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Direct Arylation of Sydnones with Aryl Chlorides towards Highly-Substituted Pyrazoles

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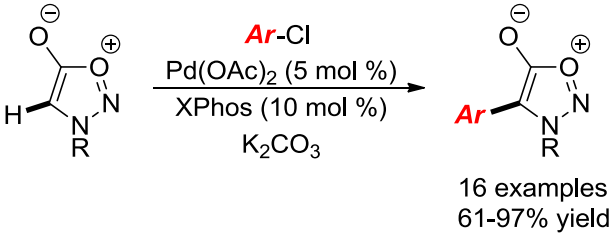
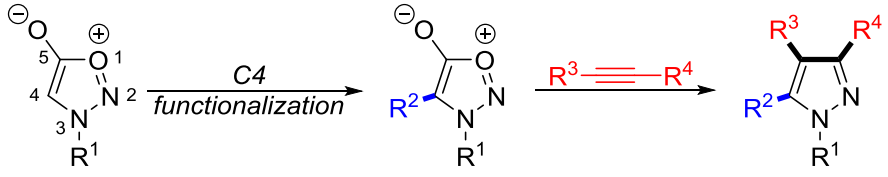


Abstract: The direct arylation of the C4 position of both N-alkyl- and N-arylsydnones with aryl/heteroaryl chlorides has been realized. The reaction is quite general and allows access to a wide range of 4-substituted sydnones. Yields of more challenging substrates can be improved through the use of aryl bromides.

Pyrazoles are common fragments in biologically active molecules, and their presence in a number of blockbuster drugs[1] and agrochemicals[2] has led to widespread interest in developing new strategies to access these valuable structures. Recent studies in our labs have focused on the use of sydnones for the preparation of functionalized pyrazoles via alkyne cycloadditions, with a particular focus on understanding the underlying reasons for reaction regioselectivity.[3, 4, 5] From a synthetic standpoint, a diverse range of pyrazoles can, in principle, be made available by a sequence involving sydnone functionalization followed by cycloaddition. As shown in Scheme 1, this strategy allows pyrazoles to be generated in two steps with the introduction of new substituents at all carbon atoms on the heteroaromatic ring.

Scheme 1: Strategy for the Preparation of Highly-Functionalized Pyrazoles

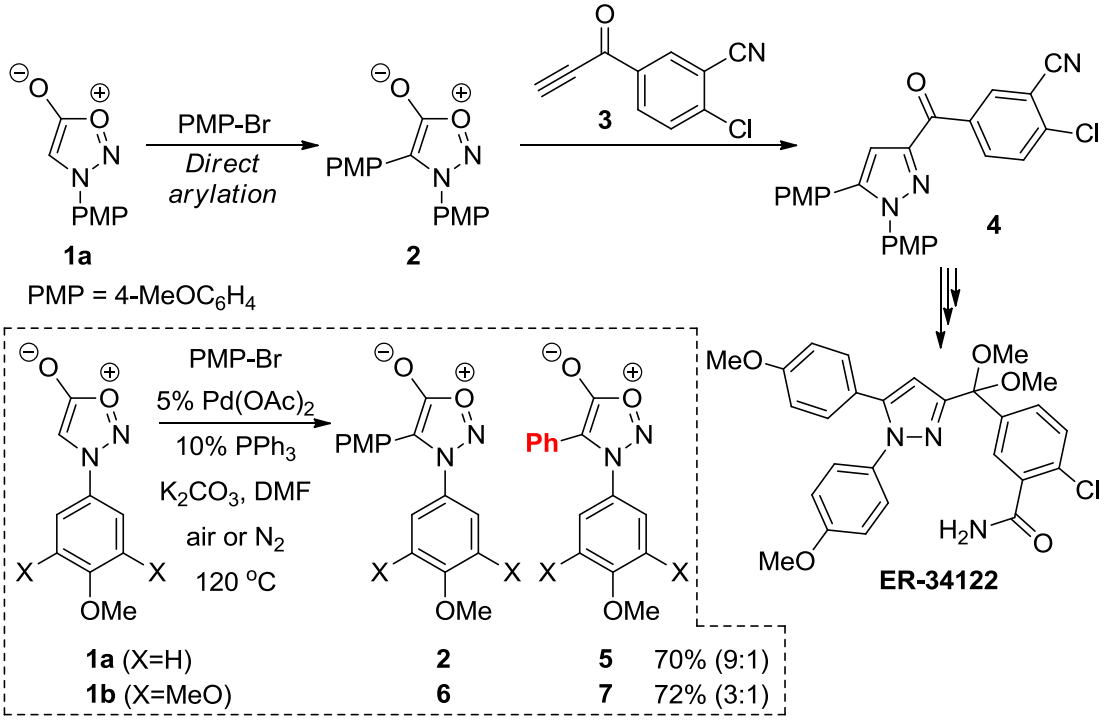


We have reported preliminary attempts to realize this idea by implementing a Suzuki-Miyaura cross-coupling reaction of 4-bromosydnones, followed by cycloaddition with a series of terminal alkynes and alkynylboronates.[6, 7] Our method was superseded however by Moran and Rodriguez who described a palladium-catalyzed direct arylation approach that avoided the need for bromination of the parent sydnone.[8, 9]

In connection with our interest in developing modular approaches to bioactive N-arylpyrazoles, we set out to employ a sequential sydnone direct arylation – cycloaddition for the synthesis of ER-34122, a potent dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity.[10] As shown in Scheme 2, employing Moran's conditions for the direct arylation provided the expected

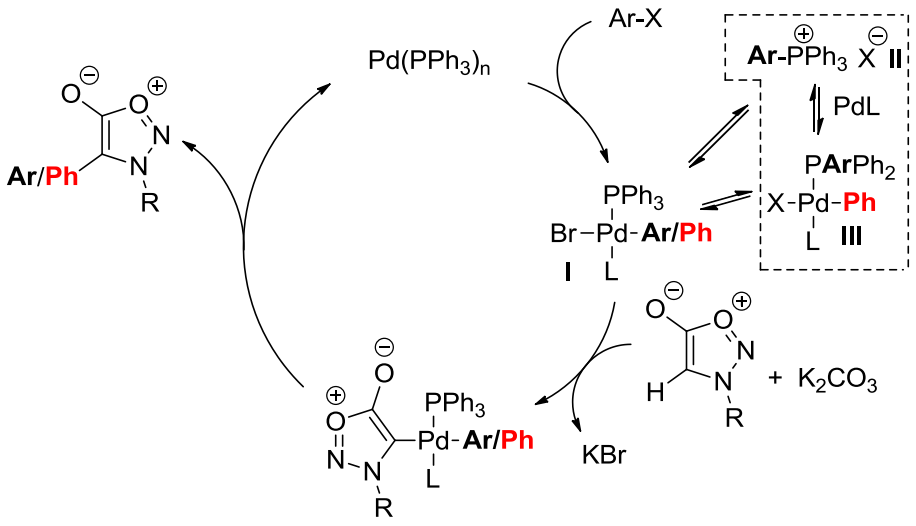
product **2** in good yield. Surprisingly however, this compound was accompanied by a small amount of the corresponding 4-Ph sydnone **5** which proved difficult to separate from **2**. Further investigation showed that this competing side reaction could become quite significant; direct arylation of **1b** provided a 3:1 mixture of **6** and **7**, albeit in high yield.

