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Palladium-catalyzed reductive N-heterocyclization of alkenyl-substituted nitroarenes as a viable method for the preparation of bicyclic pyrrolo-fused heteroaromatic compounds

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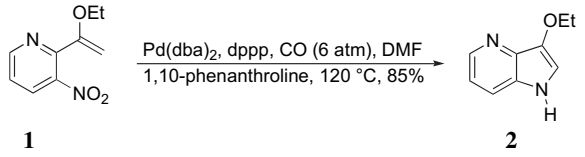
ABSTRACT

Palladium-catalyzed, carbon monoxide-mediated reductive N-heterocyclization of nitro-heteroaromatic compounds having an alkene adjacent to the nitro-group affords bicyclic pyrrolo-fused heteroaromatic molecules. This type of reaction was used to prepare the fused bicyclo[3.3.0] ring-system: thieno[3,2-*b*]pyrrole, thieno[2,3-*b*]pyrrole, furo[2,3-*b*]pyrrole, pyrrolo[3,2-*d*]thiazole, and pyrrolo[2,3-*d*]imidazole and the bicyclo[4.3.0] ring-systems: pyrrolo[3,2-*b*]pyridine, pyrrolo[2,3-*b*]pyridine, pyrrolo[3,2-*c*]pyridine, pyrrolo[2,3-*c*]pyridine, pyrrolo[3,2-*c*]pyridazine, and pyrrolo[3,2-*d*]pyrimidine in 32–94% yield.

1. Introduction

Palladium-catalyzed, carbon monoxide-mediated, cyclizations of 2-alkenyl-1-nitrobenzenes have been developed into a very versatile method for the synthesis of indole derivatives.[1] The reaction tolerates a wide variety of functional groups and high chemical yields are often realized. In some of the earlier studies in our laboratories, a handful of fused pyrrolopyridines were prepared from nitropyridines having an alkene adjacent to the nitro-group.[2] For example, reaction of **1** with carbon monoxide (6 atm) in the presence of bis(dibenzylidenacetone)palladium (6 mol %), 1,3-bis-(diphenylphosphino)propane (6 mol %), and 1,10-phenanthroline (12 mol %) gave pyrrolopyridine **2** in good isolated yield (Scheme 1).



1 **2**

Scheme 1.

A variety of methods have been developed for the synthesis of bicyclic [3.3.0] or [4.3.0] pyrrolo-fused heteroaromatic molecules. Pyrrolopyridines,[3] for example, have been prepared using classical methods such as the Reissert, Madelung, Bartoli, Hemetsberger–Knittel, and Leimgruber–Batcho syntheses in addition to the more recently developed, palladium-catalyzed, Suzuki–Miyaura,[4] Sonogashira,[5] or Kosugi–Migita–Stille[6] coupling reactions followed by cyclization. One or more of these methods have been utilized for the preparation of other ring systems including thienopyrrole, furopyrrole, pyrrolothiazole, pyrroloimidazole, pyrrolopyridazine, and pyrrolopyrimidine to be discussed herein.

Bicyclic [3.3.0] or [4.3.0] pyrrolo-fused heteroaromatic molecules are scarce in nature but a significant number of compounds have been synthesized in laboratories. The interest in pyrrolo-fused heteroaromatic compounds mainly stems from the array of interesting and potentially useful biological activity observed in many cases. We report herein an extension of the palladium-catalyzed, carbon monoxide-mediated cyclization, seen in Scheme 1, to the synthesis of a selection of bicyclic [3.3.0] and [4.3.0] pyrrolo-fused heteroaromatic compounds.

