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A Facile Synthesis of 4-Aryl-2,3-Dihydropyrroles

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Abstract: *A combination of Heck arylation of N-allylsulfonamide and subsequent hydroformylation provides a simple and flexible entry into the title compounds.*

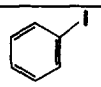
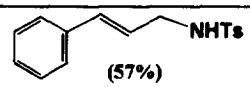
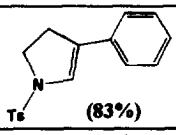
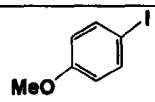
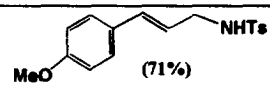
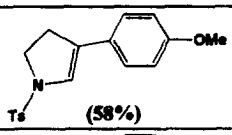
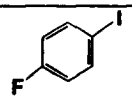
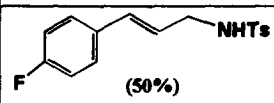
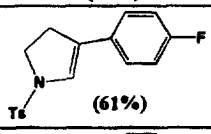
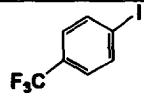
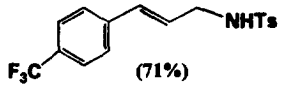
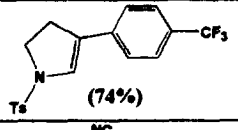
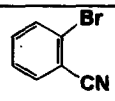
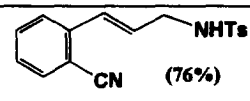
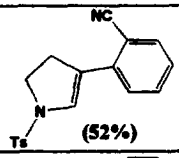
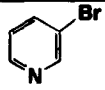
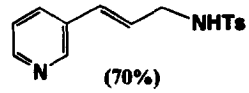
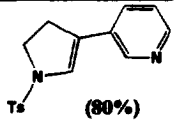
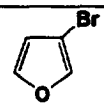
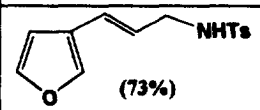
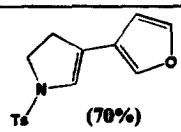
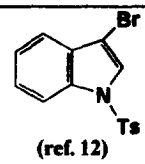
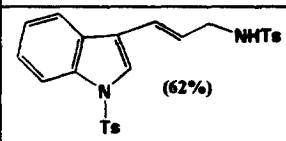
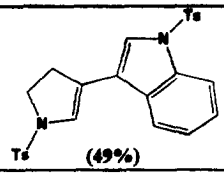
Aryl substituted dihydropyrroles have been utilized as both annelation[1] and Diels-Alder[2] substrates in the synthesis of various natural products. In the course of our work on these and related processes we desired a rapid route to a number of 4-aryl-2,3-dihydropyrroles. The most common entry to these systems has involved the cyclopropyliminium ion rearrangement first demonstrated by Stevens[1a,b] and recently used quite efficiently by Rawal.[2] Other approaches have included sequences involving electrochemical oxidation of functionalized carbamates,[3] benzyne alkylations,[4] generation of aminoaldehyde precursors,[5] and formylation of dianion[6] species. While attractive, these methods did not meet our requirements for 1) direct use of commercially available and diverse aryl halides, 2) utilization of standard, scalable experimental techniques, and 3) rapid construction. In addition, we wished to avoid reduction or oxidation of sensitive functionality.

The Heck arylation[7] reaction has emerged as an efficient and broadly applicable method for aryl-olefin bond construction. Hydroformylation is now recognized as an excellent tool for synthesis of aldehydes from olefins,[8] and Ojima[9] has ably demonstrated the utility of hydroformylation as a route to pyrrolidine and piperidine derivatives. We thus wished to determine if a new synthesis of 4-aryl-2,3-dihydropyrroles could be developed via a combination of these two powerful methodologies. Our initial work thus focused on arylation of the allylamine equivalents shown in Table 1. Allylamine **1** , (Ts)(BOC)-allylamine **2** and disilyl derivative **3** all gave very complex reaction mixtures upon Heck reaction with 4-iodoanisole. As anticipated[10] bis(BOC) compound **4** and *N*-allylphthalimide **5** each furnished arylated product (83%, 58%). Hydroformylation with ring closure to a monoprotected dihydropyrrole, however, required a deprotection or deprotection/reprotection strategy to utilize the Heck adducts derived from **4** and **5** respectively. Two monoprotected allylamines were thus examined. Mono(BOC) species **6** led unexpectedly to a mixture of positional olefin isomers, yet *N*-allyltosylamide **7** prepared *via* quantitative tosylation of allylamine, furnished the desired sulfonamide **8b** in 71% yield. It should be noted that arylation attempts under "Jeffery-Larock[11]" conditions ($Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, DMF) gave poor yields of **8b**, and only the "classical" protocol shown (eq. 1) gave the products in good yield. Heck arylation of **7** was found to be quite general, as shown in Table 2. With the olefins in hand, a number of hydroformylation protocols were examined. Two rhodium species, $RhH(CO)(PPh_3)_2$ and $RhCl_3$, three solvents (PhMe, EtOAc, and MeOH), and four ligands (PPh_3, $P(OPh)_3$, $Ph_2PC_2H_4PPh_2$, and $Ph_2PC_3H_6PPh_2$) were varied systematically. $RhCl_3$ was found to be ineffective under all conditions, as was MeOH under most catalyst/ligand combinations. Consistently faster turnover rates were observed in toluene relative to EtOAc. Ligand evaluation was similarly clear cut as PPh_3 gave superior rates to

