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Convergent Synthesis of PI3K Inhibitor GDC-0908 Featuring Palladium-Catalyzed Direct C–H Arylation toward Dihydrobenzothienooxepines

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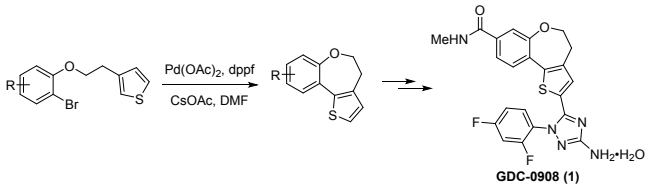


ABSTRACT: A practical convergent synthesis of PI3K inhibitor GDC-0908 (**1**) is described. The process features a dihydrobenzothienooxepine formation via palladium-catalyzed intramolecular direct C–H arylation and a Negishi coupling to construct the key C–C bonds. We further developed a general synthesis of dihydrobenzothienooxepines in good to excellent yields via palladium-catalyzed intramolecular direct C–H arylation, which tolerates both electronically and sterically diverse substituents on the phenyl ring.

INTRODUCTION

The phosphoinositide 3-kinase (PI3K) pathway, a crucial signal transduction system linking oncogenes and multiple receptor classes to many essential cellular functions, such as cell survival, proliferation and differentiation, is perhaps the most commonly activated signaling pathway in human cancer and thus one of the most attractive targets for cancer therapeutics.[1] GDC-0908 (**1**) is one of the therapeutic development agents in our pipeline targeting the PI3K pathway in cancer.[2] Its chemical structure highlights two unique and challenging heterocycles, namely a dihydrobenzothienooxepine on the northern hemisphere and a substituted 3-amino-1*H*-1,2,4-triazole in the southern hemisphere (Figure 1). Herein, we wish to report a practical and efficient synthesis of GDC-0908 (**1**) featuring a palladium-catalyzed direct C–H arylation[3] and a Negishi coupling[4] as the key steps, and further development of a general synthesis of substituted dihydrobenzothienooxepines via palladium-catalyzed intramolecular direct C–H arylation strategy.

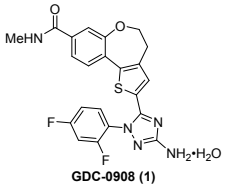
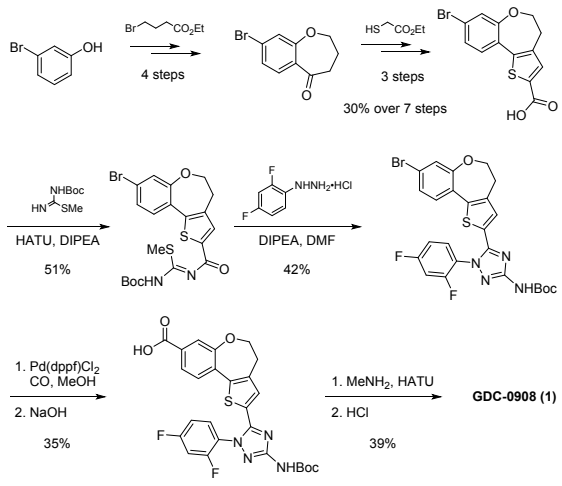


Figure 1. Structure of PI3K inhibitor GDC-0908 (1)

RESULTS AND DISCUSSION

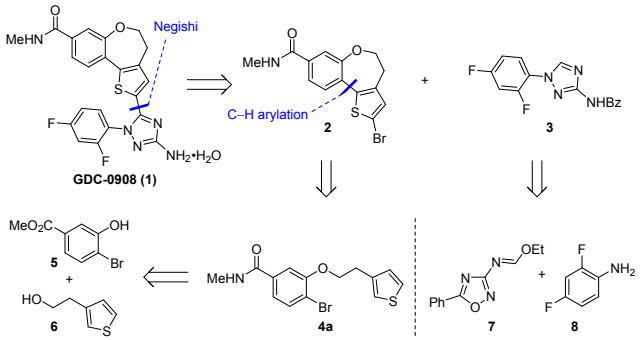
The discovery chemistry synthesis of GDC-0908 (**1**) is shown in Scheme 1. The synthesis, although proceeding in only 1% overall yield, allows flexible late stage divergent functionalization of the carboxylic acid moiety of the penultimate intermediate to afford a variety of amides used in structure–activity relationship (SAR) studies.[2]

Scheme 1. Discovery Synthesis of GDC-0908 (1)



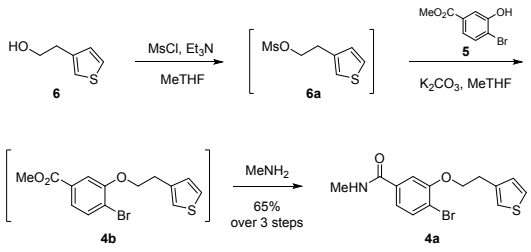
We envisioned that GDC-0908 (**1**) could be accessed via a palladium-catalyzed Negishi coupling[4] of bromodihydrobenzothienooxepine **2** and the organozinc reagent derived from benzoyl protected aminotriazole **3** (Scheme 2).[5] The corresponding bromodihydrobenzothienooxepine **2** would be generated via a palladium-catalyzed direct intramolecular C–H arylation of thiophene[6] tethered benzamide **4a** and subsequent selective bromination at 2-position of the thiophene moiety. Intermediate **4a** could be readily derived from mesylation of thienylethanol **6**, followed by S_N2 displacement with bromophenol **5** and direct ester amidation. On the other hand, benzoyl protected aminotriazole **3** would be synthesized from ethyl *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)formimidate (**7**) and 2,4-difluoroaniline (**8**) via a thermal monocyclic rearrangement reaction.[5a,7]

Scheme 2. Retrosynthetic Analysis of GDC-0908 (1)



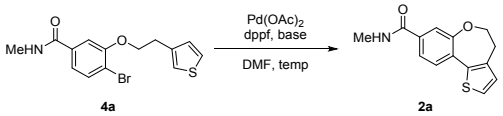
Our process research commenced with the synthesis of bromodihydrobenzothienooxepine **2**. Commercially available thienylethanol **6** was readily converted to mesylate **6a** in the presence of MsCl and Et_3N. Without isolation, mesylate **6a** was treated with commercially available bromophenol **5** and base K_2CO_3 to generate S_N2 product **4b**, which again was telescoped to a direct amidation of ester using methylamine to afford thiophene tethered benzamide **4a** in 65% yield over three steps (Scheme 3).

