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# A convenient microwave-assisted arylstannane generation-Stille coupling protocol

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**Abstract**—An efficient methodology for the synthesis of complex pyridin-3-yl-phenyl biaryl systems is described; microwave irradiation greatly enhances the rate of the two Pd-catalyzed key steps: formation of the stannane partner and its subsequent Stille coupling with a range of highly functionalized pyridines. Besides being fast and high yielding, this process also allows diversification of the pyridine at a late stage.


The biaryl motif is an important sub-unit found in many areas of medicinal chemistry. Biologically relevant entities containing a pyridine-phenyl biaryl motif include the 5HT-1A agonist Sarizotan and the HIV-1 protease inhibitor Atazanavir (Fig. 1).[1,2] Biaryls are also present in a range of natural products, agrochemicals and advanced materials.[3]

The transition-metal-catalyzed cross-coupling of organometallic reagents with halides or triflates represents a powerful method for the synthesis of this privileged scaffold.[4] Moreover, a recent evidence suggests that many of these transition-metal-catalyzed transformations, including the Stille reaction in which organostannanes are used as reaction partners,[5] can be significantly accelerated by microwave irradiation.[6]

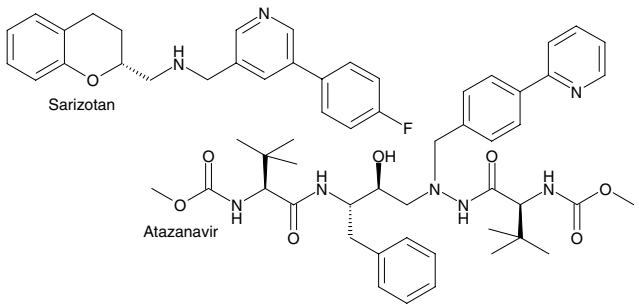


**Figure 1.** Biologically active compounds containing a phenyl-pyridine biaryl motif.

In the course of our studies on the design and synthesis of novel ligands for β4 nicotinic acetylcholine receptors, we became interested in pyridine-phenyl biaryls of type **3** (Scheme 1).[7] In addition to a highly functionalized heterobiaryl system, **3** also contains a potentially labile thioether moiety of defined stereochemistry. Therefore, we required a robust but mild synthesis to accommodate these sensitive functionalities. Additionally, we wanted to be able to introduce R and R′ late in the synthesis to allow convenient SAR exploration of this key region.

Pd-catalyzed cross-couplings were appealing to us since such reactions are known to tolerate sensitive functionalities in one or both coupling partners.[8] Although several reports of Pd-catalyzed biaryl formation describe microwave-assisted processes, these examples are most frequently related to biphenyl systems and rarely for heterobiaryls, being limited to simple unfunctionalized systems.[9] The same applies to the synthesis of heterobiaryls by Stille cross-coupling reaction with only the coupling of unsubstituted pyridine or thiophene substrates reported.[10] Herein we report the microwave-assisted synthesis of substituted pyridin-3-yl-phenyl biaryl systems **3**.

We initially envisaged forming the biaryl bond by classical Suzuki or Stille cross-coupling using conventional

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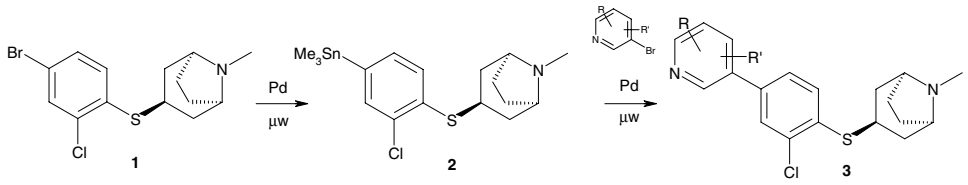
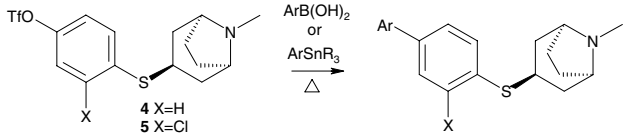


