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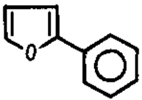
[†] We wish to dedicate this paper to Professor Herbert C. Brown on the occasion of his 70th birthday.

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



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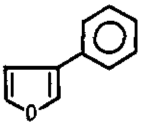

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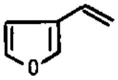

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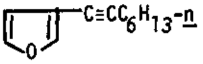

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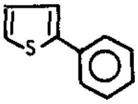

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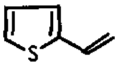

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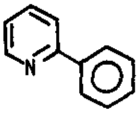

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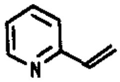

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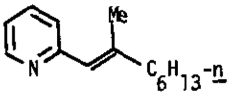

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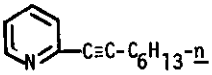

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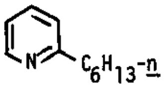

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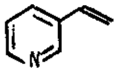

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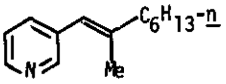

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All reactions are run at room temperature in THF in the presence of 5 mol % of $Pd(PPh_3)_4$. The need for $Pd(PPh_3)_4$ has been established in all cases by running control experiments in the absence of $Pd(PPh_3)_4$.

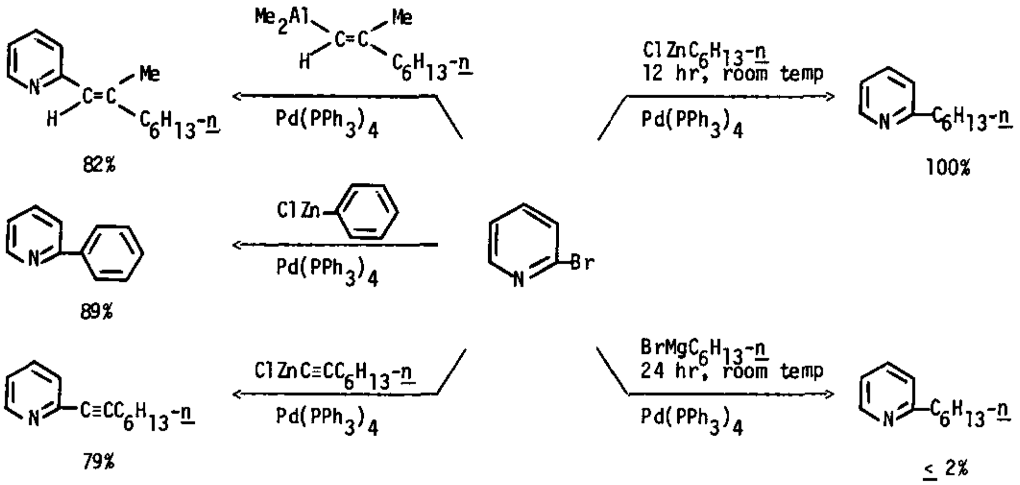
In some cases proper selection of the reagents or the charge affinity pattern is of critical importance. Thus, while both 2-iodofuran (Entry 1) and 2-furylzinc chloride (Entry 2) can be readily converted into 2-phenylfuran (1), only 3-furylzinc chloride (Entry 3), but not 3-bromofuran (Entry 4), can 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.

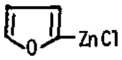
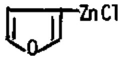
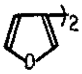
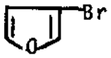
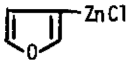
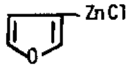
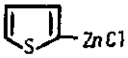
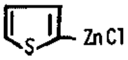
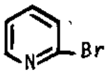
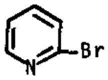
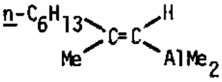
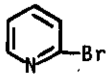
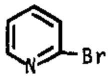
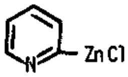
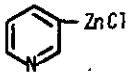
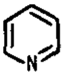
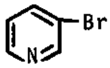
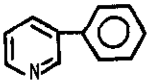
Scheme 1



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, 1.449 (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): $\underline{n}^{23}\underline{D}$ 1.5222; IR (neat) $\nu$ max 1650(s), 1585(s), 1560 (m), 1465(s), 1430(s), 1150(m), 740(m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, TMS) $\delta$ 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) $\delta$ 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$)_2$ (15%) |
| 5. |  |  | 6 | 3[f] | 80(81) | – |
| 6. |  | n-$C_6H_{13}C{\equiv}CBr$ | 1 | 4[g] | 61(62) | n-$C_6H_{13}C{\equiv}C)_2$<br>(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$)_2$ (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) $\delta$ 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) $\delta$ 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) $\delta$ 5.12 (dd, $J$ = 2 and 10 Hz, 1H), 5.42 (dd, $J$ = 2 and 19 Hz, 1H), 6.56 (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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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 $\geq$98%.

[l] Bp 98-99°C/0.1 mm Hg; $n^{24}_{D}$ 1.5220; $^{1}$H NMR ($CDCl_3$, TMS) $\delta$ 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) $\delta$ 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) $\delta$ 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) $\delta$ 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.

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