Scheme 3. Synthesis of Thiophene Tethered Benzamide 4



Next, we focused on optimizing the palladium-catalyzed intramolecular direct C–H arylation reaction of benzamide **4a**, starting with 5 mol % of $Pd(OAc)_2$ as the catalyst and 10 mol % of 1,1'-bis(diphenylphosphino)ferrocene (dppf) as the ligand in DMF at 100 °C (Table 1). A quick screening of bases (1.0 equiv) indicated that organic bases such as *N*,*N*-diisopropylethylamine (DIPEA), DBU and 2,6-lutidine only afforded low conversion and trace amount of product after 16 h (Table 1, entries 1–3). However, inorganic bases, for example, Cs_2CO_3, K_2CO_3, KOAc and CsOAc all gave essentially quantitative conversion with CsOAc being the best base, which generated 65% HPLC assay yield of the desired product **2a** in only 2 h (Table 1, entries 4–7). When the catalyst/ligand loading was reduced to 1 and 2 mol % respectively, we still observed high conversion (89%) and good assay yield (72%) in 16 h (Table 1, entry 8). Further optimization by elevating the reaction temperature to 110 °C and increasing the base CsOAc to 1.5 equiv led to the optimal conditions under which the reaction produced 82% assay yield of dihydrobenzothienooxepine **2a**. The product was readily isolated by silica gel column chromatography in 80% yield (Table 1, entries 9–10). It is worth mentioning that the use of 1 mol % of $PdCl_2$(dppf) as the catalyst system under otherwise identical optimized conditions, the reaction afforded the same 82% assay yield.[8]

Table 1. Optimization of Palladium-Catalyzed Direct C–H Arylation of 4a[a]



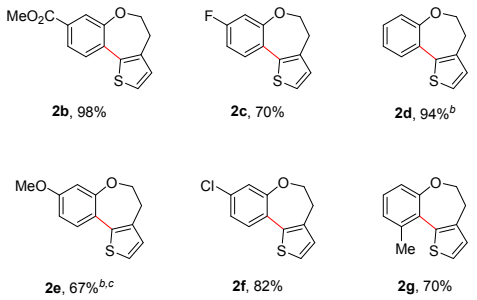
entry	cat., ligand (mol %)	base, equiv	T (°C), t (h)	conv[b] (%)	**2a**[c] (%)
1	5, 10	DIPEA, 1.0	100, 16	36	<5
2	5, 10	DBU, 1.0	100, 16	23	<5
3	5, 10	2,6-lutidine, 1.0	100, 16	16	<5
4	5, 10	Cs_2CO_3, 1.0	100, 16	>99	60
5	5, 10	K_2CO_3, 1.0	100, 16	>99	55
6	5, 10	KOAc, 1.0	100, 16	>99	62
7	5, 10	CsOAc, 1.0	100, 2	>99	65
8	1, 2	CsOAc, 1.0	100, 16	89	72
9	1, 2	CsOAc, 1.0	110, 16	>99	75
10	1, 2	CsOAc, 1.5	110, 2	>99	82(80)

[a]Reaction conditions: **4a** (200 mg, 0.59 mmol), $Pd(OAc)_2$ (1–5 mol %), dppf (2–10 mol %), base (1–1.5 equiv), DMF (2.0 mL). [b]Determined based on consumption of **4a** by HPLC analysis. [c]Assay yield based on quantitative HPLC analysis of the reaction mixture after filtration. The number in parentheses is isolated yield.

Our own interest in this unique class of tricyclic dihydrobenzothienooxepine heterocycles prompted us to further develop a more general synthetic methodology via palladium-catalyzed intramolecular direct C–H arylation. Indeed, under the optimal conditions for the transformation of **4a** to **2a** employing 1 mol % $Pd(OAc)_2$, 2 mol % dppf, 1.5 equiv CsOAc in DMF at 110 °C, a variety of electronically and sterically diverse thiophene tethered benzamides **4b**–**g** generated good to excellent yields of the desired dihydrobenzothienooxepines **2b**–**g** (Scheme

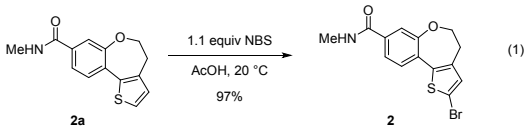
4). It is noteworthy that other than the amide functionality in **2a**, this chemistry also tolerates ester and chloride functional groups (**2b** and **2f**).

Scheme 4. Scope of C–H Direct Arylation[a]



[a]Reaction conditions: **4b–g** (1.0 mmol), $Pd(OAc)_2$ (1 mol %), dppf (2 mol %), CsOAc (1.5 equiv), DMF (5.0 mL), 110 °C. [b]$Pd(OAc)_2$ (2 mol %) and dppf (4 mol %) were employed. [c]Corrected yield. An inseparable mixture of 3.8:1 of **2e** and desBr-**4e** was isolated.

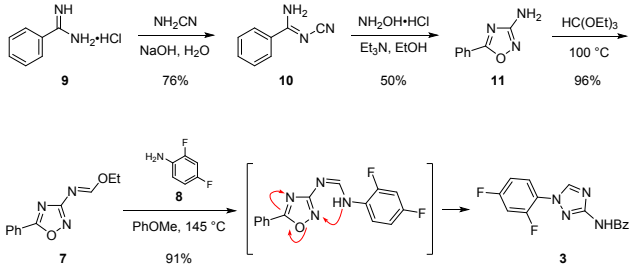
The bromination of dihydrobenzothienooxepine **2a** could be easily accomplished using 1.1 equiv NBS in acetic acid at room temperature. The reaction readily reached >99% conversion in 1 h. After the reaction was quenched with aqueous Na_2SO_3 solution, the desired product was isolated in 97% yield after filtration and drying (eq 1).



(1)

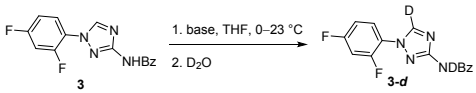
With the northern hemisphere coupling partner **2** in hand, we then turned our attention to the synthesis of aminotriazole **3** (Scheme 5). Following a literature reported procedure,[9] commercially available benzamidine•HCl (**9**) was treated with cyanamide in the presence of NaOH, affording cyanobenzamidine **10** in 76% yield. The cyclization of cyanobenzamidine **10** and hydroxylamine•HCl under improved conditions[10] employing Et_3N as base in EtOH afforded 50% yield of 3-amino-5-phenyl-1,2,4-oxadiazole (**11**), which was treated with triethylorthoformate to give 96% yield of ethyl *N*-(5-phenyl-1,2,4-oxadiazol-3-yl)formimidate (**7**). Imidate **7** then reacted with 2,4-difluoroaniline (**8**) in anisole at 145 °C, undergoing a thermal monocyclic rearrangement reaction[5a,7] to produce the desired benzoyl protected aminotriazole **3** in 91% yield.

