Supporting Information

Rh(III)-Catalyzed Oxime Ether-Directed Heteroarylation of Arene through Oxidative C–H/C–H Cross-Coupling

Dekun Qin, Jing Wang, Xurong Qin, Chunxia Wang, Ge Gao* and Jingsong You*

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, and State Key Laboratory of Biotherapy, West China Medical School, Sichuan University, 29 Wangjiang Road, Chengdu 610064, PR China
E-mail: gg2b@scu.edu.cn; jsyou@scu.edu.cn

Table of contents

I. General Remarks ...............................................................................................................S2
II. Optimization of the reaction conditions .......................................................................S2
III. General procedure for the oxidative C–H/C–H cross-coupling of oxime ethers with heteroarenes ..........................................................................................................................S5
IV. Mechanism study .........................................................................................................S6
V. Characterization of the products ...................................................................................S9
VI. References ..................................................................................................................S18
VII. Copies of 1H and 13C NMR spectra .........................................................................S19
I. General Remarks

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. [RhCp*Cl₂]₂ [1] oxime ethers [2] were prepared according to the literature procedures. All solvents were dried according to the known methods and distilled prior to use. Unless otherwise indicated, all reactions were carried out under N₂ atmosphere. NMR spectra were obtained on a Bruker AMX-400. The ¹H NMR (400 MHz) chemical shifts were measured using CDCl₃ or acetone-d₆ as the internal reference (CDCl₃: δ = 7.26 ppm; acetone-d₆: δ = 2.05 ppm). The ¹³C NMR (100 MHz) chemical shifts are given using CDCl₃ or acetone-d₆ as the internal standard (CDCl₃: δ = 77.16 ppm; acetone-d₆: δ = 29.84 ppm). High-resolution mass spectra (HR-MS) were obtained with a Waters-Q-TOF-Premier (ESI). Melting points were determined with XRC-1 and are uncorrected.

II. Optimization of the reaction conditions

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with acetophenone O-methyl oxime 1a (37.3 mg, 0.25 mmol), 2-Chlorothiophene 2a (44.5 mg, 0.375 mmol), [Rh] catalyst (0.00625 mmol, 2.5 mol%), AgSbF₆ (10 mol%, if required), oxidant (2.2 equiv), additive (50 mol%) and solvent (1.0 mL) under an N₂ atmosphere. The mixture was stirred for 5 min at room temperature, and then heated at 140-160 °C for the indicated time. After the reaction was cooled down to ambient temperature, it was diluted with 20 mL of CH₂Cl₂ and filtered through a celite pad, which was then washed with 10-20 mL of CH₂Cl₂. The combined organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether/dichloromethane = 15/1-5/1, v/v) to provide the desired product 3a.
Table S1. Screening of solvents

\[
\text{MeON} \quad + \quad \text{S} \quad \text{S} \quad [\text{Cp*RhCl}_2^2] \quad \text{(2.5 mol\%)} \\
\text{AgSbF}_6 \quad \text{(10 mol\%)} \\
\text{Cu(OAc)}_2 \quad \text{(2.2 equiv)} \\
\text{solvent (1 mL)} \\
150 \degree C, 24 h
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%) (^b)</th>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>32</td>
<td>8</td>
<td>DMSO</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>mesitylene</td>
<td>12</td>
<td>9</td>
<td>MeOH</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>22</td>
<td>10</td>
<td>NMP</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>dioxane</td>
<td>24</td>
<td>11</td>
<td>MeCN</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>o-DCB</td>
<td>22</td>
<td>12</td>
<td>THF</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>t-AmylOH</td>
<td>24</td>
<td>13</td>
<td>diglyme</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>DMA</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: acetophenone O-methyl oxime (0.25 mmol), 2-Chlorothiophene (0.375 mmol, 1.5 equiv), [Cp*RhCl]_2 (2.5 mol%), AgSbF_6 (10 mol%), Cu(OAc)_2 (2.2 equiv), solvent (1.0 mL) at 150 \degree C for 24 h under an N_2 atmosphere. \(^b\) Isolated yield.

