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Dual Selectivity: Electrophile and Nucleophile Selective Cross-Coupling Reactions on a Single Aromatic Substrate

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ABSTRACT

The development of a high yielding, both nucleophile and electrophile selective cross-coupling reaction with aromatic rings is presented. The reaction is general with respect to functional groups. Furthermore, the products still contain a boronic ester and a bromide. These two functional groups allow them to be easy-to-prepare, highly complex starting materials for further reactions, avoiding protecting group transformations.

Cross-coupling reactions are very efficient for the formation of new carbon–carbon bonds.[1] For such reactions, it is well established that the order of reactivity of the electrophilic coupling partner decreases for the leaving groups I > OTf > Br ≫ Cl.[2] This has already been used to great advantage for the development of electrophile selective cross-coupling reactions.[3] However, nucleophile selective cross-coupling reactions on aromatic dinucleophiles are almost undeveloped.[4]

We recently addressed this synthetic problem by the first systematic study of a nucleophile selective cross-coupling reaction on a single aromatic substrate.[4b,5] It was possible to synthesize a thiophene derivative **1** with both a trimethyl tin group in the 2-position and a boronic ester functional group in the 5-position. Using this compound, excellent chemoselectivity was observed in Stille coupling reactions with different brominated electrophiles in excellent yields.[4b,5]

The challenge was now to extend the degree of chemoselectivity even further: was it possible to develop both a

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(5) For a highlight on this work, see: Knochel, P.; Barl, N. M. *Synfacts* **2013**, *9*, 204.

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nucleophile and electrophile selective cross-coupling reaction? In such a reaction, a dinucleophile **M1**-Heterocycle**1**-**M2** would selectively react with a dielectrophile **X1**-Heterocycle**2**-**X2** so that only one of four potential products would be formed without the use of protecting group chemistry.

In this way, the reaction would become even more useful: Not only would the final product still contain a nucleophilic group for cross-coupling reactions but also an electrophilic site would be retained alongside any functional groups present on the aromatic rings that are tolerant toward cross-coupling reactions.

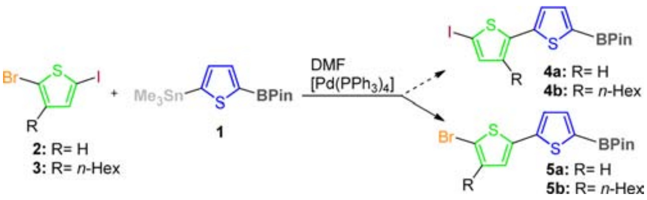
In such a reaction, it is vital to achieve not only good but quantitative selectivity, because all possible products are so similar in molecular weight and structure that their separation would be difficult or impossible. To develop a nucleophile *and* electrophile cross-coupling reaction, dinucleophile **1** was used.

As a test reaction, **1** was initially reacted with the easily accessible dielectrophile **2** which contains a bromide substituent in the 2-position and an iodide substituent in the 5-position. We screened over 40 different reaction conditions (solvents, temperatures, reaction times, catalysts, catalyst loadings; for details see Supporting Information (SI) Table SI-1).

Encouragingly, in all of those reactions—although decomposition products and low conversions did occur—the only cross-coupling product was **5a**, where the iodide had reacted in a Stille reaction. Due to this extensive screening, it was possible to identify conditions which gave excellent selectivity and a yield of 95%, using DMF as the solvent, [Pd(PPh$_3$)$_4$] as the catalyst (5 mol %) at 55 °C, and a reaction time of 18 h (Table 1, entry 1). Alternatively, at 70 °C, the reaction time could be shortened to 15 h with a yield of 96% (Table 1, entry 2). However, when we attempted to transfer these conditions to the reaction of **1** with the alkylated dielectrophile **3**, the reaction was no longer selective with respect to the electrophile: not only the iodide but also the bromide had reacted under these reaction conditions to give **4b** (Table 1, entries 3–4). This was surprising, given the increased steric bulk of the hexyl group adjacent to the bromide, and is probably due to electronic effects. Although the undesired side product **4b** occurred only in small amounts, this impurity can be expected to cause substantial problems: Its reactivity as an electrophilic cross-coupling partner compared to **5b** would be higher. Because it was not possible to separate **4b** and **5b**, it was essential to reoptimize the entire reaction. The ratio of **4b** to **5b** was independent of the catalyst loading (Table 1, entries 3–6), and therefore, low catalyst loadings of 1–2 mol % were selected for further optimizations. A breakthrough was achieved by using a microwave apparatus as the heat source. With a catalyst loading of 1–2 mol %, quantitative selectivity was found in all cases (Table 1, entries 7–11).

