ORGANIC LETTERS

2012
Vol. 14, No. 22
5644–5647

Chemoselective Cross-Coupling Reactions with Differentiation between Two Nucleophilic Sites on a Single Aromatic Substrate

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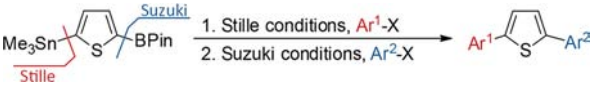
Received September 18, 2012

ABSTRACT



A new thiophene building block, containing both a stannyl group and a boronic ester, was prepared. From this starting material, a general, nucleophile-selective one-pot reaction was developed, exploiting the different reactivities of the Stille and Suzuki–Miyaura cross-coupling reactions. A series of aromatic electrophiles were used to demonstrate the high functional group tolerance.

Transition metal catalyzed cross-coupling reactions (CCRs) are among the most powerful tools in synthesis.[1] They are crucial for the preparation of many complex organic natural products,[2] pharmaceuticals, and agrochemicals.[3] In all these fields, heterocycles play an important role but thiophenes are unquestionably the most impactful.[4] The incorporation of thiophene into organic semiconducting materials for example is a highly active research area:[5] Thiophenes and their derivatives are arguably the most important monomers for semiconducting polymers[6] and oligomers[5a,7] which find already widespread use in, for example, plastic solar cells[6a,8] and organic field effect transistors.[5a,7a,c,9] The exploration of their chemistry, in particular their efficient functionalization, is therefore of great urgency.

The electrophiles used in CCRs have different reactivity, which depends on the leaving group. Typically, a gradual decrease in reactivity is observed for electrophiles containing

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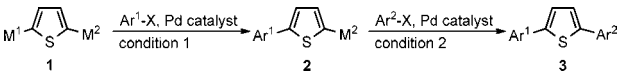
10.1021/ol302571t
Published on Web 11/02/2012

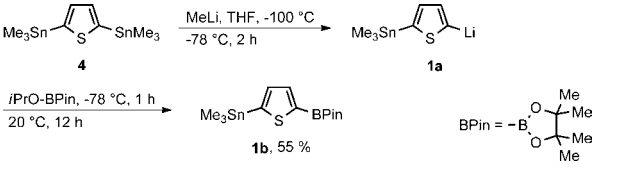
the leaving groups I > OTf > Br ≫ Cl.[10] This difference in reactivity has enabled the development of selective CCRs with respect to the electrophile.[11] In contrast, nucleophile-selective CCRs have rarely been reported and the few reports that do exist are largely associated with nonaromatic compounds.[12] There are only a few examples in which the difference in reaction rate between Stille and Suzuki–Miyaura cross-coupling has been used[13] and only one example of a chemoselective CCR involving an aromatic compound containing both tin- and boron-based substituents *at the same molecule*.[14] In that particular case, the benzene derivative *para*-$Bu_3Sn-C_6H_4-B(OR)_2$ was cross-coupled with two protected nucleosides for boron neutron capture therapy, but generality was not demonstrated. One possible reason for the striking neglect of nucleophile selective CCRs is that methods for preparing appropriate aromatic starting materials containing two different nucleophilic groups are very rare in the literature.[14] These starting materials could be used for comparing the reactivity of different metal groups, M^1 and M^2 (**1**, Scheme 1), in CCRs and could facilitate the preparation of novel molecules and materials that were not accessible before. A particularly intriguing prospect in this context would be the development of reactions that are both electrophile- and nucleophile-selective at the same time, for which work is ongoing in our laboratories.

Scheme 1. General Procedure for Chemoselective CCRs



Herein, we report the synthesis of a thiophene derivative containing both tin- and boron-based substituents and its use in the first systematic study of nucleophile-selective CCRs involving aromatic compounds. This presents a major challenge, as the nucleophilic groups are in chemically identical environments and chemoselectivity could only be derived from the nucleophilic group itself, not from any neighboring effects. We also show that the reaction products, which contain the unreactive nucleophilic metal component, can be used, in situ, in subsequent CCRs involving a second electrophile Ar^2-X (Scheme 1).