2. Results and discussion

A number of five- and six-membered heterocyclic cyclization precursors **3**–**16** were prepared using either of two procedures: (1) The Kosugi–Migita–Stille coupling reaction between ethenyltributyl tin and a nitro-heteroaromatic compound having a triflate or a bromo substituent on the adjacent carbon or (2) A Knoevenagel-type condensation between benzaldehyde and a nitro-heteroaromatic compound having a methyl group on the adjacent carbon. All the synthesized cyclization precursors are listed in Table 1. Substrates

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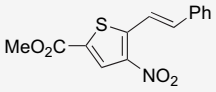
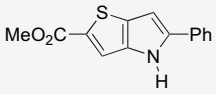
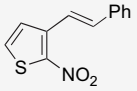
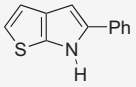
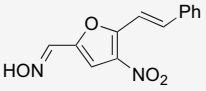
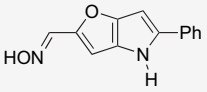
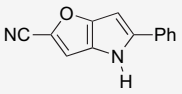
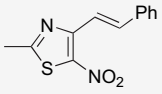
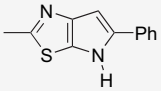
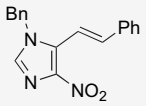
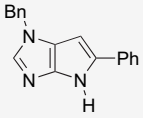
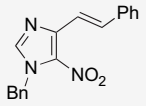
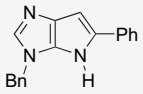
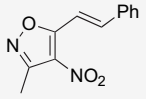
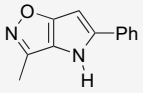
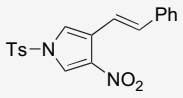
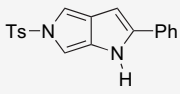
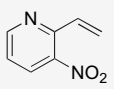
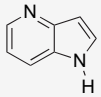
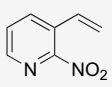
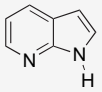
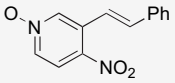
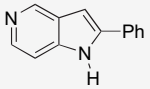
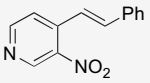
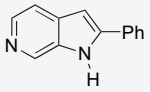
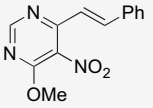
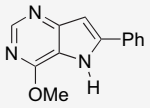
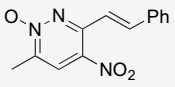
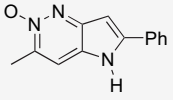
Table 1
Cyclization to give heterocycle-fused pyrroles

Entry	Nitroalkene[a,b]	Condition	Fused pyrrole[b]	
				
1	**3**	A (12 h)[c]	**17** (43%)[d]	
2		A (40 h)	**17** (71%) [70%]	
				
3	**4**	A (16 h)	**18** (94%) [40%]	
				
4	**5** (88%)	A (12 h)	**19** (63%)	
5		B (22 h)[e]	**19** (45%)	**20** (20%)
6		B (50 h)	**19** (29%)	**20** (21%)
				
7	**6**	A (72 h)	**21** (61%)	
8		B (72 h)	**21** (16%)	
				
9	**7**	B (139 h)	**22** (77%)	
				
10	**8**	B (72 h)	**23** (32%)	
				
11	**9**[10]	A (96 h)[f]	**24** (not observed)	
12	**9**	B (96 h)[g]	**24** (not observed)	
				
13	**10**	B (84 h)	**25** (not observed)	
				
14	**11**	B (42 h)	**26** (65%)	

(*continued on next page*)

Table 1 (*continued*)

Entry	Nitroalkene[a,b]	Condition	Fused pyrrole[b]
15	 **12** (73%)	B (180 h)	 **27** (41%)
16	 **13**	B (22 h)	 **28** (91%) [14%]
17	 **14**	B (24 h)	 **29** (87%)
18	 **15** (41%)	B (24 h)	 **30** (82%)
19	 **16** (30%)	B (14 h)	 **31** (57%)

[a] For experimental details, see Experimental Section.
[b] Isolated yields in parentheses. Comparison with a Cadogan–Sundberg reaction in brackets.
[c] Condition A: A catalyst system consisting of $Pd(OAc)_2$–PPh_3 in MeCN was used.
[d] 45% of **3** was recovered.
[e] Condition B: A catalyst system consisting of $Pd(dba)_2$-1,10-phenanthroline in DMF was used.
[f] A mixture of dba and **9** was observed by ^1H NMR of the crude product.
[g] 15% of **9** was recovered.

previously not described in the literature have yields by the compound number (**5**, **15**, and **16**, entries 4, 18, and 19, respectively). One compound was prepared in a new fashion (**12**, entry 15). The functionalized pyrrole **10** (entry 13) was prepared by N-tosylation of the previously described 3-nitro-4-(2-phenylethenyl)pyrrole.

