A REGIOSPECIFIC SYNTHESIS OF CARBOSUBSTITUTED HETEROAROMATIC DERIVATIVES VIA Pd-CATALYZED CROSS COUPLING[1,†]

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Abstract - The Pd-catalyzed cross-coupling reaction of either heteroarylzinc derivatives with unsaturated organic halides or heteroaryl halides with organometallic reagents containing Zn or Al can produce cleanly and regiospecifically the corresponding carbo-substituted heteroaromatic compounds in high yields.

The cross-coupling reaction of organometallic reagents with organic halides in the presence of Ni[2] or Pd[3] catalysts has emerged as a versatile and useful synthetic tool that can complement the Cu-based methodology.[4] While the applicability of the Ni-catalyzed cross coupling to the synthesis of carbo-substituted heteroaromatics has been widely examined,[5] that of the Pd-catalyzed cross-coupling is essentially unknown.[6]

We now report that a variety of carbo-substituted heteroaromatic derivatives can indeed be readily synthesized via Pd-catalyzed cross coupling involving either heteroarylmetals or heteroaryl halides. As representative heteroaromatics 2- and 3-furyl, 2-thienyl, and 2- and 3-pyridyl systems were chosen.

As indicated by the structures of the products 1 - 13 as well as by the results summarized in the Table, introduction of unsaturated organic groups, such as alkenyl, aryl, and alkynyl, in the above-mentioned positions in the heteroaromatic systems can now be readily achieved by the Pd-catalyzed cross coupling.

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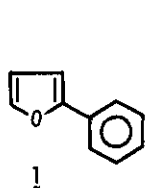
†We wish to dedicate this paper to Professor Herbert C. Brown on the occasion of his 70th birthday.

‡On leave from the Japan Tobacco & Salt Public Corporation.



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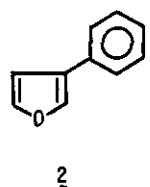

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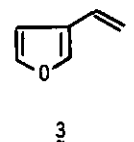

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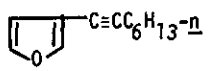

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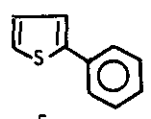

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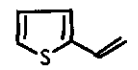

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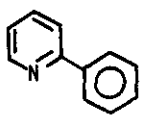

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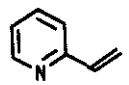

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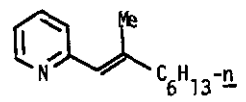

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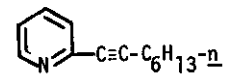

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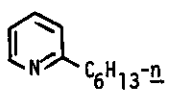

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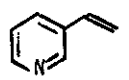

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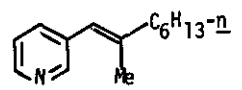

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All reactions are run at room temperature in THF in the presence of 5 mol % of $Pd(PPh_3)_4$. The need for $Pd(PPh_3)_4$ has been established in all cases by running control experiments in the absence of $Pd(PPh_3)_4$.

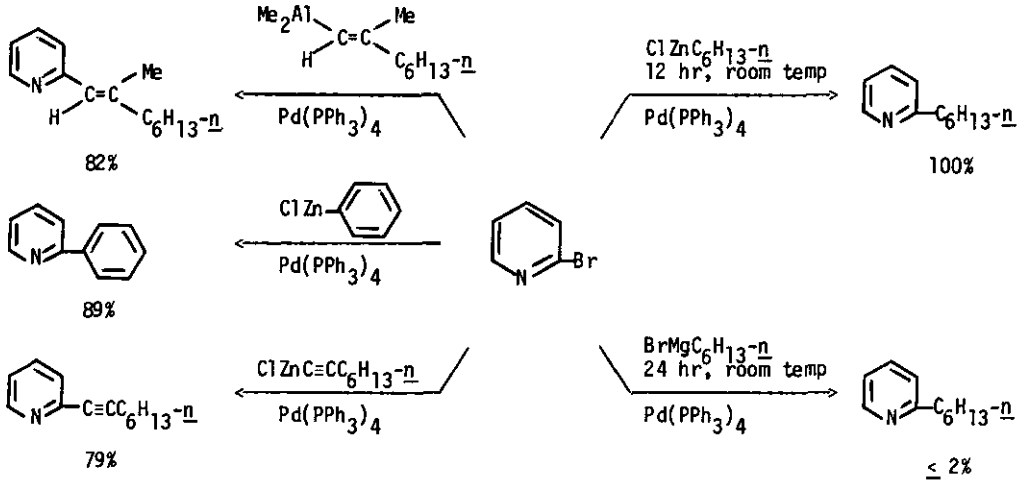
In some cases proper selection of the reagents or the charge affinity pattern is of critical importance. Thus, while both 2-iodofuran (Entry 1) and 2-furylzinc chloride (Entry 2) can be readily converted into 2-phenylfuran (1), only 3-furylzinc chloride (Entry 3), but not 3-bromofuran (Entry 4), can be converted into 3-phenylfuran. Likewise, while 3-pyridylzinc chloride (Entry 14) can be successfully employed, we have been unable to use 3-bromopyridine (Entry 15) in the Pd-catalyzed cross coupling.

