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Heteroarylation of Anthraquinone-Triflate by Suzuki Cross-coupling

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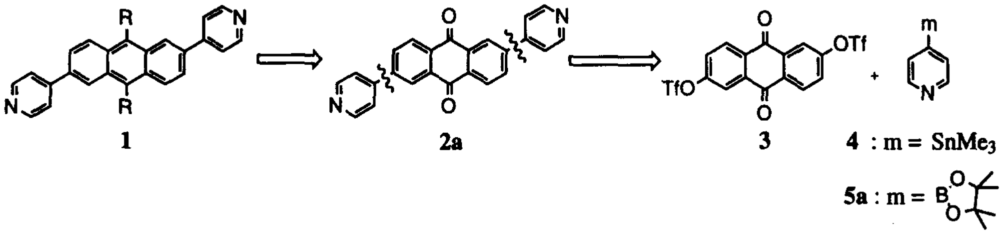
Abstract**: The reactivity of the 4-pyridylboronate 5a for $PdCl_2$(dppf)-catalysed cross-coupling reaction with an anthraquinone triflate is presented, and compared with its 2-thienyl- and phenylboronic analogues. Best results have been obtained on a small scale with anhydrous K_3PO_4 using an O_2-scavenger or under rigorously anaerobic conditions.**

Polyaromatic bridging ligands based on anthracene such as **1** represent an attractive class of rigid photochromic devices for molecular electronics. One of the most direct entries to this family of compounds is a palladium-catalysed (hetero)arylation of readily available anthraquinones bis-triflate followed by diarylanthraquinone rearomatisation (Scheme 1).



Scheme 1

We selected 4-pyridyl groups for their complexing abilities and the topographically interesting anthraflavic acid bis-triflate **3** as anthracene precursor. Since the latter was known to undergo Stille cross-coupling with phenyltrimethyltin,[1,2] we planned to use the analogous reaction, with 4-trimethylstannylpyridine **4**,[3] to introduce the pyridyl groups. However, no significant cross-coupling occured in our case whatever the conditions used.[4] Traces of the desired 2,6-di-(4-pyridyl)-anthraquinone **2a** were obtained with $PdCl_2$(dppf). This failure prompted us to explore the Suzuki reaction[5] with the latter palladium salt as catalyst, using the recently described potential synthon for such a reaction: 4-pyridylboronic acid pinacol ester **5a**.[6]

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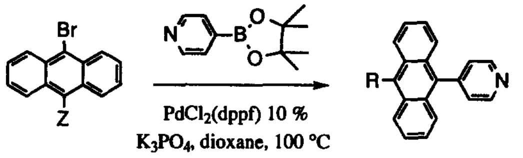
The reactivity of boronate **5a** towards aryl halides has been first tested with the bromoarenes **6a** and **6b** (Scheme 2). Mono- and and dipyridyl- anthracenes **7a** and **7b**[7] have been obtained with 63 % and 51 % yield respectively (unoptimised) with K_3PO_4 / dioxane[8,9] showing that **4a** behaves as expected.

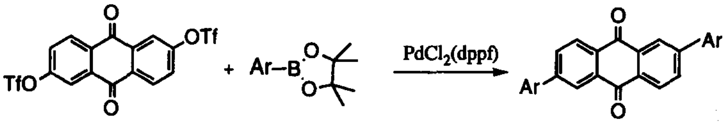


6a : Z = H
6b : Z = Br

7a : R = H
7b : R = 4-pyridyl

Scheme 2

A more complete study was then undertaken with the triflate **3**. (Scheme 3). Results are summarized in table 1.



3

5a : 4-pyridyl
5b : 2-thienyl
5c : phenyl

2a : 4-pyridyl
2b : 2-thienyl
2c : phenyl

Scheme 3

"Wet" or strong bases (entry 1 to 3)[8,10,11] predominently led to tars and triflate hydrolysis. Use of $Ba(OH)_2.8\ H_2O$ / DMF (entry 4) enabled us to obtain a poor yield of anthraquinone **2a** but reagents degradation could not be avoided. We found that triflate hydrolysis reaction could be limitted by using dioxane and anhydrous K_3PO_4 which should also prevent deboronation of the electron deficient **5a** (entry 5).[8]

Tars formation was attributed to oxidation processes despite the use of standard Schlenk techniques hence the importance of this parameter was controlled. Indeed, the addition of a O_2-scavenger, the 2,6-di-*ter*butyl-4-methylphenol (DTMP), increased the yield markedly (entry 6). The optimal quantity was found to be 0.7 eq. to triflate **3**. Similar result was achieved with a *very* careful degasing of the reaction mixture which increased the yield up to 67% (entry 7). No improvements were found by using fluoride[12] as base (entry 8).