Table S2. Screening of oxidants

\[
\text{MeON} \quad + \quad \text{S} \quad \text{S} \quad [\text{Cp*RhCl}_2^2] \quad \text{(2.5 mol\%)} \\
\text{AgSbF}_6 \quad \text{(10 mol\%)} \\
\text{oxidant (2.2 equiv)} \\
\text{DCE (1 mL)} \\
150 \degree C, 24 h
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Yield (%) (^b)</th>
<th>Entry</th>
<th>Oxidant</th>
<th>Yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)_2</td>
<td>32</td>
<td>8</td>
<td>AgOAc</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)_2 \cdot H_2O</td>
<td>24</td>
<td>9</td>
<td>AgOTf</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>CuCl_2 \cdot 2H_2O</td>
<td>N.D</td>
<td>10</td>
<td>Ag_2O</td>
<td>N.D</td>
</tr>
<tr>
<td>4</td>
<td>CuBr_2</td>
<td>N.D</td>
<td>11</td>
<td>NFSI</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Cu(O Tf)_2</td>
<td>trace</td>
<td>12</td>
<td>BQ</td>
<td>N.D</td>
</tr>
<tr>
<td>6</td>
<td>Cu(TFA)_2 \cdot H_2O</td>
<td>24</td>
<td>13</td>
<td>KcS_2O_4</td>
<td>N.D</td>
</tr>
<tr>
<td>7</td>
<td>Ag_2CO_3</td>
<td>36</td>
<td>14</td>
<td>Phl(OAc)_2</td>
<td>18</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: acetophenone O-methyl oxime (0.25 mmol), 2-Chlorothiophene (0.375 mmol, 1.5 equiv), [Cp*RhCl]_2 (2.5 mol%), AgSbF_6 (10 mol%), oxidant (2.2 equiv), DCE (1.0 mL) at 150 \degree C for 24 h under an N_2 atmosphere. \(^b\) Isolated yield.
Table S3. Screening of additives\(^a\)

\[
\begin{array}{ccc}
\text{Entry} & \text{Additive} & \text{Yield (%)}\(^b\) \\
1 & \text{PivOH} & \text{trace} \\
2 & \text{TFA} & \text{trace} \\
3 & \text{TfOH} & \text{trace} \\
4 & \text{NaOAc} & 12 \\
5 & \text{KOAc} & 16 \\
6 & \text{CsOAc} & 19 \\
7 & \text{Cs\(\text{CO}_3\)} & 28 \\
8 & \text{CsOPiv} & 25 \\
9 & \text{K_2CO}_3 & 36 \\
10 & \text{t-BuOK} & \text{trace} \\
11 & \text{KH}_2\text{PO}_4 & \text{trace} \\
12 & \text{Cu(OAc)}_2 & 47 \\
13 & \text{Cu(TFA)}_2\cdot\text{H}_2\text{O} & 50 \\
14 & \text{Cu(TFA)}_2\cdot\text{H}_2\text{O}\text{c} & 58 \\
15 & \text{Cu(TFA)}_2\cdot\text{H}_2\text{O}\text{e} & 55 \\
16 & \text{Cu(TFA)}_2\cdot\text{H}_2\text{O}\text{e} & 47 \\
\end{array}
\]

\(^a\) Reaction conditions: acetophenone O-methyl oxime (0.25 mmol), 2-Chlorothiophene (0.375 mmol, 1.5 equiv), \([\text{Cp*RhCl}_2]\) (2.5 mol%), \(\text{AgSbF}_6\) (10 mol%), \(\text{Ag}_2\text{CO}_3\) (2.2 equiv), additive (50 mol%) and \(\text{DCE}\) (1.0 mL) at \(150^\circ\text{C}\) for 24 h under an \(\text{N}_2\) atmosphere. \(^b\) Isolated yield. \(^c\) 20 mol% was used. \(^d\) 10 mol% was used. \(^e\) 100 mol% was used.

Table S4. Screening of catalysts\(^a\)

\[
\begin{array}{ccc}
\text{Entry} & \text{Catalysts} & \text{Yield (%)}\(^b\) \\
1 & \text{[Cp*Rh(MeCN)}_3][\text{SbF}_6]}\ (5 \text{ mol%}) & 42 \\
2 & \text{Rh(PPh}_3)_2\text{Cl} \ (5 \text{ mol%}) & \text{trace} \\
3 & \text{RhCp*(OAc)}_2 \ (5 \text{ mol%}) & 16 \\
4 & \text{[Cp*RhCl}_2]\_2 & \text{trace} \\
5 & \text{[Cp*RhCl}_2]\_2 & \text{trace} \\
6 & \text{[Cp*RhCl}_2]\_2 & \text{trace} \\
\end{array}
\]

\(^a\) Reaction conditions: acetophenone O-methyl oxime (0.25 mmol), 2-Chlorothiophene (0.375 mmol, 1.5 equiv), Rh source (2.5 mol%), Ag source (10 mol%), \(\text{Ag}_2\text{CO}_3\) (2.2 equiv), \(\text{Cu(TFA)}_2\cdot\text{H}_2\text{O}\) (20 mol%) and \(\text{DCE}\) (1.0 mL) at \(150^\circ\text{C}\) for 24 h under an \(\text{N}_2\) atmosphere. \(^b\) Isolated yield.
Table S5. Other reaction parameters

\[
\text{MeON} + \text{S} \quad \xrightarrow{[\text{Cp*RhCl}_2]_2 (2.5 \text{ mol\%})} \quad \text{MeON} \\
\text{1a} \quad \text{2a} \quad \text{2b} \quad \text{3a}
\]

