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# Palladium-catalyzed cross-coupling reaction of resin-bound chlorotriazines

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**Abstract**—To introduce the biaryl structure as a triazine functionality, we have developed a new synthetic route via the Suzuki cross-coupling reaction of resin-bound chlorotriazines. The Suzuki cross-coupling reaction was achieved using various arylboronic acids, Pd(PPh<sub>3</sub>)<sub>4</sub>, Cs<sub>2</sub>CO<sub>3</sub>, and dioxane. With the integration of this chemistry and our previous orthogonal methodology, the triazine library is greatly expanded to a biaryl scaffold.

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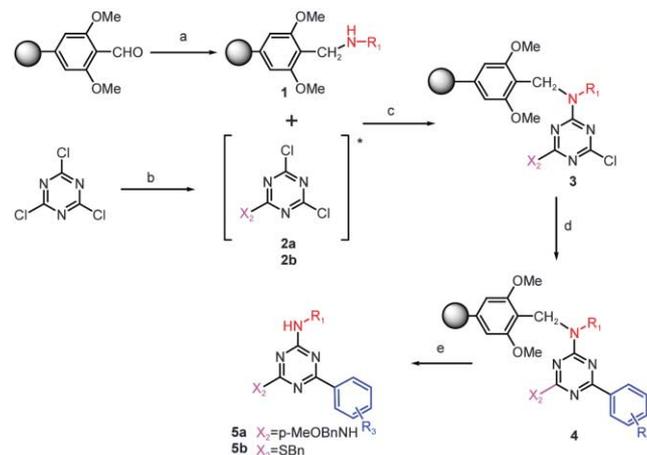
The aryl–aryl bond formation has elicited much interest in modern organic synthesis. This axially chiral bond is often found in natural products such as alkaloids,<sup>1</sup> and is prevalent in biologically active parts of pharmaceutical<sup>2</sup> and agrochemical specialties,<sup>3</sup> as well as in the materials science.<sup>4</sup> The development of synthetic methods for assembling aryl–aryl structured compounds has been aided by the advancement of transition metal catalysis, namely Suzuki cross-coupling reactions.<sup>5</sup>

Solution-phase Suzuki coupling reactions of aryl chlorides,<sup>6</sup> specifically heterocyclic chlorides, such as chloropyrimidines,<sup>7,8</sup> chloropyridines,<sup>9</sup> chloropurines,<sup>10</sup> and chlorotriazines,<sup>8,11</sup> have been reported in the literature. The Suzuki coupling was further extended to solid phase both in chloropyrimidines<sup>12,13</sup> and chloropurines,<sup>13,14</sup> yet remained unexplored for the triazine scaffold. Thus, we have developed a general method for performing palladium-catalyzed cross-coupling of solid supported chlorotriazines to provide a novel aryl–aryl containing triazine library.

In our previous research, we developed a unique solid phase synthetic pathway for a highly pure trisubstituted triazine library.<sup>15,16</sup> Interestingly, a series of compounds from the library, known as tubulyzines, demonstrated significant biological activity by the inhibition of tubulin polymerization.<sup>16</sup> However, one of our limitations was that triazine synthesis on solid support was confined to simple amine or alcohol nucleophilic reac-

tions. Herein, we report novel orthogonal reactions, which can be expanded to incorporate the Suzuki reaction (Scheme 1).

According to the orthogonal approach, a primary amine was coupled to a 4-formyl-3-dimethoxyphenoxymethyl-functionalized polystyrene resin (PAL) by reductive amination using NaBH(OAc)<sub>3</sub>. A monosubstituted 4,6-dichloro-[1,3,5]triazine, which was synthe-



**Scheme 1.** Orthogonal strategy for 1,3,5-trisubstituted triazines. (a) (i) R<sub>1</sub>NH<sub>2</sub>, HOAc:THF (1:44), rt, 1 h. (ii) NaBH(OAc)<sub>3</sub>, overnight. (b) benzenemethanethiol or *p*-methoxybenzylamine, DIEA, THF 0°C. (c) DIEA (4 equiv.), THF, 60°C, 3 h. (d) arylboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, dioxane, 90°C, 15 h. (e) 10% TFA/DCM, rt, 30 min. \*Purification was required via crystallization or column chromatography.