Scheme 2. Synthesis of Thiophene **1b** (Pin = pinacol)



Thiophene **1b** was prepared in a one-pot reaction of bis(stannyl) thiophene **4**[15] through monolithiation and in situ Li–B exchange (Scheme 2). Purification of the crude product turned out to be challenging due to contaminations with the starting material **4** and bis(borylated) thiophene. The desired product **1b** was unstable to silica gel chromatography, but it could be purified by fractional sublimation and was eventually isolated in good yields and could be stored in air at 5 °C for at least 5 months without noticeable decomposition.

To establish reaction conditions for a chemoselective CCR, we used 1-bromo-4-nitrobenzene (**5a**) as a test substrate and $Pd(PPh_3)_4$ as a catalyst in toluene at 110 °C. After 16 h, we obtained product **2a** in 70% yield following isolation (Table 1, entry 6). The isolated product was used as a calibrant for the development of a GC method for reaction monitoring and optimization. The conversion and the yield were highly dependent on the solvent and temperature. At 110 °C, although conversion for the reactions conducted in all solvents was essentially quantitative, the corresponding yields were significantly lower, owing to the formation of unidentified byproducts. The use of toluene and dioxane gave superior yields (83% and 80% respectively, Table 1). DMF was

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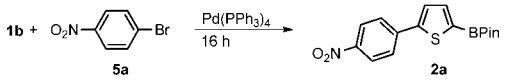
not a suitable solvent, and THF, acetonitrile, and pyridine also gave low yields (see Supporting Information (SI)).

Table 1. Optimization Studies for Chemoselective CCRs with Varying Solvent and Temperature[a]



5a 2a

entry	solvent	temp [°C]	conv[b] [%]	yield[c] [%]
1	dioxane	65	20	18
2	dioxane	110	>99	80
3	DMF	65	95	75
4	DMF	110	>99	23
5	toluene	65	16	11
6	toluene	110	>99	83[d]

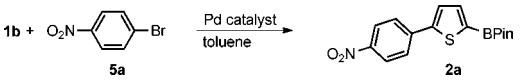
[a] **5a** (1.0 equiv), **1b** (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %). [b] Conversion; based on **5a**. [c] Determined by GC (multiple point internal standard method). [d] Yield of isolated product: 70%.

To establish mild conditions that minimize the formation of byproducts, we tested a variety of catalysts for the reaction in toluene (Table 2) and dioxane (see SI). By reducing the reaction time from 16 to 5 h, not only was the starting material completely consumed but also the product was obtained in essentially quantitative yield (Table 2, entry 2). $[Pd(dppe)Cl_2]$[16] was a poorer catalyst than $[Pd(PPh_3)_4]$: even after a reaction time of 72 h, the yield was only 61% (Table 2, entries 3−5). Although the use of $[Pd(PtBu_3)_2]$, $[Pd(dppf)Cl_2]$, and $Pd(OAc)_2$/SPhos[16] resulted in excellent conversions at 110 °C, decomposition of the product was most likely the problem (Table 2, entries 6−14). However, when using the $Pd(OAc)_2$/SPhos catalyst, this problem could be avoided by reduction of the reaction time to 80 min (Table 2, entry 12). To ensure that the cross-coupling was compatible with temperature-sensitive compounds, we optimized the reaction also at a lower temperature. When the reaction was carried out at 65 °C for 4 h, the product **2a** was obtained in 98% yield (Table 2, entry 18). However, when we attempted to isolate the product by using column chromatography or sublimation, we were unable to obtain the product without contamination with the SPhos ligand. To simplify the purification of the product, the loading of the $Pd(OAc)_2$/SPhos catalyst was reduced to 1 mol % and, following the reaction at 65 °C over the course of 18 h, the product was obtained in excellent yield (Table 2, entry 19; for further details, see the SI).

With optimized conditions established, the scope of the reaction was explored by using a variety of (hetero)aryl bromides (Table 3). To avoid the potential for product decomposition, reactions were performed at 65 °C. The use of electron-deficient benzene and furan derivatives gave good to excellent yields of the corresponding products (76−98%; Table 3, entries 1−3 and 6−8). However, close to no conversion was observed when 2- or 3-bromopyridine was used (Table 3, entries 4 and 5) and only trace

(16) dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1′-bis(diphenyl-phosphino)ferrocene; SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

Table 2. Chemoselective Cross-Coupling with Varying Catalyst, Reaction Time, and Temperature[a]



