Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 3139

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**COMMUNICATION**

# Rapid synthesis of bis(hetero)aryls by one-pot Masuda borylation–Suzuki coupling sequence and its application to concise total syntheses of meridianins A and G†‡ §

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***Received 2nd December 2010, Accepted 25th February 2011***
**DOI: 10.1039/c1ob05310h**

**3-(Hetero)aryl substituted indoles, 7-azaindoles, and pyrroles can be obtained in a very concise fashion *via* a one-pot Masuda borylation–Suzuki coupling sequence. The concise total syntheses of the marine natural products meridianins A (5) and G (4i) nicely illustrate the utility of this methodology.**

Indoles and pyrroles belong to the most important heterocycles. They are widespread in nature[1] and represent privileged structures found in a plethora of biologically and pharmacologically active compounds.[2] In particular, indoles with 5- or 6-membered heterocyclic substituents in the 3-position have aroused considerable attention due to a remarkable spectrum of biological activity. For example, meridianins[3] and variolins[4] (Fig. 1) are small marine alkaloids consisting of indole and 7-azaindole frameworks connected to a 2-aminopyrimidine ring, the essential structural element for the kinase inhibitory activity of these natural products.

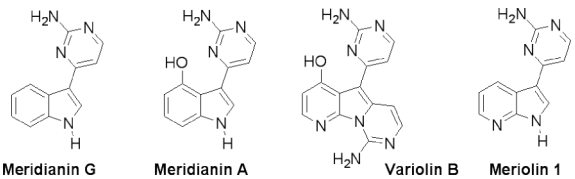


**Fig. 1** 3-Substituted indoles as natural products and bioactive compounds.

Recently, we synthesized some members of the meridianin family using the carbonylative Sonogashira coupling reaction as a key step.[5] The simplified 7-azaindole analogue of variolin B (later called meriolin 1)[6] has attracted our attention because it is very active on kinases and human cancer cell lines with $IC_{50}$ values (*i.e.* concentration reducing cell proliferation by 50%) of 0.18 and 0.14 μM against HCT116 (colon carcinoma) and A2780 (ovarian carcinoma), respectively. 7-Azaindole is an increasingly important structural motif due to its strong ability to bind to the hinge region of kinases and act as a kinase inhibitor. We are particularly interested in investigating the structure–activity relationship of 3-heteroaryl substituted 7-azaindoles. Therefore, a robust and general synthetic methodology to decorate (aza)indoles with diverse heterocyclic residues is highly desirable.

The Suzuki–Miyaura cross-coupling reaction[7] is an extremely important tool for the construction of biaryls, as emphasized by awarding the Nobel Prize 2010 to Akira Suzuki in recognition of the enormous utility of this Pd-catalyzed transformation. As the nucleophilic component of this coupling, pinacol boronic esters[8] are stable reagents and can be also accessed *via* Pd-catalyzed approaches such as Miyaura ($B_2pin_2/PdCl_2dppf/KOAc$)[9] and Masuda ($HBpin/PdCl_2dppf/NEt_3$)[10] borylations. The Masuda protocol utilizes pinacolborane,[11] thus being a more elegant and atom economical approach. The catenation of Masuda and Suzuki reactions into a one-pot fashion has been described by several groups pioneered by the work of Baudoin in 2000.[12] However, the strategy has never been generalized and no simple catalytic system has been disclosed for the flexible introduction of various heterocycles on pharmaceutically relevant heterocyclic scaffolds such as indoles or related systems.[13] Herein, we report a strikingly simple one-pot procedure which was established to efficiently synthesize a variety of 3-(hetero)aryl substituted (7-aza)indoles, pyrroles, and other electron-rich (hetero)aryls.

*N*-Boc protected (aza)indolyl[14] iodides **1** are easily accessible, stable to storage and can be successfully used as valuable building blocks in cross-coupling reactions. The direct Suzuki coupling of **1** with heteroaryl boronic acids or esters is strongly limited by the accessibility of the latter. We reasoned that iodides **1** could be converted to the corresponding pinacol esters[15] **2** and then reacted en route with heterocyclic halides **3**, which are readily available (Scheme 1).

