

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 regioselectively the corresponding carbo-substituted heteroaromatic compounds in high yields.

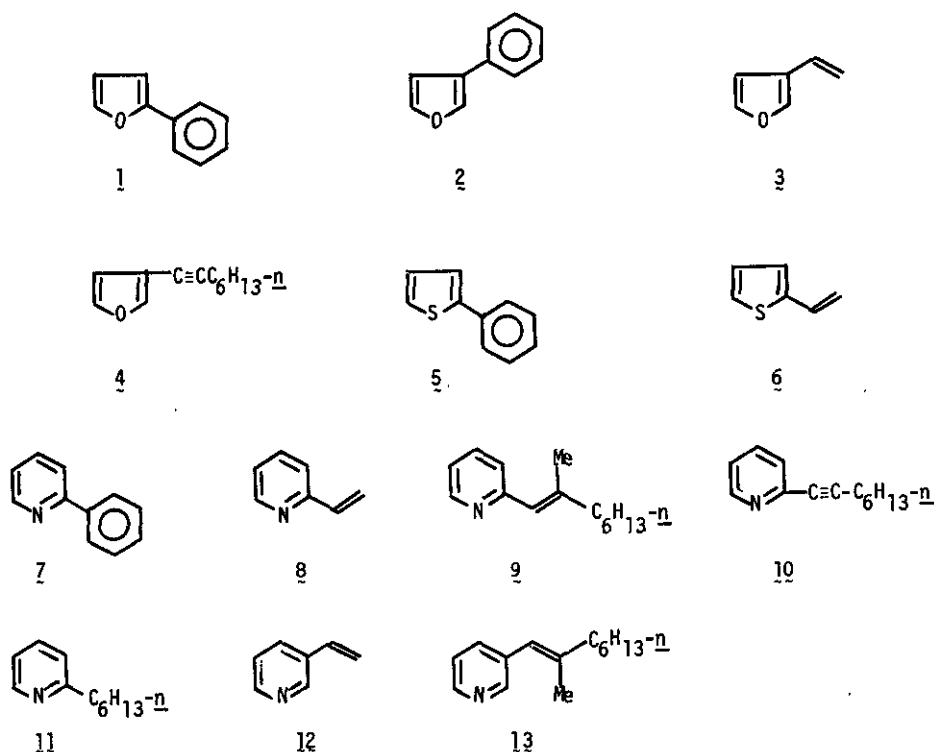
The cross-coupling reaction of organometallic reagents with organic halides in the presence of Ni² or Pd³ catalysts has emerged as a versatile and useful synthetic tool that can complement the Cu-based methodology.⁴ While the applicability of the Ni-catalyzed cross coupling to the synthesis of carbo-substituted 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.

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

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All reactions are run at room temperature in THF in the presence of 5 mol % of $\text{Pd}(\text{PPh}_3)_4$. The need for $\text{Pd}(\text{PPh}_3)_4$ has been established in all cases by running control experiments in the absence of $\text{Pd}(\text{PPh}_3)_4$.

