Supporting Information
for DOI: 10.1055/s-0031-1290602
© Georg Thieme Verlag KG Stuttgart · New York 2012
Palladium-Catalyzed Benzylic Cross-Couplings of Pyridine N-Oxides

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

Chemistry and Chemical Engineering School, Henan University of Technology, Zhengzhou Henan 450001, China

Email: wpmai@yahoo.com.cn

Supporting Information

Table of Contents

I. General Information .................................................. S2
II. Experimental Section ............................................... S3
III. References and Notes .............................................. S13
IV. NMR Spectrum Copies .............................................. S14
I. General Information

All experiments were carried out using common flask in N₂. Pd(OAc)_2, PPh₃, PCy₃, IPrS, tBu₃P-HBF₄ were purchased from commercial suppliers and used as received unless otherwise noted. All solvents and other commercially available reagents were purchased from Acros or Adaddin and used directly. Reactions were monitored by thin layer chromatography (TLC) using Qingdao Haiyang Chemical Co. Ltd. Silica gel 60 F254. Products were detected using a UV/Vis lamp (254 nm). Column chromatography was performed on Qingdao Haiyang Chemical Co. Ltd. Gel 60 (200–300 mesh) The H and C NMR spectras were obtained on a Bruker 400 MHz NMR Fourier transform spectrometer. H NMR data was reported as: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. C NMR data was reported in terms of chemical shift (δ ppm) multiplicity, and coupling constant (Hz). Hertz (Hz).The Spectra are referenced against the internal solvent (CDCl₃, δ 1H= 7.26 ppm, δ 13C= 77.0 ppm; DMSO-d6, δ 1H= 2.50 ppm, δ 13C= 40.0 ppm). Data is reported as follows: s= singlet, d= doublet, t= triplet, q=quartet and m= multiplet. ESI-MS spectra were recorded on a Bruker Esquire 3000. High resolution mass spectra (HR MS) were obtained on a Waters Micromass Q-Tof MicroTM instrument using the ESI technique.
II. Experimental Section

Starting Materials

For this study, pyridine N-oxides was purchased from commercial sources or can be synthesized according to one of the following general procedures:

Method 1\(^1\):

Pyridine (1.0 eq.) and m-Chloroperoxybenzoic acid (1.1 eq.) are dissolved in dry methylene chloride. The reaction is allowed to stir at room temperature for overnight. The solvent is then evaporated under reduced pressure and the crude reaction mixture is purified by column chromatography on silica gel with CH\(_2\)Cl\(_2\)/Me\(_2\)CO or CH\(_2\)Cl\(_2\)/MeOH mixtures.

Method 2\(^2\):

Pyridine (1.0 eq.) is dissolved in acetic acid in a round bottom flask and Hydrogen peroxide (3.0 eq.) is added in twice times at 70°C and the mixture is stirred for overnight. Then K\(_2\)CO\(_3\) was added to adjust PH > 7. The mixture is extracted twice with CH\(_2\)Cl\(_2\). The organic layer is then dried over NaSO\(_4\), filtered and evaporated under reduced pressure to afford the pyridine N-oxide often in analytically pure form.
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), tBu$_3$P-HBF$_4$ (0.1 mmol), K$_2$CO$_3$ (2.0 mmol), followed by dry toluene (3 mL). After stirring at 110°C for 18 h, The reaction mixture was filtered through celite (washed with MeOH and DCM), 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 Methanol in CH$_2$Cl$_2$: 1 ~ 5%, v/v).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>X</th>
<th>Solvent</th>
<th>Yield(%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$</td>
<td>Cl</td>
<td>Toluene</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$</td>
<td>Br</td>
<td>Toluene</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PCy$_3$</td>
<td>Cl</td>
<td>Toluene</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>PCy$_3$</td>
<td>Br</td>
<td>Toluene</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>PCy$_3$</td>
<td>Cl</td>
<td>Dioxane</td>
<td>trace</td>
</tr>
<tr>
<td>6$^b$</td>
<td>IPrS</td>
<td>Cl</td>
<td>Toluene</td>
<td>trace</td>
</tr>
<tr>
<td>7$^b$</td>
<td>IPrS</td>
<td>Cl</td>
<td>DMF</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>tBu$_3$PHBF$_4$</td>
<td>Cl</td>
<td>DMF</td>
<td>49</td>
</tr>
<tr>
<td>Entry</td>
<td>Reactants</td>
<td>Conditions</td>
<td>Yield</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>tBu3PHBF4</td>
<td>Cl</td>
<td>dioxane</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>tBu3PHBF4</td>
<td>Cl</td>
<td>Toluene</td>
<td>82</td>
</tr>
<tr>
<td>11c</td>
<td>tBu3PHBF4</td>
<td>Cl</td>
<td>Toluene</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>tBu3P</td>
<td>Cl</td>
<td>Toluene</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>tBu3PHBF4</td>
<td>Br</td>
<td>Toluene</td>
<td>43</td>
</tr>
<tr>
<td>14</td>
<td>tBu3PHBF4</td>
<td>OTs</td>
<td>Toluene</td>
<td>trace</td>
</tr>
<tr>
<td>15b</td>
<td>tBu3PHBF4</td>
<td>OTs</td>
<td>Toluene</td>
<td>trace</td>
</tr>
</tbody>
</table>