While a high reaction temperature of 120 °C led to product decomposition with longer reaction times (entries 9 and 10), the reaction gave quantitative yields at 80 °C after 3 h 30 min (Table 2, entry 7). Equally good conditions included a temperature of 100 °C, for either 20 min with 2 mol % or 30 min with 1 mol % of the catalyst (Table 2, entries 8 and 11).

Table 1. Stille Coupling Reaction with a Reagent with Competing Electrophilic Sites



entry	starting material	cat. loading (mol %)	temp (°C)	time	yield **5** (%)[a,b]	normalized ratio **5**:**4**[c]
1	**2**	5	70	15 h	96	>99.7:n[d]
2	**2**	5	55	18 h	95	>99.7:n[d]
3	**3**	5	70	18 h	68	93:7
4	**3**	5	55	39 h	73	94:6
5	**3**	2	55	30 h	79	94:6
6	**3**	10	55	30 h	76	94:6
7	**3**	2	80 (MW)	3.5h	>99	>99.7:n[d]
8	**3**	**2**	**100 (MW)**	**20 min**	**>99**	**>99.7:*n***[d]
9	**3**	2	120 (MW)	20 min	95	>99.7:n[d]
10	**3**	2	120 (MW)	30 min	85	>99.7:n[d]
11	**3**	1	100 (MW)	30 min	>99	>99.7:n[d]

[a] The reaction was controlled at regular intervals by GC, using triisopropylbenzene as internal calibration standard. [b] If the yield is < 100%, unidentified side products were formed. The starting material was fully converted in all cases. MW = microwave. [c] The amount of the undesired nonselective coupling product was calculated by NMR analysis (see Figure SI 3). [d] The limit of detection was estimated by comparative integration of the NMR signals to baseline to be $n < 0.3\%$ (see Figure SI 3). Where n is indicated in the table, no byproduct peak could be detected.

It was now important to prove that this second set of conditions really did represent a general method for cross-coupling with different dielectrophiles.

Therefore, a variety of different electrophiles containing two or even three different electrophilic functionalities (for their synthesis see SI) were reacted with the dinucleophile **1** at 100 °C in the microwave using 2 mol % of [Pd(PPh$_3$)$_4$] as the catalyst (Table 2). Thiophene dielectrophiles **2** and **3** gave the product in 20 min in high yields of 89% and 95% respectively, but if the bromide was in an *ortho*-position to the iodide (**6**), the reaction time had to be prolonged to 2 h (entries 1–3) to achieve a similar yield of 79%. This substituent effect in the *ortho*-position could also be observed for phenyl dielectrophiles **8**, **10**, and **12** where the reaction with the *ortho*-substituted **10** took more than four times as long (**12** twice as long) as the *para*-substituted **8** to proceed to completion (entries 4–6).

This effect is presumably induced by steric hindrance (compare for example entries 2 and 3 or entries 4 and 5).[6] However, despite this difference in reactivity, all of those

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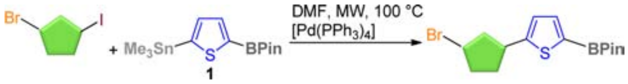
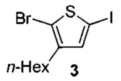
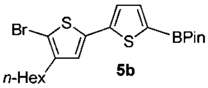
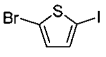
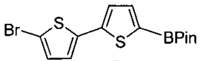
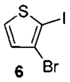
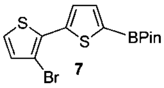
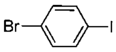
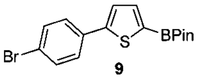
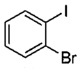
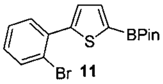
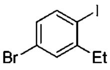
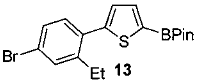
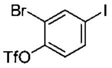
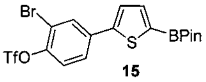
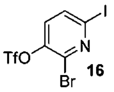
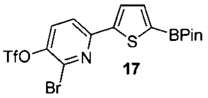
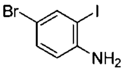
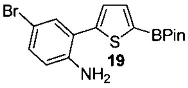
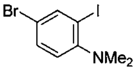
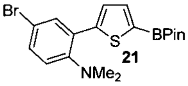
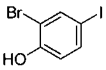
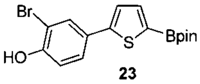
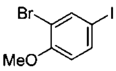
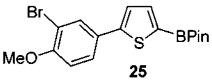
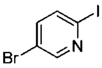
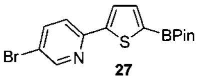
Table 2. Performing Stille Cross-Coupling Reactions with Various Dielectrophiles[a]