Unfortunately, attempts to scale up the reaction were unsuccessful, the yield being less than 30% whatever the care taken to exclude oxygen from the reaction vessel. We suspected triflate **3** to be poorly reactive so cross-coupling with other boronic acid pinacol esters (i.e. (2-thienyl)- **5b**[13] and phenyl- **5c**[14]) were tested under the same conditions as for **5a**.[15] This hypothesis was ruled out since moderate to good yields of respectively 2,6-diphenylanthraquinone **2c**[16] (entries 13, 14), and 2,6-(2-thienyl)-anthraquinone **2b** (entries 9-12) were obtained. For the thienylboronate **5b**, these results along with a lack of sensitivity to DTMP concentration (i.e. residual O_2 level) might signify that its catalytic cycle is run faster than for **5a**, limiting side-reactions.

dioxaborolane **5**	Entry	Base	Solvent	2[7] (isolated yield)
5a (4-pyridyl)-	1	"wet" K_2CO_3[13]	dioxane[a]	-
	2	^tBuOK[14]	DME[a]	-
	3	$Ba(OH)_2.8H_2O$	dioxane[a]	-
	4	$Ba(OH)_2.8H_2O$	DMF[a]	13%
	5	K_3PO_4	dioxane[a]	11%
	6	K_3PO_4, DTMP	dioxane[a]	66%
	7	K_3PO_4	dioxane[b]	68%
	8	KF[c] [15], DTMP	dioxane[a]	57%
5b (2-thienyl)-	9	K_3PO_4	dioxane[a]	64%
	10	K_3PO_4, DTMP	dioxane[a]	85%
	11	KF[c]	dioxane[a]	80%
	12	KF[c], DTMP	dioxane[a]	83%
5c phenyl-	13	K_3PO_4, DTMP	dioxane[a]	59%
	14	KF[c], DTMP	dioxane[a]	59%

a) : reagents were mixed, degassed then solvent was added, and the mixture degassed (3 cycles vacuum (5 mmHg, 2mn.)-argon) before being heated (100 °C, closed Schlenk tube) for 24 hrs. b) : reagents under dynamic vacuum for 2 hrs, then a). c) : 0.1 eq. of 18-C-6 was added.

Table 1

Suzuki cross-coupling reactions involving electron-deficient boronic acids are known to be challenging. [17] In our case, we have pointed out the effect of residual oxygen and, on a small scale, strictly anaerobic reaction conditions give excellent results while the Stille analogous reaction fails. Since **5a** is extremely easy to handle, it may be a good alternative to its tin analogue.

Acknowledgements

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References and notes

1- Tamato N., Echavarren A. M., Paredes M. C., Farina F., Noheda P., *Tetrahedron Lett.* **1990**,*31*, 5189-5192.

2- **3** is best prepared (54%, cryst. from $CHCl_3$) with Tf_2O / pyridine / 0 °C. See Chan W.-K., Cheh Y., Peng Z., Yu L., *J. Am. Chem. Soc.* **1993**, *115*, 11735-11743.

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4- Conditions tested: Pd(PPh$_3$)$_4$ (10%) / LiCl (various amount) / DMF or dioxane/ 100 °C; Pd$_2$(dba)$_3$ / dppf / LiCl / dioxane / reflux. See: Scott W. J., Stille J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033-3040 ; Farina V., Kapadia S., Krishnan B., Wang C., Liebeskind L. S., *J. Org. Chem.* **1994**, *59*, 5905-5911.