Scheme 5. Synthesis of Aminotriazole 3



Knochel reported that TMPZnCl•LiCl readily deprotonates a variety of arenes and heteroarenes and more importantly, the resulting arylzinc species can readily undergo Negishi coupling in the presence of a palladium catalyst.[11] When we treated aminotriazole **3** with 1.1 equiv of TMPZnCl•LiCl in THF and quenched the reaction with D_2O, only 7% deuterium incorporation at C5 position of **3** was observed as the most acidic proton—the amide proton readily consumes 1 equiv of the base. To our delight, 95% deuterium incorporation was detected when 2.1 equiv of TMPZnCl•LiCl was employed. For comparison, when a weaker base LDA was used, only 50% deuterium was incorporated in compound **3** (Scheme 6). The deuterium experiments clearly indicated that the zinc species was produced when aminotriazole **3** was treated with 2.1 equiv of base TMPZnCl•LiCl. Considering that the other coupling partner bromodihydrobenzothienooxepine **2** also contains an acidic proton at the amide position, we performed one last deuterium incorporation experiment by treating a 1:1 mixture of compounds **2** and **3** with 3.1 equiv of base TMPZnCl•LiCl. Gratifyingly, 94% deuterium incorporation at the C5 position of compound **3** was observed based on ^1H NMR spectroscopic analysis (Scheme 6).

Scheme 6. Deuterium Incorporation of 3

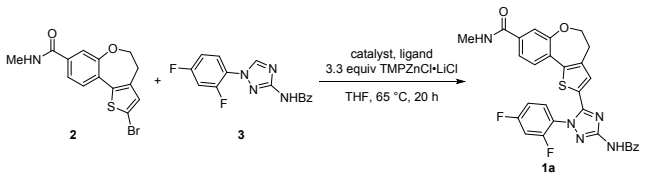


base, equiv	D% at C5 by ^1H NMR
TMPZnCl•LiCl, 1.1	7
TMPZnCl•LiCl, 2.1	95
LDA, 2.1	50
2 + **3** TMPZnCl•LiCl, 3.1	94

We then further investigated the Negishi coupling of bromodihydrobenzothienooxepine **2** and 1.1 equiv of aminotriazole **3** in the presence of 3.3 equiv of TMPZnCl•LiCl base with 5 mol % palladium catalyst (Table 2). Surprisingly, the best catalyst $PdCl_2(PPh t\text{-}Bu_2)_2$[12] in our previously reported Negishi coupling of aryl bromides and 3-aminotriazoles[5b] only afforded 32% conversion of the reaction, which attests the substrate-sensitive nature of this cross-coupling reaction (Table 2, entry 1). Other catalysts such as $PdCl_2(PPh_3)_2$, $PdCl_2(PCy_3)_2$, $PdCl_2$(dppf), all gave unsatisfactory (≤ 50%) conversions (Table 2, entries 2–4). Similarly, none of the combination of 5 mol % of $Pd(OAc)_2$ and 10 mol % of electron-rich and sterically hindered ligands, for example, $P(t\text{-}Bu)_3•HBF_4$,[13] SPhos,[14] RuPhos,[15] and XPhos,[16] produced >30% conversion of the reaction (Table 2, entries 5–8). To our delight, a catalyst system comprising of 5 mol % $Pd(OAc)_2$ and 10 mol % tri(2-furyl)phosphine (TFP) generated 90% conversion of bromide **2** in 80% assay yield of coupling product **1a** based on quantitative HPLC analysis (Table 2, entry 9). Replacing $Pd(OAc)_2$ with $PdCl_2(TFP)_2$[17] afforded 99% conversion and 95% assay yield of product **1a** (Table 2, entry 10). Further lowering the catalyst and ligand loading to 2.5 mol % and 5 mol %,

respectively, produced slightly inferior conversion and assay yield (Table 2, entry 11).

Table 2. Optimization of Palladium-Catalyzed Negishi Coupling of 2 and 3[a]

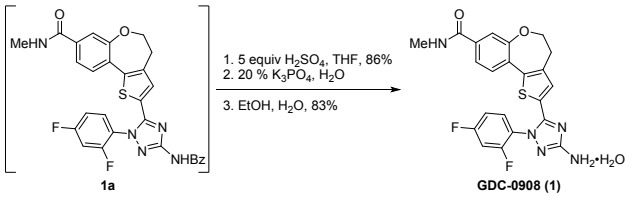


entry	catalyst, mol %	ligand, mol %	conv[b] (%)
1	$PdCl_2(PPht\text{-}Bu_2)_2$, 5	-	32
2	$PdCl_2(PPh_3)_2$, 5	-	50
3	$PdCl_2(PCy_3)_2$, 5	-	<5
4	$PdCl_2$(dppf), 5	-	26
5	$Pd(OAc)_2$, 5	$P(t\text{-}Bu)_3•HBF_4$, 10	7
6	$Pd(OAc)_2$, 5	SPhos, 10	27
7	$Pd(OAc)_2$, 5	RuPhos, 10	28
8	$Pd(OAc)_2$, 5	XPhos, 10	17
9	$Pd(OAc)_2$, 5	TFP, 10	90(80)[c]
10	$PdCl_2(TFP)_2$, 5	TFP, 10	99(95)[c]
11	$PdCl_2(TFP)_2$, 2.5	TFP, 5	94(87)[c]

[a]Reaction conditions: **2** (500 mg, 1.48 mmol), **3** (488 mg, 1.1 equiv), palladium catalyst (2.5–5 mol %), ligand (0–10 mol %), TMPZnCl•LiCl (0.65 M in THF, 7.5 mL, 3.3 equiv), THF (2.5 mL), 65 °C. [b]Determined based on consumption of **2** by HPLC analysis. [c]Assay yield based on quantitative HPLC analysis of the reaction mixture.