5a 2a

entry	catalyst	t [h]	temp [°C]	conv[b] [%]	yield[c] [%]
1	$[Pd(PPh_3)_4]$	1.33	110	95	81
2	$[Pd(PPh_3)_4]$	5	110	>99	>99
3	$[Pd(dppe)Cl_2]$	16	110	41	41
4	$[Pd(dppe)Cl_2]$	50	110	60	57
5	$[Pd(dppe)Cl_2]$	72	110	95	61
6	$[Pd(PtBu_3)_2]$	1.33	110	>99	66
7	$[Pd(PtBu_3)_2]$	5	110	>99	50
8	$[Pd(PtBu_3)_2]$	16	110	>99	18
9	$[Pd(dppf)Cl_2]$	1.33	110	>99	90
10	$[Pd(dppf)Cl_2]$	5	110	>99	85
11	$[Pd(dppf)Cl_2]$	16	110	>99	37
12	$Pd(OAc)_2$/SPhos	1.33	110	>99	>99
13	$Pd(OAc)_2$/SPhos	5	110	>99	86
14	$Pd(OAc)_2$/SPhos	16	110	>99	25
15	$Pd(OAc)_2$/SPhos	0.17	65	22	21
16	$Pd(OAc)_2$/SPhos	1.33	65	67	66
17	$Pd(OAc)_2$/SPhos	3	65	88	87
18	$Pd(OAc)_2$/SPhos	4	65	>99	98
19	$Pd(OAc)_2$/SPhos	18	65	>99	>99[d]

[a] **5a** (1.0 equiv), **1b** (1.1 equiv), Pd source (5 mol %), SPhos (10 mol % for entries 12−18). [b] Conversion; based on **5a**. [c] Determined by GC (multiple point internal standard method). [d] 1 mol % $Pd(OAc)_2$, 2 mol % SPhos. dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-biphenyl.

amounts of the corresponding products were observed by GC/MS. Increasing the reaction temperature to 110 °C did not improve the yield of product in the case of 2-bromopyridine; however, we found that 3-bromopyridine reacted smoothly within 6 h under these conditions, giving **2e** in 81% yield upon isolation (Table 3, entry 5).

The origin of this behavior could be the deactivation of the catalyst through its binding with the N-atom of the substrate.[17] The use of electron-neutral electrophiles, such as bromobenzene and 1-bromonaphthalene, also gave the corresponding products in good yields, 83% and 91%, respectively; however, the use of 1-bromonaphthalene required a longer reaction time (40 h) for completion (Table 3, entries 9 and 10), presumably owing to steric hindrance. Furthermore, electron-rich aryl bromides could also be employed as electrophiles for the nucleophile-selective CCR (Table 3, entries 11−13); however, the use of amine **5k** gave the product in moderate yield.[18] In all the reactions, the transformation was fully chemoselective with respect to the stannyl and boronic ester functional groups. The reason for this is that, in the case of Suzuki reactions, a base has to be added for the reaction to take place.

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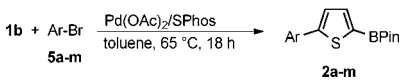
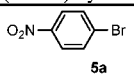
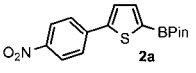
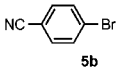
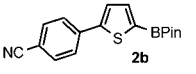
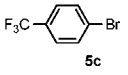
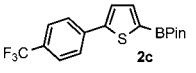
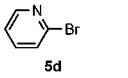
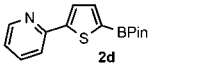
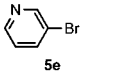
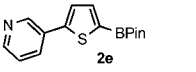
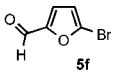
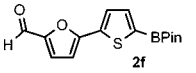
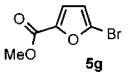
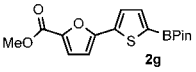
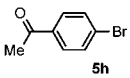
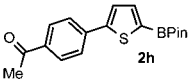
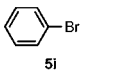
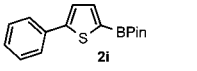
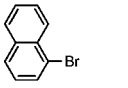
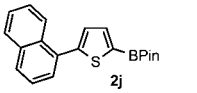
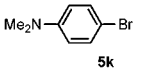
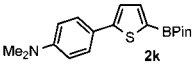
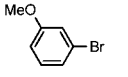
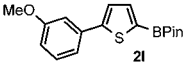
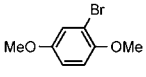
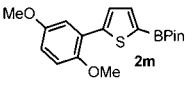
(18) The tertiary amine **5k** showed a low yield of 37% due to a low conversion. Longer reaction times and reflux conditions did not lead to higher conversion. A reason could be the binding of the amine to the Pd. For more information about tertiary amines used as ligands for Pd, see: (a) Li, J.-H.; Liu, W.-J. *Org. Lett.* **2004**, *6*, 2809. (b) Li, Y.; El-Sayed, M. A. *J. Phys. Chem. B* **2001**, *105*, 8938.0.

