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Photochemical Homologation for the Preparation of Aliphatic Aldehydes in Flow

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Supporting Information

ABSTRACT: Cheap and readily available aqueous formaldehyde was used as a formylating reagent in a homologation reaction with nonstabilized diazo compounds, enabled by UV photolysis of bench-stable oxadiazolines in a flow photoreactor. Various aliphatic aldehydes were synthesized along with the corresponding derivatized alcohols and benzimidazoles. No transition-metal catalyst or additive was required to effect the reaction, which proceeded at room temperature in 80 min.

Following the discovery of the Buchner−Curtius−Schlotterbeck reaction over a century ago,1 the interactions between carbonyl compounds and diazo compounds have been extensively studied.2,3 These methods constitute a powerful synthetic tool for C−C bond formation, especially for the extension of carbon chains and for the construction and decoration of ketones.4−6 However, the controlled formation of aldehyde products using diazo chemistry is not a simple task; carbonyl groups and diazo compounds are highly reactive coupling partners. The reliable and safe generation of nonstabilized diazo compounds is currently an area of intense research,7−10 and one our laboratory has been interested in due to the application of flow chemistry as an enabling technology11−13 to overcome the safety issues traditionally associated with diazo compounds.14−16 Following the pioneering work from Warkentin and co-workers17,18 we have recently published two reports on the use of oxadiazolines as bench-stable, nonstabilized diazo compound precursors and their application in protodeboronative and oxidative C(sp2)−C(sp3) cross-coupling with boronic acids19 and aldehyde C−H functionalization to afford unsymmetrical ketones.20 During this work, two reports in the literature caught our attention (Scheme 1). Kingsbury and co-workers demonstrated a Lewis acid catalyzed double homologation reaction by combining ex situ prepared diazo compounds and the flash-pyrolyzed preparation of anhydrous formaldehyde (Scheme 1, A),21 and Hu et al. reported an interesting three-component coupling of aryldiazooacetate, aniline, and aqueous formaldehyde (Scheme 1, B).22 Both of these reactions passed through, but did not stop at, the aldehyde oxidation state on the way to a final product, either the doubly homologated ketone or the α-aryl serine derivative. These examples encouraged us to control the homologation reaction and stop at the aldehyde product in as simple a manner as possible and without the use of a protecting group strategy. Herein, we report the controlled homologation of nonstabilized diazo compounds generated from bench-stable precursors in flow to form aldehydes and their derivatives (Scheme 1, C).
Our investigation began by combining 2-tetralone oxadiazoline 1a with different sources of formaldehyde under UV irradiation (Table 1). Common formaldehyde surrogates throughout the course of the reaction, disfavors double homologation. We further observed that over an extended period of time the corresponding carboxylic acid product was formed, most likely as a result of an aerobic oxidative transformation, which is not uncommon for aldehydes of this type.

Also owing to the volatility of some of the aldehydic products, we decided to directly reduce the crude mixture with sodium borohydride (NaBH₄), thereby converting the products into the corresponding alcohol (4a), resulting in an improved yield of 60% over two steps (Table 2, entry 1). We also saw this procedure as a way of storing these unstable aliphatic aldehydes through recycling via a secondary oxidation process back to aldehydes should this be necessary. To further exemplify the method and to better capture the unstable and sometimes volatile small-molecule products, the crude aldehydes were additionally subjected to oxidative condensation with o-phenylenediamine following a modified procedure originally reported by Jiao et al.²⁶ This procedure gave 2-substituted benzimidazole (5a) from 1,2,3,4-tetrahydronaphthalene-2-carbaldehyde (3a) via in situ generated aliphatic aldehyde in an overall 72% isolated yield (Table 2, entry 1).

With these various conditions in hand, we set about examining the scope of the reactions (Table 2). Tetrahydropyran substrate (1b) was able to produce the corresponding aldehyde (3b) in a 48% yield while providing 53% of alcohol (4b) and 76% benzimidazole (5b). Similarly, tetrahydrothiopyran (1c), tetrahydrothiophene (1d), and cyclohexyldioxole (1e) derivatives all underwent these three individual transformations to give products (3c–e, 4c–e, and 5c–e) in reasonable yields (entries 3, 4, and 5). As for nitrogen-based functional groups, Boc-protected amine (1f) and N-pyrimidinyl piperidine (1g) were also tolerated (entry 6 and 7). Bulky 2-adamantyl aldehyde (3h) was isolated in 68% yield, together with 75% of 2-adamantamethanol (4h) and 79% of 2-adamantylbenzimidazole (5h). Lastly, cyclobutyl oxadiazoline (1i) did not give useful isolated yields owing to aldehyde and alcohol volatility (3i and 4i), although the formation of 2-cyclobutylbenzimidazole was achieved in 59% yield (5i).

Except for methoxynaphthalene substrate (3j, entry 10), the α-methyl aldehydes we obtained have displayed a tendency toward hydration or aerobic oxidation, thus resulting in low crude NMR yields and difficulty in isolation (3k–p), which is well-known for similar materials. The efficiency of the reaction was generally better represented by comparing the yield of alcohols and benzimidazoles. In some cases, such as 5-hydroxy-2-methylpentanal (3k), homologated product was identified as 81% of the hydrated form when only 4% of aldehyde was observed in NMR analysis, even though 66% of alcohol product (4k) was isolated over two steps. Pyridine (1i) and furan (1m) were all successfully homologated into the corresponding products (4l, 5l, 5m), respectively (entries 12 and 13). Alkyne- and alkene-substituted oxadiazolines (1n, 1o) both gave reasonable isolated yields as aldehyde derivatives (4n, 5n, o), with alkynyl substrate produced lower yield arguably owing to larger steric hindrance (5o). Even though 2-cyclopropylpropanal (3p) and 2-cyclopropylpropan-1-ol (4p) were not able to give good isolated yields, the formation of 69% of 2-(1-cyclopropyl)benzimidazole (5p) proved the effectiveness of oxadiazolinc as a successful diazo precursor for homologation. Many of these products can be thought of as branched, or iso, aldehydes which would be difficult to prepare.

