Regioselective Pd(0)-Catalyzed Hiyama Cross-Coupling Reactions at Dihalo-Substituted Heterocycles

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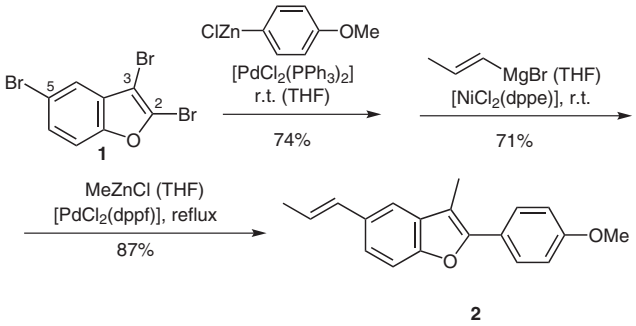
Abstract: The regioselectivity of the Hiyama cross-coupling reaction at various dihalo-substituted heterocycles has been studied. Methyl 2,3-dibromo-5-furancarboxylate and *n*-octyltrifluorosilane were employed to find optimum reaction conditions [CsF; Pd_2dba_3/P(2-furyl)$_3$ as catalyst, 80–150 °C in toluene or benzene] for the desired transformation. Subsequent experiments with the title compounds and with different primary alkyltrifluorosilanes illustrate the generality of this regiochemical process.

Key words: catalysis, cross-coupling, heterocycles, palladium, regioselectivity, silane



Scheme 1 Regioselective cross-coupling reactions employed in the synthesis of eupomatenoid 15 (**2**) from 2,3,5-tribromobenzofuran (**1**)

The preparation of multiply substituted heterocycles remains one of the most frequently occurring, yet most demanding tasks in synthetic organic chemistry.[1] There are two major routes to achieve this goal: Heterocyclic ring closure can be induced after successful introduction of the desired substituents or of suitable substituent precursors. Alternatively, the substituents can be introduced by a judicious selection of reaction steps that occur with the completed heterocyclic skeleton. Following the latter concept, the strategy of regioselective cross-coupling reactions at multiply halogenated heterocycles has become a useful tool that is attracting the attention of synthetic organic chemists.[2] The synthesis of the neolignane eupomatenoid 15 (**2**) from 2,3,5-tribromobenzofuran (**1**) by a sequence of Negishi (at C-2), Kumada (at C-5), and Negishi (at C-3) cross-coupling reactions exemplifies how straightforward this approach can be (Scheme 1).[3]

A closer look at the use of different cross-coupling variants reveals that Kumada, Negishi, Suzuki, Stille, and Sonogashira reactions have been used most often in the regioselective cross-coupling chemistry discussed above. In contrast, it is surprising to note that the versatile Hiyama cross-coupling reaction of silanes[4,5] has never been probed regarding its utility in regioselective cross-coupling reactions. This is all the more surprising because the scope of this particular cross-coupling reaction has been recently expanded to a significant extent, most notably by Fu et al.[6] and by Denmark et al.[7] A concern with the Hiyama cross-coupling is the high reaction temperature that is required in many instances, which may be detrimental to its regio- and chemoselectivity. In this study we have searched for optimized reaction conditions that achieve regioselective Hiyama cross-coupling reactions of various dihalo-substituted heterocycles and report our results in preliminary form.

In initial studies conducted with methyl 2,3-dibromo-5-furancarboxylate (**3**)[8] and *n*-octyltrifluorosilane[9] in THF, it turned out that high reaction temperatures (120 °C) are required to achieve notable conversion and that anhydrous CsF is a superior activating reagent[10] compared to tetrabutylammonium fluoride, Ag_2CO_3, $KOSiMe_3$, Ag_2O, or KO*t*Bu. Further optimization experiments were conducted using Pd_2dba_3 (dba = dibenzylidene acetone) as the Pd source, varying the solvent, the reaction temperature and the ligand (Table 1).

While the regioselectivity of the reaction was consistently in favor of the expected[11] 2-substituted product **4a**, the lack of chemoselectivity turned out to be a major issue. Hydrodebromination to product **5** was observed as a major side reaction. Only some of the ligands[12] we tested are depicted in Table 1 (entries 1–5). Tri(2-furyl)phosphane [P(2-furyl)$_3$][13] emerged from these studies as the ligand of choice. Other monodentate ligands delivered by far less desired product either due to a much slower reaction (entry 1) or, in the case of tri(*o*-tolyl)phosphane, due to hydrodebromination at C-3 as a major side reaction (entry 2). Bidentate ligands 1,1′-bis(diphenylphosphino)ferrocene (dppf) and 1,1′-bis(di-2-furylphosphino)ferrocene (dfpf) produced an increased amount of hydrodebrominated material, with dfpf performing best (entry 4). When the amount of P(2-furyl)$_3$ was further increased (entry 6),

