Palladium-Catalyzed Benzylic Cross-Couplings of Pyridine *N*-Oxides

Wenpeng Mai,* Jinwei Yuan, Zhicheng Li, Liangru Yang, Yongmei Xiao, Pu Mao, Lingbo Qu

Chemistry and Chemical Engineering School, Henan University of Technology, Zhengzhou Henan 450001, P. R. of China
Fax +86(371)67756715; E-mail: wpmai@yahoo.com.cn

Received 19 December 2011

Abstract: Palladium-catalyzed C–H couplings (C_{SP^3}–C_{SP^2}) of pyridine *N*-oxides with benzyl chloride derivatives is reported. It provides a novel and easy process for the synthesis of 2-benzylpyridine derivatives through benzylic cross-couplings of pyridine *N*-oxides.

Key words: palladium, benzylation, pyridine *N*-oxide, C–H couplings

Transition-metal-catalyzed C–H bond activation reactions for the C–C bond formation has contributed significantly to the preparation of biaryl molecules.[1] In particular, prominent reactions involve Pd-catalyzed couplings of aryl halides with aromatic C–H bonds (C_{sp^2}–C_{sp^2}) or two differential arene compounds' C–H bonds (C_{sp^2}–C_{sp^2}).[2] In this area of research, benzyl halides or aliphatic electrophiles (C_{sp^3}) coupled with aromatic rings remain rare.[3] Yu reported palladium-catalyzed *ortho* alkylation of benzoic acids,[4] and Ackermann described ruthenium-catalyzed direct benzylations or alkylation of arene through C–H activation.[5]

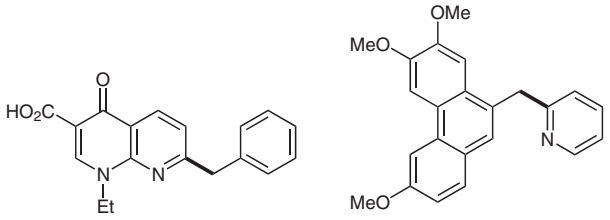
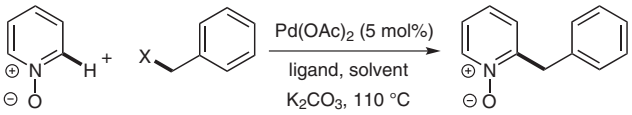


Figure 1 Bioactive 2-benzylpyridine derivatives

2-Benzylpyridine and its derivatives are important components of natural products, medicinal chemistry and material science[6] (Figure 1). The benzylic arylation of pyridines does not have effective synthetic routes.[7] Recently, Liu reported decarboxylative cross-couplings of 2-(2-pyridyl)acetates with aryl halides for the synthesis of 2-benzylpyridine derivatives.[8] 2-(2-Pyridyl)ethanol derivatives were used as substrates to obtain 2-pyridylmethyl functional group in Yorimitsu's work.[9] More recently, Knochel reported Pd-catalyzed coupling of aryl bromides with 2-picoline under the assistance of Lewis acid TMPZnCl–LiCl.[10] More synthetic routes or modified pyridine precursors and expensive reagents were required in these methods; for example, BuLi or LDA were used in Liu's and Yorimitsu's works to synthesize modified 2-picoline derivatives (Figure 2). Pyridine *N*-oxide has attracted interest due to its direct C–H activation on 2-position of pyridine.[11] Though Fagnou has reported synthesis of 2-benzylpyridine *N*-oxide using 2-methylpyridine *N*-oxide with aryl halides as substrates, methyl on pyridine core was necessary. Benzyl halides as electrophiles coupled with pyridine *N*-oxides have not been reported to date. Our study was inspired by the recent fascinating work of Fagnou et al.[12] (Figure 2). On the arylation of

Table 1 Screening of Different Conditions for Palladium-Catalyzed Coupling of Pyridine *N*-Oxide with Benzyl Chloride[a]



Entry	Ligand	X	Solvent	Yield (%)[b]
1	Ph_3P	Cl	toluene	0
2	Ph_3P	Br	toluene	0
3	Cy_3P	Cl	toluene	trace
4	Cy_3P	Br	toluene	trace
5	Cy_3P	Cl	dioxane	trace
6[c,d]	IPrS	Cl	toluene	trace
7[c,d]	IPrS	Cl	DMF	27
8	*t*-Bu_3P–HBF_4	Cl	DMF	49
9	*t*-Bu_3P–HBF_4	Cl	dioxane	64
10	*t*-Bu_3P–HBF_4	Cl	toluene	82
11[e]	*t*-Bu_3P–HBF_4	Cl	toluene	75
12	*t*-Bu_3P	Cl	toluene	77
13	*t*-Bu_3P–HBF_4	Br	toluene	43
14	*t*-Bu_3P–HBF_4	OTs	toluene	trace
15[c–e]	*t*-Bu_3P–HBF_4	OTs	toluene	trace

[a] Conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), K_2CO_3 (2.0 mmol), solvent (3.0 mL), 110 °C, under N_2, 16 h.
[b] Isolated yield.
[c] Cs_2CO_3 was used as base.
[d] IPrS = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride.
[e] $Pd_2(dba)_3$ (2.5 mol%) was used as catalyst.