Entry | Variation | Yield (%) | Entry | Variation | Yield (%) |
--- | --- | --- | --- | --- | --- |
1 | no variation | 58 | 7 | without Ag\(_2\text{CO}_3\) | N.D |
2 | DCE (0.6 mL) | 65 | 8 | without AgSbF\(_6\) | 8 |
3 | DCE (2.0 mL) | 44 | 9 | 0.25 mmol of 2a and 0.375 mmol of 1a | 48 |
4 | 140 °C | 56 | 10 | 36 h | 54 |
5 | 160 °C | 51 | 11 | 20h | 50 |
6 | without | N.D |

\[\text{a} \text{ Reaction conditions: acetophenone O-methyl oxime (0.25 mmol), 2-Chlorothiophene (0.375 mmol, 1.5 equiv), [Cp*RhCl}_2]_2 (2.5 \text{ mol\%}), AgSbF}_6 (10 \text{ mol\%}), Ag}_2\text{CO}_3 (2.2 \text{ equiv}), Cu(TFA)}_2\cdot\text{H}_2\text{O (20 mol\%) and DCE (1 mL)} \text{ at 150 °C for 24 h under an N}_2 \text{ atmosphere.} \]

\[\text{b} \text{ Isolated yield.} \]

III. General procedure for the oxidative C–H/C–H cross-coupling of oxime ethers with heteroarenes

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with oxime ethers (0.25 mmol), heteroarene (0.375 mmol), [RhCp*Cl\(_2\)]\(_2\) (3.9 mg, 0.00625 mmol), AgSbF\(_6\) (8.6 mg, 0.025 mmol), Ag\(_2\text{CO}_3\) (151.7 mg, 0.55 mmol), Cu(TFA\(_2\))\(_2\)\cdot\text{H}_2\text{O} (14.5 mg, 0.05 mmol), and DCE (0.6 mL) under an N\(_2\) atmosphere. The mixture was stirred for 5 min at room temperature, and then heated at 150 °C for 24 h. After the reaction was cooled down to ambient temperature, it was diluted with 20 mL of CH\(_2\text{Cl}_2\) and filtered through a celite pad, which was then washed with 10-20 mL of CH\(_2\text{Cl}_2\). The combined organic phase was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to provide the desired product.
IV. Mechanism study

(a) The H/D exchange experiments

The reactions were conducted by using the general procedure with (1) only 1a, (2) only 2h and (3) both in the presence of D$_2$O (5.0 mmol).

\[ \text{H} \quad [\text{RhCp*Cl}_2]_2 (2.5 \text{ mol\%}), \text{AgSbF}_6 (10 \text{ mol\%}) \quad \text{Ag}_2\text{CO}_3 (2.2 \text{ eq}), \text{Cu(TFA)}_2\text{H}_2\text{O} (20 \text{ mol\%}) \quad \text{DCE, 150}^\circ \text{C, 1 h} \]

The $^1$H NMR analysis showed that 85% hydrogen at the ortho-position of phenyl ring of acetophenone $O$-methyl oxime was deuterated.

\[ \text{H} \quad \text{D} \quad \text{H} \quad \text{NOMe} \quad \text{20 equiv} \]

(1)

\[ \text{H} \quad [\text{RhCp*Cl}_2]_2 (2.5 \text{ mol\%}), \text{AgSbF}_6 (10 \text{ mol\%}) \quad \text{Ag}_2\text{CO}_3 (2.2 \text{ eq}), \text{Cu(TFA)}_2\text{H}_2\text{O} (20 \text{ mol\%}) \quad \text{DCE, 150}^\circ \text{C, 1 h} \]

The $^1$H NMR analysis showed that 11% hydrogen at the C2-position of benzothiophene was deuterated.

\[ \text{H} \quad \text{S} \quad \text{H} \quad \text{NOMe} \quad \text{20 equiv} \]

(2)
The $^1$H NMR analysis showed that 5% hydrogen at the C2-position of benzothiophene and 73% hydrogen at the *ortho*-position of the phenyl ring of acetophenone O-methyl oxime were deuterated, respectively.
(b) Kinetic isotope experiments

Two sets of reactions were carried out in a parallel manner under the optimal conditions for only 2 h. In each case benzothiophene was allowed to react with acetophenone O-methyl oxime and its deuterated derivative, respectively. 3h was obtained in 17% yield and [D₄]-3h was obtained in 14% yield. KIE = 1.2.