*a* Isolated yield. *b* Cs₂CO₃ as base. *c* Pd₂(dba)₃ was used.

Using Conditions of Entry 10: the following pyridine N-Oxides were not effective in our catalyst system.

![Diagram of pyridine N-Oxides]

Using Conditions of Entry 10: the following pyridine N-Oxides were not effective in our catalyst system.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Products</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1f + 1c + 2e</td>
<td>3ce</td>
<td>(\text{Pd(OAc)}_2) 5%, t-Bu3PHBF4 10%, (\text{K}_2\text{CO}_3), Toluene 110°C</td>
</tr>
<tr>
<td></td>
<td>0 3fe</td>
<td></td>
</tr>
</tbody>
</table>
NMR Data of Products

2-benzylpyridine N-oxide (3aa)

(yellow solid) $^1$H NMR (400MHz, CDCl$_3$) 8.32 (d, $J = 2.8$ Hz, 1H), 7.33-7.40 (m, 2H), 7.28-7.31 (m, 3H), 6.95-7.19 (m, 2H), 6.93-6.95 (m, 1H), 4.28 (s, 2H). $^{13}$NMR (100MHz, CDCl$_3$) 151.9, 139.4, 136.2, 129.7, 128.8, 127.1, 125.8, 125.6, 123.6, 36.5

ESI-MS $[M+1]^+ = 186.0$; ESI-HRMS: $[M+H]^+$ m/z calcd for C$_{12}$H$_{12}$NO$^+$: 186.0919, found: 186.0913

2-benzylpyridine (4)$^{3,4}$

(colorless liquid) $^1$H NMR (400MHz, CDCl$_3$) 8.56-8.58 (m, 1H), 7.58 (dt, $J^1 = 1.6$Hz, $J^2 = 7.6$Hz, 1H), 7.22-7.35 (m, 5H), 7.12-7.15 (m, 2H), 4.19 (s, 2H).

$^{13}$NMR (100MHz, CDCl$_3$) 160.9, 149.2, 139.4, 136.7, 129.1, 128.6, 126.4, 123.2, 121.3, 44.6
2-(2-methylbenzyl)-pyridine N-oxide (3ab)

\[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

\[3ab\]

\[^1H\text{ NMR (400MHz, CDCl}_3\text{)}\] 8.32 (d, \(J = 6.4\text{Hz, 1H})\), 7.10-7.27 (m, 6H), 6.71 (d, \(J = 7.2\text{ Hz, 1H})\), 4.25 (s, 2H), 2.19 (s, 3H).

\[^{13}\text{NMR (100MHz, CDCl}_3\text{)}\] 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

\text{ESI-HRMS: [M+H]^+ m/z calcd for C}_{13}\text{H}_{14}\text{NO}^+: 200.1075, \text{ found: 200.1073}

2-(4-fluorobenzyl)-pyridine N-oxide (3ac)

\[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

\[3ac\]