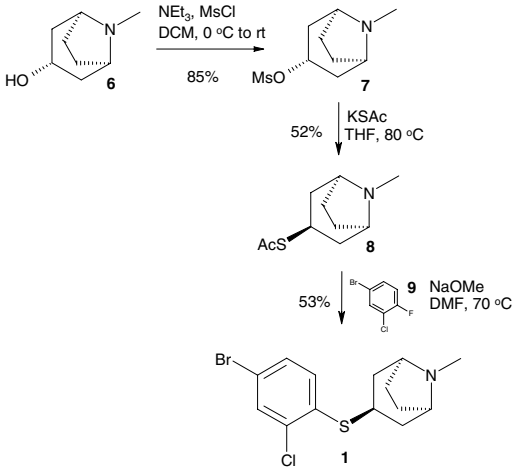

**Scheme 1.**




**Scheme 2.** Biaryl synthesis by classical Suzuki or Stille cross-coupling.

heating (Scheme 2). Attempts to couple triflate **4** to a variety of substituted aryl and heteroaryl boronic acids, including pyridines, under classical Suzuki conditions[11] ($NEt_3$, $PdCl_2(PPh_3)_2$, DMF, 90 °C, 4 h) gave unsatisfactory yields (0–15%). Slightly more promising results were obtained for the coupling of 3-chloro-triflate **5** using the Stille conditions developed by Farina.[12] The coupling of **5** with 3-tributylstannylpyridine in the presence of $Pd_2(dba)_3$, $Ph_3As$ and LiCl in NMP at 100 °C for 2 h gave the desired biaryl in a 30% yield.

Although the Stille cross-coupling seemed a better approach towards our biaryl targets, this synthetic route implied that a diversification of the pyridine substituents would require a synthesis of suitably substituted pyridyl stannanes since only a limited number of them were commercially available. We therefore envisaged synthesizing the tropane-thioaryl stannane intermediate **2** (Scheme 1), which could then be coupled to a broad range of commercially available bromopyridines. Bromide **1** was synthetically more accessible than its triflate analogue **5** and was therefore chosen as the stannane precursor. Mesylate **7** could be prepared on a multigram scale by standard manipulation of the commercially available tropine **6** followed by displacement with potassium thioacetate to give **8**. Upon treatment with sodium methoxide the thiolate was liberated and reacted in situ with commercially available fluorobenzene **9** to produce **1** in an overall 23% yield (Scheme 3).

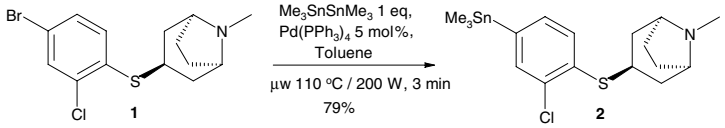



**Scheme 3.** Synthesis of bromo intermediate **1**.

After heating bromide **1** in dry toluene in the presence of hexamethylditin and $Pd(PPh_3)_4$ in a pressurized microwave vessel for 3 min at 110 °C/200 W,[13] stannane **2** was produced in a 79% yield after column chromatography on silica (Scheme 4).[14] These reaction conditions had first been optimized on a model reaction, for which microwave irradiation had led to a reduction of the reaction time from 20 h under conventional reflux to 3 min.[15] Stannane **2** could be kept for days in the fridge without any obvious degradation. To the best of our knowledge, this is the first report on the microwave-assisted synthesis of a trimethylstannane intermediate from the corresponding bromide.

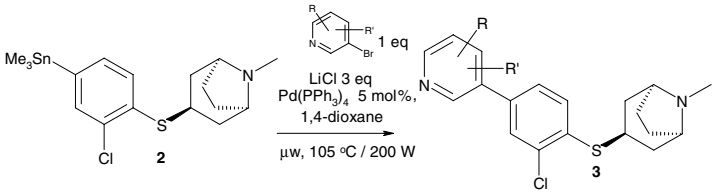
Intermediate **2** was then used in Stille cross-coupling reactions with a variety of substituted 3-bromopyridines using $Pd(PPh_3)_4$ and LiCl in a pressurized vessel under microwave irradiation (Table 1).[16]