Two sets of reactions were carried out in a parallel manner under the optimal conditions for only 2 h. In each case acetophenone O-methyl oxime was allowed to react with benzothiophene and 2-deuterio-benzothiophene, respectively. 3h was
obtained in 17% and 7% yields, respectively. KIE = 2.4.

(c) Plausible mechanism

![Scheme S1. Plausible mechanism](image)

V. Characterization of the products

1-(2-(5-chlorothiophen-2-yl)phenyl)ethanone O-methyl oxime (3a): Pale yellow oil (40.4 mg, 61%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.87$ (s, 3H), 4.00 (s, 3H), 6.86 (d, $J = 4.0$ Hz, 1H), 6.88 (d, $J = 3.6$ Hz, 1H), 7.34-7.43 (m, 4H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.5, 62.0, 126.4, 126.8, 128.4, 129.1, 129.7, 130.2, 130.6, 132.4, 137.0, 140.9, 157.8$ ppm. HRMS (ESI$^+$): calcd for C$_{13}$H$_{12}$ClNOS [M+H]$^+$ 266.0406, found 266.0406.

1-(2-(5-chlorothiophen-2-yl)-4-methylphenyl)ethanone O-methyl oxime (3b): Pale yellow oil (41.8 mg, 60%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.85$ (s, 3H), 2.38 (s, 3H), 3.98 (s, 3H), 6.84 (d, $J = 4.0$ Hz, 1H), 6.86 (d, $J = 4.0$ Hz, 1H), 7.16 (dd, $J = 8.0$ Hz, 1.2 Hz, 1H), 7.22 (s, 1H), 7.26 (d, $J = 8.0$ Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.6, 21.3, 62.0, 126.3, 126.7, 129.1, 129.7, 130.4, 130.9, 132.1, 134.3, 139.1, 141.1, 157.8$ ppm. HRMS (ESI$^+$): calcd for C$_{14}$H$_{14}$ClNOS [M+H]$^+$ 280.0563, found 280.0560.
1-(2-(5-chlorothiophen-2-yl)-5-methylphenyl)ethanone O-methyl oxime (3c): Pale yellow oil (37.0 mg, 53%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.86 (s, 3H), 2.38 (s, 3H), 4.00 (s, 3H), 6.82 (d, $J$ = 4.0 Hz, 1H), 6.86 (d, $J$ = 3.6 Hz, 1H), 7.18-7.20 (m, 2H), 7.30 (d, $J$ = 8.0 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.5, 21.2, 62.0, 126.1, 126.7, 129.5, 129.8, 130.1, 130.2, 130.3, 136.8, 138.4, 141.0, 158.0 ppm. HRMS (ESI$^+$): calcd for C$_{14}$H$_{14}$ClNOS [M+H]$^+$ 280.0563, found 280.0560.

1-(2-(5-chlorothiophen-2-yl)-4-ethylphenyl)ethanone O-methyl oxime (3e): Pale yellow oil (51.3 mg, 70%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.25 (t, $J$ = 7.6 Hz, 3H), 1.86 (s, 3H), 2.67 (q, $J$ = 7.6 Hz, 2H), 3.98 (s, 3H), 6.84 (d, $J$ = 4.0 Hz, 1H), 6.87 (d, $J$ = 3.6 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 15.6, 16.6, 28.7, 62.0, 126.3, 126.7, 127.9, 129.7, 129.8, 130.3, 132.2, 134.5, 141.2, 145.5, 157.8 ppm. HRMS (ESI$^+$): calcd for C$_{15}$H$_{16}$ClNOS [M+Na]$^+$ 316.0539, found 316.0539.

1-(4-bromo-2-(5-chlorothiophen-2-yl)phenyl)ethanone O-methyl oxime (3f): Pale yellow oil (41.1 mg, 48%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.84 (s, 3H), 3.99 (s, 3H), 6.87 (d, $J$ = 3.6 Hz, 1H), 6.88 (d, $J$ = 3.6 Hz, 1H), 7.23 (d, $J$ = 8.4 Hz, 1H), 7.47 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 7.56 (d, $J$ = 2.0 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.4, 62.1, 123.0, 126.9, 127.0, 131.2, 131.3, 131.5, 132.8, 134.2, 135.9, 139.1, 156.8 ppm. HRMS (ESI$^+$): calcd for C$_{13}$H$_{11}$BrClNOS [M+H]$^+$ 343.9512, found 343.9522.
1-(5-bromo-2-(5-chlorothiophen-2-yl)phenyl)ethanone O-methyl oxime (3g): Pale yellow oil (44.6 mg, 52%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.84 (s, 3H), 4.00 (s, 3H), 6.84 (d, $J$ = 3.6 Hz, 1H), 6.88 (d, $J$ = 4.0 Hz, 1H), 7.27 (dd, $J$ = 8.0 Hz, 0.4 Hz, 1H), 7.50-7.53 (m, 2H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.3, 62.2, 122.3, 126.7, 126.9, 131.1, 131.3, 131.6, 132.1, 132.6, 138.5, 139.6, 156.5 ppm. HRMS (ESI$^+$): calcd for C$_{13}$H$_{11}$BrClNOS [M+H]$^+$ 343.9512, found 343.9515.