Compounds **3**–**16** were treated with carbon monoxide (6 atm) in the presence of either a palladium acetate–triphenyl phosphine catalyst system in acetonitrile at 80–90 °C (conditions A) or using a bis(dibenzylideneacetone)palladium-1,10-phenanthroline catalyst system in DMF at 120 °C (conditions B). The reactions were monitored by thin layer chromatography at 12 h intervals to assure complete consumption of the substrate. No adverse effects were observed from venting, removing a TLC sample, and repressurizing the reaction vessel. Conditions B gave in most cases a higher yield of cyclized product, when comparing the same substrate, although longer reaction times were often required. Depending on the substrate, the reactions times varied from 14 h to 7.5 days for the reactions to go to completion. For example, reaction of thiophene **3** under conditions A for 12 h gave 43% of thieno[3,2-*b*]pyrrole **17** together with 45% of recovered starting material (entry 1). Extending the reaction time to 40 h furnished **17** in 71% (entry 2). The nitro-thiophene **4** gave thieno[2,3-*b*]pyrrole (**18**) in an excellent yield (entry 3).

Reductive cyclization of furanaloxime **5** gave the expected furo[2,3-*b*]pyrrole **19** using conditions B for 12 h (entry 4). A relatively clean ^1H NMR spectrum of **19** was obtained immediately after chromatography. However, the compound undergoes dehydration to give the corresponding nitrile **20** upon standing in $CDCl_3$. This is evident by the appearance of new resonances from a second ^1H NMR experiment after a few minutes. Extension of the reaction time led to a decrease in the amount of the oxime and the isolation of nitrile **20** (entries 5–6). Cyclization of **6**–**8** gave pyrrolo[3,2-*d*]thiazole (**21**), pyrrolo[3,2-*d*]imidazole (**22**), and pyrrolo[2,3-*d*]imidazole (**23**), respectively (entries 7–10). A large difference in yield was observed for the two isomeric products **22** and **23**. The reason for this difference is unclear.

No cyclization was observed in two cases, neither the isoxazole **9** nor the pyrrole **10** formed the expected products (entries 11–13). Using **9**, some starting material was observed by NMR or isolated (See Table 1). The starting material was consumed in the case of **10** leading to a complex mixture of unidentified products.

The six-membered heterocyclic substrates **11**–**16** were transformed into the anticipated products **26**–**31** in 41–91% yield using conditions B (entries 14–19). Concomitant deoxygenation of the *N*-oxide was observed for pyridine **13** but not for pyrazine **16**.

The cyclization substrate **3**–**16** were not selected with the intent to directly compare the results obtained in this study with results reported by other investigators using the related Cadogan–Sundberg reaction. However, compound **17** was obtained in an almost identical yield to a Cadogan–Sundberg reaction of **3** using triethylphosphite at elevated temperature (entry 2).[7] Reductive cyclization of **4** and **13** with triethylphosphite has been reported but in significantly lower yields (entries 3[7] and 16[8]). And finally, a complex mixture of products was obtained from the demethyl analog of **16**.[9]

In conclusion, we have shown that the palladium-catalyzed, carbon monoxide-mediated, N-heterocyclization of nitro-heteroaromatic compounds having an alkene adjacent to the nitro-group is a viable methodology for the synthesis of an array of fused heteroaromatic molecules. For the cyclization reaction, yields in the range

of 32–94% were obtained from twelve of the starting materials examined. Two additional substrates did not undergo the expected cyclization using either of the two catalyst systems examined.

3. Experimental section

3.1. General procedures

The chemical shifts are expressed in δ values relative to $SiMe_4$ (0.0 ppm, ^1H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. Results of APT (Attached Proton Test) ^{13}C NMR experiments are shown in parentheses, where relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C.

Hexanes and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted the first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Chromatography was performed on silica gel (35–75 μm).

Melting points were determined on a MelTemp and are uncorrected. Elemental analyses were performed in the Department of Chemical Engineering, College of Engineering and Mineral Resources, West Virginia University.

