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Regioselectivity in the Stille Coupling Reactions of 3,5-Dibromo-2-pyrone

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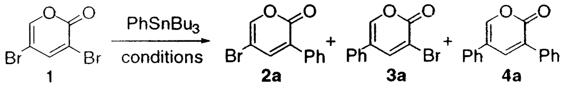
The Stille coupling reaction is a widely used carbon−carbon bond-forming synthetic method.[1] Many important advances have been reported in the literature, further expanding its scope and versatility, with the development of efficient Pd catalysts and ligands.[2] Despite the extensive usage, however, there is no standard protocol for a given coupling reaction in terms of selecting an appropriate set of reaction conditions as the reported procedures employ a wide variety of solvents, catalysts, and additives for the reactions.[1c] One of the synthetic limitations in the Stille reaction would be its high steric demand, which often slows down the subsequent Sn/Pd transmetalation in the catalytic cycle. Liebeskind et al. have reported that the addition of CuI can increase the reaction rate.[3,4] The exact nature of the rate-enhancing "copper effect" is, however, not fully understood. They suggested that the added Cu(I) salt would increase the otherwise slow transmetalation by forming organocopper species from the organotin reagent via a Sn/Cu transmetalation, when the reaction is carried out with a weak ligand in a polar solvent. The resulting organocopper species is believed to undergo Cu/Pd transmetalation at a higher rate than organotin reagents. In ethereal solvents, the CuI would facilitate the formation of the coordinatively unsaturated Pd-species formed in the oxidative addition step.[5] There are a few contrasting cases in the literature where organotin undergoes cross coupling reactions with the action of Cu(I) alone.[6]

In connection to our ongoing research program on the chemistry of 3,5-dibromo-2-pyrone, we have reported its Stille, Sonogashira, and Pd-catalyzed amination reactions, all of which underwent substitutions regioselectively at C3 over C5 position.[7] The observed regioselectivity at C3 is attributed to the lower electron density at C3, proceeding via a faster oxidative addition of Pd(0) at this position. The ^{13}C NMR spectrum of 3,5-dibromo-2-pyrone clearly indicates that C3 is more deshielded than C5 (C3: 113.8; C5: 100.0 ppm). The Stille coupling reaction with phenyl tributyltin in fact provided 3-phenyl-5-bromo-2-pyrone **2a** in 94% yield when the reaction was carried out with CuI (10 mol %) in refluxing toluene (Table 1, entry 2).[7b] Quite surprisingly, however, the Stille coupling reaction gave rise to 3-bromo-5-phenyl-2-pyrone **3a** in 75% yield when the coupling was performed with 1.0 equiv of CuI in DMF (entry 5). The structures of **2a** and **3a** were fully characterized spectroscopically and confirmed upon chemical transformations into the corresponding cycloadducts.[8] In this account, we present the details of the Stille coupling reactions of 3,5-dibromo-2-pyrone, the first report showing that the Stille couplings can be made to occur at either of two chemically different bromides, depending on the reaction conditions.

In toluene, the added CuI has no effect on the regiochemistry. The addition of CuI not only increases the reaction rate, but also changes the course of the reaction, providing more of **3a** than **2a** when the reaction was conducted in DMF (entry 5).

In DMF, the ratio of **3a** to **2a** increases in proportion to the equivalents of CuI (Table 2). No regiochemical changes were observed in toluene, regardless of the amount of CuI (data not shown).

Table 1. Stille Reactions under Various Reaction Conditions



entry	conditions	time	**2a** (%)	**3a** (%)	**4a** (%)
1	Pd(PPh$_3$)$_4$/tol/100 °C	0.5 h	81	trace	16
2	Pd(PPh$_3$)$_4$/CuI (0.1 equiv)/ tol/100 °C	0.5 h	94	trace	trace
3	Pd(PPh$_3$)$_4$/CuI (1.0 equiv)/ tol/100 °C	2 h	71	6	4
4	Pd(PPh$_3$)$_4$/CuI (0.1 equiv) /DMF/50 °C	5 h	34	20	trace
5	Pd(PPh$_3$)$_4$/CuI (1.0 equiv)/ DMF/50 °C	2 h	trace	75	trace
6	Pd(PPh$_3$)$_4$/DMF/50 °C	4 d	41	2	1
7	Pd(PPh$_3$)$_4$/LiCl(1.0 equiv)/ DMF/50 °C	1 d	50	trace	9
8	CuI (1.0 equiv)/ DMF/50 °C	3 d	trace	3	trace