1-(2-(5-chlorothiophen-2-yl)-4-fluorophenyl)ethanone O-methyl oxime (3h): Brown oil (38.9 mg, 55%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.85 (s, 3H), 3.99 (s, 3H), 6.87-6.89 (m, 2H), 7.04 (td, $J$ = 8.4 Hz, 2.8 Hz, 1H), 7.12 (dd, $J$ = 9.2 Hz, 2.4 Hz, 1H), 7.34 (dd, $J$ = 8.8 Hz, 6.0 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.6, 62.1, 115.2 (d, $J$ = 21.0 Hz), 116.9 (d, $J$ = 23.0 Hz), 126.9, 131.4, 131.7 (d, $J$ = 8.0 Hz), 133.1 (d, $J$ = 3.0 Hz), 134.4 (d, $J$ = 9.0 Hz), 139.5 (d, $J$ = 2.0 Hz), 157.0, 161.5, 164.0 ppm. HRMS (ESI$^+$): calcd for C$_{13}$H$_{11}$ClFNOS [M+H]$^+$ 284.0312, found 284.0316.

methyl 3-(5-chlorothiophen-2-yl)-4-(1-(methoxyimino)ethyl)benzoate (3i): Pale yellow oil (62.9 mg, 78%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.87 (s, 3H), 3.93 (s, 3H), 4.00 (s, 3H), 6.89-6.91 (m, 2H), 7.45 (d, $J$ = 8.0 Hz, 1H), 7.99 (dd, $J$ = 8.0 Hz, 1.6 Hz, 1H), 8.02 (d, $J$ = 1.6 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.3, 52.6, 62.2, 126.9, 127.0, 129.2, 130.0, 130.8, 131.3, 131.4, 132.7, 139.7, 141.0, 157.1, 166.4 ppm. HRMS (ESI$^+$): calcd for C$_{15}$H$_{14}$ClNO$_3$S [M+H]$^+$ 324.0461, found 324.0457.

1-(2-(5-chlorothiophen-2-yl)-4-nitrophenyl)ethanone O-methyl oxime (3j): A pale
yellow solid (51.3 mg, 70%). M.p.: 110-111 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.88$ (s, 3H), 4.02 (s, 3H), 6.78 (d, $J = 4.0$ Hz, 1H), 6.96 (d, $J = 4.0$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 8.17 (dd, $J = 8.4$ Hz, 2.4 Hz, 1H), 8.28 (d, $J = 2.4$ Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.2, 62.4, 122.8, 125.0, 127.1, 127.7, 131.1, 132.5, 134.0, 138.1, 142.8, 148.1, 156.0$ ppm. HRMS (ESI$^+$): calcd for C$_{13}$H$_7$ClN$_2$O$_3$S [M+Na]$^+$ 333.0077, found 333.0077.

3-(5-chlorothiophen-2-yl)-4-(1-(methoxyimino)ethyl)benzonitrile (3k): A brown solid (31.9 mg, 44%). M.p.: 80-82 °C. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.85$ (s, 3H), 4.00 (s, 3H), 6.90 (d, $J = 4.0$ Hz, 1H), 6.92 (d, $J = 3.6$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.62 (dd, $J = 7.6$ Hz, 1.6 Hz, 1H), 7.70 (d, $J = 1.2$ Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.1, 62.4, 113.2, 118.1, 127.1, 127.5, 130.8, 131.4, 132.3, 133.6, 133.7, 138.1, 141.2, 156.2$ ppm. HRMS (ESI$^+$): calcd for C$_{14}$H$_{11}$ClN$_2$O$_3$S [M+Na]$^+$ 313.0178, found 313.0179.

1-(2-(5-chlorothiophen-2-yl)-4-(trifluoromethyl)phenyl)ethanone O-methyl oxime (3l): Pale yellow oil (43.3 mg, 52%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.87$ (s, 3H), 4.01 (s, 3H), 6.90-6.92 (m, 2H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.60 (dd, $J = 8.0$ Hz, 1.2 Hz, 1H), 7.66 (s, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.3, 62.3, 123.8$ (q, $J = 270.9$ Hz), 124.9 (q, $J = 3.6$ Hz), 126.99, 127.00 (q, $J = 3.7$ Hz), 127.3, 130.4, 131.3 (q, $J = 32.5$ Hz), 131.8, 133.2, 139.1, 140.2, 156.6 ppm. HRMS (ESI$^+$): calcd for C$_{14}$H$_{11}$ClF$_3$NOS [M+H]$^+$ 334.0280, found 334.0280.

