Palladium-catalyzed coupling reactions on functionalized 2-trifluoromethyl-4-chromenone scaffolds. Synthesis of highly functionalized trifluoromethyl-heterocycles

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General Information.

All chemical reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich, and dried over 3 Å molecular sieves when necessary. DCM, DMF and THF were purified by passage through a bed of activated alumina. Normal phase flash column chromatography was performed using Biotage KP-Sil 50 μm silica gel columns and ACS grade solvents on a Biotage Isolera flash purification system. Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25 mm silica gel 60 F_254 plates and visualized by UV light. Proton (^1H), and carbon (^13C) NMR spectra were recorded on a 500 MHz Bruker Avance III with direct cryoprobe spectrometer. Chemical shifts were reported in ppm (δ) and were referenced using residual non-deuterated solvent as an internal standard (CDCl₃ at 7.26 ppm for ^1H NMR and 77.16 for ^13C NMR. CD₃OD at 3.31 ppm for ^1H NMR and 49.00 for ^13C NMR). The chemical shifts for ^1H NMR and ^13C NMR are reported to the second and first decimal place respectively. Proton coupling constants are expressed in hertz (Hz). The following abbreviations were used to denote spin multiplicity for proton NMR: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, dd = doublet of doublets, dt = doublet of triplets, quin = quintet, tt = triplet of triplets. In some cases, overlapping signals occurred in the ^13C NMR spectra and C-F coupling constants could also be reported (Hz). Low resolution liquid chromatography/mass spectrometry (LCMS) was performed on a Waters Acquity-H UPLC/MS system with a 2.1 mm × 50 mm, 1.7 μm, reversed phase BEH C18 column and LCMS grade solvents. A gradient elution from 95% water +0.1% formic acid/5% acetonitrile +0.1% formic acid to 95% acetonitrile +0.1% formic acid/5% water +0.1% formic acid over 2 min plus a further minute continuing this mixture at a flow rate of 0.85 mL/min was used as the eluent. Total ion current traces were obtained for electrospray positive and negative ionization (ESI+/ESI-). High-resolution mass spectra were obtained using an Agilent 6210 LC-TOF spectrometer in the positive ion mode using electrospray ionization with an Agilent G1312A HPLC pump and an Agilent G1367B autoinjector at the Integrated Molecular Structure Education and Research Center (IMSERC), Northwestern University. Melting point ranges were measured with a Büchi Melting Point M-565 apparatus and are uncorrected.
Optimization table for the Pd-catalyzed Suzuki reaction of compounds 4, 10 and 11.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standard</td>
<td>71%</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄ instead of Pd(dppf)Cl₂</td>
<td>10%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh₃)₄ instead of Pd(dppf)Cl₂ and 16 h instead of 20 min</td>
<td>56%</td>
</tr>
<tr>
<td>4</td>
<td>Dioxane:water instead of toluene:EtOH:water</td>
<td>58%</td>
</tr>
<tr>
<td>5</td>
<td>NaOAc instead of Na₂CO₃</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Compound 7 instead of 2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>65%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Compound 7 instead of 2&lt;sup&gt;c&lt;/sup&gt; and 2 h instead of 20 min</td>
<td>80%</td>
</tr>
<tr>
<td>8</td>
<td>Compound 8 instead of 2&lt;sup&gt;d&lt;/sup&gt; and 2 h instead of 20 min</td>
<td>76%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield for 4d, 10a (entry 7) and 11a (entry 8).<br><sup>b</sup>Conversion measured by LCMS.<br><sup>c</sup>Compound 10a was obtained instead of compound 4d.<br><sup>d</sup>Compound 11a was obtained instead of compound 4d.
Crystal data and refinement parameters

**Table S1: Crystal data and structure refinement for cx1274**

<table>
<thead>
<tr>
<th>Crystal data and structure refinement for compound 7 (CCDC 1840656)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identification code</strong></td>
</tr>
<tr>
<td><strong>Empirical formula</strong></td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
</tr>
<tr>
<td><strong>Temperature / K</strong></td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
</tr>
<tr>
<td><strong>Space group</strong></td>
</tr>
<tr>
<td><strong>a / Å, b / Å, c / Å</strong></td>
</tr>
<tr>
<td><strong>α°, β°, γ°</strong></td>
</tr>
<tr>
<td><strong>Volume / Å³</strong></td>
</tr>
<tr>
<td><strong>Z</strong></td>
</tr>
<tr>
<td><strong>ρ_{calc} / mg mm^{-3}</strong></td>
</tr>
<tr>
<td><strong>μ / mm^{-1}</strong></td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
</tr>
<tr>
<td><strong>Crystal size / mm³</strong></td>
</tr>
<tr>
<td><strong>2θ range for data collection</strong></td>
</tr>
<tr>
<td><strong>Index ranges</strong></td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
</tr>
<tr>
<td><strong>Independent reflections</strong></td>
</tr>
<tr>
<td><strong>Data/restraints/parameters</strong></td>
</tr>
<tr>
<td><strong>Goodness-of-fit on F²</strong></td>
</tr>
<tr>
<td><strong>Final R indexes [I&gt;2σ (I)]</strong></td>
</tr>
<tr>
<td><strong>Final R indexes [all data]</strong></td>
</tr>
<tr>
<td><strong>Largest diff. peak/hole / e Å^{-3}</strong></td>
</tr>
</tbody>
</table>
Crystal data and structure refinement for compound 12a (CCDC 1840657)

