Photoredox Synthesis of Arylhydroxylamines from Carboxylic Acids and Nitrosoarenes

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Abstract
Hydroxylamines are found in biologically active compounds and serve as building blocks for the preparation of nitrogen-containing molecules. Here the direct conversion of carboxylic acids into the corresponding alkylhydroxylamines using organo-photoredox catalysis is reported. The process relies in the generation of alkyl radicals via photoinduced oxidation-decarboxylation and their following reaction with nitrosoarenes. We have successfully applied this method to the late-stage modification of complex and biologically active acids and applied it in novel radical cascade processes.

Key words hydroxylamines, radical addition, nitrosoarenes, late-stage functionalization, radical cascade, photoredox

Hydroxylamines and their derivatives are a privileged class of compounds with applications spanning from active pharmaceutical ingredients and agrochemicals to versatile building blocks for the synthesis of complex molecules (Scheme 1, A). Despite this relevance, their preparation can still be troublesome and the development of novel strategies able to selectively introduce the hydroxylamine functionality on structurally complex molecules under mild reaction conditions is a relevant goal.

Visible-light photoredox catalysis is now an established and powerful technique to perform single-electron transfer (SET) reactions under mild conditions. In particular, the ability of harvesting carboxylic acids for the generation of sp3-C-radicals by oxidative decarboxylation has enabled the development of many C–C and C–X (X = F, N3, S…) bond-forming processes.

Owing to our ongoing interest in the preparation of hydroxylamine derivatives as nitrogen-radical precursors, we wondered if a visible-light-mediated protocol for their direct assembly from simple feedstock chemicals could be developed. In particular, we were interested in the possibility of using carboxylic acids as source of sp3-C-radicals and to exploit them in the reaction with nitrosoarenes. Such an approach would be complementary to the more established

Scheme 1 Relevance of hydroxylamines, previous ionic and radical approaches using nitrosoarenes, and this work
ionic pathways where nitrosoarenes are used as electrophiles in conjunction with organometallic reagents,\textsuperscript{7} enolates,\textsuperscript{8} and enamine\textsuperscript{9}/NHC\textsuperscript{10}-based catalytic systems (Scheme 1, B).\textsuperscript{11}
Furthermore, the preparation of hydroxylamines via radical addition onto nitrosoarenes has been considerably overlooked and only few protocols are available.\textsuperscript{12} Most notably, de Alaniz\textsuperscript{13} and Selander\textsuperscript{14} have recently developed Cu(II)-catalyzed protocols for the coupling of nitrosoarenes with radical deriving from \( \alpha \)-bromocarbonyls and sodium triflinate, respectively (Scheme 1, C).

In this paper, we describe the development of the first approach for the generation of hydroxylamines from readily available carboxylic acids and its use in the functionalization of complex and biologically active molecules (Scheme 1, D).

At the outset, we envisioned a catalytic cycle starting with the visible-light-promoted excitation of a photocatalyst and the following oxidative SET decarboxylation of acid \( A \) upon in situ deprotonation \( A \rightarrow B \) (Scheme 2, A).\textsuperscript{4} This step would deliver the C-radical \( C \) that would react with a nitrosoarene \( D \) forging the required C–N bond and delivering the persistent nitroxyl radical \( E \).\textsuperscript{15} At this point, we speculated that the final hydroxylamine \( G \) could be obtained by reductive SET of \( E \) with the reduced photoredox catalyst (to give \( F \)) and protonation.