Under the optimal Negishi coupling conditions employing bromide **2**, 1.1 equiv of aminotriazole **3**, 3.3 equiv of TMPZnCl•LiCl, 5 mol % of $PdCl_2(TFP)_2$ and 10 mol % of TFP in THF at 65 °C, the reaction was highly productive with little impurity detected. Therefore, we decided to telescope the Negishi coupling directly to the benzoyl deprotection rather than isolating the penultimate intermediate **1a**. Indeed, quenching the Negishi reaction with aqueous HCl, followed by 5 equiv of concentrated H_2SO_4 at 65 °C removed the benzoyl group, generating GDC-0908•H_2SO_4 (**1b**) in 86% isolated yield over two steps. A final K_3PO_4 salt break and crystallization of the free base in EtOH/H_2O successfully produced GDC-0908 (**1**) as the corresponding monohydrate in 83% yield and 99 A% HPLC purity (Scheme 7). It is worth noting that the residual palladium in GDC-0908 (**1**) was controlled to <20 ppm level without any scavenging operation.

Scheme 7. Endgame of GDC-0908 (1) Synthesis



CONCLUSION

In conclusion, we have developed an efficient and practical synthesis of GDC-0908 (**1**). The process features a palladium-catalyzed intramolecular direct C–H arylation to assemble the northern hemisphere dihydrobenzothienooxepine, a thermal monocyclic rearrangement to construct the southern hemisphere substituted 3-amino-1,2,4-triazole, and a palladium-catalyzed Negishi coupling to form the key C–C bond connecting two hemispheres. Overall, the convergent synthesis of GDC-0908 (**1**) involves 12 steps with 8 longest linear steps from commercially available starting materials methyl 4-bromo-3-hydroxybenzoate (**5**), 2-(thiophen-3-yl)ethan-1-ol (**6**) and benzamidine•HCl (**9**). We have also developed a general synthesis of dihydrobenzothienooxepines via palladium-catalyzed intramolecular direct C–H arylation. The chemistry tolerates both electronically and sterically diverse substituents on the phenyl ring and afforded the desired tricyclic heterocycles in good to excellent yields.

EXPERIMENTAL SECTION

General. Commercially obtained solvents and reagents were used as received. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker spectrometer. Flash column chromatography was performed using a CombiFlash ISCO instrument, using prepacked RediSep silica gel columns. HPLC analyses were performed using an Agilent 1260 Series HPLC instrument. The column used was ACE Excel 3 C18 HL, 3×50 mm; particle size 3 um; injection volume 2 µL; temperature 35 °C; flow rate 1 mL/min; mobile phase A = 0.05% trifluoroacetic acid in H_2O, mobile phase B = 0.05% trifluoroacetic acid in acetonitrile, gradient: 0–0.3' = 5% B, 0.3–3' = 5–60% B, 3–4' = 60–90% B, 4-6' = 90% B, 6–6.1' = 5% B, 6.1–7.5' = 5% B. IR spectra were recorded using a Bruker Alpha Platinum-ATR spectrometer and are reported in wavenumbers (cm^{-1}). HRMS data were obtained using a Thermo Scientific Orbitrap Fusion instrument at Genentech, Inc. Melting points (uncorrected) were measured on a Büchi Melting Point B-540 apparatus or by differential scanning calorimetry (DSC, Mettler Toledo HP DSC 1) and were reported as onset temperature.

*4-Bromo-N-methyl-3-(2-(thiophen-3-yl)ethoxy)benzamide (**4a**).* To a 2 L reactor under nitrogen were charged 2-(thiophen-3-yl)ethan-1-ol (**6**, 80.0 g, 0.624 mol), Et_3N (175 mL, 2.0 equiv) and MeTHF (560 mL) at 25 °C. The mixture was cooled to 0–5 °C and a solution of MsCl (100 g, 1.4 equiv) in MeTHF (240 mL) was added over 45 min while maintaining the reaction temperature <25 °C. The mixture was stirred at 25 °C for 2 h and HPLC analysis showed 99% conversion of the reaction. The mixture was cooled to 0–5 °C and quenched with aq citric acid solution (320 mL, 10 wt %) at <10 °C until pH = 5–6. The MeTHF phase was separated, washed with aq Na_2CO_3 solution (320 mL, 10 wt %), then aq NaCl solution (320 mL, 10 wt %) to afford a solution of mesylate **6a** in MeTHF. An analytical sample was taken and concentrated to dryness.

^{1}H NMR (400 MHz, DMSO-d_6) δ 3.02 (s, 2 H), 3.12 (s, 3 H), 4.41 (t, *J* = 6.78 Hz, 2 H), 7.06–7.12 (m, 1 H), 7.31 (br s, 1 H), 7.49 (br s, 1 H).

To a 3 L reactor under nitrogen were charged a MeTHF solution of **6a** (120.0 g by assay, 0.582 mol, ca. 800 mL), methyl 4-bromo-3-hydroxybenzoate (**5**, 144.0 g, 1.05 equiv) and K_2CO_3 (160.8 g, 2.0 equiv) at 25 °C. The mixture was stirred at 80 °C for 24 h. HPLC analysis showed 97% conversion. The reaction was cooled to 25 °C and quenched with H_2O (1200 mL). The MeTHF layer was separated and washed with H_2O (600 mL, ×3) until aqueous layer pH = 7–8. The MeTHF phase was concentrated under vacuum to afford ca. 400 mL of MeTHF solution of **4b**.

To a 2 L pressure reactor was charged MeTHF solution of **4b** (170.0 g by assay, 0.498 mol), $MeNH_2$ (33 wt % in EtOH, 760 mL, 10 equiv). The mixture was heated at 50 °C under N_2 pressure (50 psi) for 24 h. HPLC analysis showed 99% conversion. The reaction was concentrated to ca. 400 mL, diluted with MeTHF (1200 mL), and washed with H_2O (340 mL). The MeTHF phase was separated, washed with aq NaCl solution (10 wt %, 850 mL), and concentrated to ca. 630 mL under vacuum at 35 °C. The mixture was cooled to 25 °C, seeded (ca. 0.5 g), stirred for 1 h and charged with heptane (1260 mL) in 4 h. The suspension was aged for 12 h, filtered and dried at 40 °C for 8 h to afford compound **4a** as a white solid (135.6 g, 65% from **6**). M.p. 110–111 °C; FTIR (neat, cm^{-1}) 33689, 3230, 3095, 2943, 1593, 1559; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.1 Hz, 1H), 7.35 (d, *J* = 1.9 Hz, 1H), 7.28 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.17 (ddd, *J* = 3.0, 1.4, 0.7 Hz, 1H), 7.15 – 7.00 (m, 2H), 6.19 (s, 1H), 4.26 (t, *J* = 6.6 Hz, 2H), 3.26 – 3.10 (m, 2H), 2.99 (d, *J* = 4.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.3, 155.5, 138.1, 135.1, 133.2, 128.7, 125.5, 122.1, 119.1, 115.8, 112.0, 69.4, 30.1, 26.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{15}BrNO_2S$ 340.0002; Found, 339.9990.

