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FULL PAPER

Spirooxazoline Synthesis by an Oxidative Dearomatizing Cyclization

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Abstract: Spirocyclic compounds are of increasing importance owing to their potential applications in the development of new pharmaceuticals. Herein, we describe a new, rapid access to rarely seen spirooxazolines utilizing an I(I)/I(III) reaction manifold. The scope of the cyclization using phenols and naphthols is described along with the stereoselective functionalization of the spirocycles. The application of this method to the formation of dihydrooxazines is also demonstrated.

Introduction

Spirocycles are generally regarded as aesthetically pleasing molecules to synthetic chemists and their prevalence in the literature has increased massively over the past decade.[1] Many spirocycles exhibit useful properties and are of increasing interest to medicinal chemists. Indeed, several thousand different spirocyclic molecules are now commercially available.[2] There are also numerous examples of natural products that contain a spirocyclic core that have inspired elegant synthetic efforts.[3]

Spirooxazoline compounds are rarely found in nature; however, there are a few examples, such as **1a** and **1b** (Figure 1).[4] On the other hand, various spiroheterocycles are prevalent with commercial suppliers because of the interest in these compounds by medicinal chemists. Weindel et al. reported that a simple spirooxazolidine inhibits mineralocorticoid biosynthesis in z. glomerulosa cells.[5] Li and co-workers reported that spirotriptolide derivative **2** is an effective anticancer agent.[6] Researchers at Merck reported a spirooxazolidinone to be a highly effective calcitonin gene-related peptide receptor (CGRP) antagonist useful for migraine treatment.[7] Fenspiride **3** is an anti-inflammatory bronchodilator used in the treatment of respiratory disorders.[8] Lundbeck researchers reported that spirooxazoline **4** is a potent brain penetrant that displays anxiolytic activity.[9]

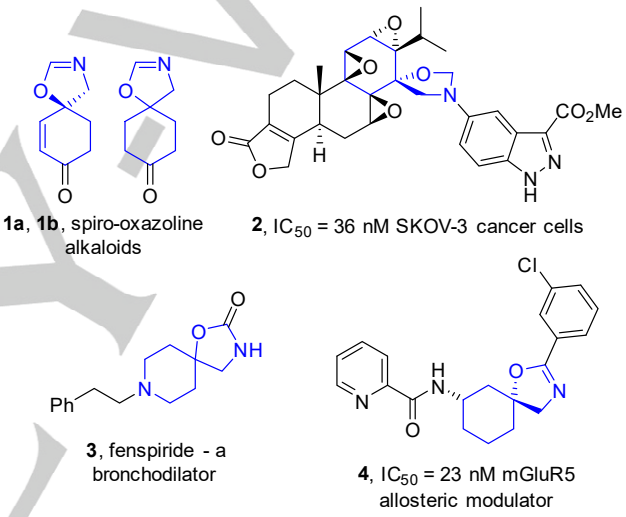

Figure 1 Examples of oxazaspirocycles.

Despite the substantial interest in the synthesis of spiroheterocyclic compounds, to the best of our knowledge, there are only two reported synthetic methods to access spirooxazoline compounds. Zhu reported a photochemical cycloaddition approach which appears to be limited to benzo-fused examples with the difluoro substitution pattern shown (Scheme 1a).[10] Lundbeck scientists described a multi-step route which converted a ketone into a spirooxazolidinone and then into the spirooxazoline (Scheme 1b).[9]

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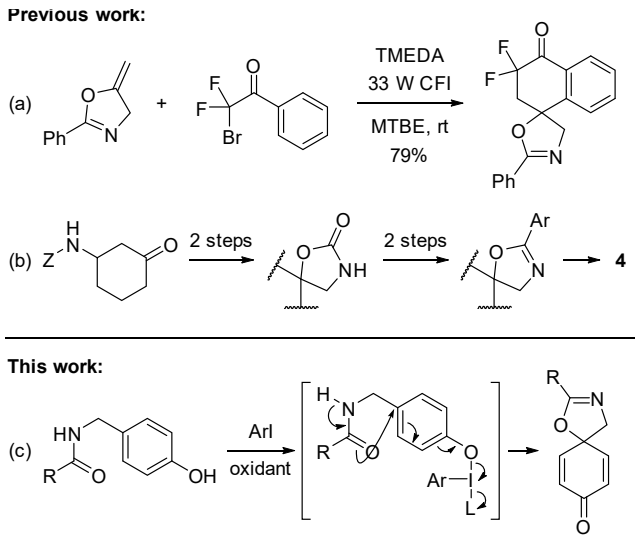


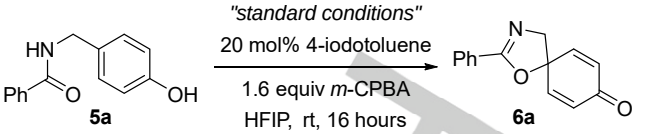
Scheme 1. Synthetic routes to spirooxazolines.

Our approach to spirooxazoline formation is by the dearomatizing cyclisation of phenols (and naphthols) mediated by in-situ generated hypervalent iodine(III) species (Scheme 1c). We envisaged that a pendent amide would cyclize on to the aromatic ring after activation of the oxygen by a λ^3-iodane. This concept was inspired by our previous work on the cyclization of amides onto alkenes and alkynes.[11,12] Oxidative dearomatization of phenols is a popular strategy in synthesis, especially using hypervalent iodine reagents under stoichiometric and catalytic conditions,[13,14] so it is surprising that this approach has not been used already to access the spirooxazoline framework.

Results and Discussion

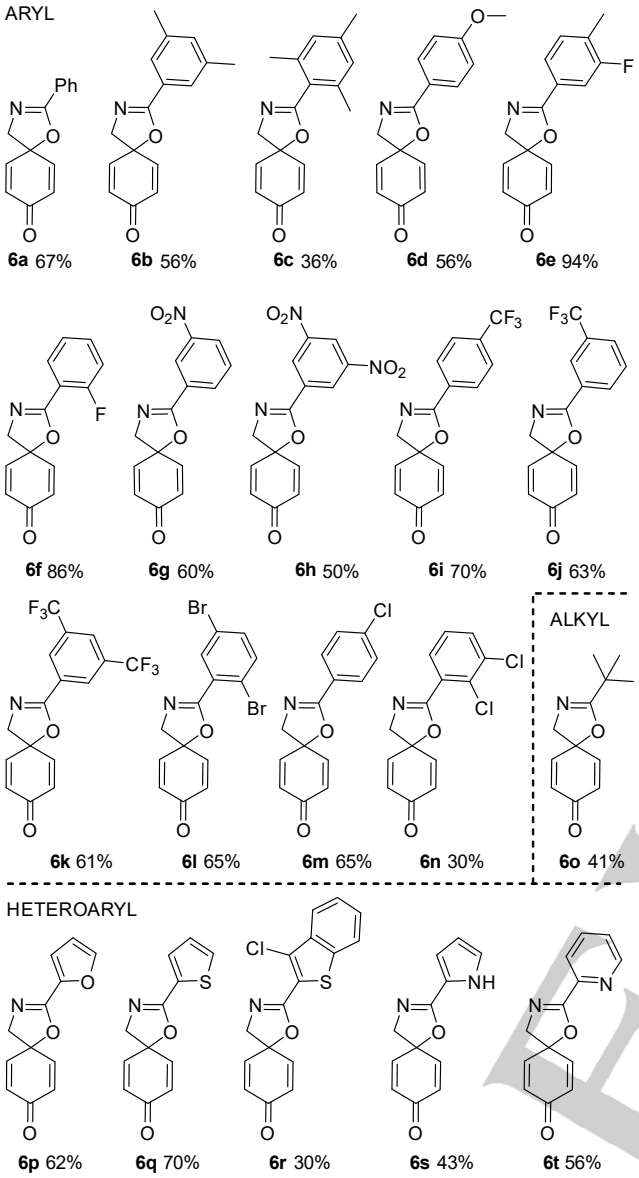
We initiated our study with amide 5a, prepared by acylation of the commercially available amine, and subjected it to conditions that would generate hypervalent iodine species in-situ (Table 1). Gratifyingly, smooth dearomatizing cyclization occurred to furnish spirocycle **6a** in 67% yield using 4-iodotoluene as the precatalyst in the presence of *m*-CPBA as oxidant in hexafluoroisopropanol (HFIP) at room temperature after 16 hours (entry 1). Increasing the amount of 4-iodotoluene did not lead to any improvement in yield (entry 2). Whereas reducing the amount of 4-iodotoluene led to a lower yield of product; however, a longer reaction time led to an augmented yield (entries 3-4). Changing the oxidant from m-CPBA to Oxone, Selectfluor or peracetic acid led to diminished yields (entries 5-7). Substituting 4-iodotoluene for 5-iodo-*m*-xylene or 2-iodoanisole was detrimental to the reaction outcome (entries 8-9) whereas iodobenzene displayed similar efficiency (entry 10). We decided to continue to use 4-iodotoluene rather than iodobenzene as the former is a solid and is easier to handle in small quantities. Changing the solvent from HFIP to MeCN was also detrimental to the yield (entry 11). Interestingly, only HFIP was found to be an effective solvent for this cyclization.[15]