We have previously found that the use of metals of intermediate electronegativity leads to highly favorable results[7] in coupling two unsaturated groups. On this basis unsaturated organozinc and organoaluminum reagents are used in the present study. The Pd-catalyzed reaction of 2-bromopyridine with n-hexylzinc chloride (Entry 12) indicates that alkylation of heteroaromatic derivatives is also feasible. In this case, the relative effectiveness of n-hexylmagnesium bromide and n-hexylzinc chloride prepared by treating the former with one equivalent of anhydrous $ZnCl_2$ has been compared. While the latter reaction is complete within 12 hr at room temperature producing 2-(n-hexyl)pyridine in essentially quantitative yield, that of the Grignard reagent merely consumed

2-bromopyridine without producing the desired product in any more than a trace (< 2%) amount under comparable reaction conditions.

As might be expected on the basis of our previous findings,[7] the Pd-catalyzed reaction of 2-bromopyridine with (E)-(2-methyl-1-octenyl)dimethylalane proceeds with complete retention of the alkenyl stereochemistry. Scheme 1 summarizes the results obtained with 2-bromopyridine and shows the versatility of the present methodology with respect to the structural types of the organic substituents introduced on the heteroaromatic rings.

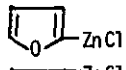
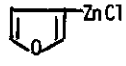
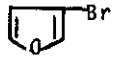
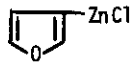
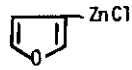
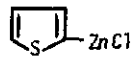
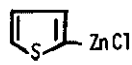
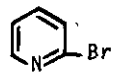
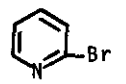
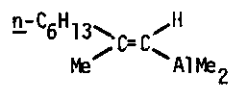
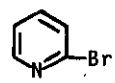
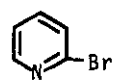
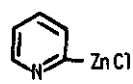
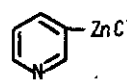
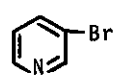
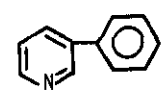
Scheme 1



The following procedure for the preparation of (E)-2-(2-methyl-1-octenyl)pyridine (9) is representative. To 1.58 g (10 mmol) of 2-bromopyridine and 0.346 g (0.3 mmol) of $Pd(PPh_3)_4$ in 50 ml of THF is added the (E)-(2-methyl-1-octenyl)dimethylalane, prepared from 1.10 g (10 mmol) of 1-octyne, 1.44g (20 mmol) of $AlMe_3$ and 0.584 g (2 mmol) of Cp_2ZrCl_2 in 20 ml of 1,2-dichloroethane.[8] After stirring the mixture for 5 hr at room temperature, it is quenched with aqueous $NaHCO_3$, and the organic layer is extracted with hexane. The extract is dried over $MgSO_4$. After filtration and evaporation, it is purified by flash column chromatography (silica gel, n-hexane: ethyl acetate = 3:1) to yield 1.66 g (82%) of 9 (99% purity): n^{23}_D 1.5222; IR (neat) ν max 1650(s), 1585(s), 1560 (m), 1465(s), 1430(s), 1150(m), 740(m) cm^{-1}; ^1H NMR ($CDCl_3$, TMS) δ 0.90 (t; J = 7 Hz, 3H), 1.2-1.8 (m, 8H), 2.07 (s, 3H), 2.1-2.4 (t, J = 7 Hz, 2H), 6.32 (s, 1H), 6.9-7.3 (m, 2H), 7.60 (t, J = 7 Hz, 1H), and 8.56 (d, J = 5 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 14.16, 18.21, 22.75, 28.07, 29.20, 31.95, 41.40, 120.31, 123.78, 124.77, 135.64, 144.28, 149.06, and 157.76 ppm.

