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Note

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Photochemical Homologation for the Preparation of Aliphatic Aldehydes in Flow

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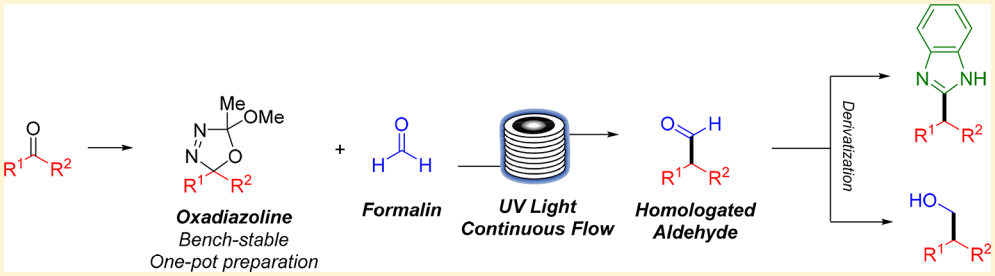
Supporting Information

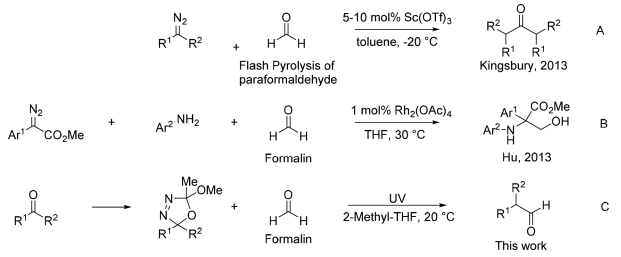


ABSTRACT: Cheap and readily available aqueous formaldehyde was used as a formylating reagent in a homologation reaction with nonstabilized diazo compounds, enabled by UV photolysis of bench-stable oxadiazolines in a flow photoreactor. Various aliphatic aldehydes were synthesized along with the corresponding derivatized alcohols and benzimidazoles. No transition-metal catalyst or additive was required to affect 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 technology[11−13] to overcome the safety issues traditionally associated with diazo compounds.[14−16] Following the pioneering work from Warkentin and co-workers,[17,18] 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(sp^2)−C(sp^3) cross-coupling with boronic acids[19] 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 aryldiazoacetate, 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).

Scheme 1. Examples of homologation reactions involving diazo and carbonyl compounds



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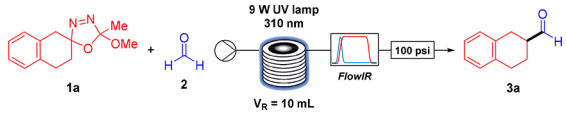
Our investigation began by combining 2-tetralone oxadiazoline **1a** with different sources of formaldehyde under UV irradiation (Table 1). Common formaldehyde surrogates

Table 1. Optimization of Aldehyde Formation



entry[a]	formaldehyde source	ox (M)	t_R (min)	T (°C)	conv (%)	yield (%)
1	dioxolane	0.1	40	20	99	0
2	trioxane	0.1	40	20	96	2
3	thermolyzed paraformaldehyde	0.1	40	20	67	55
4	37% aq	0.1	40	20	78	48
5	37% aq	0.1	40	10	72	41
6	37% aq	0.05	40	10	80	39
7	37% aq	0.1	80	20	87	60 (50)[b]
8[c]	37% aq	0.1	80	20	86	58
9[d]	37% aq	0.1	80	20	87	56
10[e]	37% aq	0.1	80	20	78	41
11[f]	37% aq	0.1	80	20	79	12

[a]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. [b]Isolated yield. [c]100 equiv of formaldehyde was used. [d]5.0 equiv of formaldehyde was used. [e]Tetrahydrofuran was used instead of 2-methyltetrahydrofuran. [f]Dichloromethane was used instead of 2-methyltetrahydrofuran.

trioxane and dioxolane both delivered only trace amounts of the desired aldehyde product **3a** despite almost complete conversion of the oxadiazoline starting material (entry 1 and 2).[23] While we established our first success using a stock solution of monomeric formaldehyde created via thermolysis of paraformaldehyde,[24] resulting in a 55% yield of the desired aldehyde (entry 3), practical considerations of the procedure and the propensity of the stock solution to polymerize without warning on warming above −78 °C made this an unattractive approach. We then turned our attention to formalin, a 37% aqueous solution of formaldehyde, which pleasingly gave a modest isolated yield (48%) of the target aldehyde (**3a**, entry 4).[25] Lowering the reaction temperature to 10 °C led to a diminished conversion and yield (entry 5), while a decrease in the reaction concentration did not result in an improved yield despite a higher conversion (entry 6). Elongating the residence time to 80 min improved both conversion (87%) as well as yield (60%) (entry 7). Formaldehyde ratio changes were ineffective (entry 8 and 9). Similarly, switching to tetrahydrofuran also marginally lowered the yield to 41%, while with dichloromethane this dropped to 12% (entry 10 and 11).

After multiple reaction optimization attempts, we accepted the isolated yield of aldehyde of around 50%, albeit with a higher conversion of the oxadiazoline. On further examination of the crude sample mixture, along with the required aliphatic aldehyde we found a significant amount of hydrated material was also present. At no time did we observe more than 10% of the doubly homologated ketone. We presume that formation of the hydrate, due to the presence of a large amount of water in the reaction media, acts as an in situ protecting group, and this, coupled with a very low concentration of diazo compound 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 ($NaBH_4$), 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 cyclohexyldioxolo (**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-adamantanemethanol (**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 (**1l**) and furan (**1m**) were all successfully homologated into the corresponding products (**4l,m**, **5l,m**), respectively (entries 12 and 13). Alkyne- and alkene-substituted oxadiazolines (**1n**, **1o**) both gave reasonable isolated yields as aldehyde derivatives (**4n**, **5n,o**), with alkyne 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-cyclopropylethyl)benzimidazole (**5p**) proved the effectiveness of oxadiazoline 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

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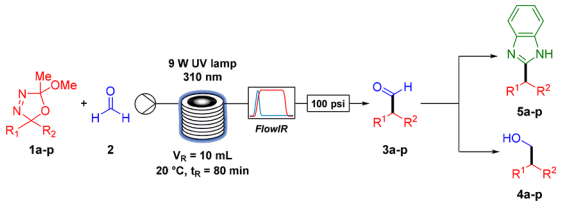
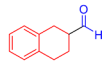
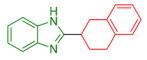
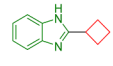
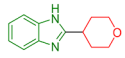
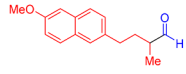
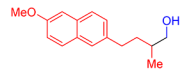
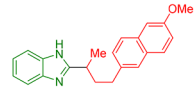
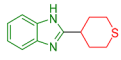
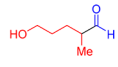
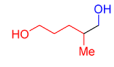
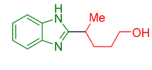
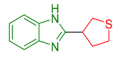
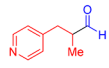
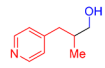
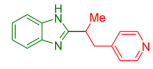
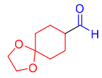
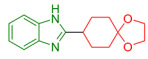
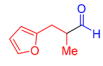
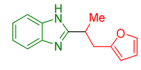
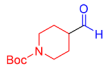
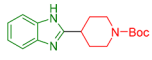
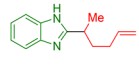
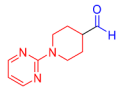
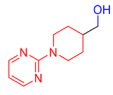
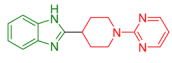
Table 2. Scope and Derivatization of Oxadiazolines and Aqueous Formaldehyde



Entry	Aldehyde 3a – h[a]	Alcohol 4a – h[b]	Benzimidazole 5a – h[c]	Entry	Aldehyde 3i – p[a]	Alcohol 4i – p[b]	Benzimidazole 5i – p[c]
1	 3a, 60%[d] (50%)	 4a, 60%	 5a, 72%	9	 3i, n.d.[e]	 4i, n.d.[e]	 5i, 59%
2	 3b, 48%	 4b, 53%	 5b, 76%	10	 3j, 57%	 4j, 75%	 5j, n.d.[e]
3	 3c, 56%	 4c, 72%	 5c, 55%	11	 3k, 85%[f]	 4k, 66%	 5k, n.d.[e]
4	 3d, 85%[d] (75%)	 4d, 89%[d] (77%)	 5d, 60%	12	 3l, 35%[d]	 4l, 50%	 5l, 48%
5	 3e, 65%	 4e, 75%	 5e, 80%	13	 3m, 25%[d]	 4m, 60%	 5m, 75%
6	 3f, 58%[d] (49%)	 4f, 53%	 5f, 49%	14	 3n, 58%[d]	 4n, 88%[d] (69%)	 5n, 73%
7	 3g, 55%[d]	 4g, 68%[d]	 5g, 72%	15	3o, 18%[d]	4o, n.d.[e]	5o, 39%
8	3h, 68%	4h, 75%	5h, 79%	16	3p, 8%[d]	4p, 58%[d]	5p, 69%

[a]Reaction conditions: oxadiazoline (1.0 equiv, 0.1 M), formaldehyde (10 equiv, 37 wt % in H_2O, 1.0 M) in 2-methyltetrahydrofuran. [b]Aldehyde reduced directly with $NaBH_4$ (10 equiv, 0.5 M) in ethanol. [c]Aldehyde reacted with *o*-phenylenediamine (1.5 equiv, 0.075 M) in toluene. [d]NMR yield, calculated using 1,3,5-trimethoxybenzene as an internal standard. [e]Not determined due to volatility or product contamination. [f]81% of the product identified as the hydrated form.

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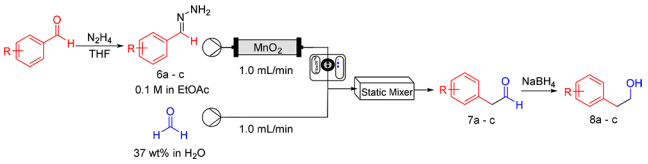
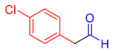
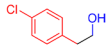
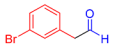
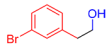
through traditional methods such as hydroformylation, particularly in the presence of alkenes or alkynes.

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.[27,28] 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

Table 3. Homologation of Aldehydes with Aqueous Formaldehyde via Hydrazine



Entry	Aldehyde –7a – c	Alcohol 8a – c[a]
1		
	7a, 53%	**8a, 57%**
2		
	7b, 58%	**8b, 66%**
3		
	7c, 57%	**8c, 66%**

[a]Aldehyde extracted with ethyl acetate then reduced directly with $NaBH_4$ (10 equiv, 0.5 M) in ethanol.

extracted and reduced directly to the corresponding alcohol in good yields (**8a–c**). No attempt was made to further exemplify this procedure, although it should be noted that the method does overcome classical issues associated with phenacetaldehyde preparation.

