Supporting Information

Palladium-catalyzed dehydrative N-benzylolation/C-H benzylation cascade of 2-morpholinoanilines on water

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Effects of catalysts and solvents (see Table 1, entry 8).

A mixture of 2-morpholinoaniline 1a (178 mg, 1 mmol), palladium(II) acetate (11 mg, 0.05 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 36 mg, 0.1 mmol) and benzyl alcohol 2a (515 μL, 5 mmol) in H₂O (4 mL) was heated at 100 °C for 20 h in a sealed tube under Ar. After the reaction mixture was cooled, 1,3,5-trimethoxybenzene (168.2 mg, 1 mmol, internal standard) was added to the reaction mixture, which was extracted with CDCl₃ (8 mL), then the organic layer was analyzed by ¹H-NMR spectroscopy.
Competitive deuterium labeling experiment (see Scheme 4A).

A mixture of \(4a\) (67.1 mg, 0.25 mmol), \(4a-d\) (68.9 mg, 0.25 mmol), \(\text{Pd(OAc)}_2\) (6 mg, 0.025 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol), benzyl alcohol \(2a\) (108 mg, 1.0 mmol), and \(2a-d\) (115 mg, 1.0 mmol) in \(\text{H}_2\text{O} (1 \text{ mL})\) and \(\text{D}_2\text{O} (1 \text{ mL})\) was heated at 100 °C for 16 h in a sealed tube under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO\(_4\) and concentrated in vacuo. The residue was washed with hexanes, then purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product \(3a\).

<table>
<thead>
<tr>
<th>Signal (\delta)</th>
<th>6.27 (Ar-H)</th>
<th>4.55 (methine-H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integral value</td>
<td>1.00 (1H)</td>
<td>0.73 (1H): (k_{iH}/k_D = 0.73/0.27 = 2.7)</td>
</tr>
</tbody>
</table>
Hammett study (see Figure 4).

\[
\begin{align*}
\text{X} = \text{CF}_3 & \quad \text{log}(k_f/k_h) = \log(1/9) = -0.95 \\
\end{align*}
\]

A mixture of 3- or 5-substituted 2-morpholinooanilines (X = Me, Cl and CF\textsubscript{3} groups) (0.25 mmol), Pd(OAc)\textsubscript{2} (6 mg, 0.025 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol) and benzyl alcohol (2a) (258 \mu L, 2.5 mmol) in H\textsubscript{2}O (2 mL) was heated at 120 °C in a sealed tube under air. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated in vacuo. The residue was analyzed by 'H-NMR spectroscopy.
Scale-up experiment (see Scheme 9).

A mixture of 2-morpholinoaniline (1.07 g, 6 mmol), palladium(II) acetate (67.4 mg, 0.3 mmol), TPPMS (218.6 mg, 0.6 mmol), and benzyl alcohol (2a, 3.09 mL, 30 mmol) in H₂O (24 mL) was heated at 100 °C for 16 h under Ar. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was recrystallized from hexane/AcOEt to give desired product 3a (1.63 g, 4.55 mmol, 76%) as a pale yellow solid.
X : parts per Million : Proton
X : parts per Million : Carbon13
S27
3I

X : parts per Million : Proton