Scheme 2: Proposed Route to ER-34122



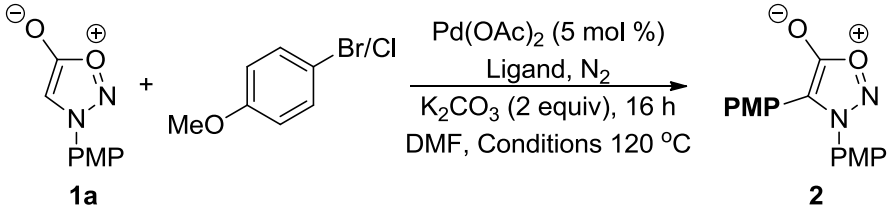
We speculated that by-products **5** and **7** formed as a result of aryl-aryl interchange from the triphenylphosphine ligand (via **I/II/III**) because of a slow transmetallation step in the cross-coupling reaction (Scheme 3). This hypothesis was based on the mechanistic studies of related aryl-aryl interchange of phosphine ligands in palladium-catalyzed cross coupling reactions reported by Novak et al.[11]

Scheme 3 Proposed Mechanistic Pathway



To overcome the issue of aryl-aryl interchange we decided to focus our optimization studies on the nature of the ligand, our results are shown in Table 1. Removing phosphine altogether resulted in a poor yield of sydnone (entry 1), while tributylphosphine furnished **2** in moderate yield (entry 2). As we had identified the transmetallation step as problematic, we postulated that Buchwald's biarylphosphine ligands could promote the cross-coupling and ultimately lead to a more general set of conditions.[12] Indeed, we were pleased to find that employing 10 mol % of XPhos with 5 mol % $Pd(OAc)_2$ afforded **2** in excellent yield (entry 3). Moreover, this catalyst system permitted previously unreactive aryl chlorides to participate in direct arylation quite smoothly under these new conditions with only a small erosion of yield (entry 4). Finally, we found the reaction to be amenable to scale up, delivering **2** on gram scale in almost quantitative yield.

Table 1: Optimization of Reaction Conditions[a]

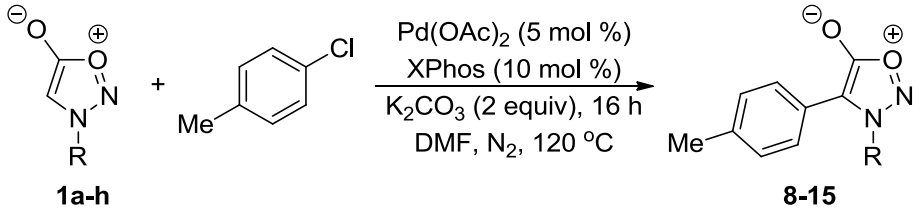


Entry[a]	Ligand	Ar-X	Yield 2[b]
1	None	4-$MeOC_6H_4Br$	28%
2	PBu_3 (50 mol %)	4-$MeOC_6H_4Br$	50%
3	XPhos (10 mol %)	4-$MeOC_6H_4Br$	86%
4	XPhos (10 mol %)	4-$MeOC_6H_4Cl$	79%
			97%[c]

[a]Reaction conditions: **1a** (0.5 mmol), 4-$MeOC_6H_4Cl$/Br (0.8 mmol), $Pd(OAc)_2$ (0.025 mmol), Ligand and K_2CO_3 (1.0 mmol) in DMF (2 mL) stirred at 120 ^oC for 16 hours under N_2. [b]Isolated yields of purified compounds. [c]5 mmol scale.

Using optimized conditions, we next decided to explore the scope of the direct arylation using 4-chlorotoluene, and a series of sydnones, our results are shown in Table 2. A range of N-aryl groups were well tolerated in the coupling (entries 1 – 5). However, it should be noted that 4-fluorophenyl sydnone **12** (entry 5) was unstable in solution and decomposed in chloroform and dichloromethane. We were also pleased to find that N-alkylsydnones coupled smoothly (entries 6-8) when a reduced reaction temperature of 80 ^oC was used. This was consistent with Moran's observations that lower temperatures were required for the coupling of N-alkylsydnones, due to thermal instability.[8]

Table 2: Sydnone Direct Arylation Scope[a]

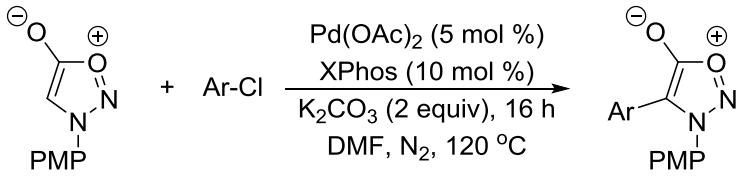


Entry	R	Product	Yield[b]
1	4-$MeOC_6H_4$; **1a**	**8**	83%
2	3,4,5-$(MeO)_3C_6H_2$; **1b**	**9**	96%
3	4-$EtOC_6H_4$; **1c**	**10**	77%
4	Ph; **1d**	**11**	83%
5	4-FC_6H_4; **1e**	**12**	68%
6	Me; **1f**	**13**	67% [c]
7	Et; **1g**	**14**	72% [c]
8	Bn; **1h**	**15**	61% [c]

[a]Reaction conditions: **1a** (0.5 mmol), 4-MeC_6H_4Cl (0.8 mmol), $Pd(OAc)_2$ (0.025 mmol), XPhos (0.05 mmol) and K_2CO_3 (1.0 mmol) in DMF (2 mL) stirred at 120 ^oC for 16 hours. [b]Isolated yields of purified compounds. [c]Reaction conducted at 80 ^oC.

We next explored the scope of the direct arylation reaction using a selection of aryl chlorides and our results are summarized in Table 3. The cross-coupling was successful for a series of aryl (entries 1-7) and heteroaromatic substrates (entries 8, 9), although 4-chloroaniline and 4-chlorophenol provided the corresponding sydnones (**19** and **20**, respectively) in poorer yields. Fortunately however, these sydnones could be obtained in much higher yields when the corresponding aryl bromides were used instead (scheme 4). We were also pleased to find that the use of an aryl bromide improved the yield of direct arylation with N-benzylsydnone, in the one example studied (scheme 4).