Table 1 demonstrates that these reaction conditions provided satisfactory yields of biaryls and are tolerant of a range of functionalities. In most cases, microwave heating at 105 °C for 15 min was sufficient to achieve complete consumption of starting stannane **2** although the sterically hindered systems (Table 1, entries h and i) required extended reaction times. Reaction progress was monitored by LCMS and the reaction stopped when complete consumption of **2** was achieved. Although LCMS analysis indicated predominant formation of biaryl product, several chromatographic methods were necessary to obtain the purity required for biological testing, thus leading to only moderate yields of isolated products. As observed for the stannylation step, micro-




**Scheme 4.** Microwave-assisted synthesis of stannane **2**.

**Table 1.** Microwave-assisted Stille cross-coupling




| Entry | R | R′ | Product | Temperature (°C) | Time (min) | Yield[a] (%) |
|---|---|---|---|---|---|---|
| a | 6-$NO_2$ | H | **3a** | 105 | 15 | 42 |
| b | 6-F | H | **3b** | 105 | 15 | 61 |
| c | 5-$CO_2$Et | H | **3c** | 105 | 15 | 61 |
| d | 5-$CONH_2$ | H | **3d** | 105 | 15 | 46 |
| e | 6-$NH_2$ | H | **3e** | 105 | 15 | 0 |
| f | 6-NHAc | 5-Me | **3f** | 110 | 15 | 40 |
| g | 2-NHAc | 5-Me | **3g** | 105 | 20 | 40 |
| h | 6-NHAc | 2-Me | **3h** | 110 | 90 | 33 |
| i | 4-*n*Bu | H | **3i** | 110 | 45 | 34 |

[a] Isolated yield after mass and/or UV guided preparative chromatography.

wave irradiation proved to greatly enhance the rate of the Stille coupling. For the preparation of nitro compound **3a** we observed that 6 h were required to achieve a complete consumption of stannane under thermal conditions compared to only 15 min in the microwave apparatus.

We found that it was essential to carry out the reactions in a sealed vessel.[17] When the synthesis of **3g** was attempted in an open vessel, no reaction was observed after 20 min of microwave irradiation. A possible reason for this is that in a pressurized vessel, under microwave irradiation the reaction mixture is able to reach temperatures much above its conventional reflux temperature.[6] The only functional group that was found to fail in the coupling study was the amino group (Table 1, entry e), which we attribute to poisoning of the catalyst. When protected as the acetamide (Table 1, entries f–h), the coupling was successful.

We are currently investigating the generation of the stannane in situ followed by Stille coupling as a one-pot process (Scheme 5). This was inspired by the methodology developed by Hitchcock et al. consisting of a tandem Pd-catalyzed cross-coupling reaction between an aryl triflate and various aryl bromides.[18] Initial studies showed that triflate **4** and 2-bromopyridine could be coupled under thermal conditions, in moderate yield, thus proving the general feasibility of this approach. We further observed a rate acceleration of this reaction under microwave irradiation.[19] Work is ongoing to determine if this microwave-assisted one-pot process represents an improvement in terms of an overall yield. A similar microwave-assisted one-pot protocol was recently reported for the Stille cross-coupling of benzylic halides with chloro-pyrazones.[20]

In conclusion, we have developed a convenient two-step protocol for the synthesis of a highly functionalized pyridin-3-yl-phenyl system with microwave enhancement of both the stannane generation step and the subsequent Stille coupling step.

## Acknowledgements

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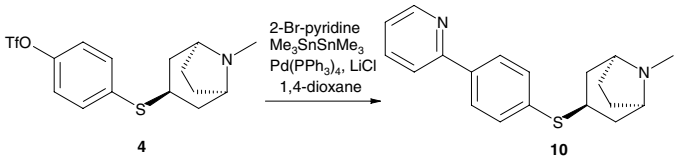
## References and notes

1. Kroesser, S.; Neugebauer, R.; Dolgos, H.; Fluck, M.; Rost, K. L.; Kovar, A. *Eur. J. Clin. Pharmacol.* **2006**, *62*, 277–284.
2. Goldsmith, D. R.; Perry, C. M. *Drugs* **2003**, *63*, 1679–1693.
3. For reviews see: (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933; (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303; (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469; (d) Bringmann, G.; Walter, R.; Weinch, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977–991.
4. (a) Kalinin, V. N. *Synthesis* **1992**, *5*, 413–432; (b) Mitchell, T. N. *Synthesis* **1992**, *9*, 803–815.