Table 1

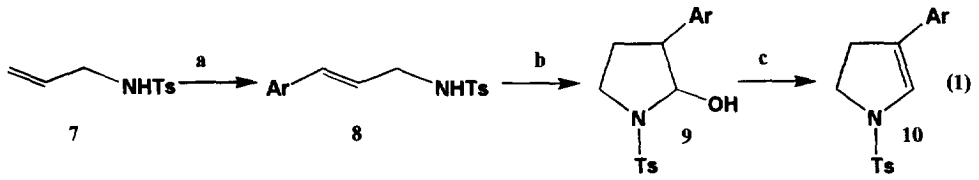
1 $R_1 = R_2 = H$
2 R_1 = Ts, R_2 = BOC
3 R_1, R_2 = disilazole
4 $R_1 = R_2$ = BOC
5 $R_1 = R_2$ = phthalimide
6 R_1 = BOC, R_2 = H
7 R_1 = Ts, R_2 = H

Table 2. Arylation of 7 and Hydroformylation/Elimination of 8.

Entry	Aryl Halide	Heck adduct 8, (yield)	mp, °C	Dihydropyrrole 10, (yield*)	mp, °C
a)		 (57%)	105-106	 (83%)	157-158
b)		 (71%)	110-111	 (58%)	129-130
c)		 (50%)	79-81	 (61%)	115-116
d)		 (71%)	145-147	 (74%)	146-148
e)		 (76%)	(oil)	 (52%)	158-160
f)		 (70%)	110-113	 (80%)	135-136
g)		 (73%)	104-105	 (70%)	131-133
h)	 (ref. 12)	 (62%)	201-203	 (49%)	224-225

* isolated yield from 8. All compounds gave satisfactory C,H,N,S analyses.

$P(OPh)_3$, and use of the two bidentate ligands led only to recovery of starting material. Additionally, it was noted that little hydroformylation occurred at pressures lower than 120 psig and temperatures below 50°C. A standard protocol was thus developed and applied to eight diverse styrenyl sulfonamides as shown (eq. 1).



a) $Pd(OAc)_2$, $(o\text{-}Tol)_3P$, ArI(Br), TEA, CH_3CN b) $RhH(CO)(PPh_3)_2$, PPh_3, H_2:CO, $PhCH_3$ c) cat. conc. HCl

Hydroformylation with ring closure proceeded smoothly in all cases to furnish the hydroxypyrrolidines **9a-h** as chromatographically isolable species. Regiocontrol for the hydroformylation was excellent, with only traces of the regioisomeric aldehyde (incapable of cyclization) visible in the crude ^1H NMR. No hydrogenation of the olefin was observed. The hydroxypyrrolidines were generally formed as ca. 2:1 trans:cis mixtures, although the 3-pyridyl adduct **9f** crystallized from the reaction mixture as the cis isomer. The relative stereochemistry was confirmed *via* x-ray crystallographic analysis. [13] The synthesis of the targets was then readily completed by dehydration with catalytic conc. HCl in THF.[14] The dihydropyrroles thus obtained were, in all cases, air stable crystalline solids. The reactivity of these dihydropyrroles is under active investigation, and will be reported in due course.

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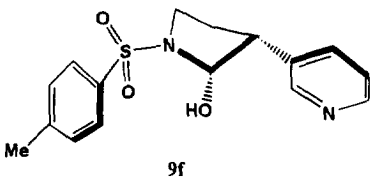
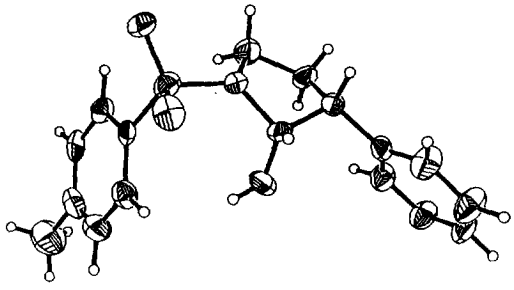
13. see x-ray structure below. Thanks to Dr. L. Tong for x-ray structure determination. Crystal data: m.p. 170-173°C; space group $P2_1$; R factor 4.2%.
14. see General Procedure for Hydroformylation/Dehydration below.