We present a mild, operationally straightforward procedure for the overall homologation of ketones and aryl aldehydes via nonstabilized diazo compounds in flow. The route complements other homologation methods while avoiding expensive and reactive transition-metal catalysts and uses formalin as a cheap and readily available source of carbon.

EXPERIMENTAL SECTION

General Information. All batch reactions were performed under an atmosphere of nitrogen using oven-dried glassware unless otherwise stated. UV flow reactions were performed using a Vaportec E-series and UV-150 system. Hydrazone flow reactions were performed using a Uniqsis FlowSyn platform. Reagents were purchased from Sigma-Aldrich, Alfa Aesar, Acros, and Fluorochem and were used as supplied unless stated otherwise. 2-Methyltetrahydrofuran (2-MeTHF, anhydrous, inhibitor free, ≥99.9%) and tetrahydrofuran (THF, anhydrous, inhibitor free, ≥99.9%) were purchased from Sigma-Aldrich and used as supplied. Workup solvents were employed directly from commercial sources, i.e., Sigma-Aldrich, 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).

^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a 600 MHz Bruker DRX-600 spectrometer. Chemical shifts (δ) are referenced to the residual solvent as $CDCl_3$ or DMSO-d_6 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 recorded 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, H_a and H_a'. ^{1}H NMR signals are reported to two decimal places and ^{13}C 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 a 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 ^{1}H 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_R = 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 FlowIR 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 FlowIR 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-Tetrahydronaphthalene-2-carbaldehyde (**3a**).* General Procedure A was followed using 5′-methoxy-5′-methyl-3,4-dihydro-1*H*,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 H_2O, 4 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 transparent oil (32 mg, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (d, J = 1.2 Hz, 1H, *H*CO), 7.13 (dt, J = 6.3, 3.5 Hz, 3H, H_{Ar}), 7.10 (q, J = 4.1, 3.5 Hz, 1H, H_{Ar}), 3.04–2.95 (m, 2H,

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ArCH_2CH$_2$), 2.94−2.82 (m, 2H, ArCH_2), 2.75−2.68 (m, 1H, HCOCH), 2.26−2.19 (m, 1H, ArCH_a), 1.84−1.75 (m, 1H, ArCH_a′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 203.9 (HCO), 136.1 (C_{Ar}), 134.4(C_{Ar}), 129.4(C_{Ar}H), 129.0(C_{Ar}H), 126.2(C_{Ar}H), 126.1(C_{Ar}H), 47.0 (HCOCH), 28.6 (ArCH$_2$CH$_2$), 28.2 (ArCH$_2$CH), 23.1 (C_a); HRMS (ESI) calcd for $C_{11}H_{12}ONa^+$ [M + Na]$^+$ 183.0780, found 183.0775; IR ν_{max} (film) 2904, 2851, 1723, 1702, 1432, 1110, 1042 cm^{-1}. The data presented are consistent with literature precedent.[29]

*Tetrahydro-2H-pyran-4-carbaldehyde (**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 H_2O, 4 mmol, 10 equiv). The crude mixture was purified via flash column chromatography (0−15% EtOAc in petroleum ether) to give the titled product as a volatile transparent oil (23 mg, 48%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.68 (d, J = 1.0 Hz, 1H, HCO), 4.00−3.92 (m, 2H, OCH_a + OCH_b), 3.48 (ddd, J = 11.5, 10.7, 2.6 Hz, 2H, OCH_a′ + OCH_b′′), 2.55−2.36 (m, 1H, HCOCH), 1.89−1.83 (m, 2H, OCH_c + OCH_d), 1.70 (dtd, J = 13.7, 10.7, 4.2 Hz, 2H, OCH_c′ + OCH_d′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 203.0 (HCO), 66.8 (C_a + C_b), 46.9 (HCOCH), 25.8 (C_c + C_d); LRMS (ESI, m/z) 115.2 ([M + H]$^+$, 100); IR ν_{max} (film) 2968, 1879, 1720, 1279, 1201, 1135, 1080, 924 cm^{-1}. The data presented are consistent with literature precedent.[30]

*Tetrahydro-2H-thiopyran-4-carbaldehyde (**3c**).* General procedure A was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (81 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H_2O, 4 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 volatile transparent oil (29 mg, 56%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.59 (s, 1H, HCO), 2.67 (dt, J = 10.2, 3.6 Hz, 4H, SCH_2), 2.34−2.22 (m, 3H, HCOCH + CH_a + CH_b), 1.75 (dtd, J = 14.3, 10.2, 4.5 Hz, 2H, CH_a′+ CH_b′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 203.3 (HCO), 49.3 (HCOCH), 27.6 (SCH$_2$), 27.2 (C_a + C_b); HRMS (ESI) calcd for $C_6H_{11}OS^+$ [M + H]$^+$ 131.0528, found 131.0531; IR ν_{max} (film) 2918, 2849, 2369, 1724, 1239, 1130, 1088, 983 cm^{-1}. The data presented are consistent with literature precedent.[31]

*Tetrahydrothiophene-3-carbaldehyde (**3d**).* General procedure A was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (37 mg, 0.2 mmol, 1.0 equiv) and formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv). An 85% NMR yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 equiv) as an internal standard. The crude mixture was purified via flash column chromatography (0−20% EtOAc in petroleum ether) to give the titled product as a colorless volatile oil (17 mg, 75%) with less than 10% of dichloromethane: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (d, J = 1.3 Hz, 1H, HCO), 3.16 (dd, J = 10.9, 5.0 Hz, 1H, SCH_cCH), 3.09−3.04 (m, 1H, HCOCH), 2.98 (dd, J = 10.9, 7.0 Hz, 1H, SCH_cCH), 2.91−2.85 (m, 1H, SCH_bCH$_2$), 2.85−2.78 (m, 1H, SCH_bCH$_2$), 2.38 (td, J = 12.7, 5.9 Hz, 1H, CHCH_a), 2.12 (dq, J = 13.4, 6.9 Hz, 1H, CHCH_a′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 201.3 (HCO), 55.1 (HCOCH), 31.1 (C_c), 30.9 (C_b), 30.5 (C_a); LRMS (ESI, m/z) 117.1 ([M + H]$^+$, 100); IR ν_{max} (film) 2944, 1720, 1416, 1235, 1028, 956 cm^{-1}. The data presented are consistent with literature precedent.[32]

*1,4-Dioxaspiro[4.5]decane-8-carbaldehyde (**3e**).* General procedure A was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4^8.2^5]tetradec-1-ene (102 mg, 0.4 mmol, 1.0 equiv) and formaldehyde (0.3 mL, 37 wt % in H_2O, 4 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 volatile oil (44 mg, 65%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.64 (d, J = 1.3 Hz, 1H, HCO), 3.94 (dd, J = 5.3, 3.4 Hz, 4H, OCH_2CH$_2$O), 2.25 (ttd, J = 9.7, 4.1, 1.4 Hz, 1H, HCOCH), 1.97−1.91 (m, 2H, CH_c + CH_d), 1.80−1.71 (m, 4H, CH_c′ + CH_d′ + CH_e + CH_f), 1.61−1.56 (m, 2H, CH_e + CH_f); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 204.2 (HCO), 108.2 (OCO), 64.5 (C_a), 64.5 (C_b), 48.4 (HCOCH), 33.5 (C_c + C_d), 23.4 (C_e + C_f); LRMS (ESI, m/z) 171.4 ([M + H]$^+$, 100); IR ν_{max} (film) 2949, 2881, 1722, 1447, 1362, 1239, 1142, 1104, 1033, 948, 881 cm^{-1}. The data presented are consistent with literature precedent.[33]

*tert-Butyl 4-Formylpiperidine-1-carboxylate (**3f**).* General procedure A was followed using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 equiv) and formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv). A 58% NMR yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 equiv) as an internal standard. 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%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (s, 1H, HCO), 3.97 (br s, 2H, NCH_c + NCH_d), 3.02−2.81 (m, 2H, NCH_c′ + NCH_d′), 2.47−2.36 (m, 1H, HCOCH), 1.98−1.80 (m, 2H, CH_a + CH_b), 1.59−1.50 (m, 2H, CH_a′ + CH_b′), 1.44 (s, 9H, C(CH_3)$_3$); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 203.1 (HCO), 154.8 (NCOO), 79.8 (C(CH$_3$)$_3$), 48.1 (HCOCH), 43.0 (br, C_c + C_d), 28.5 (C(CH_3)$_3$), 25.3 (C_a + C_b); LRMS (ESI, m/z) 214.3 ([M + H]$^+$, 100); IR ν_{max} (film) 2927, 1726, 1688, 1418, 1365, 1273, 1232, 1168, 1128, 958, 864, 769 cm^{-1}. The data presented are consistent with literature precedent.[34]

*Adamantane-2-carbaldehyde (**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 H_2O, 4 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 white solid (45 mg, 68%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.73 (s, 1H, HCO), 2.44−2.37 (m, 3H, HCOCH + HCOCHCH), 2.01−1.67 (m, 12H, CH_b + CH_c + CH_d); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 206.1 (HCO), 56.7 (HCOCH), 38.0 (C_b), 37.2 (C_d), 33.7 (C_b′), 28.3 (C_a), 28.0 (C_c), 27.6 (C_c′); HRMS (ESI) calcd for $C_{11}H_{17}O^+$ [M + H]$^+$ 165.1274, found 165.1271; IR ν_{max} (film) 2936, 2896, 1752, 1463, 1190, 1076, 912 cm^{-1}; mp 164−166 °C. The data presented are consistent with literature precedent.[35]

*4-(6-Methoxynaphthalen-2-yl)-2-methylbutanal (**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 H_2O, 4 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 transparent oil (55 mg, 57%) together with 7% of oxidized carboxylic acid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (d, J = 1.8 Hz, 1H, HCO), 7.68 (dd, J = 8.5, 3.4 Hz, 2H, H_{Ar}), 7.55 (d, J = 1.8 Hz, 1H, H_{Ar}), 7.30 (dd, J = 8.4, 1.8 Hz, 1H, H_{Ar}), 7.16−7.10 (m, 2H, H_{Ar}), 3.92 (s, 3H, OCH_3), 2.88−2.75 (m, 2H, HCOCH + ArCH_a), 2.41 (qd, J = 6.9, 1.8 Hz, 1H, ArCH_a′), 2.19−2.10 (m, 1H, ArCH$_2$CH_b), 1.78−1.70 (m, 1H, ArCH$_2$CH_b′), 1.18 (d, J = 7.1 Hz, 3H, CHCH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 205.0 (HCO), 157.4 (C_{Ar}), 136.6 (C_{Ar}), 133.2 (C_{Ar}), 129.2 (C_{Ar}), 129.0 (C_{Ar}H), 127.7 (C_{Ar}H), 127.1 (C_{Ar}H), 126.5 (C_{Ar}H), 119.0 (C_{Ar}H), 105.8 (C_{Ar}H), 55.3 (OCH_3), 45.6 (HCOCH), 33.0 (C_a), 32.1 (C_b), 13.4 (CHCH_3); HRMS (ESI) calcd for $C_{16}H_{19}O_2^+$ [M + H]$^+$ 243.1385, found 243.1386; IR ν_{max} (film) 2933, 1721, 1634, 1606, 1483, 1390, 1264, 1229, 1031, 850 cm^{-1}.