According to this strategy, the iodides **1** are reacted with pinacolborane and triethylamine as a base in 1,4-dioxane. After completed transformation (as monitiored by TLC), methanol is added which scavenges excess of pinacolborane. One equivalent of mostly commercially available halide **3** is added followed by caesium carbonate to promote the Suzuki coupling. Concurrently,

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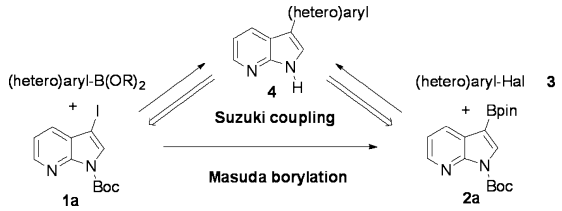
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of compounds **1a**, **1c**, **1f**, **1j**, **2a**, **4a–4u** and **5**. See DOI: 10.1039/c1ob05310h

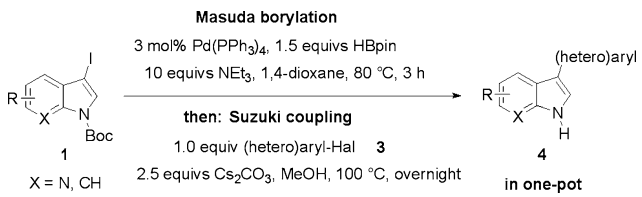
‡ Dedicated to Anna Merkul, née Seifert, on the occasion of her 60th birthday.

§ The authors cordially thank Merck Serono KGaA, Darmstadt, for the financial support.




**Scheme 1** Synthetic concept for 3-(hetero)aryl substituted 7-azaindoles **4**.

the alcoholic carbonate solution cleaves the Boc protective group, thus directly furnishing the desired products **4** without the need for an additional deprotection step (Scheme 2).




**Scheme 2** Masuda borylation–Suzuki coupling sequence.

This methodology exemplifies sequential catalysis, since a single Pd-precatalyst promotes both transformations.[16] No exotic ligands are required and no additional catalyst portion has to be added in the second reaction step. The yield did not increase upon addition of further 3 mol% $Pd(PPh_3)_4$, which performed best for the described substrates. $PdCl_2(PPh_3)_2$ was only slightly less efficient (64% *vs.* 61% for **4f**), but the typical precatalyst for Masuda borylations, $PdCl_2$dppf, failed to give the desired product in a good yield (39% for **4f**). $K_2CO_3$ can be used instead of $Cs_2CO_3$ with slightly decreased efficiency.

Interestingly, in a related approach to substituted 7-azaindolyl pyrimidines, a stepwise protocol consisting of Miyaura borylation and Suzuki coupling with two different (!) Pd-precatalysts was utilized, and the protective phenylsulfonyl group remained uncleaved.[17]

The scope of the presented sequence is remarkable since it allows the introduction of a great variety of different 6-membered aryl substituents or nitrogen heterocycles (Fig. 2). Functional groups including cyano, free hydroxy and amino groups on (hetero)aryl halides are tolerated and give good yields. (Hetero)aromatic iodides, bromides and chlorides (see the color code of Fig. 2) can be reacted according to the expected oxidative addition tendency of the halide and its position in the (hetero)cycle. Pharmacophore motifs such as 2-aminopyrimidine, 2-aminopyridine, and even 2,6-diaminopyridine can be introduced without difficulties. It should be emphasized that upon using the reverse approach, *i.e.* the direct coupling with heteroaryl boronic acids or pinacol esters, the observed functional and structural diversity can hardly be realized: especially *ortho*-nitrogen atom containing boronic reagents are particularly challenging coupling partners.[18] Not only indoles and 7-azaindoles but also iodo pyrroles[19] can be reacted and give 2,4-disubstituted pyrroles (**4k–4n**), which represent an interesting and rare substitution pattern. Furthermore, *N*-Bn 4-iodo pyrazole, 3-iodo thiophene, 2,5-disubstituted 4-iodo furan[20] as well as 2-amino 5-iodo pyridine, 2-amino 5-iodo pyrimidine and electron-rich iodo arenes can be functionalized with (hetero)aryl substituents with