In order to obtain information regarding the feasibility of our proposed process, preliminary DFT studies were conducted (Scheme 2, B). We were in fact concerned about the potential addition of the C-radical at both the N (path \( a \) – to give \( E \)) and the O atom (path \( b \) – to give \( H \)) of the nitrosoarene, an issue frequently encountered in ionic processes.\textsuperscript{7a,8c} We started by characterizing nitrosobenzene \( I \) in terms of electron donor properties by calculating its adiabatic ionization potential (IP), electron affinity (EA), and absolute electronegativity (\( \chi_{DB} \)).\textsuperscript{16} These values are in line with \( I \) being a competent radical acceptor. The preferred site of radical attack was then assessed by calculating the N and O atom Mulliken spin densities (MSDs) in the triplet state (\( \pi\pi^* \)).\textsuperscript{16} According to this study, \( I \) should display a slight
preference for the reaction at the N-atom owing to its higher MSD. Further support for this reactivity was obtained upon determination of the activation parameters for the reaction of 1 with the adamantyl radical \( \mathcal{J} \) (nucleophilic radical; \( \omega_{\mathcal{J}} = 0.34 \)).\(^{17}\) According to our study both radical pathways (\( a \): attack at the N-atom and \( b \): attack at the O-atom) are very exergonic but there is a slight preference for path \( a \), which would support our proposed process.\(^{16}\) The very low \( [\mathcal{J}] \) values also indicate that these radical additions are not influenced very much by polar effects in the transition state and should be predominantly enthalpy controlled.\(^{18}\)

To assess our working hypothesis, the reaction of adamantane carboxylic acid (1a) and nitrosobenzene was investigated using various photoredox catalysts (Figure 1) and bases in CH\(_2\)Cl\(_2\) (0.05 M) at room temperature. As illustrated in Table 1, we were pleased to find out that using mesityl perchorlate 2a (Fukuzumi’s acridinium, \( E_{1/2} = +2.06 \, \text{V vs SCE} \)) as the photoredox catalyst and Cs\(_2\)CO\(_3\), as the base under blue LEDs irradiation, the product 3a was obtained in good yield (Table 1, entry 1). We then changed the stoichiometry of the reaction (entries 2–4) and found out that a slight excess of nitrosobenzene (2.0 equiv with respect to 1a) was optimum, providing 3a in 90% yield (entry 3). Other bases were evaluated and while K\(_2\)CO\(_3\) gave 3a in a useful 62% yield (entry 5); 2,6-lutidine was not compatible and completely suppressed the reactivity (entry 6).

We also tried to run the reaction under more concentrated conditions (entries 7 and 8) but this was detrimental. Other photocatalysts 2b–d were screened but they generally provided 3a in considerably lower efficiency (if any) (entries 9–11).

Lastly, control experiments confirmed the requirement for base, light, and 2a (entries 12–14).

With the optimized reaction conditions in hand, the scope of the process using nitrosobenzene and a series of structurally different carboxylic acids was evaluated (Scheme 3). In general, tertiary carboxylic acids worked well and provided the desired hydroxylamines 3b–g in good yields. This approach tolerated several functional groups like alkyl halides, terminal olefins, carbamates and was effective for accessing C-3 and C-4 aminopiperidines, which are a frequent structural motif in many commercially available drugs (e.g., the antidiabetic alogliptin and the opioid analgesic sufentanil). Secondary carboxylic acids were tried next but unfortunately the use of a secondary mono-benzyl 3h and a primary alkyl 3i was not possible, thus representing the limitation of the strategy. Lastly, we evaluated the use of functionalized nitrosoarennes in conjunction with adamantane carboxylic acid (1a) and found them compatible. Both electron-rich 3j and ortho-substituted 3k derivatives reacted well. Substrates containing an electron-withdrawing CF\(_3\)-group 3l could also be employed, albeit in lower yield.

We were particularly keen in showcasing the utility of the methodology by using high-value and structurally complex carboxylic acids in order to provide access to the corresponding hydroxylamines. As reported in Scheme 3, this approach was successfully used to modify the blockbuster drug gemfibrozil (1j \( \rightarrow \) 3m), which is used to lower lipid levels. Furthermore, we were able to selectively introduce the hydroxylamine functionality on the core of the highly complex hepatoprotective oleanoic acid (1k \( \rightarrow \) 3n) and the antiulcer drug enoxolone (1l \( \rightarrow \) 3o). Overall, these examples show that the methodology can be used as a late-stage modification techniques, which tolerates redox active functionalities such as electron rich aromatics (which could undergo SET oxidation), enones (which can be photo-excited upon visible-light irradiation as demonstrated by Lectka)\(^{20}\) as well as free hydroxyl groups.