1-(3-(5-chlorothiophen-2-yl)biphenyl-4-yl)ethanone O-methyl oxime (3m): Yellow oil (44.0 mg, 51%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.91$ (s, 3H), 4.01 (s,
3H), 6.90 (d, J = 4.0 Hz, 1H), 6.91 (d, J = 4.0 Hz, 1H), 7.36-7.40 (m, 1H), 7.44-7.48 (m, 3H), 7.56-7.59 (m, 2H), 7.60-7.61 (m, 1H), 7.62 (d, J = 2.0 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.5, 62.1, 126.6, 126.8, 127.0, 127.3, 128.0, 129.0, 130.2, 130.7, 132.8, 135.8, 140.1, 140.8, 142.2, 157.5 ppm. HRMS (ESI$^+$): calcd for C$_{19}$H$_{16}$ClNOS [M+H]$^+$ 342.0719, found 342.0719.

1-(2-(5-chlorothiophen-2-yl)-4-methoxyphenyl)ethanone O-methyl oxime (3n):
Brown oil (37.6 mg, 51%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.84 (s, 3H), 3.83 (s, 3H), 3.98 (s, 3H), 6.85-6.89 (m, 3H), 6.92 (d, J = 2.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.7, 55.6, 61.9, 113.7, 115.6, 126.5, 126.8, 129.8, 130.6, 131.1, 133.6, 140.8, 157.6, 160.0 ppm. HRMS (ESI$^+$): calcd for C$_{14}$H$_{14}$ClNO$_2$S [M+Na]$^+$ 318.0331, found 318.0328.

1-(6-(5-chlorothiophen-2-yl)benzo[d][1,3]dioxol-5-yl)ethanone O-methyl oxime (3o): Yellow oil (42.5 mg, 55%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.84 (s, 3H), 3.97 (s, 3H), 6.03 (s, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 3.6 Hz, 1H), 6.99 (d, J = 4.0 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.8, 62.0, 101.7, 108.0, 114.7, 123.3, 126.3, 128.2, 131.2, 131.4, 133.6, 145.6, 148.1, 157.2 ppm. HRMS (ESI$^+$): calcd for C$_{14}$H$_{12}$ClNO$_3$S [M+Na]$^+$ 332.0124, found 332.0127.

1-(1-(5-chlorothiophen-2-yl)naphthalen-2-yl)ethanone O-methyl oxime (3p): Pale yellow oil (44.9 mg, 57%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.92 (s, 3H), 4.04 (s, 3H), 6.92 (d, J = 4.0 Hz, 1H), 6.94 (d, J = 4.0 Hz, 1H), 7.49-7.53 (m, 2H), 7.82-7.87 (m, 3H), 7.88 (s, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 16.9, 62.1, 126.5, 126.9,
127.1, 127.3, 127.9, 128.2, 129.1, 129.5, 129.9, 130.4, 132.7, 133.2, 134.9, 141.0, 158.1 ppm. HRMS (ESI\(^+\)): calcd for C\(_{17}\)H\(_{14}\)ClNOS [M+Na]\(^+\) 338.0382, found 338.0385.

1-(2-(5-chlorothiophen-2-yl)phenyl)propan-1-one \(O\)-methyl oxime (3q): Pale yellow oil (50.9 mg, 73%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.83\) (t, \(J = 7.6\) Hz, 3H), 2.36 (q, \(J = 7.6\) Hz, 2H), 3.99 (s, 3H), 6.87 (d, \(J = 4.0\) Hz, 1H), 6.90 (d, \(J = 4.0\) Hz, 1H), 7.29-7.44 (m, 4H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 10.3, 23.2, 62.0, 126.3, 126.8, 128.1, 129.1, 129.9, 130.4, 130.6, 132.5, 135.4, 141.0, 163.0\) ppm. HRMS (ESI\(^+\)): calcd for C\(_{14}\)H\(_{14}\)ClNOS [M+H]\(^+\) 280.0563, found 280.0564.

(2-(5-chlorothiophen-2-yl)phenyl)(phenyl)methanone \(O\)-methyl oxime (3r): A off-white solid (55.6 mg, 68%). M.p.: 47-49 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.01\) (s, 3H), 6.68 (d, \(J = 3.6\) Hz, 1H), 6.72 (d, \(J = 4.0\) Hz, 1H), 7.18-7.24 (m, 3H), 7.29-7.31 (m, 2H), 7.39-7.47 (m, 3H), 7.50-7.52 (m, 1H) ppm. \(^{13}\)C NMR (400 MHz, CDCl\(_3\)): \(\delta = 62.6, 126.0, 126.7, 127.7, 128.3, 129.2, 129.3, 130.0, 130.2, 130.5, 131.1, 133.0, 133.8, 136.7, 140.7, 156.4\) ppm. HRMS (ESI\(^+\)): calcd for C\(_{18}\)H\(_{14}\)ClNOS [M+H]\(^+\) 328.0563, found 328.0564.