Table 1. Optimization of oxidative dearomatization of phenol **5a**.



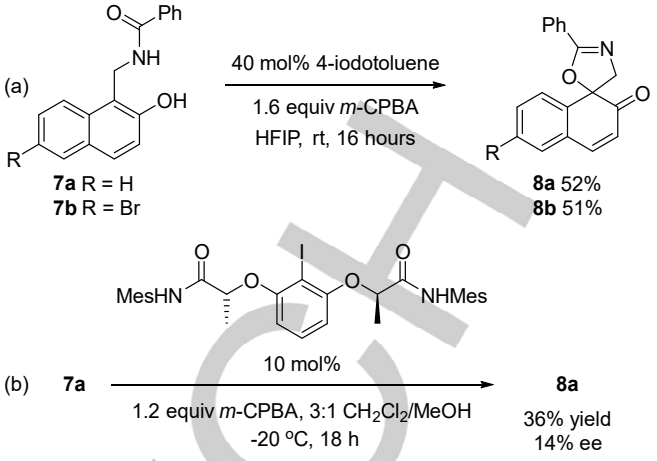
Entry	Deviation from standard conditions	Yield/%
1	none	67
2	40 mol% 4-iodotoluene	67
3	10 mol% 4-iodotoluene	33
4	10 mol% 4-iodotoluene, 48 hours	45
5	Oxone instead of *m*-CPBA	19
6	Selectfluor instead of *m*-CPBA	15
7	Peracetic acid instead of *m*-CPBA	33
8	10 mol% 5-iodo-m-xylene	22
9	20 mol% 2-iodoanisole	32
10	20 mol% iodobenzene	67
11	10 mol% 4-iodotoluene, MeCN	<5

The scope of the cyclization of phenols was investigated with a range of amides under our optimal reaction conditions (Scheme 2). Accordingly, aryl amides, alkyl amides and heteroaryl amide derivatives were prepared and these all cyclized in good yields. Alkyl and methoxy substituted phenyl amides were effective substrates and led to the formation of spirocycles **6b-d** in moderate yields. Notably, the presence of a fluorine on the phenyl ring led to higher yields of isolated compounds (**6e** and **6f**) than all of the other examples tested. The presence of one or two strongly electron-withdrawing nitro or trifluoromethyl groups was well tolerated in the cyclization (**6g-k**). Dibromide **6l**, chloride **6m** and dichloride **6n** were also readily prepared containing handles for further functionalization. *tert*-Butyl amide-derived spirocycle **6o** was obtained in moderate yield; however, the corresponding methyl amide-derived spirocycle could not be isolated as it decomposed readily during purification attempts. Heteroaromatic amides were also successfully cyclized with furan (**6p**), thiophene (**6q**), benzothiophene (**6r**), pyrrole (**6s**) and pyridine (**6t**) groups all tolerated with no unwanted over-oxidation observed.



Scheme 2. Cyclization scope with respect to the amide substituent.

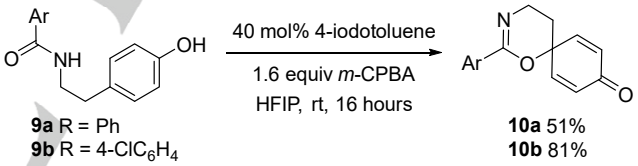
Next, we turned our attention to the oxidative dearomatization of naphthols **7a** and **7b**. Under the optimized conditions these amides furnished the expected spirocycles **8a** and **8b** in moderate yields (Scheme 3a). These cyclizations were somewhat sluggish using 20 mol% 4-iodotoluene, therefore 40 mol% was used instead. We also surveyed a range of chiral iodoarenes in an attempt to effect the enantioselective dearomatizing cyclization of **7a**. After some experimentation, **8a** was isolated with 14% ee using a known Ishihara precatalyst in 10 mol% at -20 °C (Scheme 3b).[16]



Scheme 3. (a) Oxidative dearomatization of naphthol derivatives. (b) Effect of a chiral iodoarene on the oxidative dearomatization of **7a**. Enantioselectivity determined by chiral HPLC analysis.

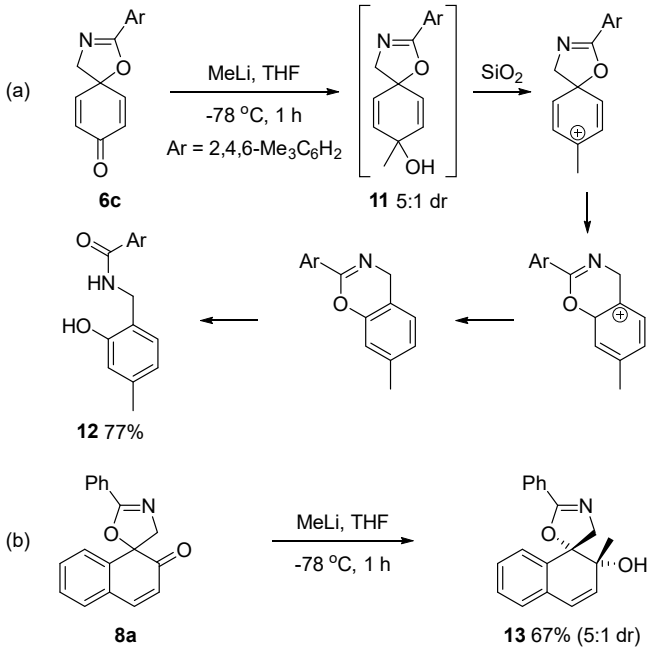
In order to probe the mechanism of this reaction, **7a** was subjected to the standard reaction conditions but in the presence of the radical inhibitors TEMPO and galvinoxyl. Product **8a** was isolated in both cases; thus suggesting that this process is not a radical one but proceeds via a mechanistic pathway similar to that shown in Scheme 1c.

The oxidative dearomatization was also amenable to the formation of [5.5]-spirocycles by the cyclization of the homologated compounds **9a** and **9b** (Scheme 4).



Scheme 4. Cyclization to form six-membered rings.

These spirocyclic compounds contain multiple points for further functionalization. For example, treatment of **6c** with MeLi led to chemoselective addition to the carbonyl group to form **11** as a 5:1 mixture of diastereomers. Attempts to purify **11** by flash chromatography with silica gel led to rearrangement to phenol **12** (Scheme 5a). Presumably the tertiary doubly allylic alcohol was protonated and water was lost which generated the stabilized carbocation. Subsequent [1,2]-rearrangement, aromatization and opening of the heterocyclic ring led to **12**.[17] Treatment of **8a** with MeLi also led to chemoselective addition to the carbon-yl group to furnish **13** in good yield and similar 5:1 diastereoselectivity (Scheme 5b). In this case, the spirocycle was stable to chromatography and the major diastereomer of **13** was isolated and assigned from the NOESY NMR spectrum (see the SI for details).