(pale yellow solid) \[^1H\text{ NMR (400MHz, CDCl}_3\text{)}\] 8.35 (d, \(J = 5.2\text{Hz, 1H})\), 7.19-7.28 (m, 4H), 6.99-7.07 (m, 3H), 4.26 (s, 2H)

\[^{13}\text{NMR (100MHz, CDCl}_3\text{)}\] 163.2, 160.7, 151.6, 149.5, 131.9, 131.2, 125.7, 123.7, 123.9, 115.8, 35.8

\text{ESI-HRMS: [M+H]^+ m/z calcd for C}_{12}\text{H}_{11}\text{FNO}^+: 204.0825, \text{ found: 204.0827}
2-(3-trifluoromethylbenzyl)-pyridine N-oxide (3ad)

![Structure of 3ad]

$^1$H NMR (400MHz, CDCl$_3$) 8.28-8.30 (m, 1H), 7.44-7.55 (m, 4H), 7.18-7.21 (m, 2H), 7.00-7.03 (m, 1H), 4.32 (s, 2H)

$^{13}$NMR (100MHz, CDCl$_3$) 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

ESI-HRMS: [M+H]$^+$ m/z calcd for C$_{13}$H$_{11}$F$_3$NO$: 254.0793, found: 254.0796

2-benzyl-3-cyanopyridine N-oxide (3ba)

![Structure of 3ba]

(pale yellow solid) $^1$H NMR (400MHz, CDCl$_3$) 8.44 (d, $J = 4$Hz, 1H), 7.54 (d, $J = 7.2$Hz, 3H), 7.25-7.35 (m, 4H), 4.53 (s, 2H)

$^{13}$NMR (100MHz, CDCl$_3$) 154.3, 143.4, 135.0, 129.3, 128.7, 128.1, 127.5, 124.2, 115.0, 113.0, 35.0

ESI-HRMS: [M+H]$^+$ m/z calcd for C$_{13}$H$_{11}$N$_2$O$: 211.0871, found: 211.0868
2-(2-methylbenzyl)-5-cyanopyridine N-oxide (3bb)

(sticky liquid) \(^1\)H NMR (400MHz, CDCl\(_3\)) 8.43 (s, 1H), 7.55 (d, \(J = 6.0\)Hz, 1H), 7.33 (s, 1H), 7.13-7.22 (m, 2H), 7.07 (t, \(J = 7.2\)Hz, 1H), 6.83 (d, \(J = 7.2\)Hz, 1H), 4.46 (s, 2H), 2.48 (s, 3H)

\(\text{\(^{13}\)NMR (100MHz, CDCl}_3\)) 154.5, 143.3, 136.9, 132.8, 130.6, 129.1, 128.2, 127.2, 126.2, 124.3, 114.7, 113.8, 32.5, 19.9

ESI-HRMS: [M+H]\(^+\) m/z calcd for C\(_{14}\)H\(_{13}\)N\(_2\)O\(^+\): 225.1028, found: 225.1027

2- (4-methylbenzyl)-4-cyanopyridine N-oxide (3ce)

(pale yellow solid) \(^1\)H NMR (400MHz, CDCl\(_3\)) 8.33 (d, \(J = 6.8\)Hz, 1H), 7.41 (dd, \(J' = 2.4\)Hz, \(J'' = 6.8\)Hz, 1H), 7.24 (d, \(J = 8.0\)Hz, 2H), 7.16 (d, \(J = 8.0\)Hz, 3H), 4.17 (s, 2H), 2.4 (s, 3H)

\(\text{\(^{13}\)NMR (100MHz, CDCl}_3\)) 154.0, 140.0, 137.5, 131.4, 129.9, 129.6, 128.4, 125.9, 116.2, 107.3, 35.9, 21.1

ESI-HRMS: [M+H]\(^+\) m/z calcd for C\(_{14}\)H\(_{13}\)N\(_2\)O\(^+\): 225.1028, found: 225.1028
2-benzylpyrazine N¹-oxide (3da)