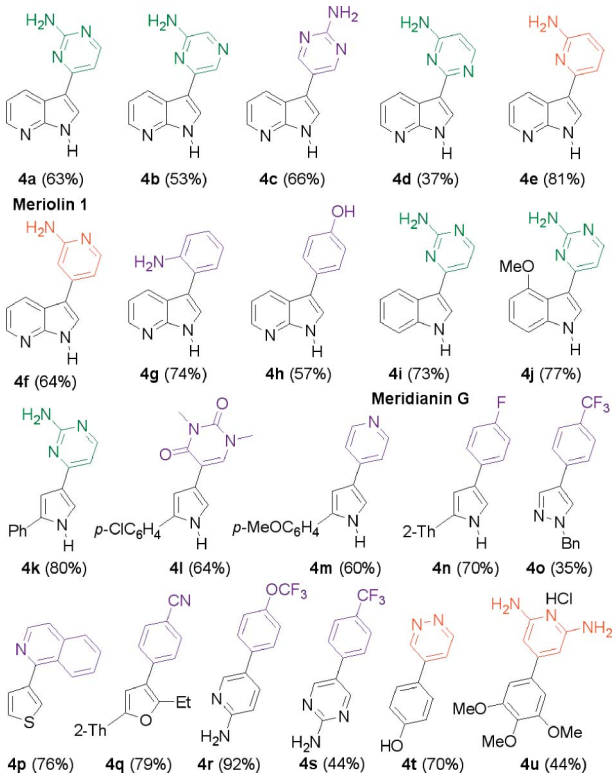


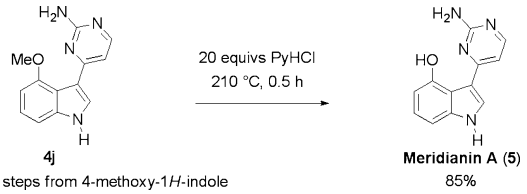

**Fig. 2** Scope of the Masuda borylation–Suzuki coupling sequence (isolated yields). Color code for the applied heterocyclic halides **3**: violet = iodide, brown = bromide, green = chloride. Th = thienyl.

comparable efficiency (**4o–4u**). Free hydroxy and amino groups on the substrates are well tolerated (**4r–4t**). The yields of the isolated products are fair to very good and the compounds can be obtained analytically pure by simple flash chromatography.

With this practical and versatile methodology in hand, we set out to perform very concise total syntheses of meridianins A (**5**)[23] and G (**4i**) in order to illustrate the utility in alkaloid synthesis. Starting from commercially available 4-methoxy-1*H*-indole, the former natural product was obtained in four steps and 54% total yield. The one-pot Masuda borylation–Suzuki coupling sequence was used as a key step to prepare *O*-Me-meridianin A (**4j**), which was then demethylated by PyHCl[21] in the final step (Scheme 3). It is worth mentioning that this strategy represents the first targeted synthesis of this natural product since the sole approach by Fresneda and Molina delivered 15% (19 mg) of meridianin A in 5 steps from 4-benzyloxy-7-bromo-1*H*-indole, which is not commercially available.[22] The presented procedure[23] gives also access to other interesting hydroxylated 3-aryl and 3-heteroaryl substituted indoles. Syntheses of further natural products can be easily envisioned and are currently underway.

The presented sequence consisting of Masuda borylation and Suzuki coupling is tailored to efficiently synthesize 3-(hetero)aryl substituted (aza)indoles, many of them are biologically active compounds. Moreover, the obtained 2,4-di(hetero)aryl substituted pyrroles represent a new promising scaffold. The most exciting feature of this preparatively extremely simple transformation is the possibility to directly connect readily available heterocyclic halides in a one-pot fashion without the need for sophisticated catalysts, ligands or additives. Considering the huge pool of




**Scheme 3** Final step of the total synthesis of meridianin A.

commercially available or easily accessible heteroaromatic halides, this methodology is a quite general concept.

The full scope of the sequence as well as structure–activity studies and the biological data of analogues based on 7-azaindole will be reported in near future.

## Notes and references


1 For recent reviews, see: A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; H. Fan, J. Peng, M. T. Hamann and J.-F. Hu, *Chem. Rev.*, 2008, **108**, 264.

2 For a recent minireview on indole alkaloid marine natural products as a source of drug leads, see: W. Gul and M. T. Hamann, *Life Sci.*, 2005, **78**, 442.

3 M. D. Lebar and B. J. Baker, *Aust. J. Chem.*, 2010, **63**, 862; A. M. Seldes, M. F. R. Brasco, L. H. Franco and J. A. Palermo, *Nat. Prod. Res.*, 2007, **21**, 555; L. H. Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A. M. Seldes and J. A. Palermo, *J. Nat. Prod.*, 1998, **61**, 1130.

4 N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro, S. Parkin and H. Hope, *Tetrahedron*, 1994, **50**, 3987; G. Trimurtulu, D. J. Faulkner, N. B. Perry, L. Ettouati, M. Litaudon, J. W. Blunt, M. H. G. Munro and G. B. Jameson, *Tetrahedron*, 1994, **50**, 3993; Recent review on variolins and related alkaloids: S. R. Walker, E. J. Carter, B. C. Huff and J. C. Morris, *Chem. Rev.*, 2009, **109**, 3080.