## Table 1. Optimization of Aldehyde Formation

<table>
<thead>
<tr>
<th>entry</th>
<th>formaldehyde source</th>
<th>ox (M)</th>
<th>tₑ (min)</th>
<th>T (°C)</th>
<th>conv (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dioxolane</td>
<td>0.1</td>
<td>40</td>
<td>20</td>
<td>99</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>trioxane</td>
<td>0.1</td>
<td>40</td>
<td>20</td>
<td>96</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>thermolysed</td>
<td>0.1</td>
<td>40</td>
<td>20</td>
<td>67</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>37% aq</td>
<td>0.1</td>
<td>40</td>
<td>20</td>
<td>78</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>37% aq</td>
<td>0.1</td>
<td>40</td>
<td>10</td>
<td>72</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>37% aq</td>
<td>0.05</td>
<td>40</td>
<td>10</td>
<td>80</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>37% aq</td>
<td>0.1</td>
<td>80</td>
<td>20</td>
<td>87</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>37% aq</td>
<td>0.1</td>
<td>80</td>
<td>20</td>
<td>86</td>
<td>58</td>
</tr>
<tr>
<td>9</td>
<td>37% aq</td>
<td>0.1</td>
<td>80</td>
<td>20</td>
<td>87</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>37% aq</td>
<td>0.1</td>
<td>80</td>
<td>20</td>
<td>78</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>37% aq</td>
<td>0.1</td>
<td>80</td>
<td>20</td>
<td>79</td>
<td>12</td>
</tr>
</tbody>
</table>

*Reaction conditions: oxadiazoline (0.4 mmol), formalin (0.3 mL, 37 wt %, 4.0 mmol), 2-methyltetrahydrofuran (4 mL). NMR yields calculated with 1,3,5-trimethoxybenzene as an internal standard. *Isolated yield. “100 equiv of formaldehyde was used. “5.0 equiv of formaldehyde was used. “Tetrahydrofuran was used instead of 2-methyltetrahydrofuran. “Dichloromethane was used instead of 2-methyltetrahydrofuran.
Table 2. Scope and Derivatization of Oxadiazolines and Aqueous Formaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alcohol</th>
<th>Benzinimidazole</th>
<th>Entry</th>
<th>Aldehyde</th>
<th>Alcohol</th>
<th>Benzinimidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3a – h&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4a – h&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5a – h&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>3b, 48%</td>
<td>4b, 53%</td>
<td>5b, 76%</td>
<td>10</td>
<td>3j, 57%</td>
<td>4j, 75%</td>
<td>5j, n.d.&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>3c, 56%</td>
<td>4c, 72%</td>
<td>5c, 55%</td>
<td>11</td>
<td>3k, 85%&lt;sup&gt;f&lt;/sup&gt;</td>
<td>4k, 66%</td>
<td>5k, n.d.&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>3d, 85%&lt;sup&gt;d&lt;/sup&gt; (75%)</td>
<td>4d, 89%&lt;sup&gt;d&lt;/sup&gt; (77%)</td>
<td>5d, 60%</td>
<td>12</td>
<td>3l, 35%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4l, 50%</td>
<td>5l, 48%</td>
</tr>
<tr>
<td>5</td>
<td>3e, 65%</td>
<td>4e, 75%</td>
<td>5e, 80%</td>
<td>13</td>
<td>3m, 25%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4m, 60%</td>
<td>5m, 75%</td>
</tr>
<tr>
<td>6</td>
<td>3f, 58%&lt;sup&gt;d&lt;/sup&gt; (49%)</td>
<td>4f, 53%</td>
<td>5f, 49%</td>
<td>14</td>
<td>3n, 58%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4n, 88%&lt;sup&gt;d&lt;/sup&gt; (69%)</td>
<td>5n, 73%</td>
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<tr>
<td>7</td>
<td>3g, 55%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4g, 68%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5g, 72%</td>
<td>15</td>
<td>3o, 18%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4o, n.d.&lt;sup&gt;e&lt;/sup&gt;</td>
<td>5o, 39%</td>
</tr>
<tr>
<td>8</td>
<td>3h, 68%</td>
<td>4h, 75%</td>
<td>5b, 79%</td>
<td>16</td>
<td>3p, 8%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>4p, 58%&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5p, 69%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: oxadiazoline (1.0 equiv, 0.1 M), formaldehyde (10 equiv, 37 wt % in H<sub>2</sub>O, 1.0 M) in 2-methyltetrahydrofuran.  
<sup>b</sup>Aldehyde reduced directly with NaBH<sub>4</sub> (10 equiv, 0.5 M) in ethanol.  
<sup>c</sup>Aldehyde reacted with o-phenylenediamine (1.5 equiv, 0.075 M) in toluene.  
<sup>d</sup>NMR yield, calculated using 1,3,5-trimethoxybenzene as an internal standard.  
<sup>e</sup>Not determined due to volatility or product contamination.  
<sup>f</sup>81% of the product identified as the hydrated form.
through traditional methods such as hydroformylation, particularly in the presence of alkenes or alkynes. The homologation reaction of oxadiazolines obtained from ketones has provided us with satisfying results toward α,α-disubstituted branched aliphatic aldehydes. However, similar oxadiazolines generated from aldehydes are difficult to obtain, which therefore obstructed the access toward linear aldehydes. To overcome this difficulty, we applied an alternative route to diazo compounds generated from hydrazones, prepared from the corresponding benzaldehydes according to our previously reported procedure.27 With the help of a glass static mixer chip, an ethyl acetate solution of diazo compound was combined with 37 wt % aqueous formaldehyde solution in line, and the resulting homologated aldehyde product was collected in the output stream and purified (Table 3, 7a-c) or extracted and reduced directly with NaBH₄ (10 equiv, 0.5 M) in ethanol.