*N-Methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide (**2a**).* To a 3 L reactor under nitrogen was charged **4a** (50.0 g, 0.147 mol), CsOAc (42.3 g, 1.5 equiv), $Pd(OAc)_2$ (0.33 g, 1 mol %), dppf (1.63 g, 2 mol %) and DMF (500 mL). The mixture was stirred at 110 °C for 2 h and HPLC analysis showed 98% conversion. The reaction was cooled to 25 °C and added MeTHF (1500 mL) and aq NaCl solution (750mL, 5 wt %). The MeTHF phase was separated and the aq layer was extracted with MeTHF (250mL). The combined organic layers were washed with aq NaCl solution (750mL, 5 wt %, ×2), decolorized with active carbon (5.0 g) at 45 °C for 2 h, filtered and concentrated to ca. 75 mL. The residue was added DCM (750 mL) and filtered through a silica gel pad (50 g). The silica gel pad was washed with DCM (250 mL), followed by DCM/EtOAc (450 mL). The combined organic solution was concentrated to ca. 250 mL under vacuum at 30 °C, seeded (ca. 0.2 g), aged for 1 h, concentrated to ca. 100 mL and added EtOAc (150 mL). The suspension was concentrated to ca. 100 mL, added heptane (300 mL) in 3 h, aged for 12 h, filtered and dried under vacuum for 16 h to afford product **2a** as an off-white solid (29.0 g, 76%). On a 200 mg scale during optimization, compound **2a** (Table 1, entry 10) was purified by silica gel column chromatography using 0-10% DCM/MeOH eluent as an off-white solid (122 mg, 80%). M.p. 152–153 °C; FTIR (neat, cm^{-1}) 3279, 3096, 3058, 2954, 2895, 1625, 1556; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.7 Hz, 1H), 7.47–7.37 (m, 2H), 7.25 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 5.2 Hz, 1H), 6.19 (s, 1H), 4.39–4.27 (m, 2H), 3.30–3.20 (m, 2H), 3.01 (d, *J* = 4.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.2, 157.3, 138.4, 134.9, 133.7, 131.0, 128.5, 127.5, 124.6, 121.5, 119.8, 69.9, 33.7, 26.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{14}NO_2S$ 260.0740; Found, 260.0739.

*2-Bromo-N-methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxamide (**2**).* To a 2 L reactor under nitrogen was added **2a** (50.0 g, 0.193 mol), AcOH (500 mL) and the mixture was stirred at 20 °C for 10 min. NBS (38.1 g, 1.1 equiv) was added in 3 portions and the mixture was stirred at 20 °C for 30 min. HPLC analysis showed >99.5% conversion. The reaction was quenched with a mixture of saturated aq solution of Na_2SO_3 (125 mL) in H_2O (500 mL), stirred at 20 °C for 30 min, filtered, washed with H_2O (150 mL, ×4), dried under vacuum at 40 °C for 48 h to afford compound **2** as a white solid (62.9 g, 97%). M.p. 164–165 °C; FTIR (neat, cm^{-1}) 3253, 3082, 2956, 2904, 1634, 1539; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.50 (m, 1H), 7.45–7.33 (m, 2H), 6.89 (d, *J* = 0.5 Hz, 1H), 6.15 (s, 1H), 4.36–4.17 (m, 2H), 3.26–3.11 (m, 2H), 3.01 (d, *J* = 4.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 157.2, 139.0, 136.4, 134.1, 133.5, 128.0, 126.7, 121.6, 119.9, 112.2, 69.7, 33.8, 26.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{14}H_{13}BrNO_2S$ 337.9845; Found, 337.9845.

*N'-Cyanobenzamidine (**10**).*[9] To a 20 L reactor under nitrogen were charged NH_2CN (661.5 g, 15.6 mol, 1.05 equiv) and H_2O (7.5 L), followed by NaOH (1200 g, 30.0 mol, 2.0 equiv) and benzamidine•HCl (2300 g, 14.7 mol). The resulting solution was stirred for 2 h at 25 °C. The precipitated solids were filtered and dried under vacuum to afford compound **10** as a white solid (1630 g, 76%). ^{1}H NMR (400MHz, DMSO-d_6) δ 9.71–8.28 (m, 2H), 7.91 (br s, 2H), 7.69–7.33 (m, 3H).

*5-Phenyl-1,2,4-oxadiazol-3-amine (**11**).*[9] To a 1 L reactor under nitrogen was charged compound **10** (85.0 g, 0.586 mol) and EtOH (190 mL). The reaction was stirred at 25 °C for 30 min, added with NH_2OH•HCl (53.5 g, 1.3 equiv), Et_3N (130 mL, 2.0 equiv) and heated at 80 °C for 3 h. HPLC analysis showed >99% conversion. The mixture was concentrated to ca. 170 mL and water (0.9 L) was charged. The solids were filtered and the crude product was slurried in heptane/MeTHF (770 mL, 6/5, v/v), filtered and dried at 35 °C under vacuum to afford compound **11** as a white solid (74.0 g, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04–7.94 (m, 2H), 7.71–7.64 (m, 1H), 7.63–7.56 (m, 2H), 6.41 (s, 2H).

*Ethyl (E)-N-(5-phenyl-1,2,4-oxadiazol-3-yl)formimidate (**7**).* To a 10 L reactor under nitrogen were charged 5-phenyl-1,2,4-oxadiazol-3-amine (**11**, 748 g, 4.64 mol) and $HC(OEt)_3$ (2.6 L). The mixture was heated at 100 °C for 4

h. ^{1}H NMR analysis showed >95% conversion. The reaction mixture was cooled to 20 °C, added with heptane (2.6 L) in 30 m and stirred at 5–10 °C for 1 h. The solids were filtered, washed with heptane (1 L) and dried under vacuum at 40 °C to afford the desired compound **7** as a white solid (936 g, 93%). Characterization data are identical to those reported in literature.[5a] M.p. 98 °C; FTIR (neat, cm^{-1}) 3071, 2983, 1630, 1565; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.13 (dd, J = 9.0, 3.0 Hz, 2H), 7.60–7.50 (m, 3H), 4.49 (qd, J = 7.1, 0.9 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 175.6, 171.1, 163.1, 132.8, 129.1, 127.9, 124.4, 64.1, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_2$ 218.0924; found, 218.0915.