Table 3. Stille CCR of (Hetero)aryl Bromides with **1b**[a]



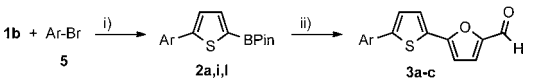
entry	(hetero)aryl-Br	product	yield[b] [%]
1	 **5a**	 **2a**	98
2	 **5b**	 **2b**	84
3	 **5c**	 **2c**	81
4	 **5d**	 **2d**	0/0[c]
5	 **5e**	 **2e**	0/81[c]
6	 **5f**	 **2f**	95
7	 **5g**	 **2g**	76
8	 **5h**	 **2h**	87
9	 **5i**	 **2i**	83
10	 **5j**	 **2j**	91[d]
11	 **5k**	 **2k**	37
12	 **5l**	 **2l**	89
13	 **5m**	 **2m**	66

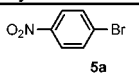
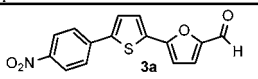
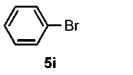
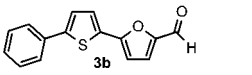
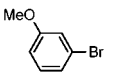
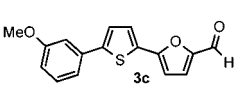
[a] $Pd(OAc)_2$ (1 mol %), SPhos (2 mol %). [b] Yields of isolated products. [c] 6 h, reflux. [d] 40 h, 65 °C.

The latest analysis on the effect of OH^- ions has shown their role to be threefold: First, they are reagents for the formation of the reactive *trans*-[ArPd(OH)$(L)_2$] from the unreactive *trans*-[ArPd(X)$(L)_2$], the product of oxidative addition. Second, the reductive elimination step is also accelerated by the reaction of OH^- with *trans*-[ArPdAr′$(L)_2$]. Third, the addition of a base can also have a retarding effect by the formation of Ar′$B(OH)_4^-$.[19]

Because the $Pd(OAc)_2$/SPhos catalyst is also known to be very effective for Suzuki–Miyaura CCRs,[20] we envisioned that the boronic ester products in the above nucleophile-selective CCRs could react with a second electrophile in a one-pot transformation. This was accomplished by adding 5-bromofuraldehyde as the second electrophile, water, and K_3PO_4 as a base to the reaction mixture upon completion of the Stille CCR and subsequently stirring the reaction mixture at 100 °C for 3 h. The yields of the products **3** were uniformly high for different aryl bromides (Table 4).

Table 4. Chemoselective One-Pot Successive CCRs of Thiophene **1b**[a]



entry	aryl bromide	product	yield[b] [%]
1	 **5a**	 **3a**	84
2	 **5i**	 **3b**	76
3	 **5l**	 **3c**	70

[a] (i) **1b** (1.0 equiv), **5** (1.0 equiv), $Pd(OAc)_2$ (1 mol %), SPhos (2 mol %), toluene, 65 °C, 18 h. (ii) 5-Bromofuraldehyde (1.0 equiv), K_3PO_4 (2.0 equiv), water, 100 °C, 3 h. [b] Yields of isolated products.

In conclusion, we prepared a thiophene dinucleophile **1b** with both a trialkyltin group and a boronic ester at the 2 and 5-positions, respectively. With this compound, we established conditions for nucleophile-selective CCRs, that is, conditions that allow a selective Stille CCR involving substrates that contain a boronic ester substituent. The resulting products, which contain the boronic ester group, were used in the same pot in a subsequent Suzuki–Miyaura CCR. We are currently developing efficient syntheses of a wide variety of aryl and heteroaryl substrates containing both tin- and boron-based substituents for their employment in nucleophile-selective CCRs.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie (FCI). J.L. and A.H. thank the Deutsche Bundesstiftung Umwelt (DBU) for a Ph.D. scholarship.

Supporting Information Available. Experimental procedures, all GC optimization reactions, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (c) Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *Organometallics* **2007**, *26*, 2183.

The authors declare no competing financial interest.