Table S2: Crystal data and structure refinement for cx1275

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<tbody>
<tr>
<td>Identification code</td>
<td>cx1275</td>
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<tr>
<td>Empirical formula</td>
<td>C_{18}H_{12}N_{3}O_{2}F_{3}</td>
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<tr>
<td>Formula weight</td>
<td>359.31</td>
</tr>
<tr>
<td>Temperature / K</td>
<td>100.01</td>
</tr>
<tr>
<td>Crystal system</td>
<td>orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>Pbcn</td>
</tr>
<tr>
<td>a / Å, b / Å, c / Å</td>
<td>27.8356(9), 5.13030(10), 21.0337(6)</td>
</tr>
<tr>
<td>α/, β/, γ/°</td>
<td>90, 90, 90</td>
</tr>
<tr>
<td>Volume / Å³</td>
<td>3003.72(14)</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>ρcalc / mg mm⁻³</td>
<td>1.589</td>
</tr>
<tr>
<td>μ / mm⁻¹</td>
<td>1.131</td>
</tr>
<tr>
<td>F(000)</td>
<td>1472</td>
</tr>
<tr>
<td>Crystal size / mm³</td>
<td>0.119 x 0.099 x 0.034</td>
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<tr>
<td>2Θ range for data collection</td>
<td>8.408 to 130.242°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-19 ≤ h ≤ 32, -5 ≤ k ≤ 6, -24 ≤ l ≤ 16</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>7133</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2531[R(int) = 0.0279]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>2531/0/244</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.043</td>
</tr>
<tr>
<td>Final R indexes [I&gt;2σ (I)]</td>
<td>R₁ = 0.0325, wR₂ = 0.0864</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>R₁ = 0.0347, wR₂ = 0.0887</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å⁻³</td>
<td>0.208/-0.261</td>
</tr>
</tbody>
</table>

![Crystal structure diagram](image-url)
NMR SPECTRA

7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (1)

$^1$H NMR

$^{13}$C NMR
4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl trifluoromethanesulfonate (2)

$^1$H NMR

$^{13}$C NMR
7-hydroxy-8-iodo-2-(trifluoromethyl)-4H-chromen-4-one (3)

\(^1\text{H NMR}\)

\[^{13}\text{C NMR}\]
7-(4-fluorophenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4a)

$^1$H NMR

$^{13}$C NMR
7-(4-hydroxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4b)

$^1$H NMR

$^{13}$C NMR
4-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzonitrile (4c)

$^1$H NMR

$^{13}$C NMR
7-(3,5-bis(trifluoromethyl)phenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4d)

$^1$H NMR

$^{13}$C NMR
3-(4-oxo-2-(trifluoromethyl)-4H-chromen-7-yl)benzamide (4e)

$^1$H NMR

$^{13}$C NMR
7-(2-chlorophenyl)-2-(trifluoromethyl)-4H-chromen-4-one (4f)

$^1$H NMR

$^{13}$C NMR
7-(2-(trifluoromethoxy)phenyl)-2-(trifluoromethyl)-4\textit{H}-chromen-4-one (4g)

\textit{\textsuperscript{1}H NMR}

\textit{\textsuperscript{13}C NMR}
7-(thiophen-3-yl)-2-(trifluoromethyl)-4H-chromen-4-one (4h)

$^1$H NMR

$^{13}$C NMR
7-cyclopropyl-2-(trifluoromethyl)-4H-chromen-4-one (4i)

$^1$H NMR

$^{13}$C NMR
7-((4-chlorophenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5a)

$^1$H NMR

$^{13}$C NMR
7-((4-hydroxyphenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5b)

$^1$H NMR

$^{13}$C NMR
7-(o-tolylamino)-2-(trifluoromethyl)-4H-chromen-4-one (5c)