Scheme 5. Functionalization of dearomatized products.

Conclusion

The oxidative cyclization of phenols containing pendent amides to form spirooxazolines mediated by in-situ generated iodine(III) species is presented. This process operates with catalytic quantities of iodoarene and is successful for a wide range of substrates. The spirooxazoline products can be derivatized in a diastereoselective manner.

Experimental Section

General

NMR spectra were recorded at room temperature in the solvent and at the frequencies stated in each case. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent peaks. Infrared (IR) spectra (cm^{-1}) were recorded on a Nicolet 380 spectrum spotlight system, equipped with a diamond probe ATR attachment. High-resolution mass spectra (*m/z*) were obtained in the electrospray (ESI) mode. All reagents and solvents were purchased from commercial sources and used without further purification except THF (dried over 3 Å molecular sieves and then freshly distilled from Na/benzophenone under nitrogen). Flash chromatographic separations were performed on SigmaAldrich silica gel 60 (35-70 µm).

General Syntheses of Benzamide Starting Materials

Procedure A: To a solution of the benzylamine (2.44 mmol, 1 equiv) and triethylamine (2.44 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added the acid chloride (2.44 mmol) and this was left to stir at room temperature for 1-2 hours. The reaction mixture was diluted with CH_2Cl_2 (50 mL), quenched with saturated aqueous $NaHCO_3$ solution (25 mL) and the organic layer was separated and concentrated under vacuum. The obtained residue was diluted with MeOH (25 mL) and CH_2Cl_2 (5 mL) then aqueous NaOH solution (1 M, 18 mL) was added. After stirring for 10 minutes at room temperature, TLC analysis indicated that any bis-acylated product was cleaved to give the desired mono-acylated product. Glacial acetic acid was added to the reaction mixture until it was pH 7 and then the mixture was concentrated under vacuum. The residue was extracted with CH_2Cl_2 (50 mL) and washed with brine (50 mL). The organic layers were separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The organic residue was purified by recrystallisation (MeOH/Petroleum) to give the desired product as a solid.

Procedure B: A solution of acid chloride (2 mmol) in THF (4 mL) was cooled to 0 °C under nitrogen. Potassium phosphate tribasic (2.5 mmol) was added in one portion followed by the benzylamine (2 mmol). The mixture was stirred for 1-2 hour at room temperature then the reaction mixture was concentrated under reduced pressure. Water (6 mL) and EtOAc (2 mL) were added, the organic layer separated and then washed with 0.5 N HCl (5 mL) followed by water (5 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by recrystallisation (EtOAc-hexanes) to give the desired product as a solid.

Procedure C: Naphthol (6.94 mmol) and *N*-(hydroxymethyl)benzamide (1.05 g, 6.94 mmol) were dissolved in anhydrous ethanol (100 mL). Concentrated sulfuric acid (10 mL) was added dropwise and the reaction mixture was stirred for 7 hours at 50 °C. The reaction mixture was cooled to room temperature and washed with 1 M NaOH solution (50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was recrystallised (EtOAc-hexanes) to afford the desired product as a solid.[18]

N-(4-Hydroxybenzyl)benzamide **5a**. White solid (1.03 g, 55%) using general procedure A. FT-IR (cm^{-1}): v = 3397, 3073, 2820, 1614. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 9.30 (br, s, 1H), 8.95 (br, s, 1H), 7.89 (d, *J* = 7.1 Hz, 2H), 7.53-7.44 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 8.4 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H). ^{13}C{H} NMR: (DMSO-d_6, 100 MHz) δ 166.0, 156.3, 134.5, 131.1, 129.9, 128.6, 128.3, 127.3, 115.0, 42.2. HRMS: m/z calc'd for $C_{14}H_{13}NO_2Na$ $[M+Na]^+$ 250.0838, found 250.0840. Melting Point: 151-153 °C.

N-(4-Hydroxybenzyl)-3,5-dimethylbenzamide **5b**. Beige solid (3.4 g, 63%) using general procedure B. FT-IR (cm^{-1}): v = 3260, 2914, 1621, 1515. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 9.28 (s, 1H), 8.82 (t, *J* = 5.9 Hz, 1H), 7.49 (s, 2H), 7.14-7.12 (m, 3H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.34 (d, *J* = 5.9 Hz, 2H), 2.30 (s, 6H). ^{13}C{H} NMR: (DMSO-d_6, 100 MHz) δ 166.2, 156.2, 137.4, 134.5, 132.4, 130.0, 128.6, 125.0, 115.0, 42.1, 20.9. HRMS: m/z calc'd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332, found 256.1339. Melting Point: 165-166 °C.

N-(4-Hydroxybenzyl)-2,4,6-trimethylbenzamide **5c**. Pale yellow solid (0.81 g, 46%) using general procedure B. FT-IR (cm^{-1}): v = 3373, 3163, 2917, 1620. ^{1}H NMR: (DMSO-d_6, 400 MHz) δ 9.26 (s, 1H), 8.58 (t, *J* = 6.0 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.82 (s, 2H), 6.70 (d, *J* = 6.0 Hz, 2H), 4.30 (d, *J* = 6.0 Hz, 2H), 2.22 (s, 3H), 2.13 (s, 6H). ^{13}C{H} NMR: (DMSO-d_6, 100 MHz) δ 168.9, 156.2, 136.9, 135.8, 133.5, 129.9, 128.8, 127.6, 114.9, 41.8, 20.6, 18.8. HRMS: m/z calc'd for $C_{17}H_{20}NO_2$ $[M+H]^+$ 270.1489, found 270.1496. Melting Point: 150-151 °C.

N-(4-Hydroxybenzyl)-4-methoxybenzamide **5d**. Off-white crystalline solid (1.29 g, 61%) using general procedure B. FT-IR (cm^{-1}): v = 3257, 3009, 2971, 2936, 2836, 1604. ^{1}H NMR: (DMSO-d_6, 300 MHz) δ 9.29 (s, 1H), 8.79 (t, *J* = 5.9 Hz, 1H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.33 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H). ^{13}C{H} NMR: (DMSO-d_6, 75 MHz) δ 165.3, 161.3, 155.9, 129.9, 128.9, 128.4, 126.5, 114.8, 113.3, 55.1, 41.9. HRMS: m/z calc'd for $C_{15}H_{16}NO_3$ $[M+H]^+$ 258.1125, found 258.1126. Melting Point: 155-156 °C.

3-Fluoro-*N*-(4-hydroxybenzyl)-4-methylbenzamide **5e**. Pink solid (1.78 g, 53%) using general procedure B. FT-IR (cm^{-1}): v = 3314, 3012, 1630. ^{1}H

NMR: (DMSO-d_6, 300 MHz) δ 9.29 (s, 1H), 8.95 (t, *J* = 5.8 Hz, 1H), 7.66-7.61 (m, 2H), 7.41-7.35 (m, 1H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J*= 8.4 Hz, 2H), 4.35 (d, *J* = 5.9 Hz, 2H), 2.28 (s, 3H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 164.3 (d, *J* = 2.3 Hz), 160.0 (d, *J* = 241 Hz), 156.0, 133.9 (d, *J* = 7.0 Hz), 131.3 (d, *J* = 5.1 Hz), 129.4, 128.4, 127.5 (d, *J* = 17.1 Hz), 122.9 (d, *J* = 3.5 Hz), 114.7, 113.4 (d, *J* = 23.3 Hz), 41.9, 13.9 (d, *J* = 3.0 Hz). HRMS: m/z calc'd for $C_{15}H_{15}FNO_2$ $[M+H]^+$ 260.1081, found 260.1086. Melting Point: 131-132 ℃.