(pale yellow solid) \( ^1 \)H NMR (400MHz, CDCl\(_3\)) 8.34 (d, \( J = 4.0 \)Hz, 1H), 8.24 (s, 1H), 8.14 (d, \( J = 4.0 \)Hz, 1H), 7.26-7.38 (m, 5H), 4.19 (s, 2H) \( ^{13} \)NMR (100MHz, CDCl\(_3\)) 147.7, 146.8, 145.3, 134.9, 133.6, 129.4, 128.9, 127.4, 33.9

ESI-HRMS: \([\text{M+H}]^+\) m/z calcd for C\(_{11}H_{11}N_2O^+\): 187.0871, found: 187.0870

2-(4-methylbenzyl)-pyrazine N¹-oxide (3dd)

\( ^1 \)H NMR (400MHz, CDCl\(_3\)) 8.35 (d, \( J = 4.0 \)Hz, 1H), 8.25 (s, 1H), 8.15 (d, \( J = 4.0 \)Hz, 1H), 7.19 (s, 4H), 4.17 (s, 2H), 2.37 (s, 3H)

\( ^{13} \)NMR (100MHz, CDCl\(_3\)) 147.6, 146.9, 145.2, 137.0, 133.5, 131.8, 129.5, 129.2, 53.6, 33.5

ESI-HRMS: \([\text{M+H}]^+\) m/z calcd for C\(_{12}H_{13}N_2O^+\): 201.1028, found: 201.1025
2-(4-fluorobenzyl)-pyrazine N\(^1\)-oxide (3dc)

(sticky pale yellow liquid) \(^1\)H NMR (400MHz, CDCl\(_3\)) 8.35 (d, \(J = 4.0\)Hz, 1H), 8.27 (s, 1H), 8.13 (d, \(J = 4.0\)Hz, 1H), 7.26-7.29 (m, 2H), 7.02-7.06 (m, 2H), 4.16 (s, 2H) \(^{13}\)NMR (100MHz, CDCl\(_3\)) 163.3, 160.8, 147.5, 146.5, 145.5, 133.7, 130.98, 130.90, 130.58, 130.55, 115.9, 115.7, 33.2

ESI-HRMS: [M+H]\(^+\) m/z calcd for C\(_{11}\)H\(_{10}\)FN\(_2\)O\(^+\): 205.0777, found: 205.0774

2-methylbenzyl isoquinoline N-oxide (3eb)

(white solid) \(^1\)H NMR (400MHz, CDCl\(_3\)) 8.28 (d, \(J = 7.2\)Hz, 1H), 7.77-7.82 (m, 2H), 7.65 (d, \(J = 7.2\)Hz, 1H), 7.56-7.58 (m, 2H), 7.23 (d, \(J = 7.4\)Hz, 1H), 7.12 (t, \(J = 7.4\)Hz , 1H), 6.97 (t, \(J = 7.4\)Hz , 1H), 6.55 (d, \(J = 7.6\)Hz , 1H), 4.74 (s, 2H), 2.54 (s, 3H)

\(^{13}\)NMR (100MHz, CDCl\(_3\)) 146.9, 136.9, 136.4, 134.9, 130.3, 129.4, 129.3, 128.9, 128.3, 127.4, 126.8, 126.5, 126.2, 124.2, 122.7, 29.4, 19.9

S11
ESI-HRMS: [M+H]^+ m/z calcd for C_{17}H_{16}NO\(^+\): 250.1232, found: 250.1235
III. References and Notes


IV. NMR Spectrum Copies

2-benzylpyridine N-oxide (3aa)
2-benzylpyridine (4)
2-(2-methylbenzyl)-pyridine N-oxide (3ab)
2-(4-fluorobenzyl)-pyridine N-oxide (3ac)
2-(3-trifluoromethylbenzyl)-pyridine N-oxide (3ad)
2-benzyl-3-cyanopyridine N-oxide (3ba)
2- (4-methylbenzyl)-4-cyanopyridine N-oxide (3ce)
2-(2-methylbenzyl)-5-cyanopyridine N-oxide (3bb)
2-benzylpyrazine N$_1$-oxide (3da)
2-(4-methylbenzyl)-pyrazine N\(^1\)-oxide (3dd)

S33
2-(4-fluorobenzyl)-pyrazine N\textsuperscript{1}-oxide (3dc)
2-methylbenzyl isoquinoline N-oxide (3eb)