**Scheme 5.** One-pot process.

5. For reviews of the Stille reaction see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *The Stille Reaction, Organic Reactions*; Wiley & Sons: New York, 1997; Vol. 50, pp 1–652; (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
6. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
7. Astles, P. C.; Baker, S. R.; Keenan, M.; Vernier, J. M.; Sanderson, A. J.; Cube, R. V.; Martinez-Perez, J. A.; Maeto Herranz, A. I.; Dell, C. P.; Gutierrez, S.; Prietro, L.; Smith, C. W. WO 2003062235, Modulators of Acetylcholine Receptors; *Chem. Abstr.* **2003**, *139*, 149805. This work has been in part presented at YCI XIII, London, UK and at ASCMC Moscow 04.
8. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
9. (a) Seganish, W. M.; Deshong, P. *Org. Lett.* **2004**, *6*, 4379–4381; (b) Solodenka, W.; Schön, U.; Messinger, J.; Glinschert, A.; Kirschning, A. *Synlett* **2004**, *10*, 1699–1702; (c) Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639–642; (d) Zhang, W.; Chen, C.; Lu, Y.; Nagashima, T. *Org. Lett.* **2004**, *6*, 1473–1476.
10. (a) Lahred, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583–5587; (b) Lahred, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222; (c) Alterman, M.; Andersson, H. O.; Garg, N.; Ahlsén, G.; Lövgren, S.; Classon, B.; Danielson, U. H.; Kvarnström, I.; Vrang, L.; Unge, T.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 3835–3844; (d) Olofsson, K.; Kim, S-Y.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539–4541.
11. Cockerill, G. S.; Easterfield, H. J.; Percy, J. M.; Pintat, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, *16*, 2591–2599.
12. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.
13. CEM Discovery. Multimode cavity system which continuously adjusts the applied wattage to maintain the desired temperature.
14. Representative procedure for synthesis of **2**: bromide **1** (600 mg, 1.73 mmol), hexamethylditin (696 mg, 1.90 mmol), $Pd(PPh_3)_4$ (112 mg, 0.086 mmol) and dry toluene (5 ml) were placed in a Pyrex tube[17] under nitrogen. The tube was closed, positioned in the microwave cavity and irradiated for 3 min, at 200 W and 110 °C. After allowing the tube to cool to room temperature within the microwave cavity for a couple of minutes, the crude mixture was concentrated and purified by flash column chromatography (silica gel column, 0–10% MeOH in $CHCl_3$) yielding **2** as a light brown solid (587 mg, 79% yield).
15. Stannylation of 4-(4-bromophenylsulfanyl)-1-methylpiperidine with hexabutylditin in the presence of $Pd(PPh_3)_4$ in toluene.
16. General procedure for Stille coupling: stannane **2** (153 mg, 0.35 mmol), aryl bromide (0.35 mmol), lithium chloride (1.07 mmol), $Pd(PPh_3)_4$ (0.017 mmol) and 1,4-dioxane (1 ml) were placed in a Pyrex tube[17] under nitrogen. The tube was closed, positioned in the microwave cavity and irradiated at 200 W for the given times. After allowing the tube to cool to room temperature within the microwave cavity for a couple of minutes, the crude mixture was concentrated and purified by flash column chromatography.
17. The reactions were performed in a heavy-walled Pyrex tube equipped with a sealable metal cap and silicon septum. The reaction volume filled no more than two thirds of the total volume, thereby allowing space for pressure build-up during the microwave treatment.
18. Hitchcock, S. A.; Mayhugh, D. R.; Gregroy, G. S. *Tetrahedron Lett.* **1995**, *36*, 9085–9088.
19. Under the conditions described, LCMS showed no sign of **10** after 2 h of conventional reflux; an aliquot was then heated in the microwave (110 °C/200 W, 5 min) after which LCMS showed full consumption of **4** and formation of **10**.
20. Appukkuttan, P.; Husain, M.; Gupta, R. K.; Parmar, V. S.; Van der Eycken, E. *Synlett* **2006**, 1491–1496.