Table 3. Homologation of Aldehydes with Aqueous Formaldehyde via Hydrazine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde –7a – c</th>
<th>Alcohol 8a – c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a, 53%</td>
<td>8a, 57%</td>
</tr>
<tr>
<td>2</td>
<td>7b, 58%</td>
<td>8b, 66%</td>
</tr>
<tr>
<td>3</td>
<td>7c, 57%</td>
<td>8c, 66%</td>
</tr>
</tbody>
</table>

*Aldehyde extracted with ethyl acetate then reduced directly with NaBH₄ (10 equiv, 0.5 M) in ethanol.

Note: unless stated otherwise. Petroleum ether refers to the fractions of petroleum ether collected between 40 and 60 °C b.p.

Flash column chromatography was performed using a Biotage SPX system with single-use disposable silica columns of the appropriate size (SiliaSep Flash Cartridges, 4 or 12 g of 40–60 μm ISO04/012). Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated glass-backed plates and visualized by ultraviolet radiation (254 nm) and appropriate dip (typically potassium permanganate or ninhydrin).

'1H NMR and 13C(1H) NMR spectra were recorded on a 600 MHz Bruker DRX-600 spectrometer. Chemical shifts (δ) are referenced to the residual solvent as CDCl₃ or DMSO-d₆ in parts per million (ppm). Signals are reported with the descriptions of their environments (e.g., ArH, NH, OH). Coupling constants (J) are quoted in hertz (Hz). Proton and carbon multiplicity is described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br) or a combinations thereof. All compounds examined were dried in vacuo to remove residual solvents. Spectra are assigned as fully as possible using 1'H-tCOSY, DEPT-135, HSQC, and 1'H NOESY where appropriate to facilitate structural determination. Multiple signals arising from (pseudo)axial/equatorial positions are suffixed, for example, H₆ and H₆′. '1H NMR signals are reported to two decimal places and 13C signals to one decimal place.

Infrared spectra were recorded neat on a PerkinElmer Spectrum One FTIR spectrometer with a universal ATR sampling accessory; selected peaks are reported.

Low-resolution mass spectrometry was performed on an Advion Expression CMS spectrometer. High-resolution mass spectrometry (HRMS) was performed using positive or negative electrospray ionization (ESI+) by the Mass Spectrometry Service for the Chemistry Department at the University of Cambridge.

Melting points were recorded on a Stanford Research Systems OptiMelt automated melting point system.

The oxadiazolines 1a–p were synthesized according to the precedent literature procedure without further modifications.19 The hydrazones 6a–c were synthesized according to the precedent procedure published by our group.28 All compounds listed in the paper are >95% purity. Some products appear to be very hydroscopic and, therefore, contain 0.2–0.5 molar equiv of water (2–5 wt %) in the '1H NMR spectra as shown below. Volatile compounds are reported with minor solvents. Inseparable impurities are noted.

Synthesis of Aliphatic Aldehydes. General Procedure A for the Synthesis of Aliphatic Aldehydes. A solution of the appropriate oxadiazoline (1.0 equiv, 0.05 mmol/mL) and formaldehyde (10 equiv of aqueous solution, 37% w/w) in 2-MeTHF (0.5 mol/mL) was pumped (0.125 mL min⁻¹, t_p = 80 min) through a Vaportec UV-150 photochemical reactor (10 mL, FEP tubing) while being irradiated by a 310 nm UV lamp (output power: 9W) held at 20 °C. The reactor output was monitored using a Mettler Toledo FlowR instrument (SiComp head, bands of interest: C=O stretch signal at 1750–1700 cm⁻¹ for methyl acetate, generated by the decomposition of oxadiazoline). Once the FlowR detector showed the signal of the reaction slug, the output stream was collected in a sealed sample vial containing a biphasic solution of dichloromethane and brine with stirring to separate excess formaldehyde and other potential impurities. The collected material was rested, and the organic phase was separated and concentrated under reduced pressure. The remaining residue was purified via flash silica gel column chromatography with appropriate eluent combination to give the desired product.

1,2,3,4-Tetrahydroxynaphthalene-2-carbaldehyde (3a). General Procedure A was followed using 5'-methoxy-5'-methyl-3,4-dihydro-1H,5'H-spiro(naphthalene-2,2'-[1,3,4]oxadiazole) (92 mg, 0.4 mmol, 10 equiv) and formaldehyde (0.3 mL, 37% w/w) in 2-MeTHF (0.5 mol/mL) was pumped (0.125 mL min⁻¹, t_p = 80 min) through a Vaportec UV-150 photochemical reactor (10 mL, FEP tubing) while being irradiated by a 310 nm UV lamp (output power: 9W) held at 20 °C. The reactor output was monitored using a Mettler Toledo FlowR instrument (SiComp head, bands of interest: C=O stretch signal at 1750–1700 cm⁻¹ for methyl acetate, generated by the decomposition of oxadiazoline). Once the FlowR detector showed the signal of the reaction slug, the output stream was collected in a sealed sample vial containing a biphasic solution of dichloromethane and brine with stirring to separate excess formaldehyde and other potential impurities. The collected material was rested, and the organic phase was separated and concentrated under reduced pressure. The remaining residue was purified via flash silica gel column chromatography with appropriate eluent combination to give the desired product.