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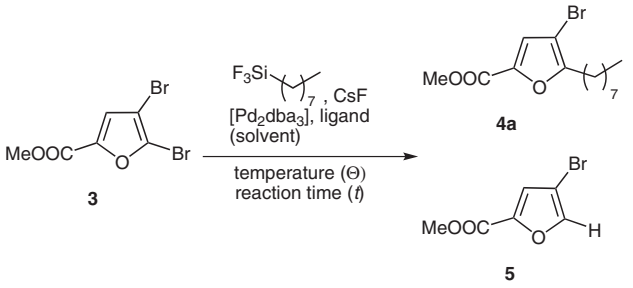
Table 1 Optimizing the Cross-Coupling Reaction **3**→**4a** and Minimizing the Hydrodebromination **3**→**5**



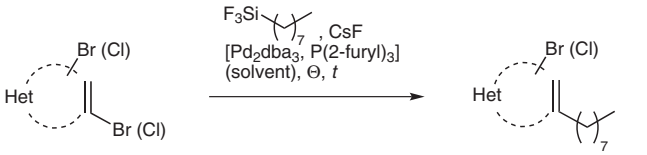
Entry	Ligand (mol%)		Solvent	Θ (°C)	*t* (h)	**4a/5**	**4a** (%)
1	PPh_3	20	THF	120	48	46:54	7
2	P(*o*-Tol)$_3$	20	THF	120	21	–	15
3	dppf	10	THF	120	48	50:50	25
4	dfpf	10	THF	120	18	63:37	28
5	P(2-furyl)$_3$	20	THF	120	22	66:34	37
6	P(2-furyl)$_3$	40	THF	120	14	93:7	54
7	P(2-furyl)$_3$	10	THF	120	19	35:65	20
8	P(2-furyl)$_3$	40	MeCN	120	16	79:21	50
9	P(2-furyl)$_3$	40	dioxane	120	16	60:40	44
10	P(2-furyl)$_3$	40	toluene	120	24	75:25	51
11	P(2-furyl)$_3$	40	toluene	100	24	87:13	65
12	P(2-furyl)$_3$	40	toluene	80	17	97:3	69
13	P(2-furyl)$_3$	40	benzene	80	15	>99:1	72

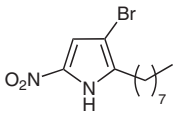
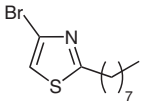
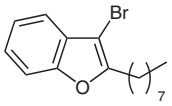
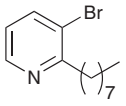
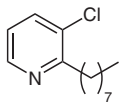
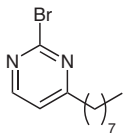
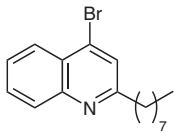
the chemoselectivity dramatically improved, while a decrease led to increased formation of the undesired product **5** (entry 7). The results seem to suggest that P(2-furyl)$_3$ not only enhances the transmetalation rate,[12] but also facilitates the reductive elimination step.

Solvent variation (entries 8–10) was initially thought to be ineffective, with the ratios **4a/5** being lower in all cases than those obtained using THF, however, the result with toluene indicated a high reactivity in this solvent with a relatively good combined yield of **4a** and **5**. Upon reduction of the reaction temperature (entries 11 and 12) the ratio **4a/5** further improved and was close to perfect at 80 °C. In the case of methyl 2,3-dibromo-5-furancarboxylate (**3**), a further improvement was achieved by changing the solvent from toluene to benzene (entry 13).

Under optimized conditions,[14] which included the use of toluene or benzene as the solvent at a substrate concentration of 0.1 M, four equivalents of CsF, two equivalents of the silane, 5 mol% Pd_2dba_3 and 40 mol% P(2-furyl)$_3$, an array of other dibromosubstituted heterocycles (Table 2, entries 1–4 and 6–7) and 2,3-dichloropyridine (Table 2, entry 5) were employed in regioselective Hiyama cross-coupling reactions. The reaction temperature was adjusted so that full conversion could be achieved in a reasonable

Table 2 Regioselective Hiyama Cross-Coupling Reactions on Dihalosubstituted Heterocycles Delivering Products **6**–**12**



Entry	Product	Solvent	Θ (°C)	*t* (h)	Yield (%)
1	 **6**	toluene	100	17	66
2	 **7**	toluene	80	17	77
3	 **8**	benzene	80	72	84
4	 **9**	toluene	100	48	70
5	 **10**	toluene	100	48	73
6	 **11**	toluene	80	48	80
7	 **12**	toluene	100	24	57

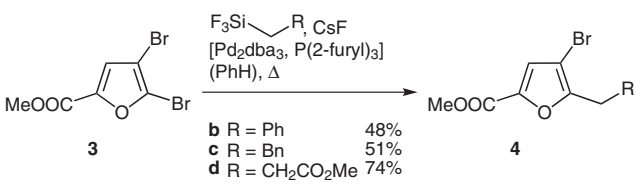
period of time. Yields varied between 57% and 84%. Reactions were conducted in high-pressure Teflon-sealed Schlenk tubes using appropriate safety conditions.