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 $NaBH_4$ (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 $MgSO_4$, 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-Tetrahydronaphthalen-2-yl)methanol (**4a**).* General procedure B 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), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 4.0 mmol, 10 equiv). The crude mixture was purified via flash column

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chromatography (10−40% EtOAc in petroleum ether) to give the titled product as a transparent oil (39 mg, 60%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.09 (app. p, J = 2.2 Hz, 4H, H_{Ar}), 3.69−3.59 (m, 2H, $HOCH_2$), 2.93−2.79 (m, 3H, $ArCH_2CH$ + $ArCH_a$), 2.52 (dd, J = 16.3, 10.7 Hz, 1H, $ArCH_a'$), 2.06−1.95 (m, 2H, $ArCH_2CH_2$), 1.55−1.39 (m, 2H, $HOCH_2CH$ + CH_2OH); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 136.8 (C_{Ar}), 136.0 (C_{Ar}), 129.3 ($C_{Ar}H$), 128.9 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 125.7 ($C_{Ar}H$), 67.8 ($HOCH_2$), 37.1 ($HOCH_2CH$), 32.5 ($ArCH_2$), 28.8 (C_a), 26.0 ($ArCH_2CH_2$); HRMS (ESI) calcd for $C_{11}H_{14}Ona^+$ $[M + Na]^+$ 185.0937, found 185.0931; IR ν_{max} (film) 3370, 2918, 1494, 1453, 1436, 1065, 1022, 900 cm^{-1}. The data presented are consistent with literature precedent.[36]

*(Tetrahydro-2H-pyran-4-yl)methanol (**4b**).* General procedure B 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), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 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 transparent oil (25 mg, 53%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.99 (ddt, J = 11.5, 4.6, 1.1 Hz, 2H, OCH_a + OCH_b), 3.51 (d, J = 6.5 Hz, 2H, $HOCH_2$), 3.41 (td, J = 11. 5, 2.1 Hz, 2H, OCH_a' + OCH_b'), 1.79−1.73 (m, 1H, $HOCH_2CH$), 1.68−1.64 (m, 2H, CH_c + CH_d), 1.38−1.32 (m, 2H, CH_c' + CH_d'); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 68.1 ($HOCH_2$), 67.8 (C_a + C_b), 37.7 ($HOCH_2CH$), 29.4 (C_c + C_d); LRMS (ESI, m/z) 115.3 ($[M - H]^-$, 100); IR ν_{max} (film) 3368, 2918, 2847, 1652, 1443, 1235, 1140, 1031, 1012, 984, 849 cm^{-1}. The data presented are consistent with literature precedent.[30]

*(Tetrahydro-2H-thiopyran-4-yl)methanol (**4c**).* General procedure B was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (81 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 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 transparent oil (38 mg, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.47 (d, J = 6.4 Hz, 2H, $HOCH_2$), 2.70 (ddd, J = 14.3, 11.9, 2.6 Hz, 2H, SCH_a + SCH_b), 2.64−2.58 (m, 2H, SCH_a' + SCH_b'), 2.07 (dd, J = 13.5, 3.5 Hz, 2H, CH_c + CH_d), 1.59 (br s, 1H, OH), 1.57−1.48 (m, 1H, $HOCH_2CH$), 1.39 (dtd, J = 13.1, 11.8, 3.5 Hz, 1H, CH_c' + CH_d'); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 68.4 ($HOCH_2$), 40.2 ($HOCH_2CH$), 30.8 (C_a + C_b), 28.3 (C_c + C_d); HRMS (ESI) calcd for $C_6H_{13}O^{32}S^+$ $[M + H]^+$ 133.0682, found 133.0681; IR ν_{max} (film) 3584, 2924, 1454, 1422, 1273, 1036 cm^{-1}. The data presented are consistent with literature precedent.[37]

*(Tetrahydrothiophene-3-yl)methanol (**4d**).* General procedure B was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). An 89% NMR yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 equiv) as an internal standard. The crude mixture was purified via flash column chromatography (0−40% EtOAc in petroleum ether) to give the titled product as a colorless oil (18 mg, 77%) with less than 5% of ethyl acetate: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.64 (dt, J = 6.8, 3.5 Hz, 2H, $HOCH_2$), 2.94 (dd, J = 10.6, 6.8 Hz, 1H, SCH_cCH), 2.87 (ddd, J = 7.2, 5.9, 1.6 Hz, 2H, SCH_bCH_2 + $SCH_b'CH_2$), 2.65 (dd, J = 10.6, 7.2 Hz, 1H, $SCH_c'CH$), 2.44 (dpd, J = 8.3, 6.8, 5.5 Hz, 1H, $HOCH_2CH$), 2.12 (dq, J = 11.9, 5.7 Hz, 1H, $CHCH_a$), 1.85−1.71 (m, 2H, OH + $CHCH_a'$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 64.8 ($HOCH_2$), 46.7 ($HOCH_2CH$), 33.8 (C_c), 33.4 (C_d), 30.9 (C_a); LRMS (ESI, m/z) 117.3 ($[M - H]^-$, 100); IR ν_{max} (film) 3336, 2928, 2860, 2355, 1438, 1264, 1210, 1079, 1049, 1028, 967, 945, 885, 684 cm^{-1}. The data presented are consistent with literature precedent.[38]

*(1,4-Dioxaspiro[4.5]decan-8-yl)metanol (**4e**).* General procedure B was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4^8.2^5]tetradec-1-ene (102 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 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 transparent oil (52 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.09−3.78 (m, 4H, OCH_2CH_2O), 3.46 (d, J = 6.5 Hz, 2H, $HOCH_2$), 1.86 (br s, 1H, HO), 1.78−1.73 (m, 4H, CH_c + CH_d), 1.52 (td, J = 13.5, 12.8, 4.6 Hz, 3H, $HOCH_2CH$ + $OCCH_a$ + $OCCH_b$), 1.26 (dtd, J = 13.5, 12.8, 11.7, 4.0 Hz, 2H, $OCCH_a'$ + $OCCH_b'$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 109.1 (OCO), 67.8 ($HOCH_2$), 64.2 (OCH_2CH_2O), 39.2 ($HOCH_2CH$), 34.2 (C_a + C_b), 26.7 (C_c + C_d); HRMS (ESI) calcd for $C_9H_{16}O_3Na^+$ $[M + Na]^+$ 195.0992, found 195.0987; IR ν_{max} (film) 3460, 2928, 2863, 1106, 1032, 928, 890 cm^{-1}. The data presented are consistent with literature precedent.[39]

*tert-Butyl 4-(Hydroxymethyl)piperidine-1-carboxylate (**4f**).* General procedure B was followed using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 titled product as a colorless oil (23 mg, 53%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12 (br s, 2H, NCH_c + NCH_d), 3.56−3.44 (m, 2H, $HOCH_2CH$), 2.69 (br s, 2H, NCH_c' + NCH_d'), 1.75−1.68 (m, 2H, CH_a + NCH_b), 1.66−1.59 (m, 1H, $HOCH_2CH$), 1.45 (s, 9H, $C(CH_3)_3$), 1.20−1.05 (m, 2H, CH_a' + CH_b'); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 155.0 (NCOO), 79.5 ($C(CH_3)_3$), 67.8 ($HOCH_2$), 43.8 (br, C_c + C_d), 39.0 ($HOCH_2CH$), 28.7 (br, C_a + C_b), 28.6 ($C(CH_3)_3$); HRMS (ESI) calcd for $C_{11}H_{22}O_3N^+$ $[M + H]^+$ 216.1594, found 216.1591; IR ν_{max} (film) 3455, 2974, 2924, 2857, 2355, 1693, 1669, 1424, 1366, 1313, 1274, 1247, 1168, 1087, 1039, 962, 864, 769 cm^{-1}. The data presented are consistent with literature precedent.[40]

*(Adamantan-2-yl)methanol (**4h**).* General procedure B 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), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (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 titled product as a transparent oil (50 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.74 (d, J = 7.1 Hz, 2H, $HOCH_2$), 1.94−1.90 (m, 1H, $HOCH_2CH$), 1.89−1.84 (m, 4H, CH_b), 1.83−1.79(m, 3H, CH_b' + CH_a), 1.79−1.77 (m, 1H, CH_a'), 1.75−1.72 (m, 2H, CH_b''), 1.57 (br s, 1H, CH_c), 1.55 (br s, 3H, CH_c' + CH_d), 1.25 (br s, 1H, HO); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 65.3 ($HOCH_2$), 47.3 ($HOCH_2CH$), 39.1 (C_b), 38.2 (C_d), 31.9 (C_b'), 29.2 (C_a), 28.4 (C_c), 27.9 (C_c'); HRMS (ESI) calcd for $C_{11}H_{18}ONa^+$ $[M + Na]^+$ 189.1250, found 189.1247; IR ν_{max} (film) 3260, 2861, 2849, 1466, 1452, 1066, 1033, 1007, 971 cm^{-1}. The data presented are consistent with literature precedent.[41]

*4-(6-Methoxynaphthalen-2-yl)-2-methylbutan-1-ol (**4j**).* General procedure B was followed using 2-methoxy-5-(2-(6-methoxynaphthalen-2-yl)ethyl)-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (98 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (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 titled product as a yellow oil (73 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.55 (s, 1H, H_{Ar}), 7.33 (dd, J = 8.3, 1.8 Hz, 1H, H_{Ar}), 7.14−7.09 (m, 2H, H_{Ar}), 3.91 (s, 3H, OCH_3), 3.56 (br s, 1H, $HOCH_c$), 3.54−3.51 (m, 1H, $HOCH_c'$), 2.89−2.79 (m, 1H, $ArCH_a$), 2.78−2.68 (m, 1H, $ArCH_a'$), 1.91−1.80 (m, 1H, CH_b), 1.76−1.66 (m, 1H, CH_b'), 1.61−1.50 (m, 2H, $HOCH_2CH$ + OH), 1.02 (d, J = 6.7 Hz, 3H, $CHCH_3$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.3 (C_{Ar}), 137.9 (C_{Ar}), 133.1 (C_{Ar}), 129.2 (C_{Ar}), 129.0 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 126.9 ($C_{Ar}H$), 126.3 ($C_{Ar}H$), 118.6 ($C_{Ar}H$), 105.6 ($C_{Ar}H$), 68.2 (C_c), 55.3 (OCH_3), 35.3 (C_a), 34.9 (C_b), 33.2 ($HOCH_2CH$), 16.5 ($CHCH_3$); HRMS (ESI) calcd for $C_{16}H_{20}O_2^+$ $[M + H]^+$ 244.1467, found 244.1463; IR ν_{max} (film) 3342, 2961, 2926, 2850, 1634, 1604, 1484, 1462, 1391, 1263, 1228 cm^{-1}.