2-Fluoro-*N*-(4-hydroxybenzyl)benzamide **5f**. Beige coloured solid (1.40 g, 54%) using general procedure B. FT-IR (cm^{-1}): v = 3400, 3224, 3078, 1614. ^1H NMR: (DMSO-d_6, 300 MHz) δ 9.30 (s, 1H), 8.75 (t, *J* = 6.3 Hz, 1H), 7.64-7.58 (m, 1H), 7.55-7.48 (m, 1H), 7.31-7.24 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.71 (d, *J* = 8.5 Hz, 2H), 4.34 (d, *J* = 6.3 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 163.6, 159.2 (d, *J* = 248 Hz), 156.3, 132.3 (d, *J* = 8.4 Hz), 130.0 (d, *J* = 3.1 Hz), 129.4, 128.5, 124.4 (d, *J* = 3.3 Hz), 124.3 (d, *J* = 14.6 Hz), 116.1 (d, *J* = 22.4 Hz), 115.0, 42.2. HRMS: m/z calc'd for $C_{14}H_{13}FNO_2$ $[M+H]^+$ 246.0925, found 246.0928. Melting Point: 129-130 ℃.

N-(4-Hydroxybenzyl)-3-nitrobenzamide **5g**. Beige powder (2.0 g, 45%) by general method A. FT-IR (cm^{-1}): v = 3080, 3022, 1634, 1530, 1344, 1223. ^1H NMR: (DMSO-d_6, 300 MHz) δ 9.32 (s, 2H), 8.71 (t, *J* = 1.9 Hz, 1H), 8.39-8.31 (m, 2H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.40 (d, *J* = 5.7 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 163.9, 156.4, 147.8, 135.9, 133.8, 130.1, 129.3, 128.8, 125.9, 122.0, 115.1, 42.5. HRMS: m/z calc'd for $C_{14}H_{13}N_2O_4$ $[M+H]^+$ 273.0870, found 273.0874. Melting Point: 168-169 ℃.

N-(4-Hydroxybenzyl)-3,5-dinitrobenzamide **5h**. Yellow solid (2.1 g, 45%) using general procedure B. FT-IR (cm^{-1}): v = 3435, 3107, 1644, 1530, 1350. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.63 (t, *J* = 5.3 Hz, 1H), 9.34 (s, 1H), 9.10 (d, *J* = 1.8 Hz, 2H), 8.94 (t, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.43 (d, *J* = 5.6 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 161.9, 156.5, 148.2, 136.9, 129.0, 128.8, 127.6, 120.8, 115.1, 42.8. HRMS: m/z calc'd for $C_{14}H_{12}N_3O_6$ $[M+H]^+$ 318.0721, found 318.0717. Melting Point: 204-205 ℃.

N-(4-Hydroxybenzyl)-4-(trifluoromethyl)benzamide **5i**. White solid (1.5 g, 78%) using general procedure A. FT-IR (cm^{-1}): v = 3355, 3193, 1635, 1190. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.30 (s, 1H), 9.17 (t, *J* = 5.8 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.14-7.12 (m, 2H), 6.73-6.70 (m, 2H), 4.38 (d, *J* = 5.7 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 164.9, 156.3, 138.2, 131.1 (q, 32 Hz), 129.5, 128.7, 128.2, 125.3 (q, 3.8 Hz), 122.6 (q, *J* = 274 Hz), 115.1, 42.3. HRMS: m/z calc'd for $C_{15}H_{13}F_3NO_2$ $[M+H]^+$ 296.0893, found 296.0896. Melting Point: 155-156 ℃.

N-(4-Hydroxybenzyl)-3-(trifluoromethyl)benzamide **5j**. Light pink solid (1.2 g, 63%) using general procedure A. FT-IR (cm^{-1}): v = 3307, 3139, 1632, 1441. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.34 (s, 1H), 9.21 (t, *J* = 5.7 Hz, 1H), 8.23 (s, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J*= 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.39 (d, *J* = 5.8 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 164.5, 156.4, 135.3, 131.4, 130.1, 129.7, 129.4, 129.3, 129.0, 127.8 (q, *J* = 32 Hz), 124.1 (q, *J* = 272 Hz), 123.9 (q, *J* = 4.0 Hz), 115.1, 42.4. HRMS: m/z calc'd for $C_{15}H_{13}F_3NO_2$ $[M+H]^+$ 296.0893, found 296.0898. Melting Point: 154-155 ℃.

N-(4-Hydroxybenzyl)-3,5-bis(trifluoromethyl)benzamide **5k**. Pink solid (2.4 g, 68%) using general procedure A. FT-IR (cm^{-1}): v = 3272, 3140, 1642, 1286, 1142. ^1H NMR: (DMSO-d_6, 300 MHz) δ 9.41 (t, *J* = 5.6 Hz, 1H), 9.33 (s, 1H), 8.53 (s, 2H), 8.31 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.41 (d, *J* = 5.7 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 162.7, 156.3, 136.0, 130.2 (q, *J* = 33 Hz), 128.7, 128.3, 127.9 (q, *J* = 2.8 Hz), 124.5 (q, *J* = 3.5 Hz), 123.0 (q, *J* = 273 Hz), 114.8, 42.4. HRMS: m/z calc'd for $C_{16}H_{12}F_6NO_2$ $[M+H]^+$ 364.0772, found 364.0770. Melting Point: 176-177 ℃.

2,5-Dibromo-*N*-(4-hydroxybenzyl)benzamide **5l**. Dark brown solid (1.93 g, 34%) using general procedure B. FT-IR (cm^{-1}): v = 3290, 3076, 1628, 1580, 1510, 1310, 1225. ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.31 (s, 1H), 8.93 (t, *J* = 5.7 Hz, 1H), 7.61-7.53 (m, 3H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.72 (d, *J* = 8.3 Hz, 2H), 4.31 (d, *J* = 5.8 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 165.6, 156.3, 140.9, 134.7, 133.5, 131.2, 128.9, 128.7, 120.5, 118.2, 115.0, 42.1. HRMS: m/z calc'd for $C_{14}H_{12}Br_2NO_2$ $[M+H]^+$ 383.9229, found 385.9231. Melting Point: 187-188 ℃.

4-Chloro-*N*-(4-hydroxybenzyl)benzamide **5m**.[19] Off-white solid (1.03 g, 49%) using general procedure A. FT-IR (cm^{-1}): v = 3353, 3176, 2921, 1630. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.29 (s, 1H), 9.01 (t, *J* = 5.9 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 4.35 (d, *J* = 6.0 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 164.9, 156.3, 136.0, 133.2, 129.6, 129.2, 128.7, 128.4, 115.0, 42.4. HRMS: m/z calc'd for $C_{14}H_{13}ClNO_2$ $[M+H]^+$ 262.0629, found 262.0631. Melting Point: 195-196 ℃ (lit: 196-197 ℃).

2,3-Dichloro-*N*-(4-hydroxybenzyl)benzamide **5n**. White solid (1.3 g, 68%) using general procedure B. FT-IR (cm^{-1}): v = 3331, 3066, 1624, 772. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.30 (s, 1H), 8.93 (t, *J* = 5.6 Hz, 1H), 7.70-7.68 (m, 1H), 7.43-7.38 (m, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 4.33 (d, *J* = 5.8 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 165.5, 156.3, 139.4, 131.9, 130.9, 129.0, 128.6, 128.5, 128.0, 127.3, 115.0, 42.0. HRMS: m/z calc'd for $C_{14}H_{12}Cl_2NO_2$ $[M+H]^+$ 296.0240, found 296.0250. Melting Point: 161-163 ℃.

N-(4-Hydroxybenzyl)pivalamide **5o**. Brown solid (0.8 g, 48%) using general method B. FT-IR (cm^{-1}): v = 3418, 3121, 2963, 2932, 1627. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.24 (s, 1H), 7.93 (t, *J* = 5.9 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.5 Hz, 2H), 4.13 (d, *J* = 6.0 Hz, 2H), 1.11 (s, 9H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 177.2, 156.0, 130.3, 128.0, 114.9, 41.6, 38.0, 27.5. HRMS: m/z calc'd for $C_{12}H_{18}NO_2$ $[M+H]^+$ 208.1332, found 208.1337. Melting Point: 135-136 ℃.