**Table 1** Optimization of the Visible Light-Mediated Synthesis of Hydroxylamine 3a from Carboxylic Acid 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>PC(^{a})</th>
<th>1a/PPhNO</th>
<th>Base</th>
<th>([M])</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>1:1</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>1:1.1</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>2:1</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>1:2</td>
<td>K(_2)CO(_3)</td>
<td>0.05</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>2a</td>
<td>1:2</td>
<td>2,6-lutidine</td>
<td>0.05</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>2a</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.1</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.2</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>2b</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>2c(^b)</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>2d(^c)</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>2a</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>–</td>
</tr>
<tr>
<td>13(^d)</td>
<td>2a</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>–</td>
<td>1:2</td>
<td>Cs(_2)CO(_3)</td>
<td>0.05</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^{a}\) Photoredox catalyst.

\(^{b}\) 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene.

\(^{c}\) \(\text{Ir}(dF(CF_3)ppy)_2(dtbpy)PF_6\).

\(^{d}\) The reaction was carried out in the dark.
We then decided to evaluate if this radical decarboxylative process could be part of a cascade sequence leading to the concomitant formation of two C–N bond across an olefin. We have recently developed a divergent photoredox imino-functionalization strategy for the assembly of polyfunctionalized pyrroline-based heterocycles. Specifically, we envisaged a cascade process starting with the SET oxidation-fragmentation of the oxime \( M \) (Scheme 4). This would deliver an iminyl radical \( O \) (\( M \rightarrow N \rightarrow O \)) that would undergo fast 5-exo-trig cyclization resulting in the C-radical \( P \). At this point, radical attack onto the nitrosoarene and SET reduction and protonation of the persistent nitroxyl radical \( Q \) would enable the formation of \( R \). Also in this case, we have evaluated the key radical reaction between nitrosobenzene \( I \) and the Ph-dimethyl-substituted C-radical \( S \) (to give \( T \)) by DFT and found it feasible. 

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**Scheme 3** Scope of the process for the synthesis of hydroxylamines 3
The implementation of this strategy was assessed using the oxime 6a, which was prepared by condensation of the ketone 4 with commercially available 2-(aminoxy)-2-methylpropanoic acid (5) on a gram-scale (Scheme 5).

As illustrated in Table 2, we were pleased to find out that by irradiating (blue LEDs) a solution of 6a and nitroso-benzene (1:2) using 2a as the photoredox catalyst, Cs2CO3 as the base in CH2Cl2 (0.1 M), the product 7a was obtained in 48% (Table 2, entry 1). In this case however, increasing the amount of nitrosobenzene with respect to 6a was detrimental (entries 2 and 3) and eventually a ratio of 1:1.1 (entry 4) and a reaction concentration of 0.05 M were identified to be optimum for this transformation (entry 5). Also in this case control experiments confirmed the requirement for base, 2a, and blue LEDs for irradiation (entries 6–8).

With this optimized conditions in hand, other iminyl radical precursors were tested (Scheme 6). We were able to engage substrate containing pyridine 6b and ester 6c functionalities giving access to pyrrolines 7b and 7c that can be used for the preparation of nicotine and proline analogues. Interestingly, in this case we were able to engage a secondarily α-ester radical 7d in the cascade cyclization-functionalization reaction.