*2-Methylpentane-1,5-diol (**4k**).* General procedure B was followed using 3-(5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazol-2-yl)-propan-1-ol (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). The crude mixture was purified via flash

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column chromatography (2% MeOH in dichloromethane) to give the titled product as a colorless oil (16 mg, 66%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.60 (t, J = 6.1 Hz, 2H, HOCH_2CH$_2$), 3.48−3.36 (m, 2H, HOCH_2CH), 3.16 (br s, 2H, OH), 1.66−1.56 (m, 2H, HOCH$_2$CH_2), 1.54−1.45 (m, 2H, CH$_2$CH_2CHCH$_3$), 1.16−1.06 (m, 1H, CHCH$_3$), 0.88 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 67.8 (HOCH_2CH$_2$), 62.8 (HOCH_2CH), 35.4 (HOCH$_2$CH_2), 29.7 (CH$_2$CH$_2$CHCH$_3$), 29.1 (CHCH$_3$), 16.7 (CH$_3$); HRMS (ESI) calcd for $C_6H_{15}O_2^+$ [M + H]$^+$ 119.1067, found 119.1066; IR ν_{max} (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 (**4l**).* General procedure B was followed using 2-methoxy-2,5-dimethyl-5-(pyridin-4-ylmethyl)-2,5-dihydro-1,3,4-oxadiazole (88 mg, 0.4 mmol, 1.0 equiv), formaldehyde (0.3 mL, 37 wt % in H_2O, 4 mmol, 10 equiv), and sodium borohydride (153 mg, 2.0 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%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (br s, 2H, H_{Ar}), 7.12 (d, J = 4.9 Hz, 2H, H_{Ar}), 3.51 (dd, J = 5.9, 1.0 Hz, 2H, HOCH_2), 2.81 (dd, J = 13.4, 6.0 Hz, 1H, CH_a), 2.40 (dd, J = 13.4, 8.4 Hz, 1H, CH_a′), 2.03−1.93 (m, 1H, HOCH$_2$CH), 1.75 (br s, 1H, OH), 0.91 (d, J = 6.8 Hz, 3H, CHCH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 150.2 ($C_{pyridine}$), 149.6 ($C_{pyridine}$H), 124.8 ($C_{pyridine}$H), 67.2 (HOCH_2), 39.0 (C_a), 37.2 (HOCH$_2$CH), 16.4 (CHCH_3); HRMS (ESI) calcd for $C_9H_{14}NO^+$ [M + H]$^+$ 152.1071, found 152.1075; IR ν_{max} (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-ylmethyl)-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 H_2O, 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 transparent oil (34 mg, 60%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, J = 1.9, 0.9 Hz, 1H, H_{Furan}), 6.29 (dd, J = 3.2, 1.9 Hz, 1H, H_{Furan}), 6.02 (dd, J = 3.2, 0.9 Hz, 1H, H_{Furan}), 3.50 (d, J = 6.0 Hz, 2H, HOCH_2), 2.73 (dd, J = 14.9, 6.4 Hz, 1H, CH_a), 2.54 (dd, J = 14.9, 7.4 Hz, 1H, CH_a′), 2.03 (dq, J = 13.2, 6.4 Hz, 1H, HOCH$_2$CH), 1.46 (br s, 1H, OH), 0.94 (d, J = 6.8 Hz, 3H, CHCH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.7 (C_{Furan}), 141.2 (C_{Furan}H), 110.3 (C_{Furan}H), 106.3 (C_{Furan}H), 67.6 (HOCH_2), 35.4 (C_a), 31.5 (HOCH$_2$CH), 16.5 (CHCH_3); HRMS (ESI) calcd for $C_8H_{11}O_2^-$ [M − H]$^-$ 139.0754, found 139.0753; IR ν_{max} (film) 3342, 2919, 1595, 1507, 1460, 1381, 1146, 1033, 927 cm^{-1}. The data presented are consistent with literature precedent.[44]

*2-Methylhex-5-en-1-ol (**4n**).* General procedure B was followed using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 2.0 mmol, 10 equiv), and sodium borohydride (76 mg, 2.0 mmol, 10 equiv). An 88% NMR yield was calculated using 1,3,5-trimethoxybenzene (11 mg, 0.066 mmol, 0.33 equiv) as an internal standard. The crude mixture was purified via flash column chromatography (0−40% EtOAc in petroleum ether) to give the titled product as a colorless oil (16 mg, 69%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H, CH$_2$=CH), 5.02 (dd, J = 17.0, 1.9 Hz, 1H, H_b), 4.95 (dd, J = 10.2, 1.9 Hz, 1H, H_a), 3.48 (ddd, J = 45.3, 10.5, 6.1 Hz, 2H, CHCH_2OH), 2.18−2.09 (m, 1H, CH$_2$=CHCH_c), 2.09−1.99 (m, 1H, CH$_2$=CHCH_c′), 1.70−1.60 (m, 1H, CH$_2$CH_dCHCH$_3$), 1.58−1.47 (m, 1H, CH$_2$CH_d′CHCH$_3$), 1.33 (br s, 1H, OH), 1.28−1.16 (m, 1H, CHCH$_3$), 0.93 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 139.0 (CH$_2$=CH), 114.6 (CH$_2$=CH), 68.3 (CHCH$_2$OH), 35.4 (C_c), 32.4 (C_d), 31.3 (CHCH$_3$), 16.6 (CH$_3$); LRMS (ESI, m/z) 113.5 ([M + H]$^+$, 100); IR ν_{max} (film) 3436, 2969, 2355, 2316, 1448, 1329, 1046 cm^{-1}. The data presented are consistent with literature precedent.[45]

Synthesis of Benzimidazoles. *General Procedure C for the Synthesis of Benzimidazoles.* The procedure was a modification of the literature procedure from Jiao et al.[26]

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 one O_2 balloon and stirred at room temperature (30 °C) for 12 h. Molecular sieves were filtered over filter paper, and the filtrate was concentrated under vacuum before being purified via flash chromatography with appropriate eluent combinations to afford the final benzimidazole derivatives.

*2-(1,2,3,4-Tetrahydronaphthalen-2-yl)-1H-benzimidazole (**5a**).* General procedure C was followed using 5′-methoxy-5′-methyl-3,4-dihydro-1*H*,5′*H*-spiro[naphthalene-2,2′-[1,3,4]oxadiazole] (46 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 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%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.06 (br s, 1H, NH), 7.76 (br s, 1H, H_{Ar}), 7.40 (br s, 1H, H_{Ar}), 7.24 (d, J = 5.5 Hz, 2H, H_{Ar}), 7.29−7.13 (m, 4H, H_{Ar}), 3.41 (tdd, J = 10.3, 5.5, 3.1 Hz, 1H, CCH), 3.35−3.20 (m, 2H, ArCH_2CH), 2.97 (qp, J = 10.3, 5.5 Hz, 2H, ArCH_2CH$_2$), 2.48−2.37 (m, 1H, CHCH_a′), 2.14 (dtd, J = 13.0, 10.3, 6.2 Hz, 1H, CHCH_c′); ^{13}C{^{1}H} NMR (151 MHz, methanol-d_4) δ 159.8 (C_{Ar}), 136.8 (C_{Ar}), 136.1 (C_{Ar}), 130.0 (C_{Ar}H), 129.9 (C_{Ar}H), 127.1 (C_{Ar}H), 126.9 (C_{Ar}H), 123.3 (C_{Ar}H), 115.4 (br, C_{Ar}H), 36.7 (CCH), 35.4 (ArCH$_2$CH), 30.0 (ArCH$_2$CH$_2$), 29.6 (C_a); One aromatic carbon is not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{17}H_{17}N_2^+$ [M + H]$^+$ 249.1387, found 249.1392; IR ν_{max} (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[4.5]dec-1-ene (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 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 transparent oil (31 mg, 76%): ^{1}H NMR (600 MHz, methanol-d_4) δ 7.51 (dd, J = 6.1, 3.2 Hz, 2H, H_{Ar}), 7.19 (dd, J = 6.1, 3.2 Hz, 2H, H_{Ar}), 4.06 (dt, J = 11.5, 3.3 Hz, 2H, OCH_c + OCH_d), 3.65−3.53 (m, 2H, OCH_c′ + OCH_d′), 3.24−3.15 (m, 1H, CCH), 2.04−1.92 (m, 4H, CH_a + OCH_b); ^{13}C{H} NMR (151 MHz, Methanol-d_4) δ 159.0 (C_{Ar}), 123.3 (C_{Ar}H), 115.2 (br, C_{Ar}H), 68.6 (C_c + C_d), 36.8 (CCH), 32.4 (C_a + C_b); one aromatic carbon is not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{12}H_{15}N_2O^+$ [M + H]$^+$ 203.1181, found 203.1184; IR ν_{max} (film) 2958, 2922, 2852, 1457, 1427, 1128, 739 cm^{-1}. Mp: 225−227 °C.