*3.1.1. 4-Nitro-5-(2-phenylethenyl)-2-furanaldoxime (**5**).* A solution of 5-methyl-4-nitro-2-furanaldoxime[11] (80 mg, 0.471 mmol) in absolute methanol (5 mL) was heated at reflux for 2 min with 100 μL of freshly distilled piperidine followed by the addition of freshly distilled benzaldehyde (247 mg, 2.33 mmol). The resulting solution was heated at reflux (3 h). An orange solid was seen appearing on the walls of the flask after about 20 min. All volatiles were removed under reduced pressure and the resulting orange solid was purified by chromatography (hexanes/EtOAc, 8:2) to yield **5** (107 mg, 0.415 mmol, 88%) as an orange solid. Mp 182–185 °C; ^1H NMR (600 MHz, acetone-d_6) δ 11.65 (br s, 1H), 7.79 (d, J=16.2 Hz, 1H), 7.69 (d, J=16.8 Hz, 1H), 7.76 (d, J=7.2 Hz, 2H), 7.62 (s, 1H), 7.47–7.50 (m, 2H), 7.45 (tt, J=7.2, 1.2 Hz, 1H), 7.73 (s, 1H); ^{13}C NMR (150 MHz, acetone-d_6) δ 152.3, 144.2, 139.1, 136.4, 135.8, 135.7, 131.1, 130.1, 128.8, 113.75, 113.70; IR (ATR) 1619, 1537, 1400, 1346 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{10}N_2O_4$ ($M+H^+$) 259.0721; found, 259.0713.

*3.1.2. 3-Nitro-4-(2-phenylethenyl)-1-tosylpyrrole (**10**).* To a solution of 3-nitro-4-(2-phenylethenyl)pyrrole[12] (190 mg, 0.888 mmol) in anhydrous DMF (10 mL), was added *t*-BuOK (132 mg, 1.18 mmol) at 0 °C and the resulting orange solution was allowed to stir at 0 °C under an inert atmosphere for 45 min. A solution of 4-methylbenzenesulfonyl chloride (224 mg, 1.18 mmol) in DMF (1 mL) was added with a syringe whereupon the solution turned yellow. After stirring for 2.5 h at 0 °C, water (25 mL) was added. The mixture was extracted with EtOAc (2×25 mL). The combined organic phases were washed with water (2×25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified on Al_2O_3 (hexanes/EtOAc, 8:2) to afford **10** (257 mg, 0.698 mmol, 79%) as a yellow solid. Mp 124–125 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.00 (d, J=2.8 Hz, 1H), 7.87 (d, J=8.5 Hz, 2H), 7.48 (d, J=8.5 Hz, 2H), 7.34–7.44 (m, 6H), 7.40 (dd, J=16.2, 0.8 Hz, 1H), 7.30 (tt, J=7.3, 1.7 Hz, 1H), 6.94 (d, J=16.5 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 147.1, 137.3, 136.5, 134.2, 132.3, 130.8, 128.9, 128.4, 127.8, 126.8, 22.3, 121.8, 117.0, 116.4, 21.9; IR (ATR) 1489, 1370, 1057, 964 cm^{-1}; HRMS calcd for $C_{19}H_{16}N_2O_4S$ ($M+H^+$) 369.0909; found 369.0903.

*3.1.3. 3-Ethenyl-2-nitropyridine (**12**)[13].* A mixture of 2-nitro-3-trifluoromethanesulfonyloxypyridine[14] (507 mg, 1.86 mmol), ethenyltributyl tin (700 mg, 2.21 mmol), tetraethylammonium chloride (305 mg, 1.84 mmol), $PdCl_2(PPh_3)_2$ (16.8 mg, 0.0239 mmol) in MeCN (10 mL) was heated at reflux (67 h). The mixture was diluted with $CHCl_3$ (10 mL) and H_2O (10 mL) and filtered through Celite. The filtrate was extracted with $CHCl_3$ (30 mL) and the organic phase was washed with 10% NH_4OH (aqueous, 3×15 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to give **12** (236 mg, 1.57 mmol, 85%) as a yellow solid. Mp 34–36 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.46 (dd, J=4.8, 1.8 Hz, 1H), 8.09 (dd, J=7.8, 1.8 Hz, 1H), 7.58 (dd, J=7.8, 4.2 Hz, 1H), 6.98 (dd, J=17.4, 11.4 Hz, 1H), 5.86 (d, J=17.4 Hz, 1H), 5.61 (d, J=10.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5 (−), 137.6 (−), 129.5 (−), 127.7 (−), 126.9 (+), 121.2 (+); IR (ATR) 1531 cm^{-1}. Anal. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03. Found: C, 56.28; H: 4.23.