N-(4-Hydroxybenzyl)furan-2-carboxamide **5p**. Pink solid (1.15 g, 65%) using general procedure B. FT-IR (cm^{-1}): v = 3119, 2815, 1633, 1591, 1513, 1221, 1184, 1038. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.28 (s, 1H), 8.80 (t, *J* = 6.0 Hz, 1H), 7.82 (s, 1H), 7.11-7.09 (m, 3H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.61-6.60 (m, 1H), 4.29 (d, *J* = 6.1 Hz, 2H). ^{13}C NMR: (DMSO-d_6, 100 MHz) δ 157.6, 156.3, 148.0, 145.0, 129.7, 128.7, 115.0, 113.3, 111.8, 41.4. HRMS: m/z calc'd for $C_{12}H_{12}NO_3$ $[M+H]^+$ 218.0812, found 218.0815. Melting Point: 162-163 ℃.

N-(4-Hydroxybenzyl)thiophene-2-carboxamide **5q**. Light brown solid (0.97 g, 51%) using general procedure B. FT-IR (cm^{-1}): v = 3073, 2827, 1613, 1548, 1510, 1239. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.28 (s, 1H), 8.92 (t, *J* = 5.8 Hz, 1H), 7.79 (d, *J* = 3.7 Hz, 1H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.15-7.11 (m, 3H), 6.72 (d, *J* = 8.4 Hz, 2H), 4.33 (d, *J* = 6.0 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 160.9, 156.3, 140.1, 130.7, 129.6, 128.6, 128.0, 127.9, 115.0, 42.0. HRMS: m/z calc'd for $C_{12}H_{12}NO_2S$ $[M+H]^+$ 234.0583, found 234.0587. Melting Point: 191-192 ℃.

3-Chloro-*N*-(4-hydroxybenzyl)benzo[*b*]thiophene-2-carboxamide **5r**. Light brown crystalline solid (0.2 g, 78%) using general procedure B. FT-IR (cm^{-1}): v = 3242, 3062, 2357, 1606, 1519, 1268, 1239. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.33 (s, 1H), 8.88 (t, *J* = 5.8 Hz, 1H), 8.11-8.09 (m, 1H), 7.90-7.88 (m, 1H), 7.60-7.56 (m, 2H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.73 (d, *J* = 8.3 Hz, 2H), 4.39 (d, *J* = 5.9 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 159.8, 156.1, 136.3, 135.7, 132.1, 128.7, 128.4, 127.1, 125.7, 123.1, 122.2, 118.4, 114.8, 42.3. HRMS: m/z calc'd for $C_{16}H_{13}ClNO_2S$ $[M+H]^+$ 318.0350, found 318.0350. Melting Point: 200-201 ℃.

N-(4-Hydroxybenzyl)-1*H*-pyrrole-2-carboxamide **6s**. Brick red powder (1.37 g, 39%) using general procedure B. FT-IR (cm^{-1}): v = 3417, 3115, 2838, 1650, 1526, 1513, 1334, 1188. ^1H NMR: (DMSO-d_6, 400 MHz) δ 11.43 (s, 1H), 9.26 (s, 1H), 8.40 (t, *J* = 6.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.84-6.78 (m, 2H), 6.70 (d, *J* = 8.4 Hz, 2H), 6.08-6.06 (m, 1H), 4.31 (d, *J* = 6.0 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 160.5, 156.1, 130.2, 128.5, 126.3, 121.2, 114.9, 109.9, 108.5, 41.4. HRMS: m/z calc'd

for $C_{12}H_{13}N_2O_2$ $[M+H]^+$ 217.0972, found 217.0976. Melting Point: 175-176 °C.

N-(4-Hydroxybenzyl)picolinamide **5t**. Brown solid (1.16 g, 61%) using general procedure B. FT-IR (cm^{-1}): v = 3175, 2850, 1632, 1531, 1514, 1231. ^1H NMR: (DMSO-d_6, 400 MHz) δ 9.27 (s, 1H), 9.14 (t, *J* = 5.8 Hz, 1H), 8.63-8.62 (m, 1H), 8.06-7.96 (m, 2H), 7.60-7.57 (m, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 6.70 (d, *J* = 8.2 Hz, 2H), 4.38 (d, *J* = 6.2 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 163.5, 156.1, 149.9, 148.3, 137.6, 129.6, 128.7, 126.3, 121.8, 114.9, 41.8. HRMS: m/z calc'd for m/z calc'd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.0972, found 229.0975. Melting Point: 182-184 °C.

N-((2-Hydroxynaphthalen-1-yl)methyl)benzamide **7a**.[17] Light brown solid (2.74 g, 71%) using general procedure C. FT-IR (cm^{-1}): v = 3265, 3130, 1660, 1650. ^1H NMR: (DMSO-d_6, 400 MHz) δ 10.28 (s, 1H), 9.11 (t, *J* = 5.1 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.90-7.88 (m, 2H), 7.81-7.76 (m, 2H), 7.53-7.41 (m, 4H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 4.88 (d, *J* = 5.2 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 167.4, 153.8, 133.6, 133.4, 131.4, 129.4, 128.2, 127.5, 126.5, 122.8, 122.6, 119.0, 115.7, 34.5. HRMS: m/z calc'd for $C_{18}H_{16}NO_2$ $[M+H]^+$ 278.1176, found 278.1181. Melting Point: 177-178 °C.

N-((6-Bromo-2-hydroxynaphthalen-1-yl)methyl)benzamide **7b**. Pale yellow solid (0.95 g, 59%) using general procedure C. FT-IR (cm^{-1}): v = 3462, 3425, 3148, 1624, 1572, 1501, 1293. ^1H NMR: (DMSO-d_6, 400 MHz) δ 10.37 (s, 1H), 9.04 (t, *J* = 5.1 Hz, 1H), 8.06 (d, *J* = 2.1 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.86-7.84 (m, 2H), 7.75 (d, *J* = 8.9 Hz, 1H), 7.56 (dd, J_1= 9.1 Hz, J_2 = 2.2 Hz, 1H), 7.51-7.47 (m, 1H), 7.45-7.40 (m, 2H), 7.22 (d, *J* = 9.0 Hz, 1H), 4.82 (d, *J* = 5.2 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 100 MHz) δ 167.2, 154.3, 133.6, 132.0, 131.4, 130.0, 129.5, 129.2, 128.6, 128.2, 127.4, 125.3, 120.1, 116.0, 115.5, 34.2. HRMS: m/z calc'd for $C_{18}H_{15}BrNO_2$ $[M+H]^+$ 356.0281, found 356.0282. Melting Point: 211-212 °C.

N-(4-Hydroxyphenethyl)benzamide **9a**. Off-white solid (2.0 g, 63%) using general procedure B. FT-IR (cm^{-1}): v = 3323, 3025, 1636, 1538, 1511, 1250. ^1H NMR: (DMSO-d_6, 300 MHz) δ 9.18 (s, 1H), 8.52 (t, *J* = 5.7 Hz, 1H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.51 7.42 (m, 3H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.68 (d, *J* = 8.3 Hz, 2H), 3.44-3.37 (m, 2H), 2.71 (t, *J* = 7.5 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 166.0, 155.6, 134.6, 131.0, 129.5, 129.4, 128.2, 127.0, 115.1, 41.2, 34.3. HRMS: m/z calc'd for $C_{15}H_{16}NO_2$ $[M+H]^+$ 242.1176, found 242.1180. Melting Point: 158-159 °C.

4-Chloro-*N*-(4-hydroxyphenethyl)benzamide **9b**. White solid (2.4 g, 68%) using general procedure B. FT-IR (cm^{-1}): v = 3307, 2871, 2797, 1650, 1592, 1511, 1240. ^1H NMR: (DMSO-d_6, 300 MHz) δ 9.19 (s, 1H), 8.62 (t, *J* = 5.5 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 3.44-3.37 (m, 2H), 2.71 (t, *J* = 7.5 Hz, 2H). $^{13}C\{H\}$ NMR: (DMSO-d_6, 75 MHz) δ 165.0, 155.6, 135.8, 133.3, 129.5, 129.4, 129.0, 128.3, 115.1, 41.3, 34.2. HRMS: m/z calc'd for $C_{15}H_{15}ClNO_2$ $[M+H]^+$ 276.0786, found 276.0790. Melting Point: 178-179 °C.