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7- Analytical data: **2a** : Mp (from AcOH) > 300 °C; ^{1}H-NMR (CDCl$_3$, 250MHz): δ 7.65 (d, 4H, 6.2); 8.09 (dd, 2H, 1.8, 8.1); 8.47 (d, 2H, 8.1); 8.61 (d, 2H, 1.9); 8.78 (d, 4H, 6.1); EI-MS: 362 (100); Anal. Calcd for $C_{24}H_{14}O_2N_2.(C_2H_4O_2)_{0.26}$, C ; H; N. **2b**: Mp: 228 °C (from AcOH); ^{1}H-NMR (CDCl$_3$) δ 7.45-7.56 (m, 6H); 7.72-7.76 (m, 4H); 8.03 (dd, 2H, 1.9, 8.1); 8.41 (d, 2H, 8.1); 8.56 (d, 2H, 1.8). EI-MS 360 (84). Anal. Calcd for $C_{26}H_{16}O_2$. $(C_2H_4O_2)_{0.12}$,C; H. **2c** Mp 265 °C. ^{1}H-NMR (CDCl$_3$) δ 7.17 (dd, 2H, 3.7; 5.0); 7.45 (dd, 2H, 1.1, 5.0); 7.60 (dd, 2H, 1.1, 3.7); 8.00 (dd, 2H, 1.9, 8.1); 8.33 (d, 2H, 8.2); 8.53 (d, 2H, 1.8). EI-MS: 372 (100). Anal. Calcd for $C_{22}H_{12}O_2S_2.(C_2H_4O_2)_{0.06}$, C ; H ; S. **7a**: Mp 190 °C; 1H-NMR (CDCl$_3$) δ 7.58-7.35 (m, 8H); 8.06 (d, 2H, 8.4); 8.54 (s, 1H); 8.85 (d, 2H, 5.8). EI-MS: 255 (100). Anal. Calcd. for $C_{19}H_{13}N$, C, 89.38; H, 5.14; N, 5.49. Found, C, 88.3 ;H, 5.98; N, 5.5 **7b**: Mp 250 °C; ^{1}H-NMR (CDCl$_3$) δ 7.36-7.41 (m, 1H); 7.44 (d, 1H, 5.8); 7.57-7.63 (m, 1H); 8.88 (d, 2H, 5.8). EI-MS: 332 (100). Anal. Calcd. for $C_{24}H_{16}N_2$, C, 86.71; H, 4.86; N, 8.43. Found, C, 86.06 ; H, 5.46 ; N, 8.28.

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9- Representative procedure : to a degased mixture of dibromide **6b** (0.9 g, 2.7 mmol.), boronate **5a** (1.2 g, 2.2 eq.), PdCl$_2$(dppf).CH$_2$Cl$_2$ (0.215 g, 10%) and K$_3$PO$_4$ (1.8 g, 3.3 eq.) in a large Schlenk tube, was added dry degased dioxane (70 mL), and the resulting slurry was heated at 100 °C for 20 hrs under argon. The reaction mixture was treated with water then extracted with CH$_2$Cl$_2$. After usual work-up, the crude product was purified by column chromatography (SiO$_2$, CH$_2$Cl$_2$- 2% MeOH). Yield : 0.45 g (51 %). Addition of LiCl inhibited the reaction.[3]

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13- As for **5a**,[6] from 2-thienyllithium. See Lipshutz B. H., Ellsworth E. L., Siahaan T.J., *J. Am. Chem. Soc.* **1989**, *111*, 1351-1358.

14- Matteson D. S., Majumdar D., *Organometallics* **1983**, *2*, 1529-1535 (Foot note 26).

15- Reagents: **3** (1 mmol) /**5** (2.2 eq.)/PdCl$_2$(dppf).CH$_2$Cl$_2$ (10%)/ base (3.2 eq. (K$_3$PO$_4$) to 4 eq. (KF))(see ref. quoted) /solvent (25 mL). Purification by column chromatography (SiO$_2$) after aqueous work-up and extraction with CHCl$_3$.

16- Negishi's conditions (i.e. **3** / PhZnCl (2.2 eq.) / PdCl$_2$(dppf)(10%) / THF rfx 16 hrs) give a 51% yield; Coudret C., Gonzalo V., unpublished results. See also ref. 1.

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