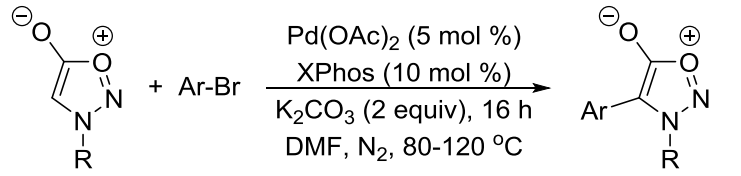
Table 3: Scope of Direct Arylation of Aryl Chlorides[a]



Entry	ArCl	Product	Yield[b]
1	Ph	**5**	83%
2	3-$O_2NC_6H_4$	**16**	85%
3	2-ClC_6H_4	**17**	94%
4	3-ClC_6H_4	**18**	79%
5	4-$H_2NC_6H_4$	**19**	22%
6	4-HOC_6H_4	**20**	Trace
7	2-thiophenyl	**21**	89%
8	4-pyridyl	**22**	78%[c]

[a]Reaction conditions: **1a** (0.5 mmol), **2a(**Br/Cl**)** (0.8 mmol), $Pd(OAc)_2$ (0.025 mmol), XPhos (0.05 mmol) and K_2CO_3 (1.0 mmol) in DMF (2 mL) stirred at 120 °C for 16 hours. [b]Isolated yields of purified compounds. [c]3 equivalents of K_2CO_3 used.

Scheme 4: Improved Yields Obtained with Aryl Bromides

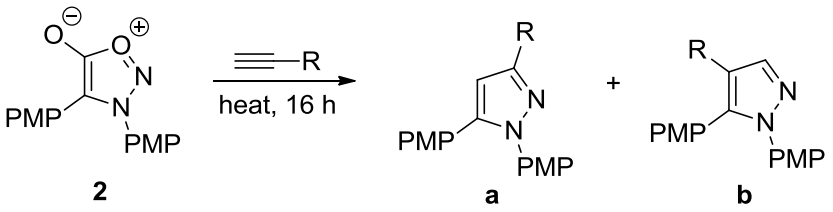


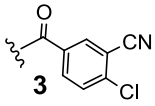
1a: R: PMP
1h: R: Bn

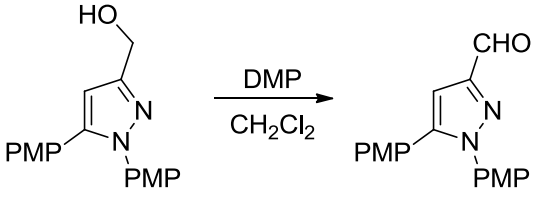
19: R: PMP, Ar: 4-$H_2NC_6H_4$; **93%**
20: R: PMP, Ar: 4-HOC_6H_4; **58%**
23: R: Bn, Ar: 4-$MeOC_6H_4$; **87%**

The incorporation of substituents at the sydnone C4 position can often reduce the efficiency of these substrates in cycloaddition reactions,[7b] and so we decided to explore the reaction of **3a** with a small selection of alkynes to evaluate the applicability of this method to access ER-34122 and analogs. As shown in Scheme 5, compound **2** reacted with ethyl propiolate to give the corresponding pyrazole as a mixture of regioisomers **24a,b** in low yield. The temperatures required in this case resulted in significant polymerization of the alkyne leading to contaminated products that could not be easily purified. In contrast, ynone **3**[13] underwent efficient cycloaddition but again provided pyrazoles **4a,b** an equal mixture of regioisomers. However, aldehyde **26**, a known precursor of ER-34122, was generated in good overall yield and regioselectivity by carrying out a cycloaddition reaction of **2** and propargyl alcohol, followed by oxidation by the Dess-Martin reagent. The minor isomer of the aldehyde was separated from **26** after column chromatography.

Scheme 5: Cycloaddition Reactions of 2



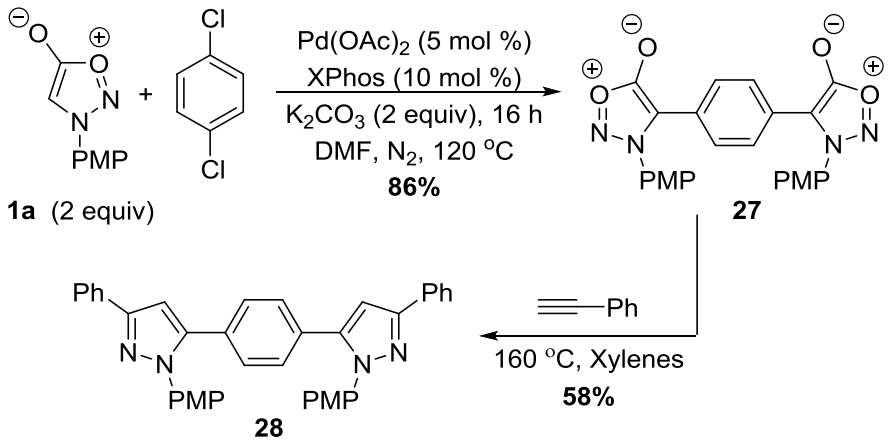
R	Conditions	Yield (a:b)
CO_2Et	1,2-$Cl_2C_6H_4$, 140-180 °C	**24;** <60% (1:1)
 **3**	1,2-$Cl_2C_6H_4$, 140 °C	**4;** 95% (1:1)
CH_2OH	xylenes, 160 °C	**25;** 97% (93:7)



25a:b (93:7) **26; 73%**

Finally, we have also found this chemistry to be applicable to the synthesis of aryl-linked sydnones. Specifically, the coupling reaction of **1a** with 1,4-dichlorobenzene provided sydnone dimer **27** in excellent yield. Moreover, the cycloaddition of **27** with phenylacetylene proceeded smoothly to afford **28** as a single regioisomer (as judged by 400 MHz ^{1}H NMR spectroscopy), albeit in moderate yield (Scheme 6). Interestingly, aryl-linked pyrazoles **28** are established organic electroluminescent molecules.[14] Therefore, aryl-linked sydnones such as **27** provide direct access to a range of these compounds, with significant potential for diversification.