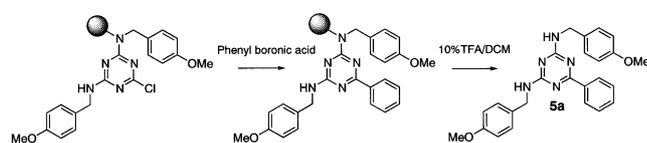
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sized in solution, was loaded on the solid support to give a chlorotriazine scaffold, through nucleophilic aromatic substitution in THF using DIEA (*N,N*-diisopropylethylamine) at 60°C. As the final derivatization step, an arylboronic acid was coupled to the triazine scaffold via the Suzuki reaction.

To optimize the reaction conditions, several palladium catalysts and bases with phenylboronic acid were first studied (Table 1). Pd<sub>2</sub>(dba)<sub>3</sub> [tris(dibenzylideneacetone) dipalladium] with carbene ligands, 1,3-bis-(2,4,6-trimethyl-phenyl)-imidazolium chloride<sup>17</sup> and Nolan,<sup>18</sup> yielded low product purity contaminated with unknown byproducts and starting material. In addition to Pd<sub>2</sub>(dba)<sub>3</sub> with carbene ligand or phosphine ligand, Pd(PPh<sub>3</sub>)<sub>4</sub> [tetrakis(triphenylphosphine)palladium] was also tested as a catalyst–ligand complex. Although the phosphine ligand<sup>19</sup> with Pd<sub>2</sub>(dba)<sub>3</sub> allowed for the reaction to proceed in comparable purity, commercially available Pd(PPh<sub>3</sub>)<sub>4</sub> with Cs<sub>2</sub>CO<sub>3</sub> was finally chosen for our catalyst to avoid unnecessary material usage and an extra preparation step. When weaker or stronger bases, such as DIEA and *t*-BuOK, were chosen for the replacement of Cs<sub>2</sub>CO<sub>3</sub>, unidentified impurities formed, leading to the conclusion that proper strength of base is necessary.

Using the optimal conditions, Pd(PPh<sub>3</sub>)<sub>4</sub> and Cs<sub>2</sub>CO<sub>3</sub> in dioxane solvent (entry 3), a variety of arylboronic acids, represented in Table 2 (entries 1–7),<sup>20</sup> were tested in the Suzuki reaction. The catalyst was stored and dispensed within a glove box to prevent oxidation of Pd(0). The reactions were heated to 90°C for 15 h under argon. Mild acidic cleavage of the resin-bound molecule by using 10% TFA/DCM gave the final trisubstituted triazine product **5**.

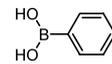
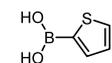
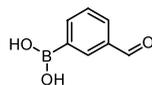
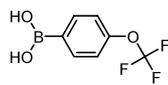
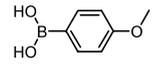
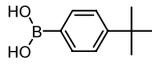
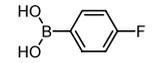
**Table 1.** Optimization of Suzuki cross-coupling reaction



	Catalyst	Ligand	Base	Solvent	% <sup>a</sup>
1	Pd <sub>2</sub> (dba) <sub>3</sub>	carbene <sup>b</sup>	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	5
2	Pd <sub>2</sub> (dba) <sub>3</sub>	carbene <sup>c</sup>	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	67
3	Pd <sub>2</sub> (dba) <sub>3</sub>	phosphine <sup>d</sup>	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	92
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	Cs <sub>2</sub> CO <sub>3</sub>	Dioxane	95
5	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	Cs <sub>2</sub> CO <sub>3</sub>	Toluene	78
6	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	<i>t</i> -BuOK	Dioxane	30
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	n/a	DIEA	Dioxane	50

<sup>a</sup> purity 1–7 of entry 1 compound **5a** of Table 2, <sup>b</sup> 1,3-Bis-(2,4,6-trimethyl-phenyl)imidazolium chloride, <sup>c</sup> Nolan ligand <sup>d</sup> biphenyl-2-yl-dicyclohexyl-phosphane.