Tetrahydro-2H-pyran-4-carboxaldehyde (3b). General procedure A was followed using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.5]-dec-1-ene (74 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H2O, 4 mol %, 10 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (23 mg, 48%, δ 203.0 (H, HCO), 4.00–3.92 (2H, OCH2 + OCH3), 2.34 (dd, J = 11.5, 10.7, 2.6 Hz, 2H, OCH2 + OCH3), 1.55–2.36 (m, 1H, HCOCH2), 1.89–1.83 (m, 2H, OCH2 + OCH3), 1.70 (dd, J = 13.7, 10.7, 4.2 Hz, 2HCH2 + OCH3).

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acids (37 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H2O, 4 mol %, 10 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (29 mg, 56%): 1H NMR (600 MHz, CDCl3) δ 9.59 (s, 1H, HCO), 2.67 (dt, J = 10.2, 6.5 Hz, 4H, SCH3), 2.34–2.22 (m, 2H, HCOCH2 + CH2CH3), 1.75 (dd, J = 14.3, 10.2, 4.5 Hz, 2H, CH2CH3 + CH2CH2).

1 1-H NMR (151 MHz, CDCl3) δ 203.0 (HCO), 44.9 (CH2), 25.8 (C3 + C4); HRMS (ESI) calcld for C16H19O2 (M + Na)+ 289.1352, found 289.1354; δ 219.4 (C = O), 165.1274, found 165.1273; IR νmax (film) 2936, 2896, 1752, 1463, 1100, 706, 10.7 Hz, 1H, HCOCH2), 1.84–1.70 (m, 3H, CH2CH3 + CH2CH2).

Adamanadane-2-carboxaldehyde (3h). General procedure A was followed using 5′-methoxy-5′-methyl-5′H-spiro[adamantane-2,2′-1,3,4]oxadiazole (94 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H2O, 4 mol %, 10 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a white solid (45 mg, 68%): 1H NMR (600 MHz, CDCl3) δ 9.73 (s, 1H, HCO), 2.44–2.37 (m, 3H, HCOCH2 + HCOCH2CH3), 2.01–1.67 (m, 12H, CH2 + CH2CH3 + CH2CH2).

4-(6-Methoxynaphthalen-2-yl)-2-methylbutan-1-ol (3j). General procedure A was followed using 2-methoxy-5-(2′-(6-methoxynaphthalen-2-yl)ethyl)-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (126 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H2O, 4 mol %, 10 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a transparent oil (55 mg, 57%) together with 7% of oxidized carboxylic acid: 1H NMR (600 MHz, CDCl3) δ 9.65 (d, J = 1.8 Hz, 1H, HCO), 7.68 (d, J = 8.5, 3.4 Hz, 2H, HAr), 7.55 (d, J = 1.8 Hz, 1H, HAr), 7.30 (d, J = 8.4, 1.8 Hz, 1H, HAr), 7.16–7.10 (m, 2H, HAr), 3.92 (s, 3H, OCH3), 2.88–2.75 (m, 2H, HCOCH2 + ArCH2), 2.41 (dd, J = 6.9, 1.8 Hz, 1H, ArCH2), 2.19–2.10 (m, 1H, HCOCH2), 1.78–1.70 (m, 1H, ArCH2CH3), 1.18 (d, J = 2.8 Hz, 3H, CH2CH3); 13C H NMR (151 MHz, CDCl3) δ 205.0 (HCO), 157.4 (C′), 136.6 (C′′), 133.2 (C′′′), 129.2 (C′), 129.0 (C′′), 127.7 (C″), 127.1 (C′′′), 126.5 (C″′), 119.0 (C′′′′), 105.8 (C′′′′′), 53.3 (OCH3), 45.6 (HCOCH3), 33.0 (C′), 32.1 (C′′), 13.4 (C′′′); HRMS (ESI) calcld for C18H12O4 (M + H)+ 289.1352. 1H NMR (film) 2936, 2896, 1752, 1463, 1100, 706, 912 cm−1; mp 164–166 °C.

Synthesis of Alcohols. General Procedure B for the Synthesis of Alcohols. The reaction slug from general procedure A was directly collected into a round-bottom flask containing NaBH4 (10 equiv) in EtOH (0.5 mmol/mL) and stirred for a further 1 h. The resulting mixture was then quenched with ice–water, extracted with ethyl acetate (2 × 20 mL), and washed with brine (2 × 20 mL). The organic phase was combined, dried over MgSO4, filtered, and concentrated under reduced pressure. The remaining residue was purified via flash column chromatography with appropriate eluents to give the desired alcohol.