Synthesis of Spirocycles

Representative Procedure for Oxidative Cyclization of Benzamides and Naphthol Amides: Synthesis of 2-phenyl-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6a**. To a stirred solution of amide 5a (227 mg, 1.0 mmol) in HFIP (6 mL) was added *m*-CPBA (~75% purity, 380 mg, 1.6 mmol) and 4-iodotoluene (43.6 mg, 0.20 mmol). The resulting mixture was stirred overnight at room temperature and then a saturated aqueous solution of $NaHCO_3$ (6 mL) was added to the reaction mixture followed by water (6 mL). The organic layer was extracted with ethyl acetate (10 mL x 3), dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (3:1 petroleum ether/EtOAc) to afford 2-phenyl-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one 6a as a brown oil (158 mg, 67%). FT-IR (cm^{-1}): v = 3160, 2991, 1668, 1650, 1630, 1251. ^1H NMR: (DMSO, 400 MHz) δ 7.89 (d, *J* = 7.4 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 9.9 Hz, 2H), 6.26 (d, *J* = 9.9 Hz, 2H), 4.12 (s, 2H). $^{13}C\{H\}$ NMR: (DMSO, 100 MHz) δ 184.5, 161.6, 147.3, 132.0, 128.8, 128.1, 128.0, 127.0, 79.0, 63.6. HRMS: m/z calc'd for $C_{14}H_{12}NO_2$ $[M+H]^+$ 226.0863, found 226.0866.

2-(3,5-Dimethylphenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6b**. Yellow oil (56 mg, 56%). FT-IR (cm^{-1}): v = 3102, 1672, 1652, 1634, 1601, 1209. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.57 (s, 2H), 7.16 (s, 1H), 6.94 (d, *J* = 10.0 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 2H), 4.11 (s, 2H), 2.35 (s, 6H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 100 MHz) δ 184.8, 163.9, 146.2, 138.4, 133.8, 128.9, 126.5, 126.3, 79.2, 64.6, 21.3. HRMS: m/z calc'd for $[M+H]^+$ $C_{16}H_{16}NO_2$ 254.1176, found 254.1180.

2-Mesityl-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6c**. Pale yellow oil (36 mg, 36 %). FT-IR (cm^{-1}): v = 3040, 2921, 2830, 1716, 1671, 1635, 1611, 1574, 1429, 1248. ^1H NMR: ($CDCl_3$, 400 MHz) δ 6.92 (d, *J* = 10.0 Hz, 2H), 6.83 (s, 2H), 6.22 (d, *J* = 10.0 Hz, 2H), 4.09 (s, 2H), 2.31 (s, 6H), 2.23 (s, 3H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 100 MHz) δ 184.4, 163.7, 145.9, 139.7, 136.8, 128.6, 128.3, 124.3, 78.6, 64.4, 21.1, 19.7. HRMS: m/z calc'd for $C_{17}H_{18}NO_2$ $[M+H]^+$ 268.1332, found 268.1341.

2-(4-Methoxyphenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6d**. Colorless oil (28 mg, 56%). FT-IR (cm^{-1}): v = 3080, 2925, 1666, 1648, 1632, 1608, 1253. ^1H NMR: ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.8 Hz, 2H), 6.95-6.91 (m, 4H), 6.27 (d, *J* = 9.9 Hz, 2H), 4.09 (s, 2H), 3.85 (s, 3H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 100 MHz) δ 184.9, 163.4, 162.7, 146.4, 130.4, 128.9, 119.2, 114.0, 79.2, 64.6, 55.6. HRMS: m/z calc'd for $C_{15}H_{14}NO_3$ $[M+H]^+$ 256.0968, found 256.0970.

2-(3-Fluoro-4-methylphenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6e**. Light brown oil (75 mg, 94%). FT-IR (cm^{-1}): v = 3056, 2961, 1678, 1632, 1602, 1389, 1283, 1252. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.64-7.56 (m, 2H), 7.28-7.22 (m, 1H), 6.93 (d, *J* = 10.1 Hz, 2H), 6.29 (d, *J* = 10.1 Hz, 2H), 4.11 (s, 2H), 2.33 (d, *J* = 1.6 Hz, 3H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 75 MHz) δ 184.7, 162.7, 161.0 (d, *J* = 245 Hz), 146.0, 131.8 (d, *J* = 5.3 Hz), 129.7 (d, *J* = 17.5 Hz), 129.0, 126.2 (d, *J* = 9.0 Hz), 124.0 (d, *J* = 3.8 Hz), 115.2 (d, *J* = 25 Hz), 79.5, 64.7, 14.9 (d, *J* = 3.6 Hz). HRMS: m/z calc'd for $C_{15}H_{13}FNO_2$ $[M+H]^+$ 258.0925, found 258.0929.

2-(2-Fluorophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6f**. Light brown oil (51 mg, 86%). FT-IR (cm^{-1}): v = 3115, 2936, 2856, 1654, 1641, 1536, 1066, 978, 756, 695. ^1H NMR: ($CDCl_3$, 300 MHz) δ 7.90-7.84 (m, 1H), 7.54-7.46 (m, 1H), 7.23-7.14 (m, 2H), 6.95 (d, *J* = 10.1 Hz, 2H), 6.30 (d, *J* = 10.1 Hz, 2H), 4.17 (s, 2H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 75 MHz) δ 184.7, 161.5 (d, *J* = 259 Hz), 159.8, 145.9, 133.8 (d, *J* = 8.9 Hz), 131.2, 129.1, 124.3 (d, *J* = 3.7 Hz), 117.0 (d, *J* = 21.7 Hz), 115.1 (d, *J* = 10.1 Hz), 78.8, 65.0. HRMS: m/z calc'd for $C_{14}H_{11}FNO_2$ $[M+H]^+$ 244.0768, found 244.0770.

2-(3-Nitrophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6g**. Pale yellow oil (30 mg, 60%). FT-IR (cm^{-1}): v = 3059, 2976, 2871, 1695, 1645, 1635, 1579, 1449, 1347, 1265, 1212. ^1H NMR: ($CDCl_3$, 400 MHz) δ 8.78 (t, *J* = 1.93 Hz, 1H), 8.40-8.37 (m, 1H), 8.30-8.28 (m, 1H), 7.65 (t, *J* = 8.20 Hz, 1H), 6.93 (d, *J* = 10.1 Hz, 2H), 6.32 (d, *J* = 10.1 Hz, 2H), 4.18 (s, 2H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 100 MHz) δ 184.5, 161.5, 145.4, 134.2, 129.9, 129.3, 128.7, 126.6, 123.7, 80.1, 64.9. HRMS: m/z calc'd for $C_{14}H_{11}N_2O_4$ $[M+H]^+$ 271.0713, found 271.0719.

2-(3,5-Dinitrophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6h**. Yellow oil (50 mg, 50%). FT-IR (cm^{-1}): v = 3069, 1664, 1632, 1538, 1342, 1281, 1251. ^1H NMR: ($CDCl_3$, 400 MHz) δ 9.19-9.18 (m, 1H), 9.10-9.09 (m, 2H), 6.93 (d, *J* = 9.9 Hz, 2H), 6.36 (d, *J* = 9.9 Hz, 2H), 4.24 (s, 2H). $^{13}C\{H\}$ NMR: ($CDCl_3$, 100 MHz) δ 184.2, 159.7, 148.8, 144.6, 130.5, 129.6, 128.5, 121.5, 80.8, 65.0. HRMS: m/z calc'd for $C_{14}H_{10}N_3O_6$ $[M+H]^+$ 316.0564, found 316.0564.

2-(4-(Trifluoromethyl)phenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6i**. Pale yellow oil (70 mg, 70%). FT-IR (cm^{-1}): v = 3048, 2934, 2850, 1715, 1673, 1635, 1620, 1575, 1412, 1320, 1249. ^1H NMR: ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 10.0 Hz, 2H),

6.32 (d, *J* = 10.0 Hz, 2H), 4.15 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.6, 162.3, 145.7, 133.6 (q, *J* = 32.7 Hz), 130.1, 129.1, 128.9, 125.3 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272 Hz), 79.7, 64.7. HRMS: m/z calc'd for $C_{15}H_{11}F_3NO_2$ $[M+H]^+$ 294.0736, found 294.0741.