Scheme 6: Preparation and Cycloaddition of Aryl-Linked Sydnone Dimer 27



In conclusion, we have developed a highly versatile and general method for the direct arylation of the sydnone C4 position. The reaction has a broad scope with respect to both coupling partners and allows aryl chlorides to be employed. The utility of the products was demonstrated in cycloaddition reactions with alkynes to form a drug compound precursor and an established class electroluminescent molecules. This robust two-step sydnone direct arylation - cycloaddition should permit the rapid construction of diverse pyrazole libraries.

Experimental Section

General Procedure for the Direct Arylation of Sydnones. A flask equipped with a reflux condenser was charged with a mixture of sydnone (1 eq.), aryl halide (1.5 eq.), palladium acetate (5 mol %), XPhos (10 mol %) and potassium carbonate (2-3 eq.) in DMF (0.1 – 0.5 M) under an atmosphere of nitrogen, and heated at 80 - 120 °C for 16 hours. The reaction was allowed to cool to ambient temperature and water was added. The resulting mixture was extracted with ethyl acetate:40-60 petroleum ether (9:1) and the combined organic layers dried over $MgSO_4$ and concentrated in vacuo. Flash silica chromatography (eluting solvent 20%-100% ethyl acetate in 40-60 petroleum ether) afforded the target 3,4-disubstituted sydnones. The compounds could be further purified by recrystallization from ethanol or dichloromethane/petrol.

3,4-Bis(4-methoxyphenyl)sydnone (**2**).[15] Sydnone **1a** (1.00 g, 5.21 mmol) and 4-chloroanisole (0.99 g, 7.8 mmol) were subjected to the general conditions affording **2** as a tan solid (1.51 g, 97%). M.p.: 136-137 °C (dec.) (lit.[15] 139–140 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (3H, s), 3.89 (3H, s), 6.79 – 6.86 (2H, m), 6.98 – 7.06 (2H, m), 7.20– 7.26 (2H, m), 7.35 – 7.43 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.4, 55.9, 108.0, 114.4, 115.2, 117.0, 126.3, 127.4, 129.0, 159.8, 162.1, 167.4.

[1,5-Bis(4-methoxyphenyl)-1H-pyrazol-3-yl](3-cyano-4-chlorophenyl)-methanone (**4a**) and [1,5-Bis(4-methoxyphenyl)-1H-pyrazol-4-yl](3-cyano-4-chlorophenyl)-methanone (**4b**). A flask was charged with **2** (183 mg, 0.614 mmol) and **3** (233 mg, 1.23 mmol) in 1,2-dichlorobenzene (4 mL) and heated at 140 ^{o}C for 24 hours. After cooling to RT, the mixture was directly loaded onto a short silica plug and 1,2-dichlorobenzene removed by elution with 100% petroleum ether, the crude material was then eluted with 100% ethyl acetate. The material was further purified by flash silica chromatography (eluting solvent: 10%– 40% EtOAc) affording **4a** as a yellow solid (130 mg, 48%) and **4b** as an orange oil (128 mg, 47%). **4a**: M.p.: 141-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (3H, s), 3.85 (3H, s), 6.86 (2H, d, J = 8.5 Hz), 6.91 (2H, d, J = 9.0 Hz), 7.15 (1H, s), 7.17 (2H, d, J = 9.0 Hz), 7.22-7.33 (2H, m), 7.64 (1H, d, J = 8.5 Hz), 8.56 (1H, dd, J = 8.5 and 2.0 Hz), 8.83 (1H, d, J = 2.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.4, 55.7, 109.7, 113.5, 114.3, 114.5, 115.8, 121.7, 126.9, 130.1, 130.3, 132.8 135.8, 136.3, 136.7, 141.0, 145.0, 150.2, 159.7, 160.2, 184.3; FTIR: ν_{max} 2932 (w), 2841 (w), 2098 (w), 1651 (s), 1611 (m), 1517 (s), 1447 (m), 1430 (m), 1253 (s), 1180 (m), 1058 (m), 1025 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{19}{}^{35}ClN_3O_3$ 444.1115, found 444.1113. **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (3H, s), 3.79 (3H, s), 6.75 (2H, d, J = 8.5 Hz), 6.83 (2H, d, J = 8.5 Hz), 7.06 (2H, d, J = 8.5 Hz), 7.16 (2H, d, J = 8.5 Hz), 7.48 (1H, d, J = 8.5 Hz), 7.86 (1H, dd, J = 8.5 and 2.0 Hz), 7.92 (1H, d, J = 2.0 Hz), 8.02 (1H, s). ^{13}C NMR (101

MHz, $CDCl_3$): δ 55.4, 55.6, 113.3, 114.1, 114.3, 115.2, 120.0, 120.4, 126.8, 130.0, 131.9, 132.1 134.1, 134.8, 137.9, 140.1, 142.5, 145.7, 159.4, 160.4, 186.7; FTIR: ν_{max} 2960 (w), 2838 (w), 1646 (m), 1610 (m), 1513 (s), 1455 (m), 1248 (s), 1177 (m), 1056 (m), 1026 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{25}H_{19}{}^{35}ClN_3O_3$ 444.1115, found 444.1109.

4-Phenyl-N-(4-methoxyphenyl)sydnone (**5**).[15] Sydnone **1a** (105 mg, 0.547 mmol) and chlorobenzene (92 mg, 0.82 mmol) were subjected to the general conditions affording **5** as a pink solid (122 mg, 83%). M.p.: 106-107 °C (dec); ^1H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 7.02 (2H, d, J = 9.0 Hz), 7.30 (5H, s), 7.39 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.9, 107.8, 115.3, 124.8, 126.3, 127.4, 127.5, 128.7, 128.9, 162.2, 167.3.

4-(4-Methoxyphenyl)-N-(3,4,5-trimethoxyphenyl)sydnone (**6**) and 4-Phenyl-N-(3,4,5-trimethoxyphenyl)sydnone (**7**). A mixture of sydnone **1b** (150 mg, 0.595 mmol), 4-bromoanisole (166 mg, 0.888 mmol), palladium acetate (7 mg, 0.03 mmol), triphenylphosphine (18 mg, 0.61 mmol) and potassium carbonate (163 mg, 1.18 mmol) in DMF (5 mL) under an atmosphere of nitrogen was heated at 120 °C for 12 hours before the reaction was allowed to cool to ambient temperature and water was added. The resulting mixture was extracted with ethyl acetate:40-60 petroleum ether (9:1) and the combined organic layers dried over $MgSO_4$ and concentrated in vacuo. Flash silica chromatography (eluting solvent 20%-100% ethyl acetate in 40-60 petroleum ether) afforded **6** as a yellow solid (117 mg, 55%) and **7** as a colorless solid (33 mg, 17%). Both **6** and **7** could be further purified by recrystallization from EtOH. **6**: M.p.: 165-168 °C (dec.); ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (6H, s), 3.79 (3H, s), 3.92 (3H, s), 6.67 (2H, s), 6.85 (2H, d, J = 9.0 Hz), 7.29 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.4, 56.6, 61.2, 102.5, 108.0, 114.3, 116.8, 128.9, 129.9, 140.6, 154.1, 159.9, 167.2; FTIR: ν_{max} 2945 (w), 1723 (s), 1505 (s), 1232 (s), 1121 (s), 1019 (m) 987 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_6$