*N-(1-(2,4-Difluorophenyl)-1H-1,2,4-triazol-3-yl)benzamide (**3**).* To a 20 L reactor under nitrogen were charged compound **12** (936 g, 4.31 mol), anisole (4.7 L) and 2,4-difluoroaniline (557 g, 4.31 mol, 1.0 equiv). The mixture was heated at 145 °C for 5 h. HPLC analysis showed >99% conversion. The reaction mixture was cooled to 20 °C and the solids precipitated. Heptane (5.5 L) was added in 30 min and the mixture was aged for 1 h. The solids were filtered, washed with heptane (2 L, ×2) and dried under vacuum at 40 °C to afford the desired compound **3** as a white solid (1163 g, 91%). M.p. 177–178 °C; FTIR (neat, cm^{-1}) 3244, 3214, 3112, 3089, 1662, 1508; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.22 (d, J = 2.6 Hz, 1H), 8.08–7.88 (m, 3H), 7.65–7.57 (m, 1H), 7.57–7.46 (m, 2H), 7.15–6.89 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.0, 161.5 (dd, J = 252.5, 11.2 Hz), 157.0, 153.8 (dd, J = 253.5, 12.3 Hz), 142.9 (d, J = 12.6 Hz), 134.1, 132.3, 128.7, 127.7, 125.8 (d, J = 9.9 Hz), 121.6 (dd, J = 11.1, 4.0 Hz), 112.6 (dd, J = 22.6, 3.7 Hz), 105.1 (dd, J = 26.8, 23.9 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}F_2N_4O$ 301.0896; Found, 301.0894.

*GDC-0908•H_2SO_4 (**1b**).* To a 2 L reactor under nitrogen were charged starting materials **2** (50.0 g, 148 mmol) and **3** (48.8 g, 1.1 equiv), THF (250 mL), TFP (3.47 g, 10 mol %) and $PdCl_2(TFP)_2$ (4.74 g, 5 mol %). The mixture was vacuumed and backfilled with nitrogen (×3) and cooled to 5 °C. A THF solution of TMPZnCl•LiCl (0.65 M, 750 mL, 3.3 equiv) was charged while maintaining the reaction temperature <10 °C. The mixture was then stirred at 65 °C for 16 h. HPLC analysis showed 97% conversion. The reaction mixture was cooled to 0–5 °C, quenched with aq HCl solution (250 mL) and added saturated aq NaCl solution (250 mL). The organic phase was separated, washed with saturated aq NaCl solution (250 mL, ×2), added THF (250 mL) and filtered. The mixture was added concentrated H_2SO_4 (42.8 mL, 5 equiv) and heated at 65 °C for 65 h. Solids precipitated and HPLC analysis showed 98% conversion. The mixture was filtered, washed with THF (100 mL, ×3) and dried under vacuum at 40 °C for 24 h to afford GDC-0908•H_2SO_4 (**1b**) as a yellow solid (70.2 g, 86%). M.p. 263–265 °C; FTIR (neat, cm^{-1}) 3385, 3348, 3081, 2904, 1631; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 4.5 Hz, 1H), 7.82 (td, J = 8.8, 6.0 Hz, 1H), 7.69 – 7.56 (m, 2H), 7.53 (dd, J = 8.2, 1.8 Hz, 1H), 7.47 (d, J = 1.7 Hz, 1H), 7.36 (ddd, J = 8.1, 2.7, 1.4 Hz, 1H), 6.79 (d, J = 5.9 Hz, 6H), 4.25 (t, J = 5.0 Hz, 2H), 3.09 (t, J = 5.0 Hz, 2H), 2.77 (d, J = 4.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 165.8, 164.0, 163.3 (dd, J = 251.5, 12.1 Hz), 157.8 (dd, J = 254.5, 13.1 Hz), 157.6, 148.3, 139.9, 137.1, 135.1, 131.9 (d, J = 10.6 Hz), 131.5, 128.4, 125.8, 122.6, 120.3, 113.5 (d, J = 23.4 Hz), 106.3 (t, J = 25.3 Hz), 70.1, 33.6, 26.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{18}F_2N_5O_2S$ 454.1144; Found, 454.1130.

*GDC-0908 (**1**).* To a 2 L reactor under nitrogen were charged GDC-0908•H_2SO_4 (**1b**, 50.0 g, 90.7 mmol), THF (1250 mL), H_2O (150 mL) and aq K_3PO_4 solution (175 mL, 20 wt %). The organic phase was separated and washed with saturated aq NaCl solution (100 mL, ×2). The mixture was distilled at 45–65 °C to KF ≤ 2.5% while maintaining total volume of ca. 850 mL, filtered at 45–55 °C and solvent exchanged to EtOH while maintaining total volume of ca. 850 mL. H_2O (90 mL) was added and the mixture was heated to 75–80 °C until a homogeneous solution was obtained. The solution was cooled to 60–65 °C, seeded (0.35 g), aged for at least 1 h and distilled to 500 mL. The mixture was cooled to 20 °C, filtered, washed with H_2O (100 mL), and dried under vacuum with filtered air until KF of the solid reached 3.9% to afford GDC-0908 (**1**) as a pale yellow solid (35.3 g, 83%). M.p. (DSC) 110.4 °C, 226.6 °C; FTIR (neat cm^{-1}) 3373, 3298, 3213, 3074, 1612, 1543; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, J = 4.6 Hz, 1H), 7.81 (td, J = 8.8, 6.0 Hz, 1H), 7.70 – 7.57 (m, 2H), 7.53 (dd, J = 8.2, 1.8 Hz, 1H), 7.47 (d, J = 1.7 Hz, 1H), 7.36 (ddd, J = 8.1, 2.8, 1.4 Hz, 1H), 6.76 (s, 1H), 5.75 (s, 2H), 4.25 (t, J = 5.0 Hz, 2H), 3.09 (t, J = 5.0 Hz, 2H), 2.77 (d, J = 4.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.0, 164.4, 163.3 (dd, J = 251.5, 12.1 Hz), 157.8 (dd, J = 253.5, 13.1 Hz), 157.6, 148.4, 139.8, 137.0, 134.9, 131.9 (d, J = 10.7 Hz), 131.4, 128.4, 127.2, 125.9, 122.7 (dd, J = 13.1, 4.0 Hz), 122.6, 120.2, 113.4 (dd, J = 22.2, 4.0 Hz), 106.3 (dd, J = 28.3, 24.2 Hz), 70.1, 33.5, 26.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{18}F_2N_5O_2S$ 454.1144; Found, 454.1145.