2-(3-(Trifluoromethyl)phenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6j**. Yellow oil (50 mg, 63%). FT-IR (cm^{-1}): v = 3046, 2936, 2836, 1714, 1670, 1635, 1626, 1571, 1409, 1320, 1250. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.21 (s, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 10.1 Hz, 2H), 6.30 (d, *J* = 10.1 Hz, 2H), 4.15 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 75 MHz) δ 184.7, 162.3, 145.7, 131.6, 131.7 (q, *J* = 33 Hz), 129.3, 129.1, 128.6 (q, *J* = 3.8 Hz), 127.6, 125.5 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 273.3 Hz), 79.8, 64.7. HRMS: m/z calc'd for $C_{15}H_{11}F_3NO_2$ $[M+H]^+$ 294.0736, found 294.0741.

2-(3,5-Bis(trifluoromethyl)phenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6k**. Blood red oil (61 mg, 61%) using general procedure D. FT-IR (cm^{-1}): v = 3078, 2980, 1674, 1636, 1602, 1396, 1280, 1250. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.40 (s, 2H), 8.01 (s, 1H), 6.94 (d, *J* = 10.0 Hz, 2H), 6.32 (d, *J* = 10.0 Hz, 2H), 4.18 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 75 MHz) δ 184.1, 161.0, 145.1, 132.4 (q, *J* = 34.4 Hz), 129.3, 129.0, 128.6 (q, *J* = 3.8 Hz), 125.4 (q, *J* = 3.7 Hz), 122.8 (q, *J* = 272.8 Hz), 80.2, 64.8. HRMS: m/z calc'd for $C_{16}H_{10}F_6NO_2$ $[M+H]^+$ 362.0610, found 362.0540.

2-(2,5-Dibromophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6l**. Light brown oil (32.5 mg, 65%). FT-IR (cm^{-1}): v = 3063, 2920, 2841, 1718, 1670, 1634, 1576, 1455, 1238. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.89 (d, *J* = 2.5 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.46 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 6.99 (d, *J* = 10.0 Hz, 2H), 6.31 (d, *J* = 10.0 Hz, 2H), 4.18 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.6, 161.5, 145.5, 135.7, 135.4, 134.4, 129.9, 129.2, 121.3, 120.9, 79.8, 64.8. HRMS: m/z calc'd for $C_{14}H_{10}Br_2NO_2$ $[M+H]^+$ 381.9073, found 381.9070.

2-(4-Chlorophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6m**. Brown solid (33 mg, 65%). FT-IR (cm^{-1}): v = 3052, 2920, 2870, 1714, 1672, 1653, 1635, 1596, 1490, 1337, 1261. ^{1}H NMR: [$CDCl_3$, 400 MHz)] δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 10.0 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 2H), 4.12 (s, 2H). ^{13}C{H} NMR: [$CDCl_3$, 100 MHz) δ 184.6, 162.8, 145.8, 138.5, 129.9, 129.0, 128.9, 125.1, 79.6, 64.4. HRMS: m/z calc'd for $C_{14}H_{11}ClNO_2$ $[M+H]^+$ 260.0473, found 260.0477.

2-(2,3-Dichlorophenyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6n**. Colorless oil (30 mg, 30%). FT-IR (cm^{-1}): v = 3060, 2991, 1667, 1634, 1414, 1195. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.70-7.67 (m, 1H), 7.63-7.60 (m, 1H), 7.31-7.27 (m, 1H), 7.00 (d, *J* = 10.0 Hz, 2H), 6.32 (d, *J* = 10.0 Hz, 2H), 4.19 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.6, 161.7, 145.6, 134.7, 133.2, 132.1, 129.7, 129.2, 128.6, 127.4, 79.7, 64.9. HRMS: m/z calc'd for $C_{14}H_{10}Cl_2NO_2$ $[M+H]^+$ 294.0083, found 294.0080.

2-(*tert*-Butyl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6o**. Colorless oil (196 mg, 41%). FT-IR (cm^{-1}): v = 2972, 2872, 1663, 1633, 1609, 1480, 1395, 1267, 1129. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 6.82 (d, *J* = 10.1 Hz, 2H), 6.23 (d, *J* = 10.1 Hz, 2H), 3.88 (s, 2H), 1.26 (s, 9H). ^{13}C{H} NMR: ($CDCl_3$, 75 MHz) δ 184.9, 174.0, 146.3, 128.7, 79.0, 64.1, 33.6, 27.8. HRMS: m/z calc'd for $C_{12}H_{16}NO_2$ $[M+H]^+$ 206.1176, found 206.1178.

2-(Furan-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6p**. Colorless oil (31 mg, 62%). FT-IR (cm^{-1}): v = 3128, 2872, 2779, 1715, 1672, 1635, 1560, 1479, 1399, 1266. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.60-7.59 (m, 1H), 7.02 (d, *J* = 3.5 Hz, 1H), 6.93 (d, *J* = 10.1 Hz, 2H), 6.54-6.53 (m, 1H), 6.30 (d, *J* = 10.1 Hz, 2H), 4.13 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.6, 155.7, 146.1, 145.6, 142.0, 129.2, 115.7, 111.9, 79.6, 64.6. HRMS: m/z calc'd for $C_{12}H_{10}NO_3$ $[M+H]^+$ 216.0655, found 216.0655.

2-(Thiophen-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6q**. Pale yellow oil (35 mg, 70%). FT-IR (cm^{-1}): v = 3090, 2861, 2760, 1667, 1648, 1633, 1428, 1250. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.63 (dd, J_1 = 3.7 Hz, J_2 = 1.1 Hz, 1H), 7.53 (dd, J_1 = 3.7 Hz, J_2 = 1.1 Hz, 1H), 7.11 (dd, J_1 = 5.0 Hz, J_2 = 3.7 Hz, 1H), 6.95 (d, *J* = 10.1 Hz, 2H), 6.30 (d, *J* = 10.1 Hz, 2H), 4.11 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.7, 159.3, 145.8, 131.4, 131.0, 129.1, 129.1, 128.0, 79.9, 64.6. HRMS: m/z calc'd for $C_{12}H_{10}NO_2S$ $[M+H]^+$ 232.0427, found 232.0429.

2-(3-Chlorobenzo[*b*]thiophen-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6r**. Pale yellow oil (15 mg, 30%). FT-IR (cm^{-1}): v = 3148, 3051, 2838, 2741, 1671, 1643, 1633, 1517, 1228. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.96-7.94 (m, 1H), 7.84-7.82 (m, 1H), 7.53-7.50 (m, 2H), 6.99 (d, J_1 = 10.1 Hz, 2H), 6.32 (d, *J* = 10.1 Hz, 2H), 4.20 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.6, 158.4, 145.6, 138.3, 137.1, 129.3, 128.0, 125.7, 125.3, 123.6, 122.8, 122.2, 79.9, 64.7. HRMS: m/z calc'd for $C_{16}H_{11}ClNO_2S$ $[M+H]^+$ 316.0194, found 316.0195.

2-(1*H*-Pyrrol-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6s**. Reddish oil (43 mg, 43%). FT-IR (cm^{-1}): v = 3100, 2942, 2830, 1671, 1635, 1620, 1448, 1270. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 10.71 (s, 1H), 6.96-6.91 (m, 3H), 6.80 (s, 1H), 6.29-6.25 (m, 3H), 4.07 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.7, 158.5, 145.9, 129.0, 123.2, 118.7, 114.3, 110.2, 79.2, 63.6. HRMS: m/z calc'd for $C_{12}H_{11}N_2O_2$ $[M+H]^+$ 215.0815, found 215.0821.