359.1243, found 359.1226. **7**: M.p.: 146-147 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (6H, s), 3.93 (3H, s), 6.66 (2H, s), 7.28-7.40 (5H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 56.6, 61.3, 102.4, 107.8, 124.6, 127.4, 128.8, 128.9, 129.9, 140.8, 154.1, 167.1; FTIR: ν_{max} 2945 (w), 2165 (w), 1746 (m), 1603 (m), 1506 (m), 1232 (s), 1125 (s), 977 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{17}N_2O_5$ 329.1137, found 329.1125.

4-(4-Tolyl)-N-(4-methoxyphenyl)sydnone (**8**). Sydnone **1a** (99 mg, 0.52 mmol) and 4-chlorotoluene (98 mg, 0.77 mmol) were subjected to the general conditions affording **8** as a tan solid (121 mg, 83%). M.p.: 106 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 3.88 (3H, s), 7.02 (2H, d, J = 9.0 Hz), 7.09 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.38 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 55.9, 108.0, 115.2, 121.8, 126.3, 127.4, 127.5, 129.5, 138.9, 162.1, 167.3; FTIR: ν_{max} 3076 (w), 2840 (w), 1736 (s), 1110 (s), 1002 (w), 968 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{14}N_2O_3$ 283.1083, found 283.1085.

4-(4-Tolyl)-N-(3,4,5-trimethoxyphenyl)sydnone (**9**). Sydnone **1b** (151 mg, 0.599 mmol) and 4-chlorotoluene (114 mg, 0.901 mmol) were subjected to the general conditions affording **9** as a colorless solid (196 mg, 96%). M.p.: 140-141 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (3H, s), 3.75 (6H, s), 3.91 (3H, s), 6.67 (2H, s), 7.10 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 8.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 56.6, 61.2, 102.5, 108.0, 121.7, 127.3, 129.5, 130.0, 139.0, 140.7, 154.1, 167.1; FTIR: ν_{max} 2942 (w), 2840 (w), 1749 (s), 1128 (s), 984 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{18}N_2O_5$ 343.1294, found 343.1283.

4-(p-Tolyl)-N-(4-ethoxyphenyl)sydnone (**10**). Sydnone **1c** (127 mg, 0.616 mmol) and 4-chlorotoluene (117 mg, 0.924 mmol) were subjected to the general conditions affording **10** as a tan solid (140 mg, 77%). M.p.: 123-124 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (3H, t, J = 7.0

Hz), 2.29 (3H, s,), 4.09 (2H, q, J = 7.0 Hz), 6.94-7.02 (2H, m), 7.08 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 7.30-7.39 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.7, 21.4, 64.3, 108.0, 115.6, 121.9, 126.2, 127.2, 127.3 129.5, 138.8, 161.5, 167.3; FTIR: ν_{max} 2981 (w), 2934 (w), 1737 (s), 1115 (m), 1041 (m), 1002 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{16}N_2O_3$ 297.1239, found 297.1249.

4-(p-Tolyl)-N-phenylsydnone (**11**).[6] Sydnone **1d** (102 mg, 0.629 mmol) and 4-chlorotoluene (119 mg, 0.940 mmol) were subjected to the general conditions affording **11** as a tan solid (131 mg, 83%). M.p.: 134-136 °C (dec.) (Lit.[6] 141-143 °C) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 7.08 (2H, d, J = 8.0 Hz), 7.16 (2H, d, J = 8.0 Hz), 7.47 (2H, d, J = 7.5 Hz), 7.57 (2H, t, J = 7.5 Hz), 7.60-7.70 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 108.2, 121.6, 125.0, 127.4, 129.5, 130.2, 132.1, 134.8, 139.0, 167.3.

4-(p-Tolyl)-N-(4-fluorophenyl)sydnone (**12**). Sydnone **1e** (100 mg, 0.555 mmol) and 4-chlorotoluene (105 mg, 0.830 mmol) were subjected to the general conditions affording **12** as an orange solid (102 mg, 68%). M.p.: 150-151 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 7.12 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 7.22-7.30 (2H, m), 7.46-7.54 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 108.3, 117.5 (d, J = 24.0 Hz), 121.3, 127.2 (d, J = 9.0 Hz), 128.6 (d, J = 223.0 Hz), 130.8 (d, J = 3.0 Hz), 139.3, 163.0, 165.5, 167.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.3; FTIR: ν_{max} 3080 (w), 2158 (w), 1738 (s), 1507 (s), 1234 (s), 1006 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O_2F$ 271.0883, found 271.0891.

4-(p-Tolyl)-N-(methyl)sydnone (**13**). Sydnone **1f** (129 mg, 1.29 mmol) and 4-chlorotoluene (245 mg, 1.94 mmol) were subjected to the general conditions affording **13** as a colorless solid (164 mg, 67%). M.p.: 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 4.11 (3H, s), 7.30 (2H, d, J =

8.0 Hz), 7.46 (2H, d, J = 8.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.4, 38.9, 108.2, 121.4, 127.6, 129.9, 139.5, 167.4; FTIR: ν_{max} 3024 (w), 2924 (w), 1719 (s), 1536 (m), 1445 (m), 1311 (m), 1087 (m), 986 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_2$ 191.0821, found 191.0813.

4-(p-Tolyl)-N-(ethyl)sydnone (**14**). Sydnone **1g** (129 mg, 1.29 mmol) and 4-chlorotoluene (173 mg, 1.37 mmol) were subjected to the general conditions affording **14** as a colorless solid (134 mg, 72%). Note: product was not stable and began to decompose after isolation. M.p.: 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.59 (3H, m), 2.40 (3H, s), 4.46 (2H, q, J = 7.5 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.41 (2H, d, J = 8.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 13.8, 21.4, 47.6, 107.2, 121.5, 128.0, 130.0, 139.3, 167.7; FTIR: ν_{max} 2820 (br), 2537 (br), 1668 (s), 1611 (m), 1417 (m), 1283 (s), 960 (m) 945 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.0977, found 205.0981.