*3.1.4. 4-Methoxy-5-nitro-6-(2-phenylethenyl) pyrimidine (**15**).* A mixture of 4-methoxy-6-methyl-5-nitropyrimidine[15] (163 mg, 0.964 mmol), benzaldehyde (125 μL, 1.23 mmol), and piperidine (50 μL, 0.506 mmol) in MeOH (5 mL) was heated at reflux (15.5 h). The resulting precipitate was removed by filtration, redissolved in acetone and purified by chromatography (hexanes/EtOAc, 6:4) to give **15** (101 mg, 0.393 mmol, 41%) as a pale yellow solid. Mp 135–137 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.17 (d, J=15.6 Hz, 1H), 7.59 (dd, J=7.8, 2.4 Hz, 2H), 7.42–7.39 (m, 3H), 7.02 (d, J=15.0 Hz, 1H), 4.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4 (+), 157.3 (−), 154.2 (+), 142.1 (+), 142.1 (−), 134.8 (+), 130.4 (−), 129.0 (−), 128.3 (−), 117.5 (−), 55.3 (−); IR (neat) 1637, 1572, 1521 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{12}N_3O_3$ ($M+H^+$) 258.0879; found, 258.0874.

*3.1.5. 6-Methyl-4-nitro-3-(2-phenylethenyl)pyridazine 1-oxide (**16**).* A solution of 3,6-dimethyl-4-nitropyridazine 1-oxide[16] (123 mg, 0.727 mmol), benzaldehyde (99.9 mg, 0.941 mmol), and piperidine (38 μL, 0.386 mmol) in MeOH (4.0 mL) was heated at reflux (21 h). Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude product by chromatography (hexanes/EtOAc, 6:4) gave **16** (56.5 mg, 0.220 mmol, 30%) as a yellow solid. Mp 170–172 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.25 (s, 1H) 8.06 (d, J=15.6 Hz, 1H), 7.76 (d, J=16.2 Hz, 1H), 7.63 (dd, J=7.8, 1.8 Hz, 2H), 7.44–7.39 (m, 3H), 2.56 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.6 (+), 143.1 (+), 141.8 (+), 135.1 (−), 134.2 (+), 130.3 (−), 129.4 (−), 129.0 (−), 128.3 (−), 116.7 (−), 17.7 (−); IR (ATR) 3057, 2666, 1314, 1214 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 61.07; H, 4.68; N, 16.28.

*3.1.6. 5-Phenyl-4H-thieno[3,2-b]pyrrole-2-carboxylic acid methyl ester (**17**).* To a threaded ACE glass pressure tube was added methyl 4-nitro-5-(2-phenylethenyl)thiophene-2-carboxylate (**3**)[4] (80 mg, 0.264 mmol), $Pd(OAc)_2$ (4 mg, 0.0178 mmol), and PPh_3 (16.3 mg, 0.062 mmol) in MeCN (5 mL). The tube was fitted with a pressure head and the solution was saturated with carbon monoxide (four cycles of 6 atm of CO). The reaction mixture was heated at 90 °C (oil bath temperature) under CO (6 atm) for 40 h, cooled to ambient temperature, depressurized and the solvent was removed under reduced pressure. The crude product was purified by chromatography (hexane/EtOAc, 8:2) to yield **17** (32 mg, 0.118 mmol, 71%) as an off-white solid. Mp 244 °C (lit.[17] 239–240 °C); ^1H NMR (600 MHz, DMSO-d_6) δ 12.03 (s, 1H), 7.78 (dd, J=8.4, 1.2 Hz, 2H), 7.67 (s, 1H), 7.45 (t, J=7.8 Hz, 2H), 7.31 (t, J=7.5 Hz, 1H), 6.97 (t, J=1.2 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.9, 141.2, 138.6, 131.8, 130.02, 128.9, 128.1, 127.5, 124.6, 117.4, 98.6, 51.8; HRMS (ESI) calcd for $C_{14}H_{12}NO_2S$ ($M+H^+$) 258.0589; found, 258.0582.