1,2,3,4-Tetrahydro-2H-naphthalene-2-yl)methanol (4a). General procedure A was followed using 5′-methoxy-5′-methyl-3,4-dihydro-1H,5′H-spiro[naphthalene-2,2′-1,3,4]oxadiazole (92 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H2O, 4 mol %, 10 equiv), and sodium borohydride (153 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a colorless oil (21 mg, 49%): 1H NMR (600 MHz, CDCl3) δ 9.65 (s, 1H, HCO), 3.97 (br s, 2H, NCH2 + NCH2), 3.02–2.81 (m, 2H, NCH2 + NCH2), 2.47–2.36 (m, 1H, HCOCH3), 1.98–1.80 (m, 2H, CH2 + CH2CH3), 1.59–1.50 (m, 2H, CH2 + CH2CH3), 1.44 (s, 9H, C(CH3)3); 13C H NMR (151 MHz, CDCl3) δ 203.1 (HCO), 154.8 (NCOO), 79.8 (C(′)(H)), 48.1 (HCOCH3), 43.0 (br, C′′ + C′′′), 28.5 (C′′′′), 25.3 (C′ + C′′); HRMS (ESI, m/z) 214.3 (M + H)+ 100; IR νmax (film) 2972, 2736, 1688, 1418, 1365, 1273, 1232, 1168, 1128, 958, 864, 769 cm−1. The data presented are consistent with literature precedent.

The product is volatile.
chromatography (10–40% EtOAc in petroleum ether) to give the title product as a transparent oil (39 mg, 60%); 1H NMR (600 MHz, CDCl₃) δ 7.09 (app. p, J = 2.2 Hz, 4H, H₄), 2.56–3.59 (m, 2H, HOCH₂CH₃), 2.93–2.79 (m, 2H, ArCH₂CH₂ + ArCH₂), 2.52 (dd, J = 16.3, 10.7 Hz, 4H, ArCH₂), 2.06–1.95 (m, 2H, ArCH₂CH₂), 1.55–1.39 (m, 2H, HOCH₂CH₂ + CH₂OH), 1.33–1.05 (m, 2H, ArC₂H₄, 11.3 (C₂H₅), 12.4, 12.5 (CH₂), 125.7 (C₆H₅), 125.7 (C₆H₅), 67.8 (HOCH₂), 37.1 (HOCH₂CH₂), 32.5 (ArCH₂), 28.8 (C₃), 26.0 (ArCH₂CH₂); HRMS (ESI) calcd for C₇H₁₃O₂N⁺ [(M + H)⁺]: 195.0932, found 195.0931; IR νₚₑₗₜ (film) cm⁻¹. The data presented are consistent with literature precedent.36

**3,4-Triazino[4,5-f]isoquinoline (4f).** General procedure B was followed using 3-methyl-3-methyl-4-oxo-2,1,2-

**ethylcarbazole (57 mg, 0.2 mmol, 1.0 equiv).** The crude mixture was purified via flash column chromatography (10–50% EtOAc in petroleum ether) to give the title product as a colorless oil (24 mg, 53%); 1H NMR (600 MHz, CDCl₃) δ 3.99 (d, Jdt = 11.5, 4.6, 1.1 Hz, 2H, OCH₂CH₂ + OCH₂); 13C{1H} NMR (153 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10–40% EtOAc in petroleum ether) to give the title product as a transparent oil (38 mg, 72%); 1H NMR (600 MHz, CDCl₃) δ 3.47 (d, J = 6.4 Hz, 2H, HOCH₂), 2.70 (dd, J = 14.3, 1.5, 3.5 Hz, 2H, CH₂OCH₂ + SCH₂); 13C{1H} NMR (151 MHz, CDCl₃) δ 68.1 (HOCH₂), 67.8 (C₃), 37.7 (HOCH₂CH₂), 29.4 (C₂ + C₃); LRMS (ESI, m/z) 115.3 (M⁻); 100; IR νₚₑₗₜ (film) cm⁻¹: 3368, 2918, 2847, 1652, 1445, 1235, 1140, 1031, 1017, 984, 849 cm⁻¹. The data presented are consistent with literature precedent.37

**1,4-Dioxoisoquinoline (4d).** General procedure B was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-

**1,4-Dioxoisoquinoline (4d).** General procedure B was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-

**2-Methylpentane-1,5-diol (4d).** General procedure B was followed using 3-(5-methoxy-2,5-dimethyl-2,5-dihydro-1,3-oxadiazol-2-yl)-propan-1-ol (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H₂O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10–50% EtOAc in petroleum ether) to give the title product as a colorless oil (24 mg, 53%); 1H NMR (600 MHz, CDCl₃) δ 4.19–3.78 (m, 4H, OCH₂CH₂O), 3.46 (d, J = 6.5 Hz, 2H, HOCH₂), 1.86 (br s, 1H, HO), 1.78–1.73 (m, 4H, CH₂ + CH₂), 1.52 (td, J = 13.5, 12.8, 4.6 Hz, 3H, HOCH₂ + OCH₂ + OCH₂), 1.26 (dd, J = 13.5, 12.8, 11.7, 4.0 Hz, 2H, OCH₂ + OCH₂); 13C{1H} NMR (151 MHz, CDCl₃) δ 109.1 (OCO), 67.8 (HOCH₂), 64.2 (OCH₂CH₂O), 39.2 (HOCH₂CH₂), 34.2 (C₂ + C₃), 33.5 (C₄), 26.7 (C₅), 26.3 (C₆), 16.1 (CH₂), 1.85–1.72 (m, 2H, CH₂), 1.57 (br s, 1H, CH₂), 1.55 (br s, 3H, CH₂ + CH₂), 1.25 (br s, 3H, HO); 13C{1H} NMR (151 MHz, CDCl₃) δ 65.3 (HOCH₂), 47.3 (HOCH₂CH₂), 39.1 (C₁), 38.2 (C₂), 31.9 (C₃), 29.2 (C₄), 28.4 (C₅), 27.9 (C₆); HRMS (ESI) calcd for C₆H₁₁O₂N⁺ [M + Na⁺]: 199.1250, found 199.1247; IR νₚₑₗₜ (film) cm⁻¹: 3260, 2861, 2849, 1466, 1452, 1066, 1033, 977 cm⁻¹. The data presented are consistent with literature precedent.41
column chromatography (2% MeOH in dichloromethane) to give the titled product as a colorless oil (16 mg, 66%): 1H NMR (600 MHz, CDCl3) δ 3.60 (t, J = 6.1 Hz, 2H, HOCH2CH3), 3.48–3.36 (m, 2H, HOCH2CH3), 1.34–1.54 (m, 2H, CH2CH2CH3), 1.16–1.06 (m, 2H, CHCH3), 0.88 (d, J = 6.7 Hz, 3H, CH3). 13C{1H} NMR (151 MHz, CDCl3) δ 67.8 (HOCH2CH3), 62.8 (HOCH2CH3), 35.4 (CH2CH2CH3), 29.7 (CH2CH2CH3), 29.1 (CH2CH2CH3), 16.7 (CH3), HRMS (ESI) calcd for C6H15O2 ([M + H]+) 119.1067, found 119.1066; IR νmax (film) 3291, 2932, 2869, 1652, 1455, 1418, 1377, 1104, 1038, 940, 897, 731 cm⁻¹. The data presented are consistent with literature precedent.42