4-(p-Tolyl)-N-(benzyl)sydnone (**15**). Sydnone **1h** (100 mg, 0.568 mmol) and 4-chlorotoluene (107 mg, 0.845 mmol) were subjected to the general conditions affording **15** as a yellow solid (93 mg, 61%). M.p.: 81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 5.49 (2H, s), 7.14-7.19 (2H, m), 7.21 (2H, d, J = 8.0 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.31-7.40 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.5, 55.3, 108.1, 121.3, 127.7, 128.5, 129.4, 129.5, 130.0, 131.6, 139.8, 167.7; FTIR: ν_{max} 3039 (w), 2994 (w), 2958 (w), 1724 (s), 991 (s), 960 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1134, found 267.1143.

4-(3-Nitrophenyl)-N-(4-methoxyphenyl)sydnone (**16**).[15] Sydnone **1a** (104 mg, 0.542 mmol) and 1-chloro-3-nitrobenzene (128 mg, 0.812 mmol) were subjected to the general conditions affording **16** as a yellow solid (144 mg, 85%). M.p.: 152-153 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (3H, s), 7.09 (2H, d, J = 9.0 Hz), 7.43 (2H, d, J = 9.0 Hz), 7.50 (1H, t, J = 8.0 Hz), 7.75 (1H, d, J = 8.0

Hz), 8.02-8.12 (2H, m); ^{13}C NMR (101 MHz, d_6-DMSO) δ 56.9, 106.5, 115.4, 121.2, 122.8, 126.5, 126.6, 127.1, 130.2, 132.8, 147.6, 161.9, 166.2.

4-(2-Chlorophenyl)-N-(4-methoxyphenyl)sydnone (**17**). Sydnone **1a** (102 mg, 0.531 mmol) and 1,2-dichlorobenzene (117 mg, 0.796 mmol) were subjected to the general conditions affording **17** as an orange oil (151 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (3H, s), 6.91 (2H, d, J = 9.0 Hz), 7.27-7.40 (6H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.8, 105.8, 115.0, 120.4, 124.0, 125.2, 127.5, 130.4, 131.5, 133.0, 135.4, 162.0, 167.2; FTIR: ν_{max} 3066 (w), 2936 (w), 2843 (w), 1757 (s), 1743 (s), 1028 (m), 1002 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O_3{}^{35}Cl$ 303.0536, found 303.0524.

4-(3-Chlorophenyl)-N-(4-methoxyphenyl)sydnone (**18**). Sydnone **1a** (100 mg, 0.521 mmol) and 1,3-dichlorobenzene (115 mg, 0.782 mmol) were subjected to the general conditions affording **18** as a yellow solid (125 mg, 79%). M.p.: 118 °C (dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (3H, s), 7.05 (2H, d, J = 9.0 Hz), 7.10 (1H, dt, J = 7.5, 1.5 Hz), 7.17-7.25 (2H, m), 7.36-7.42 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 56.0, 106.4, 115.5, 125.2, 126.2, 126.5, 127.0, 127.1, 128.7, 130.0, 134.9, 162.4, 166.9; FTIR: ν_{max} 3078 (w), 2937 (w), 2842 (w), 1749 (s), 1735 (s), 1125 (s), 1028 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}N_2O_3Cl^{35}$ 303.0536, found 303.0535.

4-(4-Aminophenyl)-N-(4-methoxyphenyl)sydnone (**19**). Sydnone **1a** (100 mg, 0.521 mmol) and 4-bromoaniline (134 mg, 0.779 mmol) were subjected to the general conditions affording **19** as a yellow solid (137 mg, 93%). M.p.: 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (2H, s), 3.88 (3H, s), 6.56 (2H, d, J = 9.0 Hz), 7.00 (2H, d, J = 9.0 Hz), 7.08 (2H, d, J = 9.0 Hz), 7.38 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.9, 108.7, 114.2, 115.0, 115.2, 126.3, 127.6, 129.0, 147.1,

162.0, 167.5; FTIR: ν_{max} 3461 (w), 3359 (m), 3232 (w), 1732 (s), 1607 (m), 1249 (s), 1182 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_3O_3$ 284.1035, found 284.1045.

4-(4-Hydroxyphenyl)-N-(4-methoxyphenyl)sydnone (**20**). Sydnone **1a** (100 mg, 0.521 mmol) and 4-bromophenol (135 mg, 0.780 mmol) were subjected to the general conditions affording **20** as a tan solid (86 mg, 58%). Note: product was not stable and began to decompose after isolation. M.p.: 212-214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (3H, s), 5.08 (1H, br), 6.76 (2H, d, J = 9.0 Hz), 7.02 (2H, d, J = 9.0 Hz), 7.19 (2H, d, J = 9.0 Hz), 7.39 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, d_6-DMSO) δ 55.8, 108.5, 115.1, 115.5, 117.6, 127.0, 129.2, 132.0, 157.9, 161.5, 166.5; FTIR: ν_{max} 3254 (br), 1710 (s), 1603 (m), 1513 (s), 1249 (s), 1171 (s), 1026 (m), 998 (m), 834 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_4$ 285.0875, found 285.0873.

4-(Thiophen-2-yl)-N-(4-methoxyphenyl)sydnone (**21**). Sydnone **1a** (101 mg, 0.526 mmol) and 2-chlorothiophene (93 mg, 0.78 mmol) were subjected to the general conditions affording **21** as an orange solid (128 mg, 89%). M.p.: 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (3H, s), 6.98 (1H, dt, J = 5.0, 4.0 Hz), 7.11 (2H, d, J = 9.0 Hz), 7.23 (1H, dd, J = 5.0, 1.0 Hz), 7.33 (1H, dd, J = 4.0, 1.0 Hz), 7.46 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 57.0, 106.6, 115.4, 125.8, 126.1, 126.2, 126.4, 127.3, 127.5, 162.8, 165.9; FTIR: ν_{max} 3080 (w), 2941 (w), 2840 (w), 1756 (s), 1735 (s), 1176 (m), 1017 (s), 991 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{10}N_2O_3S$ 275.0490, found 275.0503.

4-(4-Pyridyl)-N-(4-methoxyphenyl)sydnone (**22**). Sydnone **1a** (100 mg, 0.521 mmol) and 4-chloropyridine hydrochloride (119 mg, 0.780 mmol) were subjected to the general conditions affording **22** as a pink solid (109 mg, 78%). M.p.: 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (3H, s), 7.09 (2H, d, J = 9.0 Hz), 7.20 (2H, d, J = 9.0 Hz), 7.42 (2H, d, J = 9.0 Hz), 8.50 (2H, br);

^{13}C NMR (101 MHz, $CDCl_3$) δ 56.0, 105.0, 115.7, 119.9, 126.3, 126.9, 132.5, 150.2, 162.8, 166.4; FTIR: ν_{max} 2934 (w), 2841 (w), 1742 (s), 1596 (m), 1510 (s), 1258 (s), 1026 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{12}N_3O_3$ 270.0879, found 270.0871.