2-(Pyridin-2-yl)-1-oxa-3-azaspiro[4.5]deca-2,6,9-trien-8-one **6t**. Pale yellow oil (28 mg, 56%). FT-IR (cm^{-1}): v = 3054, 2851, 2760, 1671, 1633, 1522, 1483, 1345, 1265. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 8.76-8.74 (m, 1H), 8.07-8.04 (m, 1H), 7.84 (td, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 1H), 7.48-7.43 (m, 1H), 6.98 (d, *J* = 10.2 Hz, 2H), 6.30 (d, *J* = 10.2 Hz, 2H), 4.20 (s, 2H). ^{13}C{H} NMR: ($CDCl_3$, 75 MHz) δ 184.7, 150.2, 145.8, 137.0, 129.1, 126.3, 124.3, 80.1, 64.8. HRMS: m/z calc'd for $C_{13}H_{11}N_2O_2$ $[M+H]^+$ 227.0815, found 227.0818.

2'-Phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-one **8a**. Pale yellow oil (26 mg, 52%). FT-IR (cm^{-1}): v = 3160, 3053, 2869, 1715, 1673, 1652, 1603, 1569, 1547, 1367, 1338, 1283, 770. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.08-8.06 (m, 2H), 7.56-7.35 (m, 8H), 6.21 (d, *J* = 10.0 Hz, 1H), 4.48 (d, *J* = 15.4 Hz, 1H), 4.01 (d, *J* = 15.4 Hz, 1H). ^{13}C{H} NMR: ($CDCl_3$ 100 MHz) δ 197.8, 164.3, 145.8, 142.3, 132.0, 131.0, 129.7, 129.0, 128.9, 128.8, 128.6, 127.0, 125.7, 123.7, 86.6, 69.8. HRMS: m/z calc'd for $C_{18}H_{14}NO_2$ $[M+H]^+$ 276.1019, found 276.1019. Chiralpak IB, 254 nm, hexane/IPA gradient (100:0 to 90:10 over 35 min), 1 mL/min, retention times 12.9 & 15.1 minutes.

6-Bromo-2'-phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-one **8b**. Pale yellow oil (25.5 mg, 51%). FT-IR (cm^{-1}): v = 3273, 3060, 2922, 2869, 1718, 1679, 1655, 1602, 1579, 1556, 1483, 1367, 1338, 1283, 1246. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 8.06-8.04 (m, 2H), 7.56-7.40 (m, 6H), 7.32-7.30 (m, 1H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.47 (d, *J* = 15.0 Hz, 1H), 4.00 (d, *J* = 15.0 Hz, 1H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 197.0, 164.3, 144.1, 141.0, 133.7, 132.3, 132.1, 131.0, 128.9, 128.7, 127.4, 126.8, 125.0, 123.0, 86.3, 69.7. HRMS: m/z calc'd for $C_{18}H_{13}{}^{81}BrNO_2$ $[M+H]^+$ 356.0104, found 356.0111.

2-Phenyl-1-oxa-3-azaspiro[5.5]undeca-2,7,10-trien-9-one **10a**. Pale yellow oil (51 mg, 51%). FT-IR (cm^{-1}): v = 3067, 2925, 2867, 2761, 1672, 1655, 1653, 1536, 1346, 1279, 1219. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.90 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.38(t, *J* = 7.4 Hz, 2H), 6.97 (d, *J* = 10.2 Hz, 2H), 6.30 (d, *J* = 10.2 Hz, 2H), 3.76 (t, *J* = 6.1 Hz, 2H), 2.00 (t, *J* = 6.1 Hz, 2H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 184.7, 154.3, 146.7, 133.2, 131.0, 129.1, 128.3, 127.2, 71.7, 40.3, 30.5. HRMS: m/z calc'd for $C_{15}H_{14}NO_2$ $[M+H]^+$ 240.1019, found 240.1019.

2-(4-Chlorophenyl)-1-oxa-3-azaspiro[5.5]undeca-2,7,10-trien-9-one **10b**. Pale yellow oil (81 mg, 81%). FT-IR (cm^{-1}): v = 3053, 2867, 2740, 1673, 1656, 1638, 1596, 1536, 1486, 1398, 1346, 1278. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.83 (d, *J* = 8.6 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 10.2 Hz, 2H), 6.30 (d, *J* = 10.2 Hz, 2H), 3.73 (t, *J* = 6.2 Hz, 2H), 2.00 (t, *J* = 6.2 Hz, 2H). ^{13}C{H} NMR: ($CDCl_3$, 75 MHz) δ 184.6, 153.4, 146.4, 137.1, 131.7,

129.2, 128.6, 128.5, 71.8, 40.2, 30.4. HRMS: m/z calc'd for $C_{15}H_{13}ClNO_2$ $[M+H]^+$ 274.0629, found 274.0629.

Methylation of Spirocycles: To a solution of spirocycle (0.32 mmol, 1 equiv) in dry THF (5 mL) at -78 ˚C under a nitrogen atmosphere, was added MeLi (1.2 equiv, 1.6 M in hexane) dropwise over 5 minutes. The reaction mixture was stirred at -78 ˚C for 1 hour, then quenched with saturated aqueous NH_4Cl solution (5 mL) at -78 ˚C. The aqueous layer was extracted with ethyl acetate (2 x 5 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography (petroleum ether/ethyl acetate (4:1 then 2:1)) to yield the corresponding product.

N-(2-Hydroxy-4-methylbenzyl)-2,4,6-trimethylbenzamide **12**. Colorless oil (70 mg, 77%). FT-IR (cm^{-1}): ν = 3268, 2969, 2720, 1602, 1542, 1506, 1458, 1378, 1268. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.06 (s, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.80 (s, 2H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.30 (s, 1H), 5.90 (t, *J* = 5.5 Hz, 1H), 4.49 (d, *J* = 5.5 Hz, 2H), 2.26 (s, 9H), 2.19 (s, 3H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 170.8, 154.1, 138.7, 134.6, 134.3, 131.0, 129.4, 128.3, 126.8, 124.6, 115.3, 43.7, 21.2, 19.2, 16.0. HRMS: m/z calc'd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.1645, found 2844.1645

2-Methyl-2'-phenyl-2*H*,4'*H*-spiro[naphthalene-1,5'-oxazol]-2-ol **13**. The crude reaction mixture contained a 5:1 ratio of diastereomers. The major diastereomer was obtained as a colorless oil (60 mg, 67%). Characterization data for the major diastereomer is provided only. FT-IR (cm^{-1}): ν = 3241, 2975, 2851, 2700, 1606, 1523, 1501, 1478, 1346, 1285, 1220. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.97-7.95 (m, 2H), 7.49-7.13 (m, 8H), 6.51 (d, *J* = 9.8 Hz, 1H), 6.00 (d, *J* = 9.8 Hz, 1H), 4.43 (d, *J* = 15.4 Hz, 1H), 4.08 (d, *J* = 15.4 Hz, 1H), 2.66 (s, 1H), 1.32 (s, 3H). ^{13}C{H} NMR: ($CDCl_3$, 100 MHz) δ 163.2, 137.0, 134.5, 131.6, 131.4, 130.0, 128.6, 128.4, 128.4, 127.5, 127.5, 124.8, 90.9, 72.5, 60.5, 21.3. HRMS: m/z calc'd for $C_{19}H_{18}NO_2$ $[M+H]^+$ 292.1332, found 292.1336.

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Keywords: spirocycle • oxazoline • dearomatization • iodine • cyclization

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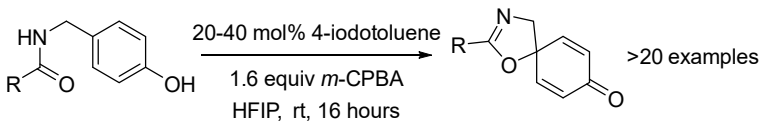

The oxidative spirocyclization of phenols and naphthols containing pendent amides is described that grants access to unusual spirooxazoline compounds. These rare spirocycles are prepared by an iodine(I)/(III) catalytic cycle.

Researcher Twitter usernames: @DrWesleyMoran; @iUmyrr

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Key topic: Hypervalent Iodine