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DIRECT SYNTHESIS OF HETEROBIARYLS BY RADICAL ADDITION TO PYRIDINE: EXPEDITIOUS SYNTHESIS OF CHELATING LIGANDS*

*** Dedicated with respect and gratitude to Dr. Pierre Potier on the occasion of his 70th birthday**

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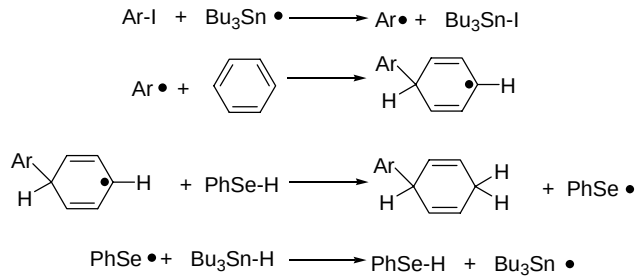
Abstract – The addition of aryl radicals to pyridine may be affected in moderate yield on exposure of aryl iodides to tributyltin hydride, AIBN, and diphenyl diselenide in hot pyridine. Mixtures of *ortho*-, *meta*-, and *para*-aryl substituted pyridines are typically obtained. When the iodide is *ortho*-substituted with a hydrogen bond donor, such as *o*-iodophenol, significantly improved selectivity for *ortho*-substituted pyridines, with potential as bidentate chelating ligands, is obtained.

INTRODUCTION

Work in our laboratory over the last several years has demonstrated how cyclohexadienyl radicals generated by aryl radical addition to benzene may be trapped by benzeneselenol leading overall to a dearomatization reaction with concomitant C-C bond formation.[1] In this chemistry the benzeneselenyl radical obtaining on quenching the cyclohexadienyl radical is itself quenched by tributylstannane, thereby rendering the process catalytic in benzeneselenol and supplying the stannyl radical necessary for chain propagation (Scheme 1).[2,3] When the initial aryl halide is an *o*-substituted phenol or aniline a subsequent cyclofunctionalization reaction affords tetrahydrodibenzofurans or tetrahydrocarbazoles, respectively, in a very efficient two step protocol.[4,5] In attempting to extent the potential of this chemistry in alkaloid chemistry we have now investigated, and report here our results on, the addition of aryl radicals to pyridine under similar, selenol-mediated stannane conditions.[6,7] Our work in this area is paralleled by, but appears to differ mechanistically from, the addition of aryl radicals to pyridine recently reported by Alvarez-Builla and co-workers[8] following their oxidative aryl radical additions to benzene.[9]

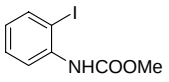
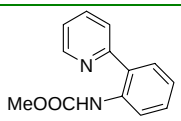
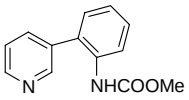
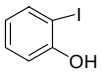
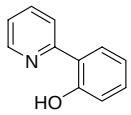
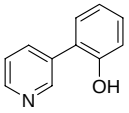
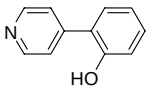
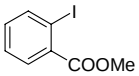
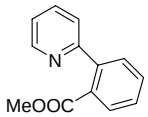
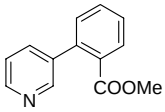
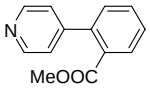
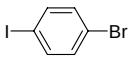
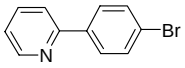
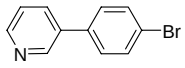
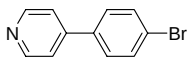
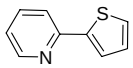
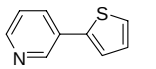
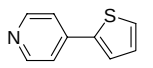
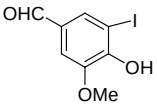
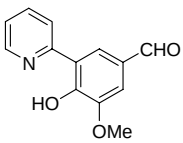
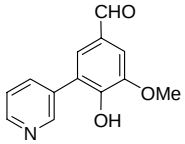
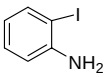
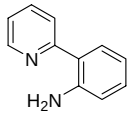
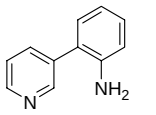
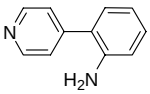
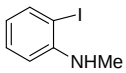
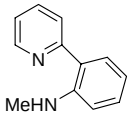
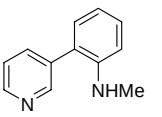
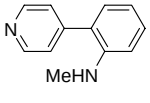
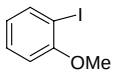
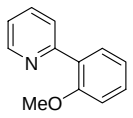
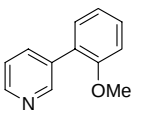
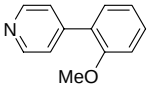
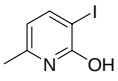
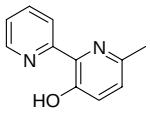
Scheme 1. Selenol-mediated Addition of Aryl Iodides to Benzene.