Other nitrosoarenes were compatible with the process as shown by the formation of products 7a–h in good to moderate yields. Also in this case, the use of highly electron poor nitrosoarene 7i as well as the trapping primary C-radicals (e.g., following cyclization onto a terminal olefin 7j) was not possible representing the limit of the strategy. Overall, this cascade process generates molecules contain-
Hydroxylamines 3a–o; General Procedure 1 (GP1)

A dry tube equipped with a stirring bar was charged with the carboxylic acid 1a–l (0.2 mmol, 1.0 equiv). The tube was capped with a Supelco aluminum crimp seal with septum (PTFE/butyl) and it was evacuated and refilled with N2 (3 ×). CH2Cl2 (anhydrous and degassed by bubbling through with N2 for 20 min; 4.0 mL) was added. The N2 inlet was then removed and the cap sealed with parafilm. The mixture was stirred at r.t. for 1 h in front of blue LEDs. The tube was opened to air and the mixture was diluted with CH2Cl2 (5 mL) and brine (5 mL). The layers were separated and the aqueous layer was extracted with CH2Cl2 (3 × 5 mL). The combined organic layers were dried (MgSO4), filtered, and evaporated. Purification by column chromatography on silica gel gave 3a–o.

N-[(3S,5S,7S)-Adamantan-1-yl]-N-phenylhydroxylamine (3a)

Following GP1, 1-adamantanecarboxylic acid (1a; 36 mg, 0.2 mmol) gave 3a (44 mg, 90%) as a brown solid, purified by column chromatography (CH2Cl2). HRMS (HESI): \[\text{m/z} = 227 \text{ (MH} - \text{OH)}^{+} \text{,} 205 \text{ [M} + \text{H}^{+}] \text{ calcd for C}_{16}\text{H}_{22}\text{NO: 244.1696; found: 244.1691}. \]

N-(1-Methylcyclohexyl)-N-phenylhydroxylamine (3b)

Following GP1, 1-methyl-1-cyclohexanecarboxylic acid (1b; 28 mg, 0.2 mmol) gave 3b (26 mg, 64%) as a brown solid, purified by column chromatography (pentane/CH2Cl2 1:1). IR (film): 2925, 2957, 2861, 1596, 1487, 1449, 1372, 1120, 1028 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ = 7.33 (2 H, br d, J = 7.8 Hz), 7.28 (2 H, t, J = 7.8 Hz), 7.17 (1 H, t, J = 7.4 Hz), 1.73–1.65 (3 H, m), 1.58–1.51 (3 H, m), 1.42–1.27 (4 H, m), 1.09 (3 H, s). HRMS (ESI): \[\text{m/z} = 227 (\text{MH} + \text{H})^{+} \text{ calcd for C}_{16}\text{H}_{22}\text{NO: 244.1696; found: 244.1691}. \]

N-Phenyl-N-(1-phenylcyclohexyl)hydroxylamine (3c)

Following GP1, 1-phenylcyclohexane-1-carboxylic acid (1c; 41 mg, 0.2 mmol) gave 3c (38 mg, 71%) as an orange solid, purified by column chromatography (pentane/CH2Cl2 1:1). IR (film): 2929, 2861, 1593, 1484, 1456, 1447, 1204, 1152, 1037 cm⁻¹. ¹H NMR (CDCl3, 400 MHz): δ = 7.32–7.11 (5 H, m), 7.15–6.99 (3 H, m), 6.71 (2 H, d, J = 7.6 Hz), 5.98 (1 H, br s), 2.41 (2 H, d, J = 12.6 Hz), 1.90 (2 H, t, J = 11.7 Hz), 1.66 (2 H, d, J = 9.5 Hz), 1.49 (1 H, d, J = 4.7 Hz), 1.39–1.12 (3 H, m). HRMS (ESI): \[\text{m/z} = 267 \text{ [MH} + \text{OH}^{+}] \text{ calcd for C}_{26}\text{H}_{28}\text{NO: 390.2024; found: 390.2018}. \]
HRMS (HESI): m/z [M + H]+ calcld for C_{16}H_{21}NO: 268.1696; found: 268.1699.

N-[(1R,3S,5R,7S)-3-Chloroadamantan-1-yl]-N-phenylhydroxylamine (3d)

Following GP1, 3-chloroadamantan-1-carboxylic acid (1d; 43 mg, 0.2 mmol) gave 3d (50 mg, 90%) as a brown solid, purified by column chromatography (pentane/CH2Cl2 1:1). IR (film): 3350, 2975, 2359, 1692, 1661, 1597, 1488, 1453, 1382, 1248, 1230, 1182, 1123, 1094, 1068 cm⁻¹.