SYNLETT 2012, 23, 938–942
Advanced online publication: 02.03.2012
DOI: 10.1055/s-0031-1290602; Art ID: W78811ST

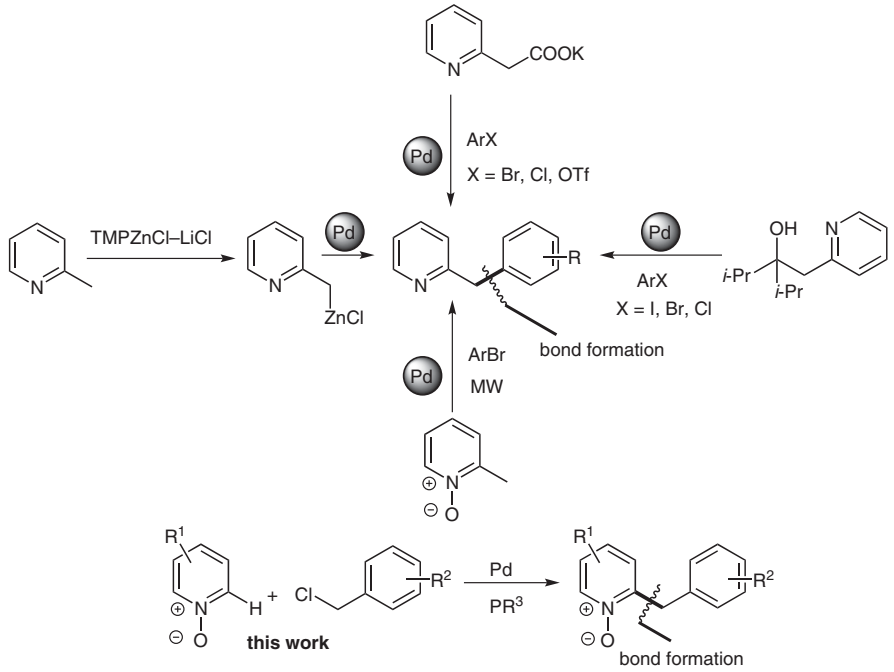


Figure 2 Overview of synthesis of 2-benzylpyridine derivatives

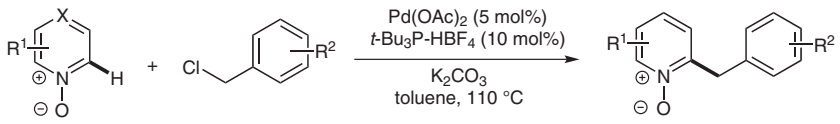
pyridine *N*-oxides, we continued our work on its 2-position through C–H activation.[13] Herein, a simple method for the synthesis of 2-benzylpyridine through palladium-catalyzed benzylic cross-couplings of pyridine *N*-oxides is described (involving both cheap crude materials and easy synthesis).

Our study began with the treatment of pyridine *N*-oxide (**1a**) with benzyl chloride (**2a**) in the presence of $Pd(OAc)_2$ (5 mol%), Ph_3P and K_2CO_3 at 110 °C under N_2 in toluene. No desired product **3aa** was found after 16 hours (Table 1, entry 1). Under the same conditions, no product was observed when using benzyl bromide as substrate coupled with **1a** (Table 1, entry 2). It was not effective for this reaction when PCy_3 was used as ligand (Table 1, entries 3–5). Only 27% yield was obtained when IPrS was used as ligand in DMF (Table 1, entry 7). The yield was improved to 49% when *t*-Bu_3P–HBF_4 was used as ligand instead of IPrS (Table 1, entry 8). After several tests for the effect of ligands and solvents in this transformation, *t*-Bu_3P–HBF_4 and toluene were found to be the most effective in this reaction, and the desired product **3aa** was obtained in 82% yield (Table 1, entry 10). Ligand *t*-Bu_3P gave a similar result as that obtained with *t*-Bu_3P–HBF_4 (Table 1, entry 12). $Pd_2(dba)_3$ as catalyst was also effective in this transformation, and 75% yield was obtained (Table 1, entry 11). Under the optimal conditions, benzyl bromide gave only moderate yield that is consistent with the previous reports by Chang's group[3a,b] (Table 1, entry 13).