2-Methyl-3-(pyridin-4-yl)propan-1-ol (4I). General procedure B was followed using 2-methoxy-2,5-dimethyl-2-(pyridin-4-yl)ethanol (38 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt% in H2O, 4 mmol, 10 equiv), and sodium borohydride (152 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (30–70% EtOAc in petroleum ether) to give the titled product as a transparent oil (30 mg, 50%): 1H NMR (600 MHz, CDCl3) δ 8.51 (br s, 2H, HOCH2CH3), 7.12 (dd, J = 13.4, 6.0 Hz, 1H, CH2), 2.40 (dd, J = 13.4, 8.4 Hz, 1H, CHCH3), 2.03–1.93 (m, 3H, HOCH2CH3), 1.75 (br s, 1H, OH), 0.91 (d, J = 6.8 Hz, 3H, CH3CH2). 13C{1H} NMR (151 MHz, CDCl3) δ 150.2 (Cpyridine), 149.6 (CpyridineH), 124.8 (CpyridineH), 67.2 (HOCH2CH3), 39.0 (Cpyridine), 37.2 (HOCH2), 16.4 (CH3CH2). HRMS (ESI) calcd for C5H10NO2+ [M + H]+ 112.0717, found 112.0710; IR νmax (film) 3353, 2924, 2348, 2185, 1605, 1043 cm⁻¹. The data presented are consistent with literature precedent.43

3-(Furan-2-yl)-2-methylpropan-1-ol (4m). General procedure B was followed using 2-(furan-2-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (84 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt% in H2O, 4 mmol, 10 equiv), and sodium borohydride (152 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (10–40% EtOAc in petroleum ether) to give the titled product as a white solid (24 mg, 76%): 1H NMR (600 MHz, methanol-d4) δ 9.06 (br s, 1H, NH), 7.76 (br s, 1H, NH), 7.40 (br s, 1H, NH), 7.24 (d, J = 5.5 Hz, 2H, H2), 7.29–7.13 (m, 4H, H4), 3.41 (tdd, J = 10.3, 5.5, 3.1 Hz, 1H, CHCH3), 3.35–3.20 (m, 2H, ArCH2CH2), 2.97 (q, J = 10.3, 5.5 Hz, 2H, ArCH2CH2), 2.48–2.37 (m, 1H, CHCH3), 2.14 (dd, J = 13.0, 10.3, 6.2 Hz, 1H, CHCH3). 13C{1H} NMR (151 MHz, methanol-d4) δ 159.8 (C3), 136.1 (C2a), 129.3 (C1a), 129.2 (C1a′), 126.9 (C5), 123.3 (C5′), 115.4 (br s, C6), 36.7 (CH3CH2), 35.4 (ArCH2), 30.0 (ArCH3), 29.6 (C1); one aromatic carbon is not seen in the 13C{1H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for C3H8N2O2+ [M + H]+ 249.1387, found 249.1392; IR νmax (film) 2921, 1423, 1275, 1009, 993, 932, 743 cm⁻¹. Mp: 239–241 °C.

2-(Tetrahydro-2H-pyran-4-yl)-1H-benzimidazole (5b). General procedure C was followed using 3-methoxy-3-methyl-4,8-dioxa-1,2-diazaspiro[4.4]non-1-ene (38 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt% in H2O, 2 mmol, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10–40% EtOAc in petroleum ether) to give the titled product as a white solid (36 mg, 72%): 1H NMR (600 MHz, CDCl3) δ 9.06 (br s, 1H, NH), 7.76 (br s, 1H, NH), 7.40 (br s, 1H, NH), 7.24 (d, J = 5.5 Hz, 2H, H2), 7.29–7.13 (m, 4H, H4), 3.41 (tdd, J = 10.3, 5.5, 3.1 Hz, 1H, CHCH3), 3.35–3.20 (m, 2H, ArCH2CH2), 2.97 (q, J = 10.3, 5.5 Hz, 2H, ArCH2CH2), 2.48–2.37 (m, 1H, CHCH3), 2.14 (dd, J = 13.0, 10.3, 6.2 Hz, 1H, CHCH3). 13C{1H} NMR (151 MHz, methanol-d4) δ 159.8 (C3), 136.1 (C2a), 129.3 (C1a), 129.2 (C1a′), 126.9 (C5), 123.3 (C5′), 115.4 (br s, C6), 36.7 (CH3CH2), 35.4 (ArCH2), 30.0 (ArCH3), 29.6 (C1); one aromatic carbon is not seen in the 13C{1H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for C21H19N2O2+ [M + H]+ 249.1387, found 249.1392; IR νmax (film) 2921, 1423, 1275, 1009, 993, 932, 743 cm⁻¹. Mp: 239–241 °C.