1H NMR (CDCl3, 400 MHz): δ = 7.26 (2 H, d, J = 8.0 Hz), 7.15 (1 H s), 6.82 (0.8 H, d, J = 13.8 Hz), 6.02 (0.8 H, d, J = 12.9 Hz), 5.38–5.70 (0.2 H, m), 3.57 (0.2 H, br s), 3.32–3.17 (0.4 H, m), 2.88 (0.8 H, d, J = 12.2 Hz), 2.65 (0.8 H, d, J = 13.9 Hz), 2.15 (0.8 H, q, J = 7.3 Hz), 1.93 (0.2 H, br s), 1.68 (1.2 H, d, J = 13.3 Hz), 1.47 (9 H, s), 1.43–1.28 (2 H, m), 0.94 (3 H, m).

13C NMR (CDCl3, 101 MHz): δ = 144.9, 135.6, 127.6, 125.2, 124.8, 117.2, 63.0, 43.6, 23.2.


HRMS (HESI): m/z [M + Na]+ calcld for C_{16}H_{24}NONa+: 283.1188; found: 283.1181.

**tert-Butyl 3-[Hydroxy(phenyl)amino]-3-methylpiperidine-1-carboxylate (3f)**

Following GP1, 1-N-Boc-3-methylpiperidine-3-carboxylic acid (1f; 49 mg, 0.2 mmol) gave 3f (34 mg, 56%) as a brown solid, purified by column chromatography (CH2Cl2).

IR (film): 3350, 2975, 2359, 1692, 1661, 1597, 1488, 1453, 1425, 1392, 1365, 1284, 1161, 1087 cm⁻¹.

1H NMR (CDCl3, 400 MHz): δ = 7.26 (4 H, m), 7.15 (1 H s), 7.12–7.07 (1 H m), 4.35 (0.8 H, d, J = 13.8 Hz), 4.02 (0.8 H, d, J = 12.9 Hz), 3.78–3.70 (0.2 H, m), 3.57 (0.2 H, br s), 3.32–3.17 (0.4 H, m), 2.88 (0.8 H, d, J = 12.2 Hz), 2.65 (0.8 H, d, J = 13.9 Hz), 2.15 (0.8 H, q, J = 7.3 Hz), 1.93 (0.2 H, br s), 1.68 (1.2 H, d, J = 13.3 Hz), 1.47 (9 H, s), 1.43–1.28 (2 H, m), 0.94 (3 H, m).

13C NMR (CDCl3, 101 MHz): δ = 157.2 (M), 154.9 (m), 149.3 (M), 148.8 (m), 127.8 (M + m), 125.4 (m), 125.0 (M), 124.5 (m), 124.4 (M), 80.2 (M + m), 61.6 (M), 61.1 (M), 53.1 (M + m), 46.3 (M), 44.3 (M), 34.9 (M), 34.4 (m), 28.6 (M + m), 21.7 (M), 21.6 (m), 17.3 (M), 16.7 (m).

MS (EI): m/z = 257 [M]+, 241, 184, 135.

HRMS (HESI): m/z [M + H]+ calcld for C_{17}H_{22}NO: 268.1726; found: 268.1725.

N-[(3S,5S,7S)-Adamantan-1-yl]-N-(4-methoxyphenyl)hydroxylamine (3j)

Following GP1, 1-adamantane-carboxylic acid (1a; 36 mg, 0.2 mmol) gave 3j (28 mg, 55%) as a red solid, purified by column chromatography (pentane/CH2Cl2/MeOH 99.5:0.5).

IR (film): 3095, 2850, 1452, 1298, 1245, 1210, 1182, 1103, 1034 cm⁻¹.

