bromides, see: M. Wasa, B. T. Worrell and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2010, **49**, 1275–1277.

10 For electron-withdrawing group-directed arylation of pyridines with aryl bromides, see: P. Guo, J. M. Joo, S. Rakshit and D. Sames, *J. Am. Chem. Soc.*, 2011, **133**, 16338–16341.

11 For radical-type arylation of pyridines with arylboronic acids, see: (*a*) I. B. Seiple, S. Su, R. A. Rodriguez, R. Gianatassio, Y. Fujiwara, A. L. Sobel and P. S. Baran, *J. Am. Chem. Soc.*, 2010, **132**, 13194–13196. For radical-type arylation of pyridines with halobenzene, see: (*b*) S. Yanagisawa, K. Ueda, T. Tanaguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673–4676. For radical-type alkylation of pyridines with alkyl iodide, see: (*c*) F. Minisci, E. Vismara, F. Fontana, G. Morini, M. Serravalle and C. Giordano, *J. Org. Chem.*, 1986, **51**, 4411–4416.

12 For ligand-promoted C3-selective arylation of pyridines with aryl halides, see: M. Ye, G.-L. Gao, A. J. F. Edmunds, P. A. Worthington, J. A. Morris and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 19090–19093.

13 For selected examples of C2-selective Rh or Ni catalytic additions with alkenes or alkynes, see: (*a*) J. C. Lewis, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2007, **129**, 5332–5333; (*b*) Y. Nakao, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2008, **130**, 2448–2449; (*c*) Y. Nakao, Y. Yamada, N. Kashihara and T. Hiyama, *J. Am. Chem. Soc.*, 2010, **132**, 13666–13668.

14 For ligand-promoted C3-selective olefination of pyridines with alkenes, see: M. Ye, G.-L. Gao and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 6964–6967.

15 (*a*) J. Kwak, Y. Ohk, Y. Jung and S. Chang, *J. Am. Chem. Soc.*, 2012, **134**, 17778–17788; (*b*) D. G. Johnson, J. M. Lynam, N. S. Mistry, J. M. Slattery, R. J. Thatcher and A. C. Whitwood, *J. Am. Chem. Soc.*, 2013, **135**, 2222–2234.

16 (*a*) Q. Shen, T. Ogata and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 6586–6596; (*b*) M. Su and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2012, **51**, 4710–4713.

17 Suzuki and co-workers described a dehydrogenative homocoupling of 4-substituted pyridines to form 2,2′-bipyridine catalyzed by diruthenium complexes. See: T. Kawashima, T. Takao and H. Suzuki, *J. Am. Chem. Soc.*, 2007, **129**, 11006–11007.

18 For Pd-catalyzed homocoupling of heteroarenes, see: (*a*) K. Masui, H. Ikegami and A. Mori, *J. Am. Chem. Soc.*, 2004, **126**, 5074–5075; (*b*) M. Takahashi, K. Masui, H. Sekiguchi, N. Kobayashi, A. Mori, M. Funahashi and N. Tamaoki, *J. Am. Chem. Soc.*, 2006, **128**, 10930–10933; (*c*) J.-B. Xia, X.-Q. Wang and S.-L. You, *J. Org. Chem.*, 2009, **74**, 456–458. For copper-promoted homocoupling of azoles, see: (*d*) Y. Li, J. Jin, W. Qian and W. Bao, *Org. Biomol. Chem.*, 2010, **8**, 326–330; (*e*) M. Zhu, K. Fujita and R. Yamaguchi, *Chem. Commun.*, 2011, **47**, 12876–12878. For Pd-catalyzed homocoupling of 2-arylpyridine, see: (*f*) K. L. Hull, E. L. Lanni and M. S. Sanford, *J. Am. Chem. Soc.*, 2006, **128**, 14047–14049.

19 For inevitable homocoupling in the Pd or Rh-catalyzed oxidative C–H/C–H cross-coupling of two heteroarenes, see: (*a*) N. Kuhl, M. N. Hopkinson and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 8230–8234; (*b*) J. Dong, Y. Huang, X. Qin, Y. Cheng, J. Hao, D. Wan, W. Li, X. Liu and J. You, *Chem.–Eur. J.*, 2012, **18**, 6158–6162. Also see ref. 7*a* and *b*.

20 CCDC 906806 (**3f**), 906804 (**3k**), 906805 (**3o**), 906808 (**4c**) and 906807 (**4f**).