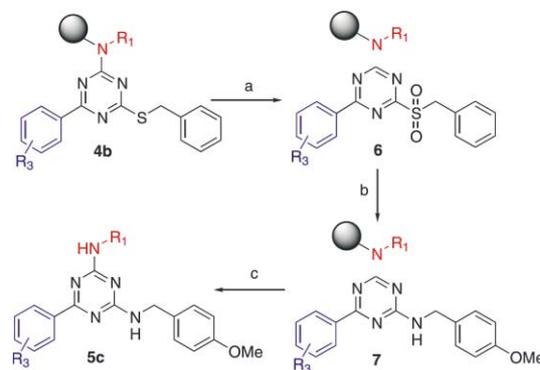
**Table 2.** Representative compounds with respective purity

Entry	Boronic acid	Purity (%)		
		<b>5a</b>	<b>5b</b>	<b>5c</b>
1		95	98	96
2		93	95	95
3		85	90	90 <sup>a</sup>
4		90	99	96
5		92	99	95
6		95	98	95
7		98	99	96

<sup>a</sup> oxidation of carbonyl yielded carboxylic acid as final **5c** product

zine product **5**. All products were analyzed for purity and identity by LC-MS equipped with a diode array detector (Table 2).

Our initial results from the Suzuki reaction, the final step in the orthogonal approach (Scheme 1, product **5a**), encouraged us to incorporate the coupling reaction into our previously developed sulfone strategy.<sup>16</sup> To test the synthetic utility of Scheme 2, we applied the Suzuki reaction, with the same optimal conditions to each of the selected arylboronic acids in the following pathway: (1) palladium-catalyzed coupling reaction



**Scheme 2.** Incorporation of Suzuki cross-coupling reaction into the sulfone strategy. (a) *m*-CPBA (10 equiv.), 1N NaOH, 1,4-dioxane, at pH 4, rt, 8 h. (b) *p*-Methoxybenzylamine (20 equiv.), DIEA (20 equiv.), BuOH:NMP (1:1), 120°C, 3 h. (c) 10% TFA/DCM, rt, 30 min.

with benzylsulfanyl as adjacent substituent (upon cleavage yields product **5b**), (2) oxidation, (3) amine replacement of sulfone and (4) cleavage, yielding product **5c**.

The purity data in Table 2 correlates to the three final cleaved products of Scheme 1 and Scheme 2, **5a**, **5b**, and **5c**, with either 4-methoxybenzylamine or benzene-methanethiol, as the X<sub>2</sub> substituent. The R<sub>1</sub> resin-bound amine for all the reactions was 4-methoxybenzylamine. The synthesis of **5c** products required oxidation with *m*-CPBA of the benzylsulfide, followed by replacement of benzylsulfone with 4-methoxybenzylamine. This served as a useful comparison for both pathways, since **5a** products and **5c** products are identical compounds.

Generally, the **5b** compounds demonstrated higher purity than the **5a** compounds. As a result, the final **5c** product exhibited high purity, as well, as it followed the pathway of Scheme 2 with sulfide intermediate **4b**. Thus, the sulfone chemistry not only offers greater accessibility for diversification, as the chemistry accommodates another site for nucleophilic amination, it also allows for greater compound purity. As a further note, the results illustrate the broad tolerance of the reaction for arylboronic acids. Our final conditions allowed for a wide variance of boronic acids with neutral, electron-withdrawing, as well as electron-donating functionalities.

In summary, we have developed two novel synthetic strategies toward making 1,3,5-trisubstituted aryl-triazines that can be applied to combinatorial triazine libraries. The previous orthogonal approach and the sulfone chemistry, in combination with the Suzuki reaction, will enable the generation of highly diversified and pure aryl-triazines. We are now in the process of constructing an extensive aryl-triazine library with biological screenings to follow.