Benzyl 4-methylbenzenesulfonate was not effective in this reaction under our conditions (Table 1, entries 14 and 15).

With the optimized conditions in hand, we explored the scope of this transformation (Table 2). As shown in Table 2, we found that benzyl chlorides with electron-withdrawing group or electron-donating group could be successfully coupled with some pyridine *N*-oxides in this reaction (Table 2, entries 2–4 and 7). 2-Methylbenzyl chloride coupled with **1a** smoothly though it has steric effect and provided the product **3ab** in high yield (Table 2, entry 2). 3-Cyanopyridine *N*-oxide and 4-cyanopyridine *N*-oxide were also coupled with **2a**, **2b** and **2e** smoothly and gave the corresponding products in 62–80% yields (Table 2, entries 5–7). It was noted that different regioselectivities for 3-cyanopyridine *N*-oxide were obtained when it was coupled with benzyl chloride and 2-methylbenzyl chloride (Table 2, entries 5 and 6). Hydrogen on 2-position of 3-cyanopyridine *N*-oxide should be more activated than that on 6-position, but 2-methylbenzyl chloride showed more steric effect if it was coupled with 3-cyanopyridine *N*-oxide on 2-position. This was found to be consistent with our previous work.[13] But entry 11 could not be explained by this conjecture. Pyrazine N^1-oxide could also undergo this coupling reaction with benzyl chloride, 4-methylbenzyl chloride and 4-fluorobenzyl chloride, and the corresponding products were obtained in good yields (Table 2, entries 8–10). The product **3eb** was obtained in 48% yield when isoquinoline *N*-oxide was used to couple with **2b** (Table 2, entry 11), but quinoline *N*-oxide could not be converted under the same conditions (Table 2, entry 12). Unfortunately, substrates with electron-donating groups on pyridine *N*-oxide were not effective in our catalyst system (see Supporting Information).

Table 2 Palladium-Catalyzed Benzylic Cross-Couplings of Pyridine *N*-Oxides[a,14]



1a–e
X = C or N

2a–e

3

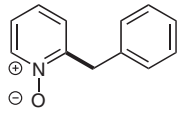
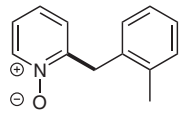
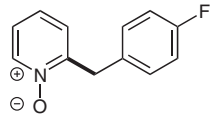
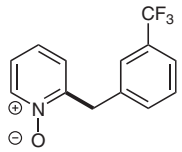
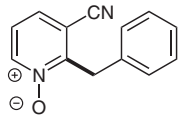
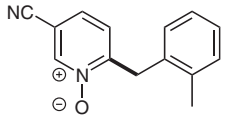
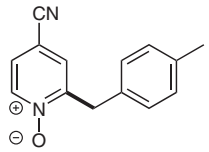
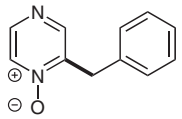
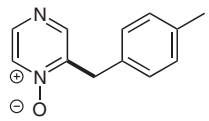
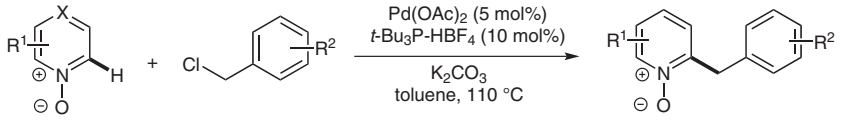
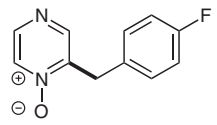
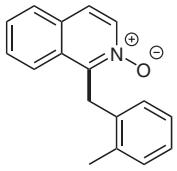
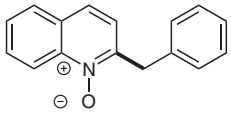
Entry	Product	Yield (%)[b]
1	 **3aa**	82
2	 **3ab**	88
3	 **3ac**	71
4	 **3ad**	72
5	 **3ba**	80
6	 **3bb**	62
7	 **3ce**	75
8	 **3da**	88
9	 **3dd**	78

Table 2 Palladium-Catalyzed Benzylic Cross-Couplings of Pyridine *N*-Oxides[a,14] (continued)