1-(2-(4-methylthiophen-2-yl)phenyl)ethanone \(O\)-methyl oxime (4a): Pale yellow oil (40.0 mg, 65%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.83\) (s, 3H), 2.28 (s, 3H), 4.01 (s, 3H), 6.89-6.92 (m, 2H), 7.30-7.40 (m, 3H), 7.45-7.47 (m, 1H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 15.9, 16.5, 62.0, 121.7, 127.8, 129.0, 129.4, 129.6, 130.3, 133.4,
136.8, 138.2, 142.0, 158.4 ppm. HRMS (ESI\(^+\)): calcd for C\(_{14}\)H\(_{15}\)NOS [M+H]\(^+\) 246.0593, found 246.0593.

5-(2-(1-(methoxyimino)ethyl)phenyl)thiophene-2-carbonitrile (4b): Yellow oil (32.0 mg, 50%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.86\) (s, 3H), 3.97 (s, 3H), 7.09 (d, \(J = 4.0\) Hz, 1H), 7.39-7.48 (m, 4H), 7.57 (d, \(J = 3.6\) Hz, 1H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 16.6, 62.1, 110.0, 114.3, 127.2, 129.3, 129.6, 129.9, 130.5, 130.8, 137.5, 137.8, 150.5, 156.8\) ppm. HRMS (ESI\(^+\)): calcd for C\(_{14}\)H\(_{13}\)NOS [M+H]\(^+\) 257.0749, found 257.0746.

1-(2-(4,5-dibromothiophen-2-yl)phenyl)ethanone O-methyl oxime (4c): Pale yellow oil (53.2 mg, 55%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.91\) (s, 3H), 4.00 (s, 3H), 6.91 (s, 1H), 7.36-7.40 (m, 4H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 16.7, 62.1, 111.8, 114.2, 129.0, 129.2, 129.3, 129.8, 130.1, 131.4, 137.0, 143.7, 157.1\) ppm. HRMS (ESI\(^+\)): calcd for C\(_{13}\)H\(_{11}\)Br\(_2\)NOS [M+H]\(^+\) 387.9006, found 387.9006.

1-(2-(5-iodothiophen-2-yl)phenyl)ethanone O-methyl oxime (4d): Pale yellow oil (44.0 mg, 50%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.84\) (s, 3H), 4.00 (s, 3H), 6.76 (d, \(J = 3.6\) Hz, 1H), 7.20 (d, \(J = 4.0\) Hz, 1H), 7.35-7.42 (m, 4H) ppm. \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 16.4, 62.0, 126.2, 127.2, 127.7, 128.0, 129.0, 129.6, 130.5, 133.2, 137.0, 142.2, 158.4\) ppm. HRMS (ESI\(^+\)): calcd for C\(_{13}\)H\(_{12}\)INOS [M+H]\(^+\) 357.9763, found 357.9758.
(2-(5-bromo-thiophen-2-yl)phenyl)(phenyl)methanone O-methyl oxime (4e): Pale yellow oil (40.8 mg, 44%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 4.00$ (s, 3H), 6.70 (d, $J = 4.0$ Hz, 1H), 6.82 (d, $J = 3.6$ Hz, 1H), 7.18-7.24 (m, 3H), 7.28-7.30 (m, 2H), 7.39-7.45 (m, 3H), 7.50-7.52 (m, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 62.6, 112.5, 127.68, 127.70, 128.3, 129.2, 129.3, 129.8, 129.9, 130.5, 131.1, 133.0, 133.8, 136.7, 143.7, 156.4$ ppm. HRMS (ESI$^+$): calcd for C$_{18}$H$_{14}$BrNOS [M+H]$^+$ 372.0058, found 372.0061.

Ethyl 5-(5-(methoxycarbonyl)-2-(1-(methoxyimino)ethyl)phenyl)thiophene-2-carboxylate (4f): off-white oil (47.0 mg, 52%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.39$ (t, $J = 7.2$ Hz, 3H), 1.82 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 4.37 (q, $J = 7.2$ Hz, 2H), 7.09 (d, $J = 4.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 3.6$ Hz, 1H), 8.04 (dd, $J = 8.0$ Hz, 2.0 Hz, 1H), 8.14 (d, $J = 1.6$ Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.5, 15.3, 52.5, 61.5, 62.2, 128.2, 129.8, 130.1, 130.8, 131.6, 132.6, 133.7, 134.7, 141.4, 148.0, 156.7, 162.2, 166.2$ ppm. HRMS (ESI$^+$): calcd for C$_{18}$H$_{19}$NO$_5$S [M+H]$^+$ 362.3062, found 362.3054.