### Acknowledgements

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### References

- (a) Bringmann, G.; Pokorny, F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 46, p. 127; (b) Furukawa, H.; Wu, T. S.; Ohta, T. *Chem. Pharm. Bull.* **1983**, *31*, 4202–4205; (c) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1–293.
- (a) Gallant, M.; Carrière, M. C.; Chateaufneuf, A.; Denis, D.; Gareau, Y.; Godbout, C.; Greig, G.; Juteau, H.; Lachance, N.; Lacombe, P.; Lamontagne, S.; Metters, K. M.; Rochette, C.; Ruel, R.; Slipetz, D.; Sawyer, N.; Tremblay, N.; Labelle, M. *Biorg. Med. Chem. Lett.* **2002**, *12*, 2583–2586; (b) Sasaki, S.; Cho, N.; Nara, Y.; Harada, M.; Endo, S.; Suzuki, N.; Furuya, S.; Fujino, M. *J. Med. Chem.* **2003**, *46*, 113–124; (c) Hotzel, A.; Schmid, D. G.; Nicholson, G. J.; Graeme, J.; Stevanovic, S.; Schimana, J.; Gebhardt, K.; Fiedler, H. S.; Jung, G. *J. Antibio.* **2002**, *55*, 571–577.
- (a) Ikegaya, K.; Ozaki, M.; Kawashima, T.; Miura, I.; Muramatsu, N. Preparation of biarylalkylencarbamic acid derivatives as agricultural and horticultural fungicides. PCT Int. Appl., WO9910317; 1999; (b) Hatanaka, Y.; Hagiwara, E.; Gouda, K.; Hiyama, T. Process of producing unsaturated organic compounds such as biaryls or arylpyridine derivative by coupling of organohalosilane with halobenzenes or halopyridines. PCT Int. Appl. WO9628401; 1996.
- (a) Bringmann, G.; Stowasser, R.; Goebel, L. *J. Organomet. Chem.* **1997**, *544*, 7–13; (b) Lee, D. H.; Im, J. H.; Lee, J. H.; Hong, J. I. *Tetrahedron Lett.* **2002**, *43*, 9637–9640; (c) Messner, M.; Kozhushkov, S.; De Meijere, A. *Eur. J. Org. Chem.* **2000**, 1137–1155.
- (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed; Wiley-VCH: New York, 1999; pp. 362–364; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
- (a) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211; (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388; (c) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020–4028; (d) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052; (e) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162–1163.
- Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125–7128.
- Cooke, G.; de Cremiers, A.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787–2789.
- (a) Ishikura, M.; Kamada, M.; Terashima, M. *Synthesis* **1984**, 936–938; (b) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273–2276; (c) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117–8126; (d) Zhang, H.; Chan, K. S. *Tetrahedron Lett.* **1996**, *37*, 1043–1044; (e) Zhang, H.; Kwong, F. Y.; Tian, Y.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 6886–6890.
- (a) Havelková, M.; Hocek, M.; Cesnek, M.; Dvorák, D. *Synlett* **1999**, 1145–1147; (b) Ding, S.; Gray, N. S.; Ding, Q.; Schultz, P. G. *Tetrahedron Lett.* **2001**, *42*, 8751–8755; (c) Havelková, M.; Dvorák, D.; Hocek, M. *Synthesis* **2001**, *11*, 1704–1710.
- (a) Janietz, D.; Bauer, M. *Synthesis* **1993**, *1*, 33–34; (b) Cocuzza, A. J.; Chidester, D. R.; Culp, S.; Fitzgerald, P.; Gilligan, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1063–1066.
- Wade, J.; Krueger, C. A. *J. Comb. Chem.* **2003**, *5*, 267–272.
- Ding, S.; Gray, N. S.; Wu, X.; Ding, Q.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 1594–1596.
- Brun, V.; Legraverend, M.; Grierson, D. S. *Tetrahedron* **2002**, *58*, 7911–7923.
- Moon, H. S.; Jacobson, E.; Khersonsky, S. M.; Luzung, M.; Walsh, D.; Xiong, W.; Lee, J. W.; Parikh, P.; Lam, J. C.; Kang, T. W.; Rosania, G. F.; Schier, A.; Chang, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 11608–11609.

16. Bork, J. T.; Lee, J. W.; Khersonsky, S. M.; Moon, H. S.; Chang, Y. T. *Org. Lett.* **2003**, *5*, 117–120.
17. (a) Zhang, C.; Haung, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805; (b) Arduengo, A. J., III, US patent 5 077 414; 1991; (c) Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530–5534.
18. Haung, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307–1309.
19. Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403–1406.
20. Representative spectroscopic data:  
(a) compound **5a**, entry 1 (*N,N'*-bis(4-methoxy-benzyl)-6-phenyl-[1,3,5]triazine-2,4-diamine):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.91 (s, 6H), 4.52–4.71 (m, 4H), 5.41 (br, 1H), 5.72 (br, 1H), 6.81–6.88 (4H, m), 7.19–7.56 (7H, m), 8.24–8.44 (2H, m).  
(b) compound **5b**, entry 1 (4-benzylsulfanyl-6-phenyl-[1,3,5]triazin-2-yl)-(4-methoxy-benzyl)-amine):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.96 (s, 3H), 4.49 (s, 2H), 4.69 (m, 2H,  $J=5.76$  Hz), 5.7 (br, 1H), 6.89 (d, 2H,  $J=7.45$  Hz), 7.26–7.38 (m, 5H), 7.38–7.56 (m, 5H), 8.37–8.54 (m, 2H).