*3.1.7. 5-Phenyl-6H-thieno[2,3-b]pyrrole (**18**).* Reaction of 2-nitro-3-(2-phenylethenyl)thiophene (**4**)[7] (72 mg, 0.311 mmol), $Pd(OAc)_2$

(6 mg, 0.026 mmol), and PPh_3 (29 mg, 0.110 mmol) in MeCN (10 mL) as described for **17** (6 atm CO, 80 °C, 16 h), gave after chromatography (hexanes/EtOAc, 9:1) **18** (58 mg, 0.291 mmol, 94%) as a pale yellow solid. Mp 179 °C (lit.[7] 186–187 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.53 (d, J=8.4 Hz), 7.40 (dt, J=8.4, 7.2 Hz), 7.25 (t, J=7.8 Hz, 1H), 7.02 (d, J=5.4 Hz, 1H), 6.85 (d, J=5.4 Hz, 1H), 6.73 (d, J=1.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.7, 134.9, 133.2, 132.6, 129.2, 126.9, 124.3, 118.5, 117.9, 99.2.

*3.1.8. 2-Cyano-5-phenyl-4H-furo[3,2-b]pyrrole (**20**) and 5-phenyl-4H-furo[3,2-b]pyrrole-2-aldoxime (**19**).* A solution of **5** (75 mg, 0.291 mmol), $Pd(dba)_2$ (10 mg, 0.0174 mmol) and 1,10-phenanthroline (7 mg, 0.0353 mmol) in anhydrous DMF (3 mL) was heated as described for **17** (6 atm CO, 120 °C, 22 h). The mixture was cooled to ambient temperature and water (10 mL) was added. The mixture was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with water (2×50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the resulting oil by chromatography (hexanes/EtOAc, 8:2) gave in order of elution **20** (12 mg, 0.058 mmol, 20%) and **19** (30 mg, 0.132 mmol, 45%). The latter compound decomposed noticeable at ambient temperature within a few minutes. Data for **20**: Mp 162–163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (br s, 1H), 7.53 (d, J=7.2 Hz, 2H), 7.48 (t, J=7.8 Hz, 2H), 7.33 (t, J=7.2 Hz, 1H), 7.10 (s, 1H), 6.47 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.7, 141.6, 132.06, 129.2, 128.1, 126.3, 124.6, 123.5, 113.4, 109.6, 90.1; IR (ATR) 3310, 2209, 1707 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_8N_2O$ ($M+H^+$) 209.0716, found 209.0709.

Partial data for **19**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.98 (s, 1H), 7.51(d, J=7.8 Hz, 2H), 7.39 (t, J=8.4 Hz, 2H), 6.64 (s, 1H), 6.46 (s, 1H).

*3.1.9. 2-Methyl-5-phenyl-4H-pyrrolo[3,2-d]thiazole (**21**).* Reaction of 2-methyl-5-nitro-4-(2-phenylethenyl)thiazole (**6**)[18] (60 mg, 0.244 mmol), $Pd(OAc)_2$ (4 mg, 0.017 mmol), and PPh_3 (19 mg, 0.0725 mmol) in MeCN (5 mL) as described for **17** (6 atm CO, 80 °C, three days) gave after chromatography (hexanes/EtOAc, 8:2) **21** (32 mg, 0.149 mmol, 61%) as a pale brown solid. Mp 257–258 °C (dec); ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.67 (d, J=7.8 Hz, 2H), 7.39 (t, J=7.8 Hz, 2H), 7.21 (t, J=7.5 Hz, 1H), 6.78 (d, J=1.8 Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 158.5, 147.3, 136.6, 132.8, 128.8, 127.1, 126.2, 123.5, 96.3; IR (ATR) 1602, 1458, 1184 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{10}N_2S$ ($M+H^+$) 215.0643; found, 215.0638.