General procedure for the synthesis of aryl ethers 4b–g

2-(Thiophen-3-yl)ethyl methanesulfonate (**6a**, 413 mg, 2 mmol), substituted *o*-bromophenol (1.05 equiv), and anhydrous K_2CO_3 (414 mg, 1.5 equiv) were charged in a septum-top vial equipped with a stir bar. The vial was purged with nitrogen and MeTHF (10 mL) was added via syringe. The reaction was stirred at 80 °C for 24 h and HPLC analysis indicated complete conversion. The reaction was cooled to 20 °C and diluted with DCM (10 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3 mL, ×3). The combined organic layers were washed with saturated aq NaCl solution (5 mL), dried over Na_2SO_4 (0.5 g), filtered, and concentrated. The crude product was purified via silica gel column chromatography using 0–20% *i*-PrOAc in heptane to afford aryl ethers **4b**–**g**.

*Methyl 4-bromo-3-(2-(thiophen-3-yl)ethoxy)benzoate (**4b**).* Compound **4b** was obtained as a clear oil (637 mg, 93%); FTIR (neat, cm^{-1}) 3100, 2949, 1716, 1578, 1480, 1435, 1413; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.0 Hz, 1H), 7.52–7.44 (m, 2H), 7.32–7.21 (m, 1H), 7.16 (dd, J = 2.9, 1.2 Hz,

1H), 7.11 (dd, *J* = 5.0, 1.3 Hz, 1H), 4.25 (t, *J* = 6.6 Hz, 2H), 3.89 (s, 3H), 3.19 (t, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.3, 155.2, 138.1, 133.3, 130.5, 128.7, 125.5, 122.9, 122.1, 117.9, 113.4, 69.4, 52.3, 30.1; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{14}H_{17}BrNO_3S$ 358.0107; Found, 358.0107.

*3-(2-(2-Bromo-5-fluorophenoxy)ethyl)thiophene (**4c**).* Compound **4c** was obtained as a cloudy oil (594 mg, 99%, ca. 93% purity based on ^1H NMR analysis) and was used directly in the next step. A retain sample (118 mg) was further purified by silica gel column chromatography to afford compound **4c** as an oil (101 mg, 86% recovery); FTIR (neat, cm^{-1}) 3103, 2931, 2877, 1604, 1580, 1482, 1421; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8.6, 6.1 Hz, 2H), 7.24 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.16–7.03 (m, 1H), 6.64–6.43 (m, 2H), 4.10 (t, *J* = 6.6 Hz, 2H), 3.13 (t, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.7 (d, *J* = 247.5 Hz), 156.1 (d, *J* = 10.1 Hz), 138.0, 133.5 (d, *J* = 8.1 Hz), 128.7, 125.5, 122.1, 108.4 (d, *J* = 22.2 Hz), 106.3 (d, *J* = 4.0 Hz), 101.3 (d, *J* = 27.3 Hz), 69.4, 30.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –111.6; HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_{10}BrFOS$ 299.9614; Found, 299.9606.

*3-(2-(2-Bromophenoxy)ethyl)thiophene (**4d**).* Compound **4d** was obtained as a clear oil (495 mg, 87%); FTIR (neat, cm^{-1}) 2928, 2875, 1584, 1480, 1464, 1441; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.22 (ddd, *J* = 17.2, 8.0, 2.3 Hz, 2H), 7.15 (d, *J* = 2.8 Hz, 1H), 7.10 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.88–6.75 (m, 2H), 4.18 (t, *J* = 6.7 Hz, 2H), 3.16 (t, *J* = 6.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.2, 138.4, 133.4, 128.8, 128.4, 125.4, 122.0, 121.9, 113.2, 112.2, 69.2, 30.2; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{12}H_{15}BrNOS$ 300.0052; Found, 300.0049.

*3-(2-(2-bromo-5-methoxyphenoxy)ethyl)thiophene (**4e**).* Compound **4e** was obtained as a clear oil (620 mg, 99%); FTIR (neat, cm^{-1}) 3101, 2934, 2834, 1579, 1487, 1463, 1442; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 1H), 7.11 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.04–6.94 (m, 2H), 6.30 (d, *J* = 2.7 Hz, 1H), 6.23 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.00 (t, *J* = 6.6 Hz, 2H), 3.60 (s, 3H), 3.01 (t, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2, 155.9, 138.4, 133.2, 128.9, 125.5, 122.1, 106.3, 103.0, 101.0, 69.2, 55.6, 30.2; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{13}H_{17}BrNO_2S$ 330.0158; found, 330.0156.

*3-(2-(2-Bromo-5-chlorophenoxy)ethyl)thiophene (**4f**).* Compound **4f** was obtained as a cloudy oil (595 mg, 94%); FTIR (neat, cm^{-1}) 3097, 2929, 2877, 1579, 1462, 1377; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.2 Hz, 1H), 7.24 (dd, *J* = 4.9, 2.9 Hz, 1H), 7.12 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.07 (dd, *J* = 4.5, 2.0 Hz, 1H), 6.83–6.73 (m, 2H), 4.11 (t, *J* = 6.6 Hz, 2H), 3.13 (t, *J* = 6.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.8, 138.0, 133.9, 133.8, 128.8, 125.6, 122.2, 121.9, 113.6, 110.3, 69.5, 30.1; HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_{10}BrClOS$ 315.9319; Found, 315.9310.

*3-(2-(2-Bromo-3-methylphenoxy)ethyl)thiophene (**4g**).* Compound **4g** was obtained as a cloudy oil (549 mg, 92%, ca. 90% purity based on ^1H NMR analysis) and was used directly in the next step. A retain sample (90 mg) was further purified by silica gel column chromatography to afford compound **4g** as an oil (75 mg, 83% recovery); FTIR (neat, cm^{-1}) 2924, 2872, 1595, 1569, 1459, 1380; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (m, 1H), 7.17–7.00 (m, 3H), 6.85–6.71 (m, 1H), 6.63 (d, *J* = 8.2 Hz, 1H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.12 (t, *J* = 6.7 Hz, 2H), 2.38 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.4, 139.8, 138.6, 128.9, 128.2, 127.5, 125.4, 123.1, 122.0, 110.4, 69.4, 30.3, 23.5; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calcd for $C_{13}H_{17}BrNOS$ 314.0209; Found, 314.0211.