entry	dielectrophile	product	time (min)	isolated yield (%)
1	 **3**	 **5b**	20	95
2	 **2**	 **5a**	20	89
3	 **6**	 **7**	120	79
4	 **8**	 **9**	60	84
5	 **10**	 **11**	270	75
6	 **12**	 **13**	120	79
7	 **14**	 **15**	90	79
8	 **16**	 **17**	300	82
9	 **18**	 **19**	120	75
10	 **20**	 **21**	210	73
11	 **22**	 **23**	60	65
12	 **24**	 **25**	120	83
13	 **26**	 **27**	300	81

[a] The reactions were performed in a 1 mmol scale: electrophile (1.00 mmol), nucleophile (1.00 mmol), and the catalyst [Pd(PPh_3)$_4$] (2 mol %) were dissolved in DMF (4 mL) and stirred at 100 °C in the microwave for the specified time.

dielectrophiles gave complete selectivity and high yields (> 75%). The products of these reactions are particularly interesting, as they lead to regioisomers: it is well established in medicinal chemistry,[7] agrochemistry,[8] and materials chemistry[9] that regioisomers of otherwise the same molecules can have dramatic effects on the bioactivity of a compound or, respectively, on the materials properties of the material derived from it.[10] Starting materials **14** and **16** are trielectrophiles, with an iodide, a trifluoromethansulfonyl group, and a bromide present, and even in those cases, only the desired cross-coupling products **15** and **17** were obtained in excellent yields of 79% and 82% respectively (entries 7 and 8). Such compounds are highly valuable because the additional electrophilic group can be used for further modifications. The reaction appears to be very robust toward both electron-rich and -deficient dielectrophiles: amine substituted starting materials (**18** and **20**, entries 9 and 10), a phenol (**22**, entry 11), and a methoxysubstituted reagent (**24**, entry 12) react in similar yields (> 65%) to electron-deficient starting materials such as pyridines (**16** and **26**, entries 8 and 13, yields > 81%). The relatively long reaction times for the latter of 5 h are likely to be a consequence of catalyst deactivation due to the lone pair of the nitrogen of the pyridine *ortho* to the reacting iodide.[11]

The development of this dually selective coupling reaction led to compounds comprised of two aromatic (hetero)cycles, containing a boronic ester, a bromide, and one other functionality.

A further aspect was to test if the reaction was electrophile selective even with competing electrophiles: in the reactions discussed so far, the first substitution during the coupling reaction changes the reactivity of the second electrophilic site.

To prove that selectivity can be demonstrated even if entirely equal electrophiles were used, equimolar amounts of competing arylbromides and -iodides (Table 3) were used. For these electrophiles, 2-halothiophenes (**28a** and **28b**), halobenzenes (**30a** and **30b**), and 2-halopyridines (**32a** and **32b**), in the order of increasing electron deficiency, only the aryliodide reacted—with quantitative selectivity and in high yields (78–92%), although the more electron-deficient substrates required longer reaction times.

The compounds prepared via this nucleophile and electrophile selective cross-coupling reaction bear both an electrophilic and a nucleophilic group. They therefore resemble monomers that can be used for living cross-coupling polymerization reactions to give semiconducting

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(7) (a) Chaurasia, C. S.; Li, K.; Doughty, M. B. *J. Med. Chem.* **1993**, *36*, 272. (b) Rao, P. N. P.; Uddin, J.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 3972. (c) Cosyn, L.; Palaniappan, K. K.; Kim, S.-K.; Duong, H. T.; Gao, Z.-G.; Jacobson, K. A.; Calenbergh, S. V. *J. Med. Chem.* **2006**, *49*, 7373. (d) Bailly, C.; Dassonneville, L.; Colson, P.; Houssier, C.; Fukasawa, K.; Nishimura, S.; Yoshinari, T. *Cancer Res.* **1999**, *59*, 2853.