4-(4-Methoxyphenyl)-N-benzylsydnone (**23**).[16] Sydnone **1j** (100 mg, 0.568 mmol) and 4-bromoanisole (159 mg, 0.850 mmol) were subjected to the general conditions affording **23** as a colorless solid (139 mg, 87%). M.p.: 107 °C. (Lit.[16] 102-104 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 5.45 (2H, s), 6.91 (2H, d, J = 9.0 Hz), 7.12-7.18 (2H, m), 7.27 (2H, d, J = 9.0 Hz), 7.30-7.36 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.2, 55.4, 107.9, 114.7, 116.3, 127.6, 129.3, 129.4, 130.2, 131.5, 160.5, 167.8.

1-(4-Methoxyphenyl)-3-(methylalcohol)-5-(4-methoxyphenyl)pyrazole (**25a**) and 1-(4-methoxyphenyl)-4-(methylalcohol)-5-(4-methoxyphenyl)pyrazole (**25b**). A Schlenk tube was charged with **2** (200 mg, 0.670 mmol), propargyl alcohol (150 mg, 2.68 mmol) and xylenes (0.67 mL) and sealed. The mixture was heated at 160 ^{o}C for 16 hours before being allowed to cool to ambient temperature. The mixture was directly loaded on to a short silica plug and xylenes removed by elution with 100% petroleum ether, the crude material was then eluted with 100% ethyl acetate. The material was further purified by flash silica chromatography (eluting solvent: 100% petrol – 100% EtOAc) affording **25a** and **25b** as an inseparable mixture (93:7) as an orange oil (202 mg, 97%). Only characterization data for the major isomer is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 3.80 (3H, s), 4.76 (2H, d, J = 6.0 Hz), 6.43 (1H, s), 6.79-6.87 (4H, m), 7.13 (2H, d, J = 9.0 Hz), 7.19 (2H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.4, 55.6, 59.3, 106.3, 114.0, 114.2, 123.0, 126.8, 130.1, 133.4, 144.1, 152.6, 158.9, 159.6; FTIR: ν_{max} 3352 (br), 2934 (w), 2837 (w), 1612 (m), 1518 (s), 1251 (s), 1179 (m), 1033 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3$ 311.1396, found 311.1406.

1,5-Bis(4-methoxyphenyl)-1H-pyrazole-3-carboxaldehyde (**26**). To a solution of **25a** and **25b** (93:7, 424 mg, 1.37 mmol) in CH_2Cl_2 (6 mL) at 0 ^oC was added Dess-Martin periodinane (638 mg, 1.50 mmol). The mixture was allowed to warm to room temperature and stirred for one hour. Water was added and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and volatiles removed in vacuo. The crude material was purified by flash silica chromatography (eluting solvent 10%-40% ethyl acetate) affording **26** as an orange oil (285 mg, 73%). **26**. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (3H, s), 3.82 (3H, s), 6.83 (2H, d, J = 9.0 Hz), 6.88 (2H, d, J = 9.0 Hz), 6.92 (1H, s), 7.12 (2H, d, J = 9.0 Hz), 7.24 (2H, d, J = 9.0 Hz), 10.03 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.3, 55.6, 106.8, 114.1, 114.4, 121.7, 126.7, 130.2, 132.7, 145.3, 151.4, 159.6, 160.0, 187.0; FTIR: ν_{max} 3055 (w), 3005 (w), 2936 (m), 2960 (m), 2838 (m), 1696 (s), 1613 (s), 1515 (s), 1434 (s), 1252 (s), 1179 (s), 1031 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_3$ 309.1239, found 309.1254.

4,4'-(1,4-phenylene)-bis-N-(4-methoxyphenyl)sydnone (**27**). Sydnone **1a** (102 mg, 0.531 mmol) and 1,4-dichlorobenzene (117 mg, 0.796 mmol) were subjected to the general conditions affording **27** as a yellow solid (104 mg, 86%). M.p.: 247-250 °C (dec.); ^1H NMR (400 MHz, $CDCl_3$) δ 3.91 (6H, s), 7.04 (4H, d, J = 9.0 Hz), 7.25 (4H, s), 7.37 (4H, d, J = 9.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 56.0, 104.3, 107.0, 115.6, 124.7, 126.3, 127.1, 162.5, 167.1; FTIR: ν_{max} 3082 (w), 2940 (w), 2838 (w), 1712 (s), 1021 (m), 998 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{19}N_4O_6$ 459.1305, found 459.1319.

5,5'-(1,4-phenylene)bis[1-(4-methoxyphenyl)-3-phenyl]-1H-pyrazole (**28**). A Schlenk tube was charged with **27** (33 mg, 0.072 mmol), phenylacetylene (59 mg, 0.58 mmol) and xylenes (72 μL) and sealed. The mixture was heated at 160 ^oC for 16 hours before being allowed to cool to ambient temperature. The mixture was directly loaded on to a short silica plug and xylenes removed by

elution with 100% petroleum ether, the crude material was then eluted with 100% ethyl acetate. The material was further purified by flash silica chromatography (eluting solvent: 20-40% EtOAc) affording **28** (>98:2 regioselectivity) as a yellow solid (24 mg, 58%). The product could be further purified by recrystallization from CH_2Cl_2/40-60 petroleum ether. M.p.: 258-259 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (6H, s), 6.84 (2H, s), 6.88 (4H, d, J = 9.0 Hz), 7.22 (4H, s), 7.28 (4H, d, J = 9.0 Hz), 7.34 (2H, t, J = 7.5 Hz), 7.43 (4H, t, J = 7.5 Hz), 7.89-7.94 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ 55.6, 104.8, 114.3, 125.9, 126.9, 128.1, 128.7, 128.8, 130.3, 133.1, 133.4, 143.7, 151.9, 159.1; FTIR: ν_{max} 3009 (w), 2936 (w), 2838 (w), 1606 (w), 1512 (s), 1485 (m), 1461 (s), 1249 (s), 843 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{38}H_{30}N_4O_2$ 575.2447, found 575.2432.