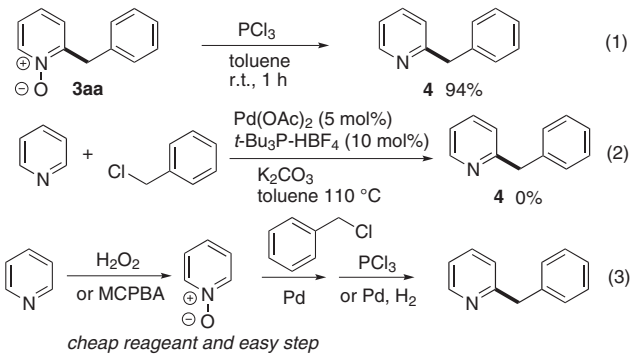


1a–e X = C or N **2a–e** **3**

Entry	Product	Yield (%)[b]
10	 **3dc**	74
11	 **3eb**	48
12		trace

[a] Conditions: **1** (1.5 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol, 11 mg), *t*-Bu_3P–HBF_4 (0.1 mmol, 29 mg), K_2CO_3 (2.0 mmol, 276 mg), toluene (3.0 mL), 110 °C, under N_2, 16 h.
[b] Isolated yield.

The coupled products were easily deoxygenated to obtain the corresponding 2-benzyl pyridines in one step. For example, when product **3aa** was treated with PCl_3 at room temperature in toluene, product **4** was obtained in 94% isolated yield after one hour (Equation 1 in Scheme 1). But no desired product **4** was found when using pyridine as substrate under our current catalyst system (Equation 2 in Scheme 1). When compared with the previous results for the synthesis of 2-benzylpyridine derivatives, our method has its advantages, no air-sensitive and water-sensitive reagents were needed and all reagents used here are cheap. It is a novel and easy route to synthesize 2-benzylpyridine though the last step seems to be inferior (Equation 3 in Scheme 1).



Scheme 1

In summary, we have developed a novel and easy method to synthesize 2-benzylpyridine derivatives by palladium-catalyzed benzylic cross-couplings with pyridine *N*-oxides through C–H activation. Only simple modification on pyridine was needed. Investigations on more efficient catalyst systems toward the scope of pyridine *N*-oxides are under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We gratefully acknowledge NSFC (No. 21172055) and the Henan University of Technology for financial support.

References and Notes

(1) (a) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (b) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (d) Chen, X.; Engle, K.-M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094. (e) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (f) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (h) Ranjit, S.; Liu, X. *Chem. Eur. J.* **2010**, *17*, 1105. (i) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 2387. (j) Han, W.; Mayer, P.; Ofial, A. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 2178. (k) Pintori, D. G.; Greaney, M. F. *J. Am.*

Chem. Soc. **2011**, *133*, 1209. (l) Wang, G. W.; Yuan, T. T.; Li, D. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 1380. (m) Li, H.; Liu, J.; Sun, C. L.; Li, B. J.; Shi, Z. J. *Org. Lett.* **2011**, *13*, 276. (n) Ciana, C. L.; Phipps, R. J.; Brandt, J. R.; Meyer, F. M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 458. (o) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160.

(2) (a) Join, B.; Yamamoto, T.; Itami, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 3644. (b) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (c) Beck, E. M.; Grimster, N. P.; Hatlev, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (d) Campeau, L.-C.; Staurt, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (e) Chen, X.; Goodhue, C. E.; Yu, J. Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (f) Scarborough, C. C.; McDonald, R. I.; Hartmann, C.; Sazama, T.; Bergant, A.; Stahl, S. S. *J. Org. Chem.* **2009**, *65*, 914. (g) Wang, Z.; Li, K. Z.; Zhao, D. B.; Lan, J. B.; You, J. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5365. (h) Bugaut, X.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 7479. (i) Xi, P. H.; Yang, F.; Qin, S.; Zhao, D. B.; Lan, J. B.; Gao, G.; Hu, C. W.; You, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 1822.

(3) (a) Hwang, S. J.; Kim, H. J.; Chang, S. *Org. Lett.* **2009**, *11*, 4588. (b) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (c) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360. (d) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4160. (e) Verrier, C.; Hoarau, C.; Marsais, F. *Org. Biomol. Chem.* **2009**, *7*, 647.

(4) Zhang, Y. H.; Shi, B. F.; Yu, J. Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 6097.

(5) (a) Ackermann, L.; Novak, P.; Vicente, R.; Hofmann, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 6045. (b) Ackermann, L.; Novák, P. *Org. Lett.* **2009**, *11*, 4966.