*2-(Tetrahydro-2H-thiopyran-4-yl)-1H-benzimidazole (**5c**).* General procedure C was followed using 3-methoxy-3-methyl-4-oxa-8-thia-1,2-diazaspiro[4.5]dec-1-ene (40 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (24 mg, 55%): ^{1}H NMR (600 MHz, methanol-d_4) δ 7.51 (br s, 2H, H_{Ar}), 7.20 (dd, J = 6.1, 3.1 Hz, 2H, H_{Ar}), 4.59 (s, 1H, NH), 3.00 (ddd, J = 12.0, 8.7, 3.3 Hz, 1H, CCH), 2.92−2.85 (m, 2H, SCH_c + SCH_d), 2.73 (d, J = 14.0 Hz, 2H, SCH_c′ + SCH_b′), 2.37 (dd, J = 13.6, 3.1 Hz, 2H, CH_a + CH_b), 2.06 (qd, J = 12.5, 3.2 Hz, 2H, CH_a + CH_b); ^{13}C{^{1}H} NMR (151 MHz, methanol-d_4) δ 159.7 (C_{Ar}), 123.3 (br, C_{Ar}H), 39.5 (CCH), 33.8 (C_a + C_b), 29.2 (C_c + C_d); two aromatic carbons are not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{12}H_{15}N_2S^+$ [M + H]$^+$ 219.0956, found 219.0955; IR ν_{max} (film) 3394, 2924, 1709, 1432, 1274, 1047, 951, 744 cm^{-1}; mp 220−222 °C.

*2-(Tetrahydrothiophene-3-yl)-1H-benzimidazole (**5d**).* General procedure C was followed using 3-methoxy-3-methyl-4-oxa-7-thia-1,2-diazaspiro[4.4]non-1-ene (38 mg, 0.2 mmol, 1.0 equiv), form-

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aldehyde (0.15 mL, 37 wt % in H_2O, 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 (29 mg, 72%): ^{1}H NMR (600 MHz, methanol-d_4) δ 7.55−7.38 (m, 2H, H_{Ar}), 7.21−7.13 (m, 2H, H_{Ar}), 3.60 (ddd, J = 15.8, 9.7, 6.3 Hz, 1H, CC*H*), 3.23 (dd, J = 10.4, 6.9 Hz, 1H, CCHCH_a), 3.14 (dd, J = 10.4, 9.3 Hz, 1H, CCHCH_a′), 2.98 (dd, J = 8.4, 5.0 Hz, 2H, SCH_2CH$_2$), 2.52 (dt, J = 10.4, 5.1 Hz, 1H, CCHCH_b), 2.36−2.26 (m, 1H, CCHCH_b′); ^{13}C{^{1}H} NMR (151 MHz, methanol-d_4) δ 156.4 (C_{Ar}), 123.4 (C_{Ar}H), 115.4 (br, C_{Ar}H), 45.0 (CCH), 37.0 (C_b), 36.0 (C_a), 31.2 (SCH$_2$CH$_2$); one aromatic carbon is not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{11}H_{13}N_2S^+$ [M + H]$^+$ 205.0805, found 205.0799; IR ν_{max} (film) 2923, 2356, 2348, 2158, 2034, 1420, 740 cm^{-1}; mp 242−244 °C.

*2-(1,4-Dioxaspiro[4.5]decan-8-yl)-1H-benzimidazole (**5e**).* General procedure C was followed using 3-methoxy-3-methyl-4,9,12-trioxa-1,2-diazadispiro[4.2.4^8.2^5]tetradec-1-ene (51 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 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 (41 mg, 80%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.51 (m, 2H, H_{Ar}), 7.20 (dd, J = 6.1, 3.1 Hz, 2H, H_{Ar}), 4.01−3.90 (m, 4H, OCH_2CH_2O), 3.02 (tt, J = 11.8, 3.7 Hz, 1H, CC*H*), 2.21−2.13 (m, 2H, CHCH_a + CHCH_b), 2.07−1.97 (m, 2H, CHCH_a′ + CHCH_b′), 1.90−1.83 (m, 2H, CCH_c + CCH_d), 1.68 (td, J = 13.2, 4.3 Hz, 2H, CCH_c′ + CCH_d′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.9 (C_{Ar}), 122.4 (C_{Ar}H), 114.8 (br, C_{Ar}H), 108.1 (OCO), 64.5 (C_e), 64.4 (C_f), 37.3 (CCH), 34.4 (C_c + C_d), 29.2 (C_a + C_b); one aromatic carbon is not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2^+$ [M + H]$^+$ 259.1457, found 259.1447; IR ν_{max} (film) 2988, 2945, 1678, 1588, 1402, 1344, 1249, 1219, 1089, 1013, 967, 838, 735 cm^{-1}; mp 230−232 °C.

*tert-Butyl 4-(1H-Benzimidazol-2-yl)piperidine-1-carboxylate (**5f**).* General procedure C was followed using *tert*-butyl 3-methoxy-3-methyl-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene-8-carboxylate (57 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (30 mg, 49%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.02 (br s, 1H, N*H*), 7.71 (br s, 1H, H_{Ar}), 7.41 (br s, 1H, H_{Ar}), 7.22 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 4.23 (br s, 2H, NCH_c + NCH_d), 3.10 (tt, J = 11.8, 3.8 Hz, 1H, CC*H*), 2.89 (br s, 2H, NCH_c′ + NCH_d′), 2.13−2.04 (m, 2H, CH_a + CH_b), 1.85 (qd, J = 12.2, 4.3 Hz, 2H, CH_a′ + CH_b′), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.0 (C_{Ar}), 154.9 (NCOOC(CH_3)$_3$), 143.2 (br, C_{Ar}), 122.5 (br, C_{Ar}H), 119.1 (br, C_{Ar}H), 110.7 (br, C_{Ar}H), 80.0 (C(CH$_3$)$_3$), 44.1 (br, C_c + C_d), 37.1 (CCH), 30.9 (br, C_a + C_b), 28.6 (C(CH_3)$_3$); HRMS (ESI) calcd for $C_{17}H_{24}O_2N_3^+$ [M + H]$^+$ 302.1869, found 302.1869; IR ν_{max} (film) 2976, 1692, 1536, 1425, 1366, 1272, 1231, 1166, 1123, 980, 861, 768, 742 cm^{-1}; mp 226−228 °C.

*2-[1-(Pyrimidin-2-yl)piperidin-4-yl]-1H-benzimidazole (**5g**).* General procedure C was followed using 3-methoxy-3-methyl-8-(pyrimidin-2-yl)-4-oxa-1,2,8-triazaspiro[4.5]dec-1-ene (55 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (40 mg, 72%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.75 (br s, 1H, N*H*), 8.30 (d, J = 4.6 Hz, 2H, $H_{pyrimidine}$), 7.54 (br s, 2H, H_{Ar}), 7.22 (dd, J = 5.9, 3.1 Hz, 2H, H_{Ar}), 6.47 (t, J = 4.6 Hz, 1H, $H_{pyrimidine}$), 4.86 (d, J = 13.5 Hz, 2H, NCH_c + NCH_d), 3.22 (tt, J = 11.8, 3.7 Hz, 1H, CC*H*), 3.10−2.99 (m, 2H, NCH_c′ + NCH_d′), 2.19 (d, J = 11.3 Hz, 2H, CH_a + CH_b), 1.92 (qd, J = 12.4, 3.9 Hz, 2H, CH_a′ + CH_b′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.7 ($C_{pyrimidine}$), 157.9 ($C_{pyrimidine}$H), 157.2 (C_{Ar}), 122.6 (br, C_{Ar}H), 110.0 ($C_{pyrimidine}$H), 43.9 (C_c + C_d), 37.3 (CCH), 30.7 (C_a + C_b); two aromatic carbons are not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{16}H_{18}N_5^+$ [M + H]$^+$ 280.1557, found 280.1546; IR ν_{max} (film) 2936, 2346, 1982, 1584, 1541, 1518, 1481, 1456, 1426, 1358, 1304, 1272, 1233, 1105, 1050, 977, 798, 741 cm^{-1}; mp 222−224 °C.

*2-(Adamantan-2-yl)-1H-benzimidazole (**5h**).* General procedure C was followed using 5′-methoxy-5′-methyl-5′*H*-spiro[adamantane-2,2′-[1,3,4]oxadiazole] (47 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 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 dark yellow solid (40 mg, 79%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (br s, 2H, H_{Ar}), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 3.27 (s, 1H, CC*H*), 2.66−2.59 (m, 2H, CH_a), 2.08−1.94 (m, 7H, CH_c + CH_b), 1.87−1.86 (m, 1H, CH_c′), 1.83 (br s, 2H, C$_d$), 1.77−1.70 (m, 2H, C$_b$); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.2 (C_{Ar}), 122.3 (C_{Ar}H), 44.6 (CCH), 38.4 (C_b), 37.6 (C_d), 33.1 (C_b′), 31.0 (C_a), 27.8 (C_c), 27.7 (C_c′); two aromatic carbons are not seen in the ^{13}C{^{1}H} NMR spectrum due to peak broadening; HRMS (ESI) calcd for $C_{17}H_{21}N_2^+$ [M + H]$^+$ 253.1705, found 253.1700; IR ν_{max} (film) 2922, 1422, 1275, 1009, 993, 743 cm^{-1}; mp 244−246 °C.

*2-Cyclobutyl-1H-benzimidazole (**5i**).* General procedure C was followed using 7-methoxy-7-methyl-8-oxa-5,6-diazaspiro[3.4]oct-5-ene (31 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (20 mg, 59%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, J = 6.0, 3.2 Hz, 2H, H_{Ar}), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 3.80 (p, J = 8.7 Hz, 1H, CC*H*), 2.58−2.47 (m, 2H, CH_a + CH_b), 2.47−2.38 (m, 2H, CH_a′ + CH_b′), 2.14−2.01 (m, 1H, CH_c), 1.99−1.91 (m, 1H, CH_c′); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.1 (C_{Ar}), 138.6 (br, C_{Ar}), 122.3 (C_{Ar}H), 114.8 (br, C_{Ar}H), 34.3 (CCH), 28.2 (C_a + C_b), 18.8 (C_c); HRMS (ESI) calcd for $C_{11}H_{13}N_2^+$ [M + H]$^+$ 173.1073, found 173.1069; IR ν_{max} (film) 2942, 1537, 1455, 1419, 1328, 1272, 982, 740 cm^{-1}; mp 186−188 °C. The data presented are consistent with literature precedent.[46]

*2-[1-(Pyridin-4-yl)propan-2-yl]-1H-benzimidazole (**5l**).* General procedure C was followed using 2-methoxy-2,5-dimethyl-5-(pyridin-4-ylmethyl)-2,5-dihydro-1,3,4-oxadiazole (44 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−100% EtOAc in petroleum ether) to give the titled product as a yellow solid (23 mg, 48%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.14 (br s, 1H, N*H*), 8.40−8.36 (m, 2H, $H_{Pyridine}$), 7.73 (br s, 1H, H_{Ar}), 7.34 (br s, 1H, H_{Ar}), 7.23 (s, 2H, H_{Ar}), 7.00−6.98 (m, 2H, $H_{Pyridine}$), 3.35 (p, J = 7.0 Hz, 1H, CC*H*), 3.28 (dd, J = 13.4, 7.5 Hz, 1H, CHCH_a), 3.00 (dd, J = 13.4, 6.8 Hz, 1H, CHCH_a′), 1.47 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.3 (C_{Ar}), 149.5 ($C_{Pyridine}$H), 148.8 ($C_{Pyridine}$), 143.1 (br, C_{Ar}), 124.5 ($C_{Pyridine}$H), 122.3 (br, C_{Ar}H), 110.5 (br, C_{Ar}H), 41.8 (C_a), 35.9 (CCH), 19.4 (CH$_3$). HRMS (ESI) calcd for $C_{15}H_{16}N_3^+$ [M + H]$^+$ 238.1344, found 238.1344; IR ν_{max} (film) 3051, 2969, 1603, 1559, 1535, 1484, 1454, 1419, 1328, 1272, 1219, 1110, 1070, 1043, 993, 907, 843, 795, 768, 747 cm^{-1}; mp 188−190 °C.