Synthesis of Benzimidazoles. General Procedure C for the Synthesis of Benzimidazoles. The procedure was a modification of the literature procedure from Jiao et al.46

The reaction slug from general procedure A was collected into a round-bottom flask containing a biphasic solution of brine and toluene with stirring. Upon resting, the toluene phase was syringed out and injected into another open round-bottom flask charged with freshly activated 4 Å molecular sieves. The mixture was stirred for another 1 min before o-phenylenediamine (1.5 equiv) was added. The reaction mixture was then bubbled with O2 gas and stirred at room temperature (30 °C) for 12 h. Molecular sieves were filtered out and injected into another open round-bottom flask charged with freshly activated 4 Å molecular sieves. The mixture was stirred for another 1 min before being purified via flash chromatography with appropriate eluent combinations to afford the final benzimidazole derivatives.
aldehyde (0.15 mL, 37 wt % in H₂O, 2 mL, 10 equiv), and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography (10–40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 72%). ¹H NMR (600 MHz, methanol-d4) δ 7.55–7.38 (m, 2H, H Ar), 7.21–7.13 (m, 2H, H Ar), 3.60 (dd, J = 15.8, 9.7, 6.3 Hz, 1H, CCH), 3.23 (dd, J = 10.4, 6.9 Hz, 1H, CCHCH₂), 3.14 (dd, J = 10.4, 9.3 Hz, 1H, CCHCH₂), 2.98 (dd, J = 8.4, 5.0 Hz, 2H, SCH₂CH₃), 2.52 (dt, J = 10.4, 5.1 Hz, 1H, CCHCH₂), 2.36–2.26 (m, 1H, CCHCH₂). The data presented are consistent with literature precedent.⁴⁶

Note

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(C<sub>49</sub>H<sub>54</sub>N<sub>2</sub>O<sub>4</sub>) was passed through the column reactor (Omni Procedure D for the Synthesis of Aldehydes from Aryl Hydrazones. Petroleum ether) to give the titled product as a white solid (26 mg, 1.45 equiv). The crude mixture was purified via flash column chromatography (10–40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 73%).<sup>31</sup> 1H NMR (600 MHz, CDCl<sub>3</sub>) δ 10.18 (br s, 1H, NH), 7.55 (br s, 2H, H<sub>2</sub>Ar), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H<sub>2</sub>Ar), 5.75 (d<sup>−</sup>dd, J = 17.0, 10.2, 6.6 Hz, 1H, CH=CH<sub>2</sub>), 4.97 (dd, J = 17.0, 1.8 Hz, 1H, H<sub>2</sub>Ar), 4.93 (dd, J = 10.2, 1.8 Hz, 1H, H<sub>1</sub>Ar), 3.14 (h<sup>−</sup> J = 7.0 Hz, 1H, CCH<sub>2</sub>), 2.14–2.05 (m, 2H, CH<sub>2</sub>CHCH<sub>2</sub>), 2.04–1.97 (m, 1H, CCHCH<sub>2</sub>), 1.85–1.77 (m, 1H, CCH<sub>2</sub>CH<sub>2</sub>), 1.45 (d<sup>−</sup>, J = 7.1 Hz, 3H, CH<sub>3</sub>); LRMS (ESI, m/z calcd for C<sub>12</sub>H<sub>15</sub>N<sub>2</sub>O<sub>4</sub> [M + H<sup>+</sup>] 206.0984, found 206.0981; IR ν<sub>max</sub> (film) 3074, 2968, 2932, 2736, 1816, 1640, 1538, 1454, 1426, 1320, 1272, 906, 745, 729 cm<sup>−1</sup>; mp 182–183 °C."

The data presented are consistent with literature precedent.<sup>46</sup>

2-3-Bromophenylacetaldehyde (2b). General Procedure D was followed using 3-bromobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt % in H<sub>2</sub>O, 1.0 mL/min). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (34 mg, 53%): 1H NMR (600 MHz, CDCl<sub>3</sub>) δ 9.76 (t, J = 2.1 Hz, 1H, HCO), 7.45 (d, J = 8.4 Hz, 2H, H<sub>2</sub>Ar), 7.15 (d, J = 8.3 Hz, 2H, H<sub>2</sub>Ar), 3.68 (dd, J = 2.1 Hz, 2H, CH=CH), 3.13 (C<sub>1</sub>H<sub>3</sub>); one aromatic carbon is not seen in the 13C{1H} NMR spectrum; HRMS (ESI, m/z calcd for C<sub>9</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> [M + H<sup>+</sup>] 155.0775, found 155.0777; IR ν<sub>max</sub> (film) 2827, 1723, 1568, 1474, 1427, 1072, 782, 692 cm<sup>−1</sup>.) The data presented are consistent with literature precedent.<sup>46</sup>