1H NMR (CDCl3, 400 MHz): δ = 7.11 (2 H, d, J = 8.2 Hz), 6.78 (2 H, d, J = 8.2 Hz), 3.82 (3 H, s), 2.05 (3 H, s), 1.74 (6 H, s), 1.59 (6 H, q, J = 12.1 Hz).

13C NMR (CDCl3, 101 MHz): δ = 154.9, 135.4, 125.3, 111.8, 59.6, 54.7, 44.7, 37.8, 35.8, 35.4, 30.0, 28.7.

MS (EI): m/z = 257 [M+H]+, 242 (M - OMe), 214, 200, 163, 135.

HRMS (HESI): m/z [M + H]+ calcld for C_{18}H_{21}NO: 273.1723; found: 273.1726.

N-[(3S,5S,7S)-Adamantan-1-yl]-N-(o-tolyl)hydroxylamine (3k)

Following GP1, 1-adamantane-carboxylic acid (1a; 36 mg, 0.2 mmol) gave 3k (28 mg, 55%) as a red solid, purified by column chromatography (pentane/CH2Cl2 3:1).

IR (film): 2905, 2850, 1487, 1452, 1356, 1307, 1103, 1080 cm⁻¹.

1H NMR (CDCl3, 400 MHz): δ = 7.41 (1 H, s), 7.30 (4 H, m), 6.55 (1 H, br s), 2.08 (3 H, br s), 1.75 (6 H, s), 1.63 (3 H, d, J = 11.6 Hz), 1.55 (3 H, d, J = 11.5 Hz).
N-[5-(2,5-Dimethylphenoxy)-2-methylpentan-2-yl]-N-phenylhydroxylamine (3m)

Following GP1, gemfibrozil (1j: 50 mg, 0.2 mmol) gave 3m (42 mg, 68%) as a brown solid, purified by column chromatography (CH₂Cl₂).

IR (film): 2945, 1486, 1463, 1386, 1364, 1263, 1028 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 7.24 (4 H, m), 7.13 (1 H, t, J = 6.9 Hz), 5.63 (0.2 H, d), 5.55 (0.8 H, s), 3.23 (1 H, dd, J = 10.6, 5.6 Hz), 2.79 (1 H, dt, J = 13.5, 3.5 Hz), 2.16–1.98 (2 H, m), 1.86–1.72 (2 H, m), 1.74–1.55 (8 H, m), 1.49–1.32 (5 H, m), 1.33 (3 H, s), 1.12 (7 H, m), 1.09 (3 H, s), 1.01 (3 H, s), 0.95 (2 H, m), 0.86–0.68 (6 H, m).

13C NMR (CDCl₃, 101 MHz): δ = 148.5, 129.8 (q, J = 31.9, 31.3 Hz), 127.9, 127.7, 124.0 (q, J = 273.1 Hz), 121.7, 121.4, 60.8, 38.4, 36.4, 29.3.

19F NMR (CDCl₃, 376 MHz): δ = -62.5.

MS (EI): m/z = 311 [M⁺], 295, 275, 238, 135.

HRMS (APCI): m/z [M + H⁺] calcd for C₁₉H₂₁F₃NO: 312.1567; found: 312.1566.

N-[5-(2,5-Dimethylphenoxy)-2-methylpentan-2-yl]-N-phenylhydroxylamine (3n)

Following GP1, gemfibrozil (1j: 50 mg, 0.2 mmol) gave 3n (58 mg, 67%) as a brown solid, purified by column chromatography (CH₂Cl₂/MeOH 98:2); dr = 5:1.