*2-[1-(Furan-2-yl)propan-2-yl]-1H-benzimidazole (**5m**).* General procedure C was followed using 2-(furan-2-ylmethyl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (42 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.15 mL, 37 wt % in H_2O, 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 (34 mg, 75%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (dd, J = 6.1, 3.2 Hz, 2H, H_{Ar}), 7.30−7.27 (m, 1H, H_{Furan}), 7.23−7.18 (m, 2H, H_{Ar}), 6.24 (dd, J = 3.2, 1.9 Hz, 1H, H_{Furan}), 5.96 (d, J = 3.2 Hz, 1H, H_{Furan}), 3.51 (h, J = 7.1 Hz, 1H, CC*H*), 3.24 (dd, J = 15.0, 7.2 Hz, 1H, CHCH_a), 3.06 (dd, J = 15.0, 7.2 Hz, 1H, CHCH_a′), 1.48 (d, J = 7.0 Hz, 3H, CHCH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.1

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(C_{Furan}), 153.3 (C_{Ar}), 141.5 ($C_{Furan}H$), 122.4 ($C_{Ar}H$), 115.1 (br, $C_{Ar}H$), 110.5 ($C_{Furan}H$), 107.1($C_{Furan}H$), 34.6 (C_a), 34.1 (CCH), 19.3 (CH_3); one aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum; HRMS (ESI+): m/z calcd for $C_{14}H_{15}N_2O^+$ $[M + H]^+$ 227.1177, found 227.1184; IR ν_{max} (film) 2921, 1423, 1275, 1009, 993, 932, 743 cm^{-1}; mp 180−182 °C.

*2-(Hex-5-en-2-yl)-1H-benzimidazole (**5n**).* General procedure C was followed using 2-(but-3-en-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (37 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (29 mg, 73%). ^1H NMR (600 MHz, $CDCl_3$) δ 10.18 (br s, 1H, N*H*), 7.55 (br s, 2H, H_{Ar}), 7.21 (dd, J = 6.0, 3.1 Hz, 2H, H_{Ar}), 5.75 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H, CH_2=C*H*), 4.97 (dd, J = 17.0, 1.8 Hz, 1H, H_a), 4.93 (dd, J = 10.2, 1.8 Hz, 1H, H_b), 3.14 (h, J = 7.0 Hz, 1H, CC*H*), 2.14−2.05 (m, 2H, CH_2=CHCH_2), 2.04−1.97 (m, 1H, CCHCH_c), 1.85−1.77 (m, 1H, CCHCH_c′), 1.45 (d, J = 7.1 Hz, 3H, CH_3); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.3 (C_{Ar}), 137.9 (CH_2=CH), 122.3 ($C_{Ar}H$), 115.3 (CH_2=CH), 35.6 (C_c), 34.2 (CCH), 31.6 (CH_2=CHCH_2), 19.8 (CH_3); two aromatic carbons are not seen in the $^{13}C\{^1H\}$ NMR spectrum; HRMS (ESI) calcd for $C_{13}H_{17}N_2^+$ $[M + H]^+$ 201.1386, found 201.1379; IR ν_{max} (film) 3074, 2968, 2932, 2736, 1818, 1640, 1538, 1454, 1426, 1330, 1272, 989, 906, 745, 729 cm^{-1}; mp 182−185 °C.

*2-(4,4-Dimethylhept-6-yn-2-yl)-1H-benzimidazole (**5o**).* General procedure C was followed using 2-(2,2-dimethylpent-4-yn-1-yl)-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (45 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (19 mg, 39%): ^1H NMR (600 MHz, $CDCl_3$) δ 9.68 (br s, 1H, N*H*), 7.71 (br s, 1H, H_{Ar}), 7.38 (br s, 1H, H_{Ar}), 7.21 (dd, J = 6.2, 2.9 Hz, 2H, H_{Ar}), 3.29−3.21 (m, 1H, CC*H*CH_3), 2.12 (dd, J = 14.4, 8.9 Hz, 1H, CHCCH_b), 2.07 (dd, J = 16.2, 3.2 Hz, 1H, CHCCH_a), 2.02−1.93 (m, 2H, C*H*CCH_2 + CHCCH_a′), 1.72 (dd, J = 14.4, 4.0 Hz, 1H, CHCCH_b′), 1.44 (d, J = 7.1 Hz, 3H, CHCH_3), 0.92 (d, J = 17.9 Hz, 6H, C(CH_3)$_2$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.7 (C_{Ar}), 122.3 (br, $C_{Ar}H$), 110.7 (br, $C_{Ar}H$), 82.6 (CHCCH$_2$), 70.5 (CHCCH$_2$), 47.1 (C_b), 34.0 (C(CH$_3$)$_2$), 31.9 (C_a), 31.2 (CCHCH$_3$), 27.3 (C(CH_3)$_2$), 27.1 (C(CH_3)$_2$), 23.3 (CCHCH_3); one aromatic carbon is not seen in the $^{13}C\{^1H\}$ NMR spectrum; HRMS (ESI) calcd for $C_{16}H_{21}N_2^+$ $[M + H]^+$ 241.1699, found 241.1690; IR ν_{max} (film) 3311, 2965, 2752, 2367, 1538, 1453, 1424, 1335, 1269, 994, 746 cm^{-1}; mp 191−192 °C.

*2-(1-Cyclopropylethyl)-1H-benzimidazole (**5p**).* General procedure C was followed using 2-cyclopropyl-5-methoxy-2,5-dimethyl-2,5-dihydro-1,3,4-oxadiazole (34 mg, 0.2 mmol, 1.0 equiv), formaldehyde (0.16 mL, 37 wt % in H_2O, 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 (10−40% EtOAc in petroleum ether) to give the titled product as a white solid (26 mg, 69%): ^1H NMR (600 MHz, $CDCl_3$) δ 9.49 (br s, 1H, N*H*), 7.73 (br s, 1H, H_{Ar}), 7.41 (br s, 1H, H_{Ar}), 7.22 (dd, J = 6.1, 3.1 Hz, 2H, H_{Ar}), 2.36 (dq, J = 9.6, 7.0 Hz, 1H, CC*H*), 1.56 (d, J = 7.0 Hz, 3H, CH_3), 1.10 (dddd, J = 13.0, 9.6, 8.0, 4.9 Hz, 1H, CHC*H*CH$_2$), 0.71−0.63 (m, 2H, CH_a + CH_a′), 0.44−0.38 (m, 1H, CH_b), 0.36−0.30 (m, 1H, CH_b′); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 158.7 (C_{Ar}), 143.4 (br, C_{Ar}), 133.5 (br, C_{Ar}), 122.3 ($C_{Ar}H$), 119.4 (br, $C_{Ar}H$), 110.4 (br, $C_{Ar}H$), 39.5 (CCH), 19.0 (CH_3), 16.6 (CCHCH), 4.8 (C_a), 4.4 (C_b); HRMS (ESI) calcd for $C_{12}H_{15}N_2^+$ $[M + H]^+$ 187.1230, found 187.1221; IR ν_{max} (film) 2969, 2317, 2135, 1456, 1414, 1274, 1076, 744 cm^{-1}; mp 187−189 °C.

Synthesis of Aldehydes from Aryl Hydrazones. *General Procedure D for the Synthesis of Aldehydes from Aryl Hydrazones.* **Conditioning phase**: A solution of triethylamine in MeOH (5 mL, 20% v/v) was passed through the column reactor (Omnifit column, 6.6 mm i.d. × 50 mm length), packed with activated MnO_2 (1.0 g), at a flow rate of 1.0 mL/min for 5 min (phase 1), and the reactor output was monitored using a Flow-IR device. The flow was switched to EtOAc for 10 min (phase 2). The column was then ready for the generation of the diazo compound.

Generation phase: A solution of hydrazone (2 mmol, 0.1 M) in EtOAc (20 mL) was passed through a conditioned column reactor (Omnifit column, 6.6 mm i.d. × 50 mm length) (phase 3) at a flow rate of 1.0 mL/min. When the Mettler Toledo FlowIR instrument (SiComp head) showed that the intensity of the diazo peak (region 2060−2080 cm^{-1}) was stable, 4 mL of the stream of diazo was combined with 4 mL of aqueous formaldehyde (37 wt %, 1.0 mL/min) in a UQ5102 Uniqsis Glass Static Mixer at room temperature. The output stream was extracted with extra EtOAc (20 mL × 2) and washed with water (20 mL). The combined organic phase was dried over $MgSO_4$, concentrated under vacuum, and purified over silica gel using appropriate eluent combinations to yield the desired aldehyde.