2-3,4-Dihydroquinoline-3-carboxaldehyde (3a). General Procedure D was followed using 3-(4-chlorobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt % in H<sub>2</sub>O, 1.0 mL/min). The crude mixture was purified via flash column chromatography (10–40% EtOAc in petroleum ether) to give the titled product as a white solid (34 mg, 53%). The reaction slug from general procedure D was extracted with extra EtOAc (20 mL) and formaldehyde (0.16 mL, 37 wt % in H<sub>2</sub>O, 2.0 mmol, 10 equiv) and o-phenylenediamine (32 mg, 0.3 mmol, 1.5 equiv). The crude mixture was purified via flash column chromatography. The output stream was extracted with extra EtOAc (20 mL) and washed with water (20 mL). The combined organic phase was dried over MgSO<sub>4</sub> and concentrated under vacuum, and purified over silica gel using appropriate eluent combinations to yield the desired aldehyde. 2,3-Dihydro-2-oxindole-3-carboxaldehyde (4a). General Procedure D was followed using 4-chlorobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt % in H<sub>2</sub>O, 1.0 mL/min). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (46 mg, 58%); 1H NMR (600 MHz, CDCl<sub>3</sub>) δ 9.74 (t, J = 2.1 Hz, 1H, HCO), 7.34 (d, J = 8.4 Hz, 2H, H<sub>2</sub>Ar), 7.15 (d, J = 8.3 Hz, 2H, H<sub>2</sub>Ar), 3.68 (dd, J = 2.1 Hz, 2H, CH=CH), 3.13 (C<sub>1</sub>H<sub>3</sub>); one aromatic carbon is not seen in the 13C{1H} NMR spectrum; HRMS (ESI, m/z calcd for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub> [M + H<sup>+</sup>] 198.1042, found 198.1048; IR ν<sub>max</sub> (film) 2827, 1723, 1568, 1474, 1427, 1072, 782, 692 cm<sup>−1</sup>.) The data presented are consistent with literature precedent.<sup>46</sup>

The reaction slug from general procedure D was extracted with extra EtOAc (20 mL × 2) and washed with water (20 mL). The combined organic phase was concentrated under reduced pressure and filtered through a 0.45 μm syringe filter before use.
column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (36 mg, 57%): 1H NMR (600 MHz, CDCl3) δ 7.28 (d, J = 8.4 Hz, 1H, Hα), 7.17 (d, J = 8.4 Hz, 1H, Hβ), 3.85 (t, J = 6.5 Hz, 2H, HOCH2), 2.84 (t, J = 6.5 Hz, 2H, ArCH2), 1.39 (br s, 1H, HO), 13C{1H} NMR (151 MHz, CDCl3) δ 132.5 (Cα), 130.5 (Cβ), 128.8 (Cγ, H), 63.6 (HOCH2), 38.6 (ArCH2); LRMS (ESI, m/z) 157.1 ([M + H]+, 100); IR νmax (film) 3355, 2932, 1492, 1406, 1090, 1046, 1015, 810 cm⁻¹. The data presented are consistent with literature precedent.49

2-(3-Bromophenyl)ethan-1-ol (8B). General procedure E was followed using (3-bromobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt % in H2O, 1.0 mL/min), and NaBH4 (152 mg, 10.0 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (53 mg, 66%): 1H NMR (400 MHz, CDCl3) δ 7.47 (m, 3H, HAr), 7.22–7.06 (m, 2H, HAr), 3.85 (t, J = 6.5 Hz, 2H, HOCH2), 2.83 (t, J = 6.5 Hz, 2H, ArCH2), 1.56 (s, 1H); 13C{1H} NMR (100 MHz, CDCl3) δ 141.1 (Cα), 132.2 (Cβ, H), 120.2 (Cγ, H), 129.7 (Cγ, Cα), 122.7 (Cβ, Cγ), 63.4 (HOCH2), 38.9 (ArCH2); LRMS (ESI, m/z) 201.0 ([M + H]+, 100); IR νmax (film) 3333, 2945, 1595, 1567, 1473, 1425, 1200, 1071, 1046, 810, 777, 692, 570 cm⁻¹. The data presented are consistent with literature precedent.50

2-(2-Toly)ethan-1-ol (8C). General procedure E was followed using (2-methylbenzylidene)hydrazine (1.0 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt % in H2O, 1.0 mL/min), and NaBH4 (152 mg, 10.0 equiv). The crude mixture was purified via flash column chromatography (0–20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (53 mg, 66%): 1H NMR (400 MHz, CDCl3) δ 7.74–7.29 (m, 2H, HAr), 7.22–7.06 (m, 2H, HAr), 3.85 (t, J = 6.5 Hz, 2H, HOCH2), 2.83 (t, J = 6.5 Hz, 2H, ArCH2), 1.56 (s, 1H); 13C{1H} NMR (100 MHz, CDCl3) δ 141.1 (Cα), 132.2 (Cβ, H), 120.2 (Cγ, H), 129.7 (Cγ, Cα), 122.7 (Cβ, Cγ), 63.4 (HOCH2), 38.9 (ArCH2); LRMS (ESI, m/z) 201.0 ([M + H]+, 100); IR νmax (film) 3333, 2945, 1595, 1567, 1473, 1425, 1200, 1071, 1046, 810, 777, 692, 570 cm⁻¹. The data presented are consistent with literature precedent.50

■ ASSOCIATED CONTENT

## Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at: 10.1021/acs.joc.8b02721.

NMR spectra (PDF)

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The authors declare the following competing financial interest(s): D.C.B. is an employee and stockholder of Pfizer, Inc.

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Additional data related to this publication is available at the University of Cambridge Institutional Data Repository: https://doi.org/10.17863/CAM.27522.

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