1-(5-(2-((methoxyimino)(phenyl)methyl)phenyl)thiophen-2-yl)ethanone (4g): Yellow oil (45.2 mg, 54%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.48$ (s, 3H), 3.98 (s, 3H), 6.97 (d, $J = 4.0$ Hz, 1H), 7.15-7.23 (m, 3H), 7.28-7.30 (m, 2H), 7.44 (d, $J = 3.6$ Hz, 1H), 7.46-7.47 (m, 3H), 7.52-7.56 (m, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 26.8, 62.7, 127.7, 128.5, 129.0, 129.3, 129.4, 130.0, 130.7, 131.3, 132.4, 132.9, 133.7, 136.8, 144.2, 151.0, 156.1, 190.7$ ppm. HRMS (ESI$^+$): calcd for C$_{20}$H$_{17}$NO$_2$S
1-(2-(benzo[b]thiophen-2-yl)phenyl)ethanone O-methyl oxime (4h): Pale yellow oil (43.5 mg, 62%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.88$ (s, 3H), 4.04 (s, 3H), 7.32 (s, 1H), 7.33-7.47 (m, 5H), 7.58-7.60 (m, 1H), 7.80 (dd, $J = 7.2$ Hz, 1.6 Hz, 1H), 7.85 (d, $J = 7.6$ Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.6, 62.0, 122.2, 123.8, 123.9, 124.5, 124.6, 128.5, 129.1, 129.7, 130.8, 133.2, 137.4, 140.3, 140.5, 142.6, 158.1$ ppm. HRMS (ESI$^+$): calcd for C$_{17}$H$_{15}$NOS [M+H]$^+$ 282.0953, found 282.0946.

1-(2-(6-bromobenzo[b]thiophen-2-yl)phenyl)ethanone O-methyl oxime (4i): Pale yellow oil (55.1 mg, 62%). $^1$H NMR (400 MHz, acetone-$d_6$): $\delta = 1.83$ (s, 3H), 3.91 (s, 3H), 7.40 (s, 1H), 7.43-7.54 (m, 4H), 7.61 (d, $J = 7.6$ Hz, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 8.16 (s, 1H) ppm. $^{13}$C NMR (100 MHz, acetone-$d_6$): $\delta = 16.6, 62.0, 118.6, 124.1, 125.4, 126.1, 128.7, 129.5, 129.9, 130.6, 131.3, 133.2, 138.3, 140.0, 142.7, 144.2, 157.3$ ppm. HRMS (ESI$^+$): calcd for C$_{17}$H$_{14}$BrNOS [M+H]$^+$ 360.0058, found 360.0058.

1-(2-(benzofuran-2-yl)-4-nitrophenyl)ethanone O-methyl oxime (4j): Yellow oil (50.4 mg, 65%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.04$ (s, 3H), 4.06 (s, 3H), 6.98 (s, 1H), 7.29 (td, $J = 7.6$ Hz, 0.8 Hz, 1H), 7.38 (td, $J = 8.4$ Hz, 1.2 Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.65 (d, $J = 7.6$ Hz, 1H), 8.21 (dd, $J = 8.4$ Hz, 2.0 Hz, 1H), 8.74 (d, $J = 2.4$ Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 16.2, 62.4, 107.4, 111.6, 121.7,$
ethyl 5-(2-(1-(methoxyimino)ethyl)phenyl)furan-2-carboxylate (4k): Pale yellow oil (32.3 mg, 45%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.40$ (t, $J = 7.2$ Hz, 3H), 2.02 (s, 3H), 3.98 (s, 3H), 4.38 (q, $J = 7.2$ Hz, 2H), 6.58 (d, $J = 3.6$ Hz, 1H), 7.22 (d, $J = 3.6$ Hz, 1H), 7.34 (dd, $J = 7.6$ Hz, 1.6 Hz, 1H), 7.37 (td, $J = 7.6$ Hz, 1.2 Hz, 1H), 7.44 (td, $J = 7.2$ Hz, 1.6 Hz, 1H), 7.79 (dd, $J = 8.0$ Hz, 1.2 Hz, 1H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.5$, 16.7, 61.1, 62.0, 110.7, 119.6, 128.1, 129.0, 129.1, 129.7, 136.2, 144.3, 155.9, 157.6, 158.9 ppm. HRMS (ESI$^+$): calcd for C$_{16}$H$_{17}$NO$_4$ [M+Na]$^+$ 310.1055, found 310.1058.

XII. References


XIII. Copies of $^1$H and $^{13}$C NMR spectra