*3.1.10. 1-Benzyl-1,4-dihydro-5-phenylpyrrolo[3,2-d]imidazole (**22**).* Reaction of 1-benzyl-5-(2-phenylethenyl)-4-nitroimidazole (**7**)[19] (58 mg, 0.190 mmol), $Pd(dba)_2$ (7 mg, 0.012 mmol), and 1,10-phenanthroline (5 mg, 0.134 mmol) in anhydrous DMF (2 mL) as described for **19**/**20** (6 atm CO, 120 °C, 139 h) gave after chromatography (hexanes/EtOAc, 8:2, followed by EtOAc) **22** (40 mg, 0.146 mmol, 77%) as a brown solid. Mp 244–247 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 10.33 (s, 1H), 7.65 (d, J=7.2 Hz, 2H), 7.53 (s, 1H), 7.39–7.29 (m, 7H), 7.13 (t, J=7.2 Hz, 1H), 6.29 (s, 1H), 5.32 (s, 2H); ^{13}C NMR (150 MHz, acetone-d_6) δ 138.7, 138.5, 135.3, 135.25, 133.7, 129.58, 129.63, 128.7, 128.67, 126.5, 124.5, 88.85, 88.8, 50.9; IR (ATR) 1599, 3111, 1470, 1452 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_3$ ($M+H^+$) 274.1344; found, 274.1338.

*3.1.11. 3-Benzyl-3,4-dihydro-5-phenylpyrrolo[2,3-d]imidazole (**23**).* Reaction of 1-benzyl-4-(2-phenylethenyl)-5-nitroimidazole (**8**)[16] (125 mg, 0.409 mmol), $Pd(dba)_2$ (15 mg, 0.012 mmol), and 1,10-phenanthroline (27 mg, 0.1361 mmol) in anhydrous DMF (3 mL) as described for **19**/**20** (6 atm CO, 120 °C, three days) gave after chromatography (hexanes/EtOAc, 8:2, followed by EtOAc) **23** (36 mg, 0.132 mmol, 32%) as a brown solid. Mp 216 °C (dec); ^{1}H NMR (600 MHz, acetone-d_6) δ 10.28 (s, 1H), 7.58 (dd, J=8.4, 2.4 Hz, 2H), 7.36–7.28 (m, 7H), 7.44 (s, 1H), 7.12 (t, J=7.2 Hz, 1H), 6.55 (s, 1H), 5.37 (s, 2H); ^{13}C NMR (150 MHz, acetone-d_6) δ 138.5, 138.0, 136.2, 135.4, 129.7, 129.6, 128.6, 128.0, 126.3, 124.3, 95.9, 95.8, 49.4; IR (ATR) 1599, 1383, 1219 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_3$ ($M+H^+$) 274.1344; found, 274.1338.

*3.1.12. 1H-Pyrrolo[3,2-b]pyridine (**26**).* A solution of 2-ethenyl-3-nitropyridine[20] (**11**) (190 mg, 1.27 mmol), $Pd(dba)_2$ (36.1 mg, 0.0628 mmol), and 1,10-phenanthroline (25.0 mg, 0.126 mmol) in anhydrous DMF (4 mL) was heated as described for **19**/**20** (6 atm CO, 120 °C, 42 h). The solvent was removed by bulb-to-bulb distillation under reduced pressure and the resulting crude product was purified by chromatography (hexanes/EtOAc, 3:7) to give **26** (97.6 mg, 0.826 mmol, 65%) as a pale yellow solid. Mp 126–128 °C (lit.[21] 127 °C).

*3.1.13. 1H-Pyrrolo[2,3-b]pyridine (**27**).* Reaction of **12** (506 mg, 3.37 mmol), $Pd(dba)_2$ (95.8 mg, 0.167 mmol), and 1,10-phenanthroline (67.1 mg, 0.338 mmol) in DMF (4 mL), as described for **19**/**20** (6 atm CO, 120 °C, 7.5 days), gave after chromatography (EtOAc/MeOH, 9:1), **27** (163 mg, 1.38 mmol, 41%) as a pale yellow solid. Mp 103–104 °C (lit.[22] 105–106 °C).