*2-(4-Chlorophenyl)acetaldehyde (**7a**).* General procedure D was followed using (4-chlorobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt % in H_2O, 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 (33 mg, 53%): ^1H NMR (600 MHz, $CDCl_3$) δ 9.74 (t, J = 2.1 Hz, 1H, *H*CO), 7.34 (d, J = 8.4 Hz, 2H, H_{Ar}), 7.15 (d, J = 8.3 Hz, 2H, H_{Ar}), 3.68 (d, J = 2.1 Hz, 2H, CH_2); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 198.8 (HCO), 133.6 (C_{Ar}), 131.1 ($C_{Ar}H$), 130.4 (C_{Ar}), 129.3 ($C_{Ar}H$), 49.9 (CH_2); LRMS (ESI, m/z) 155.3 ($[^{35}M + H]^+$, 100). The data presented are consistent with literature precedent.[47]

*2-(3-Bromophenyl)acetaldehyde (**7b**).* General procedure D was followed using (3-bromobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt % in H_2O, 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, $CDCl_3$) δ 9.75 (t, J = 2.1 Hz, 1H, *H*CO), 7.45 (d, J = 8.0 Hz, 1H, H_{Ar}), 7.39 (t, J = 1.8 Hz, 1H, H_{Ar}), 7.24 (t, J = 7.9 Hz, 1H, H_{Ar}), 7.15 (d, J = 7.6 Hz, 1H, H_{Ar}), 3.68 (d, J = 2.2 Hz, 2H, CH_2); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 198.5 (HCO), 134.2 (C_{Ar}), 132.8 ($C_{Ar}H$), 130.8 ($C_{Ar}H$), 130.6 ($C_{Ar}H$), 128.4 ($C_{Ar}H$), 123.1 (C_{Ar}), 50.1 (CH_2); LRMS (ESI, m/z) 199.1 ($[^{79}M + H]^+$, 100); IR ν_{max} (film) 2827, 1723, 1568, 1474, 1427, 1072, 782, 692 cm^{-1}. The data presented are consistent with literature precedent.[46]

*2-(o-Tolyl)acetaldehyde (**7c**).* General procedure D was followed using (2-methylbenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min) and formaldehyde (37 wt % in H_2O, 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 (31 mg, 57%): ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (t, J = 2.3 Hz, 1H, *H*CO), 7.24−7.20 (m, 3H, H_{Ar}), 7.19−7.15 (m, 1H, H_{Ar}), 3.71 (d, J = 2.3 Hz, 2H, CH_2), 2.28 (s, 3H, CH_3); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 199.4 (HCO), 143.3 (C_{Ar}), 137.3 (C_{Ar}), 130.8 ($C_{Ar}H$), 130.7 ($C_{Ar}H$), 127.9 ($C_{Ar}H$), 126.6 ($C_{Ar}H$), 48.9 (CH_2), 19.9 (CH_3); LRMS (ESI, m/z) 135.3 ($[M + H]^+$, 100); IR ν_{max} (film) 2827, 1723, 1568, 1474, 1427, 1072, 782, 692 cm^{-1}. The data presented are consistent with literature precedent.[48]

Synthesis of Alcohols from Aryl Hydrazones. *General Procedure E for the Synthesis of Alcohols from Aryl Hydrazones.* 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 and redissolved in EtOH (8 mL). $NaBH_4$ (10 equiv) was added portionwise, and the reaction mixture was stirred for a further 1 h. The resulting mixture was then quenched with ice−water, extracted with ethyl acetae (2 × 20 mL), and washed with brine (2 × 20 mL). The organic phase was combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining residue was purified via flash column chromatography with appropriate eluents to give the desired alcohol.

*2-(4-Chlorophenyl)ethan-1-ol (**8a**).* General procedure E was followed using (4-chlorobenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt % in H_2O, 1.0 mL/min), and $NaBH_4$ (152 mg, 10.0 equiv). The crude mixture was purified via flash

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column chromatography (0−20% EtOAc in petroleum ether) to give the titled product as a colorless liquid (36 mg, 57%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 1H, H_{Ar}), 7.17 (d, J = 8.4 Hz, 1H, H_{Ar}), 3.85 (t, J = 6.6 Hz, 1H, $HOCH_2$), 2.84 (t, J = 6.5 Hz, 1H, $ArCH_2$), 1.39 (br s, 1H, HO); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 137.2 (C_{Ar}), 132.5 (C_{Ar}), 130.5 ($C_{Ar}H$), 128.8 ($C_{Ar}H$), 63.6 ($HOCH_2$), 38.6 ($ArCH_2$); LRMS (ESI, m/z) 157.1 ([^{35}M + H]$^+$, 100); IR ν_{max} (film) 3335, 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 H_2O, 1.0 mL/min), and $NaBH_4$ (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%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.29 (m, 2H, H_{Ar}), 7.22−7.06 (m, 2H, H_{Ar}), 3.85 (t, J = 6.5 Hz, 2H, $HOCH_2$), 2.83 (t, J = 6.5 Hz, 2H, $ArCH_2$), 1.56 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.1 (C_{Ar}), 132.2 ($C_{Ar}H$), 130.2 ($C_{Ar}H$), 129.7 ($C_{Ar}H$), 127.8 ($C_{Ar}H$), 122.7 (C_{Ar}), 63.4 ($HOCH_2$), 38.9 ($ArCH_2$); LRMS (ESI, m/z) 201.0 ([^{79}M + H]$^+$, 100); IR ν_{max} (film) 3333, 2945, 1595, 1567, 1473, 1425, 1200, 1071, 1044, 997, 853, 806, 777, 692, 570 cm^{-1}. The data presented are consistent with literature precedent.[50]

*2-(o-Tolyl)ethan-1-ol (**8c**).* General procedure E was followed using (2-methylbenzylidene)hydrazine (0.1 M in EtOAc, 1.0 mL/min), formaldehyde (37 wt % in H_2O, 1.0 mL/min), and $NaBH_4$ (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 (36 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.02 (m, 4H, H_{Ar}), 3.84 (t, J = 6.9 Hz, 2H, $HOCH_2$), 2.90 (t, J = 6.9 Hz, 2H, $ArCH_2$), 2.35 (s, 3H, CH_3); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.7 (C_{Ar}), 136.6 (C_{Ar}), 130.6 ($C_{Ar}H$), 129.8 ($C_{Ar}H$), 126.7 ($C_{Ar}H$), 126.2 ($C_{Ar}H$), 62.8 ($HOCH_2$), 36.5 ($ArCH_2$), 19.6 (CH_3); LRMS (ESI, m/z) 137.3 ([M + H]$^+$, 100); IR ν_{max} (film) 3328, 3017, 2944, 2874, 1604, 1492, 1455, 1379, 1167, 1112, 1040, 938, 853, 741, 612 cm^{-1}. The data presented are consistent with literature precedent.[51]

■ ASSOCIATED CONTENT

Supporting Information

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NMR spectra (PDF)

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■ REFERENCES

(1) Buchner, E.; Curtius, T. Ueber die Einwirkung von Diazoessigäther auf aromatische Kohlenwasserstoffe. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2377.

(2) Candeias, N. R.; Paterna, R.; Gois, P. M. P. Homologation Reaction of Ketones with Diazo Compounds. *Chem. Rev.* **2016**, *116*, 2937.

(3) Guttenberger, N.; Breinbauer, R. CH and CC bond insertion reactions of diazo compounds into aldehydes. *Tetrahedron* **2017**, *73*, 6815.

(4) Mock, W. L.; Hartman, M. E. Synthetic scope of the triethyloxonium ion catalyzed homologation of ketones with diazoacetic esters. *J. Org. Chem.* **1977**, *42*, 459.

(5) Allwood, D. M.; Blakemore, D. C.; Ley, S. V. Preparation of Unsymmetrical Ketones from Tosylhydrazones and Aromatic Aldehydes via Formyl C−H Bond Insertion. *Org. Lett.* **2014**, *16*, 3064.

(6) Moebius, D. C.; Kingsbury, J. S. Catalytic Homologation of Cycloalkanones with Substituted Diazomethanes. Mild and Efficient Single-Step Access to α-Tertiary and α-Quaternary Carbonyl Compounds. *J. Am. Chem. Soc.* **2009**, *131*, 878.

(7) Hock, K. J.; Koenigs, R. M. The Generation of Diazo Compounds in Continuous-Flow. *Chem. - Eur. J.* **2018**, *24*, 10571.

(8) Rulliere, P.; Benoit, G.; Allouche, E. M. D.; Charette, A. B. Safe and Facile Access to Nonstabilized Diazoalkanes Using Continuous Flow Technology. *Angew. Chem., Int. Ed.* **2018**, *57*, 5777.

(9) Mastronardi, F.; Gutmann, B.; Kappe, C. O. Continuous Flow Generation and Reactions of Anhydrous Diazomethane Using a Teflon AF-2400 Tube-in-Tube Reactor. *Org. Lett.* **2013**, *15*, 5590.

(10) Rossi, E.; Woehl, P.; Maggini, M. Scalable in Situ Diazomethane Generation in Continuous-Flow Reactors. *Org. Process Res. Dev.* **2012**, *16*, 1146.

(11) Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming hazardous chemistry by continuous flow technology. *Chem. Soc. Rev.* **2016**, *45*, 4892.

(12) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-Flow Technology—A Tool for the Safe Manufacturing of Active Pharmaceutical Ingredients. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688.

(13) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The Hitchhiker's Guide to Flow Chemistry. *Chem. Rev.* **2017**, *117*, 11796.

(14) Müller, S. T. R.; Wirth, T. Diazo Compounds in Continuous-Flow Technology. *ChemSusChem* **2015**, *8*, 245.

(15) Deadman, B. J.; Collins, S. G.; Maguire, A. R. Taming Hazardous Chemistry in Flow: The Continuous Processing of Diazo and Diazonium Compounds. *Chem. - Eur. J.* **2015**, *21*, 2298.

(16) Kockmann, N.; Thenee, P.; Fleischer-Trebes, C.; Laudadio, G.; Noel, T. Safety assessment in development and operation of modular continuous-flow processes. *React. Chem. Eng.* **2017**, *2*, 258.

(17) Pezacki, J. P.; Wagner, B. D.; Lew, C. S. Q.; Warkentin, J.; Lusztyk, J. Δ3−1,3,4-Oxadiazolines: Photochemical Precursors to Diazoalkanes and sec-Alkanediazonium Ions in Acidic Solution1. *J. Am. Chem. Soc.* **1997**, *119*, 1789.