The regioselectivity of the reaction was assessed by ^{13}C NMR spectroscopy. Upon cross-coupling a significant deshielding ($\Delta\delta \geq 20$ ppm) is observed at the carbon atom where the substitution occurred.[2] In ambiguous cases, the product was debrominated by halogen–lithium exchange and the regioselectivity of the cross-coupling was derived from the $^1H/^1H$ and $^1H/^{13}C$ coupling pattern in one- and two-dimensional NMR spectra. In general, all substrates underwent substitution at the same position as occurred in previous cross-coupling reactions, i.e., the most electro-

philic position.[2,15] While it is unlikely that the oxidative addition is rate-determining for the Hiyama cross-coupling reaction, the preference for substitution to occur at the most electrophilic position may still be attributed to this process as long as there are no other factors slowing down the subsequent steps that take place at this position.

Despite successful reactions with most substrates, a few heterocycles reacted either sluggishly or with insufficient regioselectivity. In particular, thiophenes (2,3-dibromo- and 2,4-dibromothiophene) were not suitable as substrates; in these cases, either no products were obtained or significant amounts of hydrodebrominated material resulted, even under optimized conditions. The reactions of 2,4-dibromopyridine suffered from low regioselectivity[16,17] due to the similar reactivity at the two electrophilic positions.

In a preliminary series of experiments we tested whether other primary silanes could also be employed as nucleophiles in the regioselective Hiyama cross-coupling reaction (Scheme 2). Benzyltrifluorosilane,[18] (2-phenylethyl)-trifluorosilane,[9,18a] and methyl 3-(trifluorosilyl)propanoate,[4b,18a] all reacted smoothly to yield the expected 2-substituted products **4b–d**.



Scheme 2 Reaction of methyl 2,3-dibromo-5-furancarboxylate (**3**) with various silanes in a regioselective Hiyama cross-coupling reaction to products **4b–d**

In summary, conditions of the Hiyama cross-coupling reaction were successfully varied to achieve moderate to high yields in regioselective reactions of various dihalo-substituted heterocycles. The method opens a new route to multiply substituted heterocycles and allows researchers to take advantage of the known benefits of using Hiyama cross-coupling reactions (easily accessible starting materials, high stability to air and heat, low cost, and low toxicity).

Acknowledgment

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(10) Activating reagents were screened in the reaction of substrate **3** with *n*-octyltrifluorosilane in THF at 100 °C, employing Pd_2dba_3/P(2-furyl)$_3$ as the catalyst. Almost no conversion was achieved with the given activating reagents, while anhydrous CsF delivered a significant conversion after 18 h (26% **4a**, 34% **5**).

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(12) Other ligands that have been tested include tri-*tert*-butylphosphonium tetrafluoroborate (P*t*Bu$_3$·HBF$_4$), tricyclohexylphosphane (PCy$_3$), 1,2-bis(diphenylphosphino)ethane (dppe), 1,2-bis(di-2-furylphosphino)ethane (dfpe), and 1,4-bis(diphenylphosphino)butane (dppb).

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(14) Typical procedure: A flame-dried Schlenk tube was charged with Pd_2dba_3 (9.2 mg, 0.01 mmol), P(2-furyl)$_3$ (18.6 mg, 0.08 mmol) and benzene (2 mL) under an atmosphere of argon. The solution was stirred at r.t. for 15 min then *n*-octyltrifluorosilane (74 μL, 0.40 mmol) and CsF (122 mg, 0.80 mmol, which was stored and weighed in a glove box) were added, followed by dibromofuran **3** (56.8 mg, 0.20 mmol). The tube was closed with a Teflon screw plug, situated behind an explosion shield (CAUTION!), heated to 80 °C and stirred for 15 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (5 mL) and H_2O (5 mL). After separation of the layers, the aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by flash column chromatography (silica gel; pentane–Et_2O, 99:1) yielded compound **4a** (45.6 mg, 0.14 mmol, 72%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 7.0 Hz, 3 H), 1.20–1.36 (m, 10 H), 1.68 (quint,

^3J = 7.5 Hz, 2 H), 2.70 (t, ^3J = 7.5 Hz, 2 H), 3.88 (s, 3 H), 7.11 (s, 1 H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 14.1, 22.6, 26.5, 27.5, 29.0, 29.1, 29.1, 31.8, 52.0, 97.9, 121.2, 142.6, 158.3, 158.5; HRMS: *m*/*z* calcd for $C_{14}H_{21}BrO_3$: 316.0674; found: 316.0673.

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