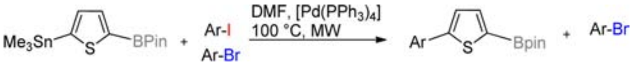
(8) Ladner, D. W. *Pestic. Sci.* **1990**, *29*, 317.

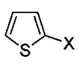
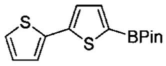
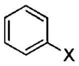
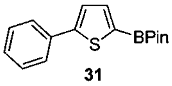
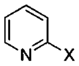
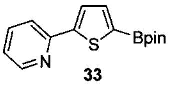
(9) Dubey, R. K.; Efimov, A.; Lemmetyinen, H. *Chem. Mater.* **2011**, *23*, 778.

(10) From single molecule conductivity measurements, the importance of positional connectivity is well known, but bulk measurements barely exist, due to the inaccessibility of such materials so far. See: Lemasson, F.; Berton, N.; Tittmann, J.; Hennrich, F.; Kappes, M. M.; Mayor, M. *Macromolecules* **2012**, *45*, 713.

(11) Solano, C.; Svensson, D.; Olomi, Z.; Jensen, J.; Wendt, O. F.; Wärnmark, K. *Eur. J. Org. Chem.* **2005**, 3510.

Table 3. Stille Coupling Reaction with Competitive Electrophiles (Yield Estimated by GC)[a]



entry	electrophiles[b]	product	time (min)	conv[c] I:Br	yield[d] (%)
1	 **28 a, b**	 **29**	20	100: n[e]	78
2	 **30 a, b**	 **31**	20	100: n[f]	92
3	 **32 a, b**	 **33**	300	100: n[g]	89

[a] The dinucleophile (1.00 mmol) the bromide (1.00 mmol) and the iodide (1.00 mmol) reacted under the described reaction conditions for the specified reaction time. [b] X = Br (a) or I (b), 1:1. [c] The conversion was monitored by GC and reported in % with respect to the standard, triisopropylbenzene. [d] The yield was isolated. [e] The method detection limit (see SI):[12] n = 0.4%; the unselective product was not observed. [f] The method detection limit (see SI):[12] n = 0.4%; the unselective product was not observed. [g] The method detection limit (see SI):[12] n = 0.7%; the unselective product was not observed.

polymers.[13] Because thiophene and its derivatives[14] belong to the best understood semiconducting polymers, we chose compound **5b** as the monomer for a proof-of-concept polymerization. Upon addition of a solution of a catalyst, [Pd(PtBu$_3$)$_2$], in THF to a solution of the monomer **5b** in THF in the presence of a base, the reaction mixture changed its color from light green to dark red within 6 min and a dark red precipitate formed. As Suzuki cross-coupling reactions with arylbromides catalyzed by [Pd(PtBu$_3$)$_2$] typically do not show such a color change, it is likely to be indicative of the formation of an elongated π-system. The product could be isolated by precipitation in a yield of the crude product of 61%. Although the material was too poorly soluble to obtain an NMR spectrum, by MALDI-MS, we could detect oligomers of up to 10 repeating units (M = 2483 m/z). The low solubility of polymer may be attributed to the absence of an alkyl chain on every other thiophene unit, compared to the soluble P3HT. This may lead to an increased propensity for crystallization of the polymer.

In conclusion, we developed the first nucleophile *and* electrophile selective one-pot cross-coupling reaction on aromatic rings. We found high selectivities for a broad range of electrophiles, high yields, and comparatively short reaction times. The type of product which is now available is highly functionalized with substituents that are still reactive toward further transformations, without any additional protection group operations. This new reaction strategy allows the convergent syntheses of complex molecules which is particularly useful if a large library of building blocks is desired, for example for screening the biological potency of a class of compounds or testing the influence of regioisomers on the performance of a material. In principle, the products of this reaction may be polymerized. Although the solubility of the resulting polymer was low, oligomers could be unequivocally identified. Work is ongoing to increase the solubility of the polymers, to exploit the wide range of new monomers which are now accessible and to establish conditions where this process can become a living polymerization.

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Supporting Information Available. Experimental section and NMR spectra are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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