RESULTS AND DISCUSSION

Dropwise addition of Bu_3SnH (1.75 equiv.) and AIBN (0.2 equiv.) to a solution of *N*-methoxycarbonyl-*o*-iodoaniline (**1)** in pyridine at reflux gave 38% of the *o*-substitution product (**11**) and 3% of the *m*-isomer (**12**) (Table 1). Likewise, *o*-iodophenol (**2**), *o*-iodoaniline (**7**), and *o*-iodo-*N*-methylaniline (**8**) all afforded predominantly the *o*-products (Table 1). In contrast, with methyl *o*-iodobenzoate (**3**), *p*-bromoiodobenzene (**4**), 2-iodothiophene (**5**), *o*-iodovanillin (**6**), and *o*-iodoanisole (**9**) the *ortho*/*meta* ratio of products was much lower. In most cases, minor amounts of the *p*-isomers were also isolated (Table 1). The additions to pyridine reported here obviously differ from our earlier additions to benzene in so far as the products are those of oxidative addition rather than the anticipated dihydro analogues.[10] Nevertheless, the presence of the diphenyl diselenol-based catalyst was found to be advantageous in terms of overall yield, indicating that this chemistry is subtly different from that of Alvarez-Builla, which employs no selenol/diselenide and which makes use of two full equivalents of AIBN. It is not clear how the aromatization of the adduct radical takes place, something that is common to all oxidative radical additions to arenes:[11] one possibility is the quenching of the azacyclohexadienyl radical by diphenyl diselenide to give an aryl phenylselenyl azacyclohexadiene which spontaneously eliminates benzeneselenol to give the final product.[12,13] Another possibility is the oxidation of the electron-rich azacyclohexadienyl to the corresponding cation by an organoselenium species, such as diphenyl diselenide, or tributylstannyl phenyl selenide. The improved ratios in favor of the *o*-substituted product seen with **1**, **2, 7,** and **8** are attributed to hydrogen bonding of the substrate to pyridine resulting in both an activating and a directing effect. The exception, *o*-iodovanillin (**6**), is explained by preferential intramolecular hydrogen bonding to the methoxy group. The yields obtained in this chemistry are only modest, but the simplicity of the protocol, and the availability of the starting materials, make it an attractive entry into aryl substituted pyridines. This chemistry is especially suited to aryl iodides bearing a hydrogen bonding group in the *o*-position when it affords improved selectivity for *o*-substituted pyridines: the 2'-substituted 2-arylpyridines generated in this very direct and facile synthesis may enjoy use as bidentate chelating ligands.

Table 1. Synthesis of Arylpyridines

Substrate	**Products** (yield %)[a]		
			
1	**11** (38)	**12** (3)	
			
2	**13** (36)	**14** (16)	**15** (10)
			
3	**16** (20)	**17** (22)	**18** (9)
			
4	**19** (18)	**20** (12)	**21** (5)
			
5	**22** (19)	**23** (24)	**24** (7)
			
6	**25** (17)	**26** (17)	
			
7	**27** (18)	**28** (4)	**29** (4)
			
8	**30** (25)	**31** (7)	**32** (5)
			
9	**33** (20)	**34** (23)	**35** (10)
			
10	**36** (13)		

a) With the exception of **11**,[14] **12**,[15] **25**,[16] **26**,[17] **30**,[18] **31**,[19] **32**,[20] and **36**,[21] all products had physical characteristics consistent with literature data.[22]

EXPERIMENTAL

Typical Protocol. A solution of aryl iodide (1 mmol), diphenyl diselenide (62 mg, 0.2 mmol) and pyridine (20 mL) is sparged with argon for 45 min, followed by heating to 95 ^{o}C with stirring. A solutionof AIBN (33 mg, 0.2 mmol) and Bu_3SnH (693 mg, 1.75 mmol) in degassed pyridine (10 mL) is added *via* syringe pump over 16 h, after which heating is continued for 1 h, before the reaction mixture is cooled to rt and concentrated. The residue is taken up in 20% EtOAc in hexane (50 mL) and extracted with 2N HCl (50 mL). The aqueous phase is neutralized with 3M NaOH and extracted (EtOAc). The extracts are washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (eluent: EtOAc/hexane).