(6) (a) Baglev, M. C.; Glover, C.; Merritt, E. A. *Synlett* **2007**, 2459. (b) Nicolaou, K. C.; Scarpelli, R.; Bollbuck, B.; Werschkun, B.; Pereira, M. M. A.; Wartmann, M.; Altmann, K. H.; Zaharevitz, D.; Gussio, R.; Giannakakou, P. *Chem. Biol.* **2000**, *7*, 593. (c) Quiroga, J.; Trilleras, J.; Insuasty, B.; Abonia, R.; Nogueras, M.; Marchal, A.; Cobo, J. *Tetrahedron Lett.* **2010**, *51*, 1107. (d) Nolan, E. M.; Jaworski, J.; Okamoto, K. I.; Hayashi, Y.; Sheng, M.; Lippard, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 16812. (e) Oliva, B.; Miller, K.; Caggiano, N.; O'Neill, A. J.; Guny, G. D.; Hoemann, M. Z.; Hauske, J. R.; Chopra, I. *Antimicrob. Agents Chemother.* **2003**, *47*, 458. (f) Baxter, P. N. W.; Lehn, J. M.; Fischer, J.; Youinou, M. T. *Angew. Chem. Int. Ed.* **1994**, *106*, 2432. (g) Lehn, J. M. *Science* **2002**, *295*, 2400.

(7) (a) Burton, P. M.; Morris, J. A. *Org. Lett.* **2010**, *12*, 5359. (b) Rizk, T.; Bilodeau, E. J.-F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325. (c) Ohmiva, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2004**, *33*, 1240. (d) Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1614.

(8) Shang, R.; Yang, Z. W.; Wang, Y.; Zhang, S. L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391.

(9) Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 2643.

(10) Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 7686.

(11) (a) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430. (d) Duric, S.; Tzschucke, C. C. *Org. Lett.* **2011**, *13*, 2310. (e) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194. (f) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Bel, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292.

(12) Campeau, L. C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266.

(13) Mai, W. P.; Yuan, J. W.; Li, Z. C.; Sun, G. C.; Qu, L. B. *Synlett* **2012**, *23*, 145.

(14) **General Procedure**: An 50-mL vial was charged with magnetic stir bar, pyridine *N*-oxide (**1a**; 1.5 mmol), benzyl chloride (**2a**; 1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), *t*-Bu_3P–HBF_4 (0.1 mmol), K_2CO_3 (2.0 mmol), followed by anhyd toluene (3 mL). After stirring at 110 °C for 16 h, the reaction mixture was filtered through Celite (washed with MeOH and CH_2Cl_2). The combined organic phase was then evaporated under reduced pressure and the isolated yield was obtained by flash chromatography column on silica gel (gradient eluent of MeOH in CH_2Cl_2: 1–5%).

2-Benzylpyridine *N*-Oxide (3aa): yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 2.8 Hz, 1 H), 7.33–7.40 (m, 2 H), 7.28–7.31 (m, 3 H), 6.95–7.19 (m, 2 H), 6.93–6.95 (m, 1 H), 4.28 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 139.4, 136.2, 129.7, 128.8, 127.1, 125.8, 125.6, 123.6, 36.5. MS (ESI): *m/z* = 186.0 $[M + 1]^+$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{12}NO^+$: 186.0919; found: 186.0913.

2-(2-Methylbenzyl)pyridine *N*-Oxide (3ab): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 6.4 Hz, 1 H), 7.10–7.27 (m, 6 H), 6.71 (d, *J* = 7.2 Hz, 1 H), 4.25 (s, 2 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.3, 139.4, 137.2, 134.4, 130.6, 127.5, 126.5, 125.7, 125.9, 125.1, 123.4, 34.4, 19.3. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{14}NO^+$: 200.1075; found: 200.1073.

2-(4-Fluorobenzyl)pyridine *N*-Oxide (3ac): pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 5.2 Hz, 1 H), 7.19–7.28 (m, 4 H), 6.99–7.07 (m, 3 H), 4.26 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 160.7, 151.6, 149.5, 131.9, 131.2, 125.7, 123.7, 123.9, 115.8, 35.8. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{11}FNO^+$: 204.0825; found: 204.0827.

2-(3-Trifluoromethylbenzyl)pyridine *N*-Oxide (3ad): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.30 (m, 1 H), 7.44–7.55 (m, 4 H), 7.18–7.21 (m, 2 H), 7.00–7.03 (m, 1 H), 4.32 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.8, 139.6, 137.3, 137.1, 133.0, 131.2, 130.9, 128.6, 129.3, 126.2, 126.17, 126.13, 126.1, 125.9, 125.7, 125.4, 124.1, 123.99, 123.95, 123.91, 122.66, 36.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{11}F_3NO^+$: 254.0793; found: 254.0796.