Table 2. Effect of CuI in DMF[a]

entry	CuI	time	ratio (**2a**:**3a**)	total yield (%)
1	none	4 d	100:0	41
2	0.1	5 h	63:37	54
3	0.2	5 h	45:55	76
4	0.3	4.5 h	19:81	64
5	0.4	2.5 h	15:85	66
6	0.5	2.5 h	0:100	64
7	1.0	2 h	0:100	75

[a] Reaction condition: Pd(PPh$_3$)$_4$/DMF/50 °C.

Table 3. Effect of Solvent Polarity with 1 Equiv of CuI[a]

entry	solvent	temp/time	ratio (**2d**:**3d**)[9]	total yield (%)
1	toluene	100 °C/1.5 h	86:14	71
2	1,4-dioxane	100 °C/1.5 h	81:19	53
3	CH$_2$Cl$_2$	100 °C/0.5 h	77:23	97
4	DMF	50 °C/0.5 h	12:88	68
5	DMSO	50 °C/5 min	8:92	39
6	NMP[b]	50 °C/5 min	39:61	46

[a] Pd(PPh$_3$)$_4$ (5 mol %). [b] PdCl$_2$(PhCN)$_2$ (5 mol %)/AsPh$_3$.

With 1.0 equiv of CuI, the ratio (**3d**:**2d**) increases as the solvent polarity increases (Table 3). In these experiments, we used 2-furyl tributyltin instead of phenyl tributyltin for easier chromatographic separation of the two regioisomeric products.

A similar trend was observed with other stannanes (Table 4). Condition C was used for the coupling with vinyltin (entry 9) as the product decomposes under condition A.[10] In entry 2, no isolable products were seen under condition B. Apparently, the Stille couplings took place at the electron-rich C5, rather than the usual C3 position under condition B, which may not be readily explainable with the level of current mechanistic understanding.[11]

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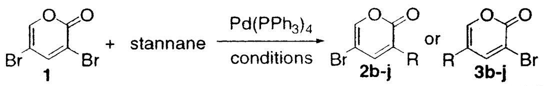
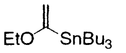
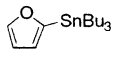
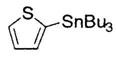
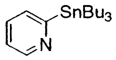
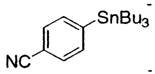
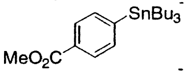
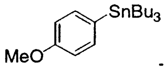
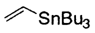
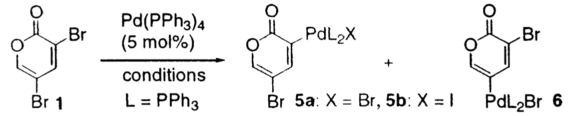
Table 4. Regiocontrolled Stille Couplings with Other Stannanes[a]



entry	stannane	condition	2	3
1		**A** (0.5 h)	50%	trace
		B (0.5 h)	trace	50%
2	TMS–≡–SnBu$_3$	**A** (10 min)	67%	0%
		B (6 h)	trace	trace
3		**A** (20 min)	61%	trace
		B (0.5 h)	trace	60%
4		**A** (20 min)	72%	trace
		B (20 min)	trace	68%
5		**A** (10 min)	51%	trace
		B (12 h)	trace	33%
6		**A** (1 h)	80%	trace
		B (20 min)	trace	79%
7		**A** (1.5 h)	79%	trace
		B (0.5 h)	trace	75%
8		**A** (7 h)	61%	trace
		B (0.5 h)	trace	55%
9		**C** (2 h)	57%	trace
		B (2 h)	trace	52%

[a] **A**: Pd(PPh$_3$)$_4$/CuI (0.1 equiv)/PhMe/100 °C, **B**: Pd(PPh$_3$)$_4$/CuI (1.0 equiv)/DMF/50 °C, **C**: Pd$_2$dba$_3$/P(*t*-Bu)$_3$/PhMe/rt[2].