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10. Inspection of crude reaction mixtures by ^{1}H-NMR spectroscopy gave no evidence for the formation of dihydropyridines.
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12. Benzeneselenol is generated in situ from diphenyl diselenide by reduction with tributyltin hydride.[2,3]
13. Blank experiments omitting the diphenyl diselenide/benzeneselenol gave reduced substrate conversion and reduced yields indicating an important mechanistic role for a selenium-based catalyst.
14. **11:** mp 32-34 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.76 (s, 3H), 7.12 (dt, *J* = 7.0, 1.0 Hz, 1H), 7.26 (ddd, *J* = 7.5, 4.5, 1.0 Hz, 1H), 7.40 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.63 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.81 (dt, *J* = 8.0, 2.0 Hz, 1H), 8.33 (br d, *J* = 8.5 Hz, 1H), 8.65 (br d, *J* = 6.0 Hz, 1H), 11.52 (br s, 1H). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30. Found: C, 68.37; H, 5.19.
15. **12:** mp 108-110 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.71 (s, 3H), 6.52 (br s, 1H), 7.20 (m, 2H), 7.41 (m, 2H), 7.70 (d, *J* = 7.5 Hz, 1H), 8.05 (br s, 1H), 8.63 (m, 2H). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30. Found: C, 68.24; H, 5.20.
16. **25:** mp 160-161 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.96 (s, 3H), 7.32 (ddd, *J* = 12.5, 5.0, 1.0 Hz, 1H), 7.39 (d, *J* = 1.5 Hz, 1H), 7.90 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 8.0 (d, *J* = 8.5 Hz, 1H), 8.52 (ddd, *J* = 5.3, 2.0, 0.5 Hz, 1H), 9.85 (s, 1H). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84. Found C, 67.83; H, 4.70.
17. **26:** mp 162-163 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.99 (s, 3H), 7.39 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.98 (td, *J* = 8.0, 2.0 Hz, 1H), 8.58 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.87 (d, *J* = 2.5 Hz, 1H), 9.87 (s, 1H); *m/z* (ESI) ($M + H^+$): Calcd 230.0817, found 230.0815.
18. **30:** ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.93 (s, 3H), 6.75 (m, 2H), 7.17 (m, 1H), 7.32 (m, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.67 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.75 (m, 1H), 8.02 (br s, 1H), 8.60 (dd, *J* = 5.0, 1.0 Hz, 1H); *m/z* (ESI) ($M + H^+$): Calcd 185.1079, found 185.1075.
19. **31**: mp 71-73 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.80 (s, 3H), 3.80 (br s, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.80 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.07 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.31 (dt, *J* = 8.5, 2.0 Hz, 1H), 7.37 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.76 (td, *J* = 7.5, 2.0 Hz, 1H), 8.59 (dd, *J* = 5.0, 2.0 Hz, 1H), 8.67 (d, *J* = 2.0 Hz, 1H); *m/z* (ESI) ($M + H^+$): Calcd 185.1079, found 185.1084.
20. **32:** mp 133-135 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.82 (s, 3H), 3.93 (br s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.80 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.09 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.32 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.39 (dd, *J* = 6.0, 2.0 Hz, 2H), 8.66 (dd, *J* = 6.0, 2.0 Hz, 2H); *m/z* (ESI) ($M + H^+$): Calcd 185.1079, found 185.1075.
21. **36:** mp 47-48 °C; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.53 (s, 3H), 7.08 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.31 (ddd, *J* = 11.5, 5.0, 1.5 Hz, 1H), 7.89 (dt, *J* = 7.5, 2.0 Hz, 1H), 8.50 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 14.01 (br s, 1H). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41. Found C, 70.89; H, 5.39.

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