General Procedure for Arylation. A 100mL RB flask was charged with 2.63g allyltosylamide 7 (12.5 mmol, 1 eq), 0.145g $Pd(OAc)_2$ (0.625 mmol, 0.05 eq), 0.379g $(o\text{-Tol})_3P$ (1.25 mmol, 0.10 eq), 30 mL MeCN, 3.52 mL TEA (25.0 mmol, 2 eq), and 1.12 mL 3-bromofuran (12.5 mmol, 1 eq) in the order given. The resulting homogeneous reaction mixture was heated to reflux for 3 h under N_2. At this time an additional 0.48 mL 3-bromofuran (5.30 mmol), 0.075g $Pd(OAc)_2$ (0.323 mmol), and 0.190g $(o\text{-Tol})_3P$ (0.63 mmol) were added in the order given. The mixture was refluxed an additional 6 h, cooled to 23°C, diluted with 100 mL H_2O, and extracted with EtOAc (3X50 mL). The combined EtOAc layers were dried ($MgSO_4$), and the solvents removed *in vacuo* to give a brown residue. This material was then immediately chromatographed on silica gel eluting with 10-40% EtOAc/hexane to give 2.51g of **8g** (73%) as a crystalline solid, m.p. 104-105°C. ^1H NMR (270 MHz, $CDCl_3$): δ 7.77 (d, *J*=8.3 Hz, 2H), 7.32-7.30 (m, 2H), 7.28 (d, *J*=8.1 Hz, 2H), 6.37 (s, 1H), 6.29 (d, *J*=15.7 Hz, 1H), 5.73 (dt, *J*=15.7, 6.4 Hz, 1H), 5.06 (t, *J*=6.1 Hz, 1H), 3.66 (dt, *J*=6.3, 1.2 Hz, 2H), 2.39 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 143.36 (d), 143.33 (s), 140.49 (d), 136.85 (s), 129.55 (d), 127.03 (d), 123.61 (d), 123.11 (s), 122.63 (d), 107.27 (d), 45.17 (t), 21.31 (q). Anal. Calc'd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05; S, 11.54. Found: C, 60.59; H, 5.25; N, 4.91; S, 11.60.

General procedure for hydroformylation/dehydration. A 300 mL stainless steel bomb was charged with 0.472g PPh_3 (1.8 mmol, 0.5 eq), 0.165g $Rh(H)(CO)(PPh_3)_2$ (0.18 mmol, 0.05 eq), 1.10g sulfonamide **8c** (3.60 mmol, 1 eq), and 25 mL PhMe. The bomb was sealed and pressurized to 300 psig with 1:1 H_2:CO, stirred 5 min, cautiously vented, and again pressurized to 300 psig with the same gas mixture. The contents were then heated at 70°C under pressure for 70 h, cooled to 0°C, and cautiously vented. The solvent was removed *in vacuo*, and the residue chromatographed on silica gel (deactivated with 5% TEA in hexane before use) eluting with 30% EtOAC/hexane to give 0.743g of hydroxypyrrolidine **9c** as a pale yellow oil. This oil was dissolved in 15 mL THF under N_2 at 23°C, and 4 drops of conc. HCl was added. After 30 min, TLC indicated complete dehydration had occurred. The volatiles were removed *in vacuo* and the residue partitioned between EtOAc and 0.5N NaOH. The EtOAc was dried ($MgSO_4$), and the solvents removed *in vacuo* to give 0.696g pure **10c** (61%) as a white crystalline solid, m.p. 115-116°C. ^1H NMR (270 MHz, $CDCl_3$): δ 7.70 (d, *J*=6.7 Hz, 2H), 7.22 (d, *J*=8.1 Hz, 2H), 7.15 (m, 2H), 7.02 (m, 2H), 6.80 (t, *J*=1.7 Hz, 1H), 3.64 (t, *J*=8.8 Hz, 2H), 2.81 (dt, *J*=8.9, 1.8 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 161.6 (d, $^1J(^{13}C\text{-}^{19}F)$=246 Hz), 143.9 (s), 132.6 (s), 129.7 (d), 127.5 (d), 126.0 (d, $^3J(^{13}C\text{-}^{19}F)$=7.7 Hz), 124.9 (d), 123.2 (s), 115.3 (d, $^2J(^{13}C\text{-}^{19}F)$=21.8 Hz), 47.4 (t), 30.4 (t), 21.4 (q). Two singlet carbon lines are coincident. Anal. Calc'd for $C_{17}H_{16}FNO_2S$: C, 64.33; H, 5.08; N, 4.41; S, 10.10. Found: C, 64.36; H, 5.04; N, 4.27; S, 9.93.



9f



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