Table 5. Regiocontrolled Oxidative Additions



entry	conditions	ratio (**5**:**6**)[12]
1	toluene/100 °C	100:0
2	toluene/CuI(1.0 equiv)/100 °C	100:0
3	DMF/50 °C	100:0
4	DMF/CuI(1.0 equiv)/50 °C	30:70

A set of control experiments demonstrated that it is the favorable oxidative addition of "PdL$_2$" at C5, together with higher reactivity of the resulting Pd intermediate **6** (vide infra) that determines the regiochemical outcome under condition B. Table 5 summarizes the effects of solvent and CuI on the regiochemistry of the oxidative adducts. Heating in toluene without CuI provided exclusively **5a** (entry 1), accompanied with small amount **5b** formed from the halogen exchange on Pd when CuI was added (entry 2), with no traceable **6** in either case. In DMF, CuI plays a decisive role, providing mainly **6** under the conditions representing the actual catalytic conditions (entry 4). The palladium complexes **5a**, **5b**, and **6** are sufficiently stable for the silica gel column chromatography and subsequent recrystallization for X-ray crystallography. The isolated **5a** produced **2a** in 91% yield when reacted with phenyltributyltin, while the same reaction with **6** provided **3a** in 99% yield.

The Pd intermediate **6** undergoes much faster coupling reaction than **5**; an equimolar mixture of **5a** (or **5b**), **6**, and phenyltributyltin provided exclusively **3a** in quantitative yield after 30 min at 50 °C in DMF (**5a** or **5b** remained intact). Similar regiochemical outcomes were obtained when CuBr was used in lieu of CuI, excluding the possible involvement of iodine in the reaction.

In summary, we have found that 3,5-dibromo-2-pyrone undergoes Stille coupling reactions regioselectively at either C3 or C5, depending on the reaction conditions. The preferred formation of the Pd intermediate **6** and its higher reactivity would account for the regioselective substitutions at C5 when the Stille couplings are conducted under condition B. Further study is underway to elucidate the exact nature of the Cu(I) effect on the oxidative addition of Pd(0) in a polar solvent.

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Supporting Information Available: Spectral data for **2a**–**2j**, **3a**–**3j**, **5a**, **5b**, and **6** (PDF) and X-ray structures of **5a**, **5b**, and **6** in CIF format.This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (c) Farina, V.; Roth, G. P. *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, 1996; Vol. 5, p 1. (d) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652. (e) Mitchell, T. N. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 4. (f) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ntepe, A. N.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212.

(2) Littke, A. F.; Schwarz, L.; Fu, G. *J. Am. Chem. Soc.* **2002**, *124*, 6343.

(3) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359.

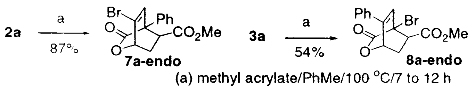
(4) (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748. (b) Barchin, B. M.; Valenciano, J.; Cuadro, A. M. Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **1999**, *1*, 545.

(5) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(6) (a) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609. (b) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973. (c) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

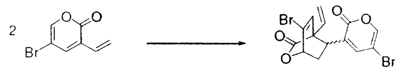
(7) (a) Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, *4*, 1171. (b) Lee, J.-H.; Kim, W.-S.; Lee, Y. Y.; Cho, C.-G. *Tetrahedron. Lett.* **2002**, *43*, 5779. (c) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 9015 (d) Lee, J.-H.; Cho, C.-G. *Tetrahedron Lett.* **2003**, *44*, 65.

(8) **2a** and **3a** produced **7a-endo** and **8a-endo**, respectively, upon cycloadditions with methyl acrylate. The cycloadduct from the cycloaddition of **1** with methyl acrylate has been shown to undergo the coupling reaction with phenyl tributyltin at the vinyl bromide position to give **8a-endo**: Lee, H.-S.; Kim, D.-S.; Won, H.; Choi, J. H.; Lee, H.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 5591.



(9) **2d**: 3-(2-furyl)-5-Br-2-pyrone, **3d**: 5-(2-furyl)-3-Br-2-pyrone.

(10) The initially formed coupling product underwent dimerization via a Diels–Alder cycloaddition during the column chromatography.



(11) (a) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598. (b) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. (c) Cotter, W. D.; Barbour, L.; McNamara, K. L.; Hechter, R.; Lachicotte, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 11016. (d) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232. (e) Ricci, A.; Angelucci, F.; Bassetti, M.; Sterzo, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 1060. (f) Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2002**, *67*, 9304.

(12) The ratio was determined by ^{1}H NMR spectroscopy and isolation.

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