General procedure for the synthesis of dihydrobenzothienooxepines 2b–g via palladium-catalyzed direct C–H arylation

Aryl ethers **4b–g** (1.0 mmol), CsOAc (288 mg, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 1 mol %), and dppf (11.1 mg, 2 mol %) were charged in a septum-top vial equipped with a stir bar. The vial was purged with nitrogen, and DMF (5 mL) was added via syringe. The reaction was stirred at 110 °C for 2 h and monitored by HPLC. The reaction was cooled to 20 °C and diluted with H_2O (10 mL) and DCM (10 mL). The organic layer was separated and the aqueous layer extracted with DCM (5 mL, ×3). The combined organic layers were washed with saturated aq NaCl solution (5 mL), dried over Na_2SO_4 (0.2 g), filtered, and concentrated. The crude product was purified by silica gel column chromatography using 0–10% *i*-PrOAc in heptane to afford the desired products **2b–g**.

*Methyl 4,5-dihydrobenzo[b]thieno[2,3-d]oxepine-8-carboxylate (**2b**).* Aryl ether **4b** (341 mg, 1 mmol) was employed. Product **2b** was obtained as a white solid (256 mg, 98 %); M.p. 79–80 ^0C; FTIR (neat, cm^{-1}) 2934, 2834, 1579, 1487, 1462, 1442, 1422, 1381; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.70 (m, 1H), 7.69–7.63 (m, 2H), 7.26 (d, *J* = 5.1 Hz, 1H), 6.91 (d, *J* = 5.2 Hz, 1H), 4.37–4.28 (m, 2H), 3.90 (s, 3H), 3.24 (p, *J* = 4.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 157.2, 138.9, 134.9, 131.1, 129.2, 129.1, 128.2, 125.1, 124.2, 122.5, 69.9, 52.1, 33.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{14}H_{13}O_3S$ 261.0580; Found, 261.0572.

*8-Fluoro-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (**2c**).* Aryl ether **4c** (301 mg, 1 mmol) was employed. Product **2c** was obtained as a clear oil (175 mg, 70 %); FTIR (neat, cm^{-1}) 3104, 2897, 1604, 1580, 1544, 1495, 1441, 1413; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.58 (m, 1H), 7.15 (d, *J* = 5.2 Hz, 1H), 6.86 (d, *J* = 5.2 Hz, 1H), 6.80–6.61 (m, 2H), 4.32 (t, *J* = 4.8 Hz, 2H), 3.20 (t, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 248.5 Hz), 158.6 (d, *J* = 9.1 Hz), 136.3, 135.0, 130.8, 129.3 (d, *J* = 9.8 Hz), 123.3, 121.0, 110.4 (d, *J* = 21.8 Hz), 108.3 (d, *J* = 23.1 Hz), 70.2, 33.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{10}FOS$ 221.0431; Found, 221.0431.

*4,5-Dihydrobenzo[b]thieno[2,3-d]oxepine (**2d**).* Aryl ether **4d** (1 mmol, 283 mg), 2 mol % of $Pd(OAc)_2$ (4.5 mg) and 4 mol % of dppf (23 mg) were employed. Product **2d** was obtained as a yellow oil (191 mg, 94 %); FTIR (neat, cm^{-1}) 3058, 2896, 1543, 1487, 1447, 1418, 1213; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.16 (d, *J* = 5.2 Hz, 1H), 7.15 – 7.09 (m, 1H), 7.01 (dtd, *J* = 8.3, 3.7, 1.4 Hz, 2H),

6.87 (d, *J* = 5.3 Hz, 1H), 4.37 – 4.22 (m, 2H), 3.21 (t, *J* = 5.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.6, 137.0, 135.9, 130.8, 128.4, 127.9, 124.7, 123.5, 123.2, 121.2, 70.0, 33.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{12}H_{11}OS$ 203.0525; Found, 203.0526.

*8-Methoxy-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (**2e**).* Aryl ether **4e** (1 mmol, 313 mg), 2 mol % of $Pd(OAc)_2$ (4.5 mg) and 4 mol % of dppf (23 mg) were employed. Product **2e** was obtained as a light yellow oil (196 mg, 67 % corrected) as a 3.8:1 inseparable mixture of **2e** and 3-(2-(3-methoxyphenoxy)ethyl)thiophene (desBr-**4e**) based on LCMS and ^1H NMR analyses; FTIR (neat, cm^{-1}) 2949, 1716, 1577, 1480, 1435, 1413, 1381; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.7, 1.3 Hz, 1H), 7.11 (d, *J* = 5.2 Hz, 1H), 6.85 (dt, *J* = 5.1, 0.8 Hz, 1H), 6.61 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 4.38 – 4.25 (m, 2H), 3.79 (s, 3H), 3.20 (t, *J* = 5.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.5, 158.6, 135.2, 130.7, 129.2, 122.3, 117.5, 109.8, 105.8, 100.9, 70.0, 55.4, 33.6; HRMS (ESI-TOF) m/z: $[M+HCO_2]^-$ calcd for $C_{14}H_{13}O_4S$ 277.0540; Found, 277.0545.

*8-Chloro-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (**2f**).* Aryl ether **4f** (1 mmol, 318 mg) was employed. Product **2f** was obtained as a clear oil (194 mg, 82 %); FTIR (neat, cm^{-1}) 2936, 2834, 1593, 1489, 1463, 1440; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 5.2 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.96 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.83 (d, *J* = 5.1 Hz, 1H), 4.26 (p, *J* = 4.7 Hz, 2H), 3.16 (p, *J* = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.9, 137.2, 134.9, 132.7, 130.9, 129.1, 123.8, 123.3, 121.4, 70.1, 33.6; HRMS (ESI-TOF) m/z: $[M]^+$ calcd for $C_{12}H_9ClOS$ 236.0057; Found, 236.0052.

*10-Methyl-4,5-dihydrobenzo[b]thieno[2,3-d]oxepine (**2g**).* Aryl ether **4g** (1 mmol, 297 mg) was employed. Product **2g** was obtained as a clear oil (151 mg, 70 %); FTIR (neat, cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.17 (ddt, *J* = 2.9, 1.5, 0.8 Hz, 1H), 7.14 – 7.04 (m, 2H), 6.85 (ddq, *J* = 7.5, 1.3, 0.6 Hz, 1H), 6.70 (ddd, *J* = 8.2, 1.5, 0.7 Hz, 1H), 4.19 (t, *J* = 6.7 Hz, 2H), 3.19 (td, *J* = 6.7, 0.9 Hz, 2H), 2.41 (d, *J* = 0.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.3, 139.8, 138.5, 128.8, 127.4, 125.3, 123.0, 121.9, 114.8, 110.3, 69.3, 30.2, 23.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{13}OS$ 217.0682; Found, 217.0683.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^1H and ^{13}C NMR spectra of compounds **1–4**, **1b**, **2b–g**, **4b–g, 7** (PDF)

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Notes

The authors declare no competing financial interest.

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