Although the number of examples reported in this paper is limited, the Pd-catalyzed cross coupling involving organozinc and organoaluminum derivatives promises as a potentially general and convenient route to carbo-substituted heteroaromatics.

Table. The Preparation of Carbo-substituted Heteroaromatic Derivatives via Pd-catalyzed Cross Coupling[a]

Entry	Heteroaromatic reagent	Organic reagent[b]	Time hr	Product	Yield[c] %	Byproducts %
1.		PhZnCl	1	1[d]	– (91)	–
2.		PhI	1	1	89(94)	–
3.		PhI	10	2[e]	85(89)	 (3%)
4.		PhZnCl	36	2	– (0)	$Ph\rangle_2$ (15%)
5.			6	3[f]	80(81)	–
6.		n-$C_6H_{13}C{\equiv}CBr$	1	4[g]	61(62)	n-$C_6H_{13}C{\equiv}C\rangle_2$ (10%)
7.		PhI	1	5[h]	75(81)	 (14%)
8.			1	6[i]	66(70)	 (13%)
9.		PhZnCl	1	7[j]	89(99)	–
10.			1	9[k]	82(94)	–
11.		n-$C_6H_{13}C{\equiv}CZnCl$	3	10[l]	79(100)	–
12.		n-$C_6H_{13}ZnCl$	0.5	11[m]	85(100)	–
13.			6	8[n]	73(82)	–
14.			6	12[o]	77(89)	 (13%)
15.		PhZnCl	24		– (0)	$Ph\rangle_2$ (6%)

[a] All reactions were carried out in THF at room temperature in the presence of 5 mol % of $Pd(PPh_3)_4$.

[b] Unsaturated organozinc derivatives were prepared by treating the corresponding organolithiums with one equivalent of dry $ZnCl_2$ in THF. n-Hexylzinc reagent was prepared by treating n-$C_6H_{13}MgBr$ with $ZnCl_2$.

[c] Isolated yields of pure products. The numbers in parentheses are yields by GLC.

[d] Bp 85-86°/4.5 mm Hg (lit.[9] bp 92-95°/10 mm Hg); n^{24}_D 1.5916 (lit.[9] n^{20}_D 1.5920); ^{1}H NMR ($CDCl_3$, TMS) δ 6.35 (dd, J = 3 and 5 Hz, 1H), 6.59 (d, J = 5 Hz, 1H) 7.15-7.5 (m, 4H), and 7.5-7.75 (m with doublet-like peaks at 7.60 and 7.70 ppm, 2H) ppm.

[e] Mp 53-54°C (lit.[10] bp 140-145°C/10 mm Hg); ^{1}H NMR ($CDCl_3$, TMS) δ 6.6-6.7 (m, 1H), 7.1-7.55 (m, 6H), 7.6-7.8 (m, 1H) ppm.

[f] Bp 84.5-85°C; n^{25}_D 1.4664; ^{1}H NMR ($CDCl_3$, TMS) δ 5.12 (dd, J = 2 and 10 Hz, 1H), 5.42 (dd, J = 2 and 19 Hz, 1H), 5.56 (dd, J = 10 and 19 Hz, 1H), 6.53 (s, 1H), 7.35 (s, 1H), and 7.39 (s, 1H) ppm. High resolution mass spectroscopy calcd for C_6H_6O: 94.042. Found: 94.042.