*3.1.14. 2-Phenyl-1H-pyrrolo[3,2-c]pyridine (**28**).* Reaction of 4-nitro-3-(2-phenylethenyl)pyridine *N*-oxide[23] (**13**) (102 mg, 0.421 mmol), $Pd(dba)_2$ (11.5 mg, 0.0200 mmol), and 1,10-phenanthroline (8.3 mg, 0.042 mmol) in DMF (5 mL), as described for **19**/**20** (6 atm CO, 120 °C, 22 h), gave after chromatography (EtOAc) **28** (74.4 mg, 0.383 mmol, 91%) as a yellow solid. Mp 282–283 °C (lit.[8] 282–283 °C).

*3.1.15. 2-Phenyl-1H-pyrrolo[2,3-c]pyridine (**29**).* Reaction of 3-nitro-4-(2-phenylethenyl)pyridine[24] (**13**) (131 mg, 0.579 mmol), $Pd(dba)_2$ (16.6 mg, 0.0289 mmol), and 1,10-phenanthroline (11.6 mg, 0.0585 mmol) in anhydrous DMF (4 mL), as described for **19**/**20** (6 atm CO, 120 °C, 24 h), gave after chromatography (EtOAc/MeOH, 9:1) **29** (98.5 mg, 0.507 mmol, 87%) as a pale yellow solid. Mp 224–226 °C (lit.[4] 223–225 °C).

*3.1.16. 4-Methoxy-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine (**30**).* Reaction of **15** (251 mg, 0.976 mmol), $Pd(dba)_2$ (27.7 mg, 0.0482 mmol), and 1,10-phenanthroline (19.3 mg, 0.973 mmol) in anhydrous DMF (5 mL), as described for **19**/**20** (6 atm CO, 120 °C, 24 h), gave after chromatography (in order hexanes/EtOAc, 2:8; EtOAc; EtOAc/MeOH, 9:1) **30** (180 mg, 0.799 mmol, 82%) as a white solid. Mp 222–223 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.3 (br s, 1H), 8.41 (s, 1H), 8.01 (dd, J=9.0, 1.2 Hz, 2H), 7.49 (t, J=8.4 Hz, 2H), 7.40 (t, J=7.8 Hz, 1H), 7.05 (d, J=1.8 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.2 (+), 150.8 (+), 149.4 (−), 142.4 (+), 131.0 (+), 128.9 (−), 128.7 (−), 126.1 (−), 115.5 (+), 99.3 (−), 53.1 (−); IR (ATR) 2754, 1624, 1526, 1457, 1393, 1345, 1293, 1120 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92. Found: C, 69.61; H, 5.19.

*3.1.17. 6-Methyl-2-phenyl-5H-pyrrolo[3,2-c]pyridazine 5-N-oxide (**31**).* Reaction of **16** (45.9 mg, 0.178 mmol), $Pd(dba)_2$ (5.40 mg, 0.00939 mmol), and 1,10-phenanthroline (3.80 mg, 0.0192 mmol) in anhydrous DMF (4 mL), as described for **19**/**20** (6 atm CO, 120 °C, 14 h), gave after chromatography (EtOAc, followed by EtOAc/MeOH, 9:1) **31** (22.8 mg, 0.101 mmol, 57%) as a yellow solid. Mp >250 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.3 (br s, 1H) 7.95 (d, J=7.2 Hz, 2H), 7.87 (s, 1H), 7.53 (t, J=7.8 Hz, 2H), 7.44 (t, J=7.8 Hz, 1H), 7.01 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 146.1 (+), 144.4 (+), 137.4 (+), 130.4 (−), 129.1 (−), 129.0 (−), 125.8 (−), 124.4 (+), 115.4 (−), 95.5 (+), 18.6 (−); IR (ATR) 3057, 2666, 1314, 1214 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{12}N_3O$ ($M+H^+$) 226.0980; found, 274.0975.

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