Hydroxylamines 7; General Procedure 2 (GP2)

A dry tube equipped with a stirring bar was charged with the carboxylic acid 6a-d (0.1 mmol, 1.0 equiv), 2a (2.0 mg, 5 mol%), Cs₂CO₃ (33 mg, 0.1 mmol, 1.0 equiv), and the requisite nitrosoarene (0.11 mmol, 1.1 equiv). The tube was capped with a Supelco aluminum crimp seal with septum (PTFE/butyl) and was evacuated and re-filled with N₂(3 ×). CH₂Cl₂ (anhydrous and degassed by bubbling through with N₂ for 20 min) (2.0 mL) was added. The N₂ inlet was then removed and the cap sealed with parafilm. The mixture was stirred at rt. for 1 h in front of blue LEDs. The tube was opened to air and the mixture was diluted with CH₂Cl₂ (5 mL) and brine (5 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried (MgSO₄), filtered, and evaporated. Purification by column chromatography on silica gel gave 7a-h.

N-Phenyl-N-[2-(5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)propan-2-yl]hydroxylamine (7a)

Following GP2, 6a (58 mg, 0.2 mmol) gave 7a (39 mg, 67%) as a brown oil, purified by column chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 99.8:0.2).

IR (film): 3212, 2978, 1618, 1596, 1576, 1486, 1448, 1432, 1168, 1063 cm⁻¹.

1H NMR (CDCl₃, 101 MHz): δ = 7.89 (2 H, dd, J = 8.0, 1.4 Hz), 7.49–7.39 (5 H, m), 7.30 (2 H, t, J = 7.9 Hz), 7.13 (1 H, t, J = 7.3 Hz), 4.37 (1 H, t, J = 8.2 Hz), 3.04 (1 H, ddd, J = 16.8, 10.3, 3.0, 2.5 Hz), 2.83 (1 H, tdt, J = 11.6, 9.5, 2.3 Hz), 2.07 (1 H, ddd, J = 11.3, 9.8, 8.0, 3.3 Hz), 1.85–1.74 (1 H, m), 1.27 (3 H, s), 1.11 (3 H, s).

13C NMR (CDCl₃, 101 MHz): δ = 173.3, 149.2, 133.5, 131.2, 128.7, 129.0, 127.8, 125.2, 125.0, 78.6, 65.1, 34.1, 25.4, 25.1, 18.2.

MS (EI): m/z = 278 (MH⁻), 170, 144, 134, 77.


N-Phenyl-N-[2-(5-(pyridin-3-yl)-3,4-dihydro-2H-pyrrol-2-yl)propan-2-yl]hydroxylamine (7b)

Following GP2, 6b (29 mg, 0.1 mmol) gave 7b (15 mg, 51%) as a brown oil, purified by column chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 99.5:0.5).

IR (film): 2979, 1620, 1594, 1485, 1413, 1377, 1358, 1342, 1168, 1071, 1026 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 9.00 (1 H, d, J = 2.2 Hz), 8.70 (1 H, dd, J = 4.8, 1.7 Hz), 8.25 (1 H, dt, J = 7.9, 2.0 Hz), 7.41–7.35 (3 H, m), 7.33–7.24 (2 H, m), 7.15–7.10 (1 H, m), 4.43 (1 H, tt, J = 8.2, 2.4 Hz), 3.05 (1 H, ddd, J = 17.3, 10.4, 3.5, 2.3 Hz), 2.93–2.79 (1 H, m), 2.11 (1 H, ddd, J = 13.2, 9.8, 8.0, 3.5 Hz), 1.87 (1 H, ddt, J = 13.1, 10.3, 6.8 Hz), 1.24 (3 H, s), 1.08 (3 H, s).

13C NMR (CDCl₃, 101 MHz): δ = 171.1, 151.8, 149.3, 149.1, 135.0, 129.4, 127.8, 125.1, 125.1, 123.6, 79.0, 65.3, 34.2, 25.1, 23.9, 18.3.

HRMS (ASAP): m/z [M + H]⁺ calcd for C₁₈H₂₃N₂O₇: 324.1832; found: 324.1836.

**N-(4-Chlorophenyl)-N-[2-(5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)propan-2-yl]hydroxylamine (7g)**

Following GP2, 6a (29 mg, 0.1 mmol) gave 7g (23 mg, 70%) as a brown oil, purified by column chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 99.5:0.5).