[g] Bp 44-46°C/1 mm Hg; n^{23}_D 1.4879; ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (t, J = 7 Hz, 3H), 1.1-1.8 (m, 8H), 2.36 (t, J = 7 Hz, 2H), 6.39 (d, J = 1 Hz, 1H), 7.32 (t, J = 1 Hz, 1H), and 7.54 (d, J = 1 Hz, 1H) ppm.

[h] Mp 32-33°C (lit.[11] mp 34-35°C); ^{1}H NMR ($CDCl_3$, TMS) δ 7.0-7.1 (m, 1H), 7.2-7.5 (m, 5H), and 7.55-7.65 (m, 2H) ppm.

[i] $n^{23.5}_D$ 1.5725; ^{1}H NMR ($CDCl_3$, TMS) δ 5.07 (dd, J = 2 and 10 Hz, 1H), 5.51 (dd, J = 2 and 16 Hz, 1H), and 6.6-7.2 (m, 4H) ppm.

[j] Bp 70-71°C/0.05 mm Hg (lit.[12] bp 190°C/20 mm Hg); n^{26}_D 1.6195; ^{1}H NMR ($CDCl_3$, TMS) δ 7.0-7.25 (m, 1H), 7.25-7.55 (m, 3H), 7.55-7.8 (m, 2H), 7.8-8.15 (m, 2H), and 8.5-8.8 (m, 1H) ppm.

[k] n^{23}_D 1.5222; ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (t, J = 7 Hz, 3H), 1.2-1.8 (m, 8H), 2.06 (s, 3H), 2.16 (q, J = 7 Hz, 2H), 6.32 (s, 1H), 6.9-7.3 (m, 2H), 7.4-7.7 (m, 1H), and 8.5-8.7 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, TMS) δ 14.16, 18.21, 22.75, 28.07, 29.20, 31.95, 41.40, 120.31, 123.78, 124.77, 135.64, 144.28, 149.06, and 157.76 ppm. The steroisomeric purity based on ^{13}C and ^{1}H NMR is ≥98%.

[l] Bp 98-99°C/0.1 mm Hg; n^{24}_D 1.5220; ^{1}H NMR ($CDCl_3$, TMS) δ 0.90 (t, J = 6 Hz, 3H), 1.15-1.85 (m, 8H), 2.45 (t, J = 7 Hz, 2H), 7.05-7.75 (m, 3H), and 8.45-8.6 (m, 1H) ppm.

[m] n^{23}_D 1.4820; ^{1}H NMR ($CDCl_3$, TMS) δ 0.86 (t, J = 7 Hz, 3H), 1.1-1.5 (m, 6H), 1.5-1.9 (m, 2H), 2.79 (t, J = 7 Hz, 2H), 6.9-7.2 (m, 2H), 7.4-7.7 (m, 1H), and 8.45-8.65 (m, 1H) ppm.

[n] Bp 67-68°C/29 mm Hg (lit.[13] bp 68-72°C/30 mm Hg); n^{24}_D 1.5449; ^{1}H NMR ($CDCl_3$, TMS) δ 5.44 (d, J = 10 Hz, 1H), 6.19 (d, J = 17 Hz, 1H), 6.82 (dd, J = 10 and 17 Hz, 1H), 7.1-7.8 (m, 3H), and 8.57 (d, J = 4.5 Hz, 1H) ppm.

[o] Bp 80-81.5°C/32 mm Hg (lit.[14] bp 57-66°C/2.7 mm Hg); n^{24}_D 1.5384; ^{1}H NMR ($CDCl_3$, TMS) δ 5.36 (d, J = 11 Hz, 1H), 5.81 (d, J = 17 Hz, 1H), 6.73 (dd, J = 11 and 17 Hz, 1H), 7.22 (dd, J = 4.5 and 8 Hz, 1H), 7.71 (d, J = 8 Hz, 1H), 8.49 (d, J = 4.5 Hz, 1H), and 8.61 (s, 1H) ppm.

Acknowledgments are made to the National Science Foundation, the National Institutes of Health, and the Japan Tobacco & Salt Public Corporation for support of this research.

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Received, 24th September, 1981