DOI: 10.1021/acs.joc.8b02721
J. Org. Chem. XXXX, XXX, XXX−XXX

(18) Majchrzak, M. W.; Bekhazi, M.; Tse-Sheepy, I.; Warkentin, J. Photolysis of 2-alkoxy-.DELTA.3−1,3,4-oxadiazolines. A new route to diazoalkanes. *J. Org. Chem.* **1989**, *54*, 1842.
(19) Greb, A.; Poh, J.-S.; Greed, S.; Battilocchio, C.; Pasau, P.; Blakemore, D. C.; Ley, S. V. A Versatile Route to Unstable Diazo Compounds via Oxadiazolines and their Use in Aryl−Alkyl Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2017**, *56*, 16602.
(20) Dingwall, P.; Greb, A.; Crespin, L. N. S.; Labes, R.; Musio, B.; Poh, J.-S.; Pasau, P.; Blakemore, D. C.; Ley, S. V. C−H functionalisation of aldehydes using light generated, non-stabilised diazo compounds in flow. *Chem. Commun.* **2018**, *54*, 11685.
(21) Wommack, A. J.; Kingsbury, J. S. Synthesis of Acyclic Ketones by Catalytic, Bidirectional Homologation of Formaldehyde with Nonstabilized Diazoalkanes. Application of a Chiral Diazomethyl-(pyrrolidine) in Total Syntheses of Erythroxylon Alkaloids. *J. Org. Chem.* **2013**, *78*, 10573.
(22) Wang, C.; Liu, S.; Xing, D.; Wang, X.; Wu, X.; Hu, W. Efficient synthesis of α-aryl serine derivatives via three-component reactions of aryldiazoacetates, anilines and formaldehyde. *Tetrahedron* **2013**, *69*, 11203.
(23) Hamilton, J. Y.; Morandi, B.; Carreira, E. M. Homologative Trifluoromethylation of Acetals. *Synthesis* **2013**, *45*, 1857.
(24) Gilman, H.; Catlin, W. E. *Org. Synth.* **1926**, *6*, 22.
(25) Further experimentation using in-line IR monitoring allowed us to quantify that the formation of the diazo compound was insensitive to both water content and dissolved oxygen.
(26) Zhang, C.; Zhang, L.; Jiao, N. Catalyst free approach to benzimidazoles using air as the oxidant at room temperature. *Green Chem.* **2012**, *14*, 3273.
(27) Tran, D. N.; Battilocchio, C.; Lou, S.-B.; Hawkins, J. M.; Ley, S. V. Flow chemistry as a discovery tool to access sp2−sp3 cross-coupling reactions via diazo compounds. *Chemical Science* **2015**, *6*, 1120.
(28) Roda, N. M.; Tran, D. N.; Battilocchio, C.; Labes, R.; Ingham, R. J.; Hawkins, J. M.; Ley, S. V. Cyclopropanation using flow-generated diazo compounds. *Org. Biomol. Chem.* **2015**, *13*, 2550.
(29) Shi, Z.-C.; Devasagayaraj, A.; Gu, K.; Jin, H.; Marinelli, B.; Samala, L.; Scott, S.; Stouch, T.; Tunoori, A.; Wang, Y.; Zang, Y.; Zhang, C.; Kimball, S. D.; Main, A. J.; Sun, W.; Yang, Q.; Nouraldeen, A.; Yu, X.-Q.; Buxton, E.; Patel, S.; Nguyen, N.; Swaffield, J.; Powell, D. R.; Wilson, A.; Liu, Q. Modulation of Peripheral Serotonin Levels by Novel Tryptophan Hydroxylase Inhibitors for the Potential Treatment of Functional Gastrointestinal Disorders. *J. Med. Chem.* **2008**, *51*, 3684.
(30) Kazem Shiroodi, R.; Dudnik, A. S.; Gevorgyan, V. Stereo-controlled 1,3-Phosphatyloxy and 1,3-Halogen Migration Relay toward Highly Functionalized 1,3-Dienes. *J. Am. Chem. Soc.* **2012**, *134*, 6928.
(31) Cabrera-Pardo, J. R.; Trowbridge, A.; Nappi, M.; Ozaki, K.; Gaunt, M. J. Selective Palladium(II)-Catalyzed Carbonylation of Methylene β-C−H Bonds in Aliphatic Amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 11958.
(32) Boehm, J., Charles; Busch-Petersen, J.; Fu, W.; Jin, Q.; Kerns, J. K.; Li, H.; Lin, G.; Lin, X.; Neipp, C. E. Indole Carboxamides as IKK2 Inhibitors. WO2008118724 (A1), 2008.
(33) Tseng, C.-C.; Noordali, H.; Sani, M.; Madhani, M.; Grant, D. M.; Frenneaux, M. P.; Zanda, M.; Greig, I. R. Development of Fluorinated Analogues of Perhexiline with Improved Pharmacokinetic Properties and Retained Efficacy. *J. Med. Chem.* **2017**, *60*, 2780.
(34) Vallone, A.; D'Alessandro, S.; Brogi, S.; Brindisi, M.; Chemi, G.; Alfano, G.; Lamponi, S.; Lee, S. G.; Jez, J. M.; Koolen, K. J. M.; Dechering, K. J.; Saponara, S.; Fusi, F.; Gorelli, B.; Taramelli, D.; Parapini, S.; Caldelari, R.; Campiani, G.; Gemma, S.; Butini, S. Antimalarial agents against both sexual and asexual parasites stages: structure-activity relationships and biological studies of the Malaria Box compound 1-[5-(4-bromo-2-chlorophenyl)furan-2-yl]-N-[(piperidin-4-yl)methyl]methanamine (MMV019918) and analogues. *Eur. J. Med. Chem.* **2018**, *150*, 698.
(35) Madder, A.; Sebastian, S.; Van Haver, D.; De Clercq, P. J.; Maskill, H. Mechanism of esterification of 1,3-dimethylamino alcohols by N-acetylimidazole in acetonitrile and the influence of alkyl and geminal dialkyl substitution upon the rate. *J. Chem. Soc., Perkin Trans. 2* **1997**, *2*, 2787.
(36) Jones, G. B.; Wright, J. M.; Plourde, G. W.; Hynd, G.; Huber, R. S.; Mathews, J. E. A Direct and Stereocontrolled Route to Conjugated Enediynes. *J. Am. Chem. Soc.* **2000**, *122*, 1937.
(37) Callahan, J. F.; Kerns, J. K.; Li, P.; Li, T.; McCleland, B. W.; Nie, H.; Pero, J. E.; Davies, T. G.; Grazia Carr, M.; Griffiths-Jones, C. M.; Heightman, T. D.; Norton, D.; Verdonk, M. L.; Woolford, A. J.-A.; Willems, H. M. G. Biaryl Pyrazoles as NRF2 Regulators. WO2017/60854, 2017.
(38) Della, E. W.; Graney, S. D. The Regiochemistry of Cyclization of α-Sulfenyl-, α-Sulfinyl-, and α-Sulfonyl-5-hexenyl Radicals: Procedures Leading to Regioselective Syntheses of Cyclic Sulfones and Sulfoxides. *J. Org. Chem.* **2004**, *69*, 3824.
(39) Kitbunnadaj, R.; Hoffmann, M.; Fratantoni, S. A.; Bongers, G.; Bakker, R. A.; Wieland, K.; Jilali, A. e.; De Esch, I. J. P.; Menge, W. M. P. B.; Timmerman, H.; Leurs, R. New high affinity H3 receptor agonists without a basic side chain. *Bioorg. Med. Chem.* **2005**, *13*, 6309.
(40) Renou, J.; Dias, J.; Mercey, G.; Verdelet, T.; Rousseau, C.; Gastellier, A.-J.; Arboléas, M.; Touvrey-Loiodice, M.; Baati, R.; Jean, L.; Nachon, F.; Renard, P.-Y. Synthesis and in vitro evaluation of donepezil-based reactivators and analogues for nerve agent-inhibited human acetylcholinesterase. *RSC Adv.* **2016**, *6*, 17929.
(41) Kawamoto, T.; Fukuyama, T.; Ryu, I. Radical Addition of Alkyl Halides to Formaldehyde in the Presence of Cyanoborohydride as a Radical Mediator. A New Protocol for Hydroxymethylation Reaction. *J. Am. Chem. Soc.* **2012**, *134*, 875.
(42) Jackson, W.; Moffat, M.; Perlmutter, P.; Tasdelen, E. The Stereochemistry of Organometallic Compounds. XXXVIII. Regio- and Stereo-control in the Rhodium-Catalyzed Hydroformylation of Some Alkenyl Phosphites. *Aust. J. Chem.* **1992**, *45*, 823.
(43) Nacsa, E. D.; MacMillan, D. W. C. Spin-Center Shift-Enabled Direct Enantioselective α-Benzylation of Aldehydes with Alcohols. *J. Am. Chem. Soc.* **2018**, *140*, 3322.
(44) Harmata, M.; Gamlath, C. B.; Barnes, C. L.; Jones, D. E. Intramolecular [4 + 3] Cycloadditions. Studies of Relative Asymmetric Induction. *J. Org. Chem.* **1995**, *60*, 5077.
(45) Peram, P. S.; Vences, M.; Schulz, S. A synthetic dodecanolide library for the identification of putative semiochemicals emitted by mantellid frogs. *Org. Biomol. Chem.* **2017**, *15*, 6967.
(46) Genovino, J.; Lian, Y.; Zhang, Y.; Hope, T. O.; Juneau, A.; Gagné, Y.; Ingle, G.; Frenette, M. Metal-Free-Visible Light C−H Alkylation of Heteroaromatics via Hypervalent Iodine-Promoted Decarboxylation. *Org. Lett.* **2018**, *20*, 3229.
(47) Nakaoka, S.; Murakami, Y.; Kataoka, Y.; Ura, Y. Maleimide-assisted anti-Markovnikov Wacker-type oxidation of vinylarenes using molecular oxygen as a terminal oxidant. *Chem. Commun.* **2016**, *52*, 335.
(48) Kavanagh, S. A.; Piccinini, A.; Fleming, E. M.; Connon, S. J. Urea derivatives are highly active catalysts for the base-mediated generation of terminal epoxides from aldehydes and trimethylsulfonium iodide. *Org. Biomol. Chem.* **2008**, *6*, 1339.
(49) Cui, X.; Li, Y.; Topf, C.; Junge, K.; Beller, M. Direct Ruthenium-Catalyzed Hydrogenation of Carboxylic Acids to Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 10596.
(50) Peng, D.; Zhang, M.; Huang, Z. A General, Practical Triethylborane-Catalyzed Reduction of Carbonyl Functions to Alcohols. *Chem. - Eur. J.* **2015**, *21*, 14737.
(51) Toyao, T.; Siddiki, S. M. A. H.; Touchy, A. S.; Onodera, W.; Kon, K.; Morita, Y.; Kamachi, T.; Yoshizawa, K.; Shimizu, K.-i. TiO2-Supported Re as a General and Chemoselective Heterogeneous Catalyst for Hydrogenation of Carboxylic Acids to Alcohols. *Chem. - Eur. J.* **2017**, *23*, 1001.

DOI: 10.1021/acs.joc.8b02721
J. Org. Chem. XXXX, XXX, XXX−XXX