IR (film): 3184, 2977, 1618, 1576, 1482, 1448, 1379, 1370, 1343, 1169, 1090, 1011 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 9.27 (1 H, br s), 7.87 (2 H, d, J = 7.4 Hz), 7.46 (3 H, m), 7.33 (2 H, d, J = 8.6 Hz), 7.25 (2 H, d, J = 8.7 Hz), 4.33 (1 H, t, J = 6.8 Hz), 3.09–2.99 (1 H, m), 2.84 (1 H, m), 2.12–2.03 (1 H, m), 1.84–1.72 (1 H, m), 1.22 (3 H, s), 1.10 (3 H, s).

HRMS (ASAP): m/z [M + Na]⁺ calcd for C₁₆H₁₄ClNO₄Na: 351.1235; found: 351.1241.

**N-(2-(5-Phenyl-3,4-dihydro-2H-pyrrol-2-yl)propan-2-yl)-N-[3-(trifluoromethyl)phenyl]hydroxylamine (7h)**

Following GP2, 6a (29 mg, 0.1 mmol) gave 7h (36 mg, 75%) as a brown oil, purified by column chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 99.5:0.5).

IR (film): 3285, 2970, 1615, 1502, 1463, 1447, 1342, 1296, 1245, 1165, 1033 cm⁻¹.

1H NMR (CDCl₃, 400 MHz): δ = 7.91 (2 H, d, J = 6.8 Hz), 7.52–7.44 (3 H, m), 7.37 (2 H, d, J = 8.8 Hz), 6.86 (2 H, d, J = 8.8 Hz), 4.41 (1 H, t, J = 8.1 Hz), 3.82 (3 H, s), 3.06 (1 H, ddt, J = 16.4, 10.4, 2.8 Hz), 2.92–2.79 (1 H, m), 2.15–2.03 (1 H, m), 1.90–1.73 (1 H, m), 1.26 (3 H, s), 1.08 (3 H, s).

13C NMR (CDCl₃, 101 MHz): δ = 173.3, 157.1, 142.0, 133.5, 131.1, 128.6, 128.0, 126.5, 113.0, 78.5, 65.1, 55.5, 34.2, 25.3, 24.7, 18.0.

MS (EI): m/z = 308 (MH → OH), 265, 164, 115, 91.


**N-(4-Methoxyphenyl)-N-[2-(5-phenyl-3,4-dihydro-2H-pyrrol-2-yl)propan-2-yl]hydroxylamine (7e)**

Following GP2, 6a (29 mg, 0.1 mmol) gave 7e (18 mg, 56%) as a brown oil, purified by column chromatography (CH₂Cl₂ → CH₂Cl₂/MeOH 99.5:0.5).

IR (film): 3184, 2977, 1618, 1576, 1482, 1448, 1379, 1370, 1343, 1169, 1090, 1011 cm⁻¹.
1H NMR (CDCl₃, 400 MHz): δ = 7.89 (2 H, d, J = 6.9 Hz), 7.70 (1 H, d, J = 7.9 Hz), 7.45 (3 H, m), 7.19 (2 H, d, J = 8.1 Hz), 7.10 (1 H, t, J = 7.3 Hz), 4.62 (1 H, t, J = 8.1 Hz), 3.06 (1 H, ddt, J = 16.2, 10.2, 2.7 Hz), 2.95–2.85 (1 H, m), 2.45 (3 H, s), 2.20–2.06 (1 H, m), 1.93–1.81 (1 H, m), 1.27 (3 H, s), 0.95 (3 H, s).

13C NMR (CDCl₃, 101 MHz): δ = 173.2, 147.9, 135.7, 133.7, 131.0, 130.3, 128.6, 128.5, 126.7, 126.7, 80.1 (br), 66.2, 34.4, 25.2, 22.4, 19.2, 17.1 (br).


HRMS (APCI): m/z [M + H]^+ calc for C_{30}H_{34}N_{10}O_{2}: 308.1883; found: 308.1887.

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**Supporting Information**

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