5 A. S. Karpov, E. Merkul, F. Rominger and T. J. J. Müller, *Angew. Chem., Int. Ed.*, 2005, **44**, 6951.

6 A. Echalier, K. Bettayeb, Y. Ferandin, O. Lozach, M. Clément, A. Valette, F. Liger, B. Marquet, J. C. Morris, J. A. Endicott, B. Joseph and L. Meijer, *J. Med. Chem.*, 2008, **51**, 737.

7 M. Prieto, E. Zurita, E. Rosa, L. Muoz, P. Lloyd-Williams and E. Giralt, *J. Org. Chem.*, 2004, **69**, 6812; N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.

8 C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482.

9 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508.

10 M. Murata, T. Oyama, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 2000, **65**, 164; M. Murata, S. Watanabe and Y. Masuda, *J. Org. Chem.*, 1997, **62**, 6458.

11 For a method for practical large-scale preparation of pinacolborane, see: T. Kikuchi, Y. Nobuta, J. Umeda, Y. Yamamoto, T. Ishiyama and N. Miyaura, *Tetrahedron*, 2008, **64**, 4967.

12 For reported one-pot Masuda borylation–Suzuki coupling sequences, see: P.-E. Broutin, I. Čerňa, M. Campaniello, F. Leroux and F. Colobert, *Org. Lett.*, 2004, **6**, 4419; M. Penhoat, V. Levacher and G. Dupas, *J. Org. Chem.*, 2003, **68**, 9517; O. Baudoin, D. Guénard and F. Guéritte, *J. Org. Chem.*, 2000, **65**, 9268.

13 For a sequence applied in a bisindole synthesis using XPhos, see: H. A. Duong, S. Chua, P. B. Huleatt and C. L. L. Chai, *J. Org. Chem.*, 2008, **73**, 9177.

14 B. Witulski, N. Buschmann and U. Bergsträßer, *Tetrahedron*, 2000, **56**, 8473.

15 For a direct Ir-catalyzed borylation of *N*-Boc protected heterocycles, see: V. A. Kallepalli, F. Shi, S. Paul, E. N. Onyeozili, R. E. Maleczka Jr. and M. R. Smith III, *J. Org. Chem.*, 2009, **74**, 9199.

16 T. J. J. Müller, *Top. Organomet. Chem.*, 2006, **19**, 149.

17 S. Huang, R. Li, P. J. Connolly, S. Emanuel and S. A. Middleton, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4818.

18 For strategies developed for the Suzuki coupling of 2-pyridyl pinacolboronates, see: D. X. Yang, S. L. Colletti, K. Wu, M. Song, G. Y. Li and H. C. Shen, *Org. Lett.*, 2009, **11**, 381; J. Z. Deng, D. V. Paone, A. T. Ginnetti, H. Kurihara, S. D. Dreher, S. A. Weissman, S. R. Stauffer and C. S. Burgey, *Org. Lett.*, 2009, **11**, 345.

19 For a one-pot preparation of 2-substituted *N*-Boc 4-iodo pyrroles, see: E. Merkul, C. Boersch, W. Frank and T. J. J. Müller, *Org. Lett.*, 2009, **11**, 2269.

20 For a one-pot preparation of (di)substituted (3)4-iodo furans, see: A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Chem. Commun.*, 2005, 2581; A. S. Karpov, E. Merkul, T. Oeser and T. J. J. Müller, *Eur. J. Org. Chem.*, 2006, 2991.