Ethyl 2-((3,4,5-trimethoxyphenyl)amino)acetate. To a suspension of 3,4,5-trimethoxyaniline (10.0 g, 54.6 mmol) and sodium acetate (17.8 g, 217 mmol) in ethanol (100 mL) was added ethyl bromoacetate (18.2 g, 109 mmol) and the mixture heated at reflux for 4 hours. The solvent was then removed in vacuo, followed by the addition of CH_2Cl_2 and filtration. The solvent was removed in vacuo. Flash silica chromatography (eluting solvent 30% ethyl acetate) afforded ethyl 2-((3,4,5-trimethoxyphenyl)amino)acetate as a colorless solid (12.1 g, 82%). M.p.: 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (3H, t, J = 7.0 Hz), 3.75 (3H, s), 3.82 (6H, s), 3.88 (2H, s), 4.25 (2H, q, J = 7.0 Hz), 5.84 (2H, s); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.4, 46.5, 56.1, 61.2, 61.5, 90.8, 130.8, 144.0, 154.1, 171.2; FTIR: ν_{max} 3374 (m), 2979 (w), 2937 (w), 1727 (s), 1012 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{13}H_{20}NO_5$ 270.1341, found 270.1331.

2-((3,4,5-trimethoxyphenyl)amino)acetic acid. To a suspension of the ethyl 2-((3,4,5-trimethoxyphenyl)amino)acetate (12.1 g, 44.9 mmol) in water:ethanol (150 mL, 9:1) was added sodium hydroxide (2.7g, 67.5 mmol) and the mixture heated at reflux for 1 hour. The reaction was allowed to cool to RT before acidifying to pH 4-6 with concentrated hydrochloric acid, leading to

product precipitation. The brown solid was isolated and dried in vacuo before recrystallization from ethanol affording 2-((3,4,5-trimethoxyphenyl)amino)acetic acid as an orange solid (9.9 g, 91% yield). M.p.: 111-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.76 (3H, s), 3.82 (6H, s), 3.96 (2H, s), 5.86 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 46.3, 56.2, 61.2, 91.1, 131.2, 143.5, 154.2, 175.3; FTIR: ν_{max} 3400 (w), 2945 (w), 2837 (w), 1730 (s), 997 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{15}NO_5$ 242.1028, found 242.1017.

N-(3,4,5-trimethoxyphenyl)sydnone (**1b**). To a suspension of 2-((3,4,5-trimethoxyphenyl)amino)acetic acid (4.37 g, 18.1 mmol) in DME (40 mL) was added isopentyl nitrite (IAN) (2.33 g, 19.9 mmol) and the reaction stirred for 3 hours at room temperature. The mixture was concentrated in vacuo followed by the addition of petroleum ether:diethyl ether(15:1) and the liquor decanted to provide the crude nitrosamine precipitate. **CAUTION: Nitrosamine intermediates are highly toxic and suspected carcinogens**. The crude material was suspended in CH_2Cl_2 (40 mL) under nitrogen and trifluoroacetic anhydride (TFAA) (5.70 g, 27.1 mmol) was carefully added at 0 °C. The reaction allowed to warm to room temperature and stirred for 90 minutes, after which the reaction was carefully quenched with saturated sodium bicarbonate solution followed by solid sodium bicarbonate and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and volatiles removed in vacuo affording the crude sydnone. The crude material was purified by recrystallization from ethanol affording **1b** as an orange solid (4.05 g, 89%). M.p.: 179-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (3H, s), 3.93 (6H, s), 6.75 (1H, s), 6.93 (2H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ 56.8, 61.2, 94.1, 99.2, 130.4, 141.3, 154.3, 169.0; FTIR: ν_{max} 3136 (w), 2944 (w), 1752 (s), 1604 (s), 1241 (s), 1126 (s), 999 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_2O_5$ 253.0824, found 253.0817.

3-cyano-4-chloro-α-ethynylbenzenemethanol. A suspension of 2-chloro-5-methylbenzonitrile (1.42 g, 9.35 mmol), freshly recrystallized N-bromosuccinamide (5.49 g, 30.9 mmol) and AIBN (9 mg 0.05 mmol) in CH_2Cl_2 (18 mL) was irradiated with a tungsten lamp for 2 hours at room temperature. The resulting mixture was filtered, aqueous sodium bisulfite added and the mixture extracted with CH_2Cl_2. The combined aqueous layers were dried over $MgSO_4$, filtered and the solvent removed in vacuo. The crude material was suspended in DMSO (100 mL) and water (20 mL) and heated at 120 ^oC for 16 hours. The reaction was allowed to cool to room temperature before being poured into water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed in vacuo. The crude material was dissolved in THF (10 mL), cooled at -78 ^oC before the dropwise addition of ethynyl magnesium bromide (0.5 M in THF) (20 mL, 10 mmol). The reaction was allowed to warm to room temperature and stirred for a further 2 hours. The mixture was then poured in aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and volatiles removed in vacuo. The crude material was purified by flash silica chromatography (eluting solvent 10%-40% ethyl acetate) affording 3-cyano-4-chloro-α-ethynylbenzenemethanol as a colorless solid (874 mg, 49%). M.p.: 57-59 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 2.73 (1H, d, J = 2.0 Hz), 3.22 (1H, d, J = 5.5 Hz), 5.47 (1H, br), 7.50 (1H, d, J = 8.5 Hz), 7.71 (1H, dd, J = 8.5 and 2.0 Hz), 7.86 (1H, d, J = 2.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 62.6, 76.1, 82.2, 113.2, 115.9, 130.2, 132.1, 132.4, 136.7, 140.0; FTIR: ν_{max} 3466 (s), 3256 (m), 3102 (w), 2235 (m), 1475 (s), 1404 (m), 1051 (s), 967 (m); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_6{}^{35}ClNO$ 191.0132, found 191.0124.

1-(3-cyano-4-chlorophenyl)-2-propyn-1-one (**3**). To a solution of 3-cyano-4-chloro-α-ethynylbenzenemethanol (300 mg, 1.57 mmol) in CH_2Cl_2 (6 mL) at 0 ^oC was added the Dess-Martin periodinane (730 mg, 1.72 mmol). The mixture was allowed to warm to room temperature

and stirred for one hour. Water was added and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and volatiles removed in vacuo. The crude material was purified by flash silica chromatography (eluting solvent 10%-20% ethyl acetate) affording **3** as a colorless solid (251 mg, 84%). M.p.: 82-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (1H, s), 7.68 (1H, d, J = 8.5 Hz), 8.27 (1H, dd, J = 8.5 and 2.0 Hz), 8.43 (1H, d, J = 2.0 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 79.2, 83.1, 114.4, 115.0, 130.8, 134.0, 135.1, 135.3, 143.1, 174.1; FTIR: ν_{max} 2967 (w), 2839 (w), 2098 (w), 1697 (s), 1515 (m), 1463 (m), 1245 (s), 1024 (s); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_4{}^{35}ClNO$ 188.9976, found.

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Supporting Information Available: ^{1}H, ^{13}C, ^{19}F NMR spectra for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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