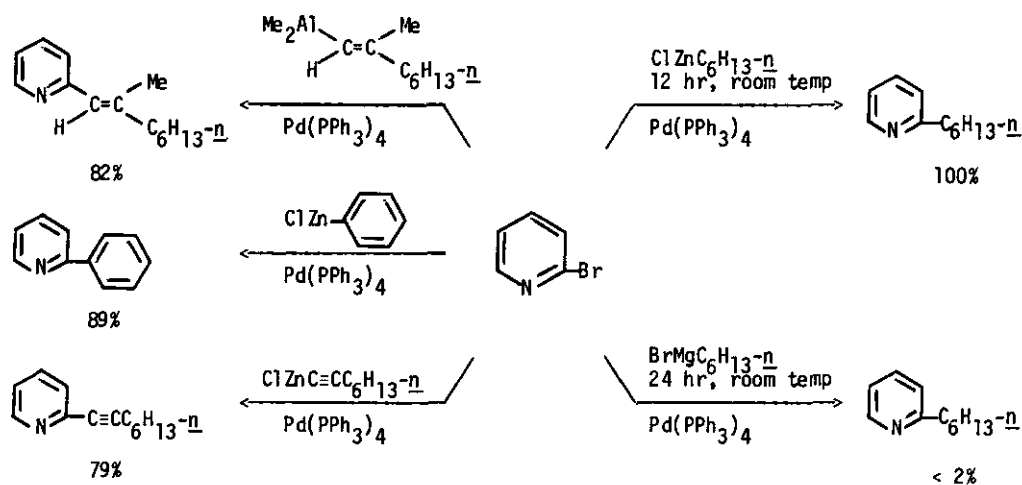
In some cases proper selection of the reagents or the charge affinity pattern is of critical importance. Thus, while both 2-iodofuran (Entry 1) and 2-furylzinc chloride (Entry 2) can be readily converted into 2-phenylfuran (1), only 3-furylzinc chloride (Entry 3), but not 3-bromofuran (Entry 4), can 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 results⁷ 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.

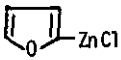
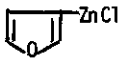
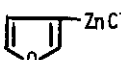
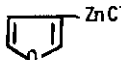
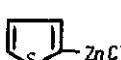
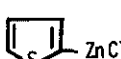
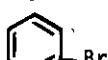
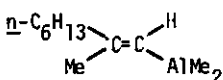
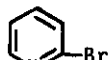
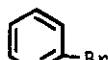
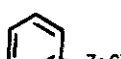
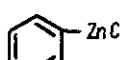
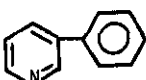
Scheme 1



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 $\text{Pd(PPh}_3)_4$ 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): n_D^{23} 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 ₂ (15%)
5.		 Br	6	3 ^f	80 (81)	—
6.		<i>n</i> -C ₆ H ₁₃ C≡CBr	1	4 ^g	61 (62)	<i>n</i> -C ₆ H ₁₃ C≡C ₂ (10%)
7.		PhI	1	5 ^h	75 (81)	 (14%)
8.		 Br	1	6 ⁱ	66 (70)	 (13%)
9.		PhZnCl	1	7 ^j	89 (99)	—
10.			1	9 ^k	82 (94)	—
11.		<i>n</i> -C ₆ H ₁₃ C≡CZnCl	3	10 ^l	79 (100)	—
12.		<i>n</i> -C ₆ H ₁₃ ZnCl	0.5	11 ^m	85 (100)	—
13.		 Br	6	8 ⁿ	73 (82)	—
14.		 Br	6	12 ^o	77 (89)	 (13%)
15.		PhZnCl	24		— (0)	Ph ₂ (6%)

^aAll reactions were carried out in THF at room temperature in the presence of 5 mol % of Pd(PPh₃)₄.

^bUnsaturated organozinc derivatives were prepared by treating the corresponding organolithiums with one equivalent of dry ZnCl₂ in THF. *n*-Hexylzinc reagent was prepared by treating *n*-C₆H₁₃LiBr with ZnCl₂.

^cIsolated 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_D^{24} 1.5916 (lit.⁹ n_D^{20} 1.5920); ^1H 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); ^1H 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_D^{25} 1.4664; ^1H NMR (CDCl_3 , TMS) δ 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 $\text{C}_6\text{H}_6\text{O}$: 94.042. Found: 94.042.

g Bp 44-46°C/1 mm Hg; n_D^{23} 1.4879; ^1H 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); ^1H 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 $n_D^{23.5}$ 1.5725; ^1H 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_D^{26} 1.6195; ^1H 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_D^{23} 1.5222; ^1H 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 stereoisomeric purity based on ^{13}C and ^1H NMR is $\geq 98\%$.

l Bp 98-99°C/0.1 mm Hg; n_D^{24} 1.5220; ^1H 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_D^{23} 1.4820; ^1H 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_D^{24} 1.5449; ^1H 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_D^{24} 1.5384; ^1H 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.

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