21 C. R. Schmid, C. A. Beck, J. S. Cronin and M. A. Staszak, *Org. Process Res. Dev.*, 2004, **8**, 670.

22 P. M. Fresneda, P. Molina and J. A. Bleda, *Tetrahedron*, 2001, **57**, 2355.

23 Typical procedure (Compound **4j**): tetrakis(triphenylphosphane)-palladium(0) (35 mg, 0.03 mmol, 3 mol%) and *tert*-butyl 3-iodo-4-methoxy-1*H*-indole-1-carboxylate (**1c**) (373 mg, 1.00 mmol) were placed under argon atmosphere in a dry screw-cap vessel with septum. Then, 5 mL of dry 1,4-dioxane were added and the mixture was degassed with argon. Dry triethylamine (1.39 mL, 10.0 mmol) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol) were successively added to the mixture which was stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), 5 mL of dry methanol, 2-amino-4-chloropyrimidine **3a** (134 mg, 1.00 mmol) and caesium carbonate (823 mg, 2.50 mmol) were successively added and the mixture was stirred at 100 °C (preheated oil bath) overnight for 15 h. Then, after cooling to room temperature (water bath) the solvents were removed *in vacuo* and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with dichloromethane–methanol-aqueous ammonia to give after drying *in vacuo* at 70 °C overnight 185 mg (77%) of the analytically pure compound **4j** as a colorless solid, mp 221–222 °C. $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ (ppm) 3.87 (s, 3 H), 6.27 (s, 2 H, N$H_2$), 6.63 (d, $J$ = 6.9 Hz, 1 H), 7.06–7.12 (m, 2 H), 7.26 (dd, $J$ = 5.4 Hz, $J$ = 0.9 Hz, 1 H), 7.85 (d, $J$ = 2.5 Hz, 1 H), 8.15 (d, $J$ = 5.4 Hz, 1 H), 11.6 (br, 1 H, N$H$). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ (ppm) 55.0 ($CH_3$), 101.2 (CH), 105.5 (CH), 109.7 (CH), 114.4 ($C_{quat}$), 115.4 ($C_{quat}$), 122.7 (CH), 127.5 (CH), 138.8 ($C_{quat}$), 153.2 ($C_{quat}$), 157.0 (CH), 161.8 ($C_{quat}$), 163.2 ($C_{quat}$). EI MS (*m*/*z* (%)): 240 ($M^+$, 50), 239 ($M^+$ – H, 21), 211 ($M^+$ – $CH_3O$ + H, 20), 202 ($M^+$ – $C_2H_2N$ + 2 H, 11), 58 ($CH_4N_3^+$, 41), 43 ($C_2H_3O^+$, 100). IR (KBr): $\tilde{\nu}$ 3465 (m) cm$^{-1}$, 3313 (m), 3165 (m), 1644 (m), 1624 (m), 1575 (s), 1555 (s), 1506 (s), 1459 (s), 1414 (m), 1320 (m), 1245 (m), 1088 (m), 733 (m). Anal. calcd for $C_{13}H_{12}N_4O$ (240.3): C 64.99, H 5.03, N 23.32. Found: C 64.86, H 4.85, N 23.25. Synthesis of meridianin A (**5**): pyridinium hydrochloride (1.18 g, 10.0 mmol) was placed in a dry screw-cap vessel under argon atmosphere. Then, **4j** (120 mg, 0.50 mmol) was added and the mixture was heated to 210 °C (preheated oil bath). After 0.5 h the mixture was cooled to 50 °C (preheated oil bath) and methanol was added to dissolve the residue. The solvents were removed *in vacuo* and the residue was adsorbed onto Celite® and purified chromatographically on silica gel with dichloromethane–methanol–aqueous ammonia to give after drying *in vacuo* at 70 °C overnight 96 mg (85%) of the analytically pure meridianin A (**5**) as a bright yellow fine crystalline solid, mp 264–276 °C. (Lit.:[3,22] 164–168 °C). $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta$ (ppm) 6.39 (dd, $J$ = 7.9 Hz, $J$ = 0.9 Hz, 1 H), 6.76 (s, 2 H, N$H_2$), 6.82 (dd, $J$ = 8.2 Hz, $J$ = 0.9 Hz, 1 H), 7.00 (t, $J$ = 7.9 Hz, 1 H), 7.14 (d, $J$ = 5.4 Hz, 1 H), 8.14 (d, $J$ = 5.4 Hz, 1 H), 8.25 (d, $J$ = 3.2 Hz, 1 H), 11.8 (br, 1 H, N$H$), 13.62 (s, 1 H, O$H$). $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta$ (ppm) 102.3 (CH), 104.3 (CH), 105.5 (CH), 113.7 ($C_{quat}$), 114.3 ($C_{quat}$), 124.4 (CH), 128.4 (CH), 139.2 ($C_{quat}$), 152.0 ($C_{quat}$), 158.4 (CH), 160.4 ($C_{quat}$), 161.7 ($C_{quat}$). EI MS (*m*/*z* (%)): 226 ($M^+$, 100), 225 ($M^+$ – H, 13), 209 ($M^+$ – OH, 2), 197 ($M^+$ – COH, 6), 185 ($M^+$ – $CH_2N_2$ + H, 18), 158 ($M^+$ – $C_3H_4N_2$, 6). IR (KBr): $\tilde{\nu}$ 3429 (m) cm$^{-1}$, 3342 (m), 1638 (m), 1593 (s), 1562 (m), 1532 (m), 1469 (m), 1444 (m), 1401 (m), 1321 (m), 1227 (m), 719 (m). Anal. calcd for $C_{12}H_{10}N_4O$ (226.2): C 63.71, H 4.46, N 24.76. Found: C 63.48, H 4.61, N 24.72.