$^1$H NMR

$^{13}$C NMR
7-((2,6-dimethylphenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5d)

$^1H$ NMR

$^{13}C$ NMR
2-(trifluoromethyl)-7-((3,4,5-trimethoxyphenyl)amino)-4H-chromen-4-one (5e)

$^1$H NMR

$^{13}$C NMR
7-((3,4-dichlorophenyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5f)

$^1$H NMR

$^{13}$C NMR
7-(1H-indol-1-yl)-2-(trifluoromethyl)-4H-chromen-4-one (5g)

$^1$H NMR

$^{13}$C NMR
7-(indolin-1-yl)-2-(trifluoromethyl)-4H-chromen-4-one (5h)

$^1$H NMR

$^{13}$C NMR
7-(pyridin-2-ylamino)-2-(trifluoromethyl)-4H-chromen-4-one (5i)

$^1$H NMR

$^{13}$C NMR
7-((4-bromophenyl)(methyl)amino)-2-(trifluoromethyl)-4H-chromen-4-one (5j)

$^1$H NMR

$^{13}$C NMR
7-(2-(m-tolyl)hydrazinyl)-2-(trifluoromethyl)-4H-chromen-4-one (5k)

$^1$H NMR

$^{13}$C NMR
7-(4-chlorophenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6a)

$^1$H NMR

$^{13}$C NMR
7-(4-acetylphenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6b)

$^1$H NMR

$^{13}$C NMR
7-(4-aminophenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6c)

$^1$H NMR

$^{13}$C NMR
7-(o-tolyloxy)-2-(trifluoromethyl)-4H-chromen-4-one (6d)

$^1$H NMR

$^{13}$C NMR
7-(3,4-dimethoxyphenoxy)-2-(trifluoromethyl)-4H-chromen-4-one (6e)

$^1$H NMR

$^{13}$C NMR
(7-(phenylthio)-2-(trifluoromethyl)-4H-chromen-4-ylidene)oxonium (6f)

$^1$H NMR

$^{13}$C NMR
8-iodo-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (7)

$^1H$ NMR

$^{13}C$ NMR
7-(benzyloxy)-8-iodo-2-(trifluoromethyl)-4H-chromen-4-one (8)

\(^1\)H NMR

\(^{13}\)C NMR
8-(3,5-bis(trifluoromethyl)phenyl)-7-hydroxy-2-(trifluoromethyl)-4H-chromen-4-one (9)

$^1$H NMR

$^{13}$C NMR
8-(3,5-bis(trifluoromethyl)phenyl)-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (10a)

$^1$H NMR

$^{13}$C NMR
4-(7-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzamide (10b)

$^1$H NMR

$^{13}$C NMR
3-(7-methoxy-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzonitrile (10c)

$^1$H NMR

$^{13}$C NMR
8-(2-chlorophenyl)-7-methoxy-2-(trifluoromethyl)-4H-chromen-4-one (10d)

$^1$H NMR

$^{13}$C NMR
7-(benzyloxy)-8-(3,5-bis(trifluoromethyl)phenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11a)

\(^1\)H NMR

\[ \text{Chemical Structure} \]

\[ \text{NMR Spectrum} \]

\[^{13}\)C NMR

\[ \text{Chemical Structure} \]

\[ \text{NMR Spectrum} \]
4-(7-(benzyloxy)-4-oxo-2-(trifluoromethyl)-4H-chromen-8-yl)benzamide (11b)

$^1$H NMR

$^{13}$C NMR
7-(benzyloxy)-8-(4-hydroxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11c)

$^1$H NMR

$^{13}$C NMR
7-(benzyloxy)-8-(3-methoxyphenyl)-2-(trifluoromethyl)-4H-chromen-4-one (11d)

$^1$H NMR

$^{13}$C NMR
7-(benzyloxy)-8-(pyridin-4-yl)-2-(trifluoromethyl)-4H-chromen-4-one (11e)

$^1$H NMR

$^{13}$C NMR
2'-hydroxy-6'-methoxy-3'-(3-(trifluoromethyl)-1H-pyrazol-5-yl)-[1,1'-biphenyl]-3-carbonitrile (12a)

$^1H$ NMR

$^{13}C$ NMR
4-(2-amino-6-( trifluoromethyl)pyrimidin-4-yl)-2'-chloro-[1,1'-biphenyl]-3-ol (12b)

$^1$H NMR

$^{13}$C NMR
6-(2-hydroxy-4-(o-tolyloxy)phenyl)-4-(trifluoromethyl)pyrimidine-2(1H)-thione (12c)

$^1$H NMR

$^{13}$C NMR