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One-Pot Synthesis of Diazine-Bridged Bisindoles and Concise Synthesis of the Marine Alkaloid Hyrtinadine A

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Dedicated to Prof. em. Dr. Leonhard Birkofer on the occasion of his 100th birthday

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Diazine-bridged bisindoles are readily obtained from *N*-Boc-protected 3-iodoindoles and 3-iodo-7-azaindole in a pseudo three-component reaction involving a one-pot Masuda borylation–Suzuki arylation sequence. Some of the title compounds display promising cytotoxic properties. The versatility of this methodology is illustrated by a very concise total synthesis of the marine alkaloid hyrtinadine A.

Introduction

Heterocycles bridging two identical indole substituents are common scaffolds in many pharmaceutically interesting natural products,[1] such as hamacanthins,[2] nortopsentins,[3] and lynamicins.[4] Inspired by marine alkaloids of the meridianin and variolin family,[5,6] we identified the structurally related, novel bisindole alkaloid hyrtinadine A (Scheme 1)[7] as a suitable target to scrutinize the scope of the Masuda borylation–Suzuki coupling sequence[8] of nitrogen heterocycles, which we applied recently in a concise synthesis of meridianin A and 7-azaindole analogues. Hyrtinadine A, isolated from an Okinawan marine sponge of the *Hyrtios* genus, was found to be highly cytotoxic against murine leukemia L1210 and human epidermoid carcinoma KB cell lines. The sole total synthesis of hyrtinadine A was realized by a Pd-catalyzed coupling of indiumorganyls as a key step.[9] Although a twofold cross-coupling with heterocyclic substrates and an unsymmetrical substitution of the pyrimidyl core were achieved, this methodology appears to be very limited. A major drawback is the overstoichiometrical use of the precious indolyl organoindium reagent, which is also associated with the need for organolithium or organomagnesium precursors not tolerant towards functional groups. Herein we report the adaptation of the Masuda borylation–Suzuki coupling sequence to diheteroaryl-substituted diazines and its application to a concise total synthesis of hyrtinadine A.

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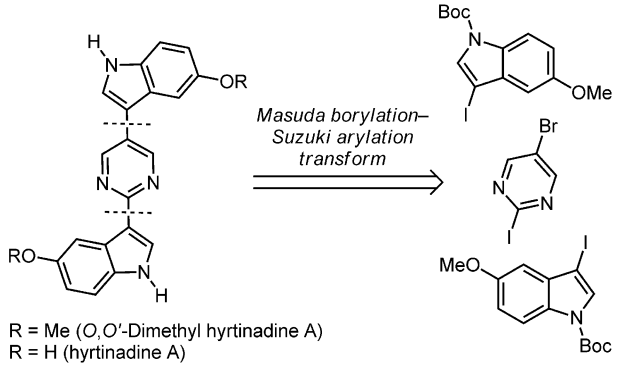
Results and Discussion

The Suzuki–Miyaura cross-coupling reaction is one of the most versatile tools for the preparation of biaryls in a short and efficient manner.[10] Pinacolboronates[11] are stable esters and can be readily applied as coupling partners in Suzuki coupling reactions. Most advantageously, their preparation proceeds by palladium-catalyzed Miyaura[12] or Masuda[13] borylation under mild conditions and tolerates a lot of polar functionality. The Masuda borylation has the advantage of using pinacolborane as a borylating agent, which is definitely more atom economical and elegant than applying bispinacolato diboron. Therefore, the advantages of performing a Masuda borylation and a subsequent Suzuki coupling in a one-pot sequence lie at hand. Prior to our studies, this sequence has not generally been used for the preparation of heteroaromatic biaryls.[14] Just recently, we established this conceptually elegant sequence for N-heterocycles, such as indoles and pyrroles,[8] which are both ubiquitous in nature and constitute important building

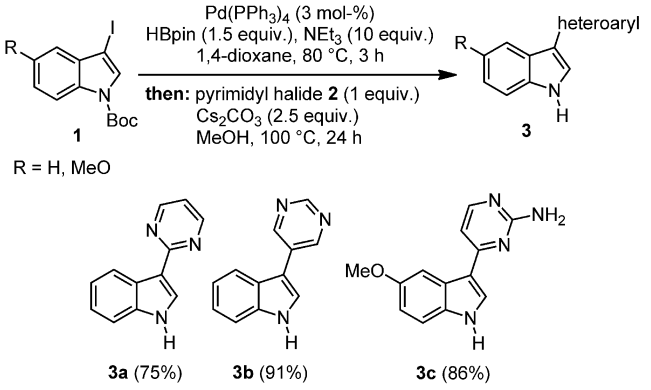


Scheme 1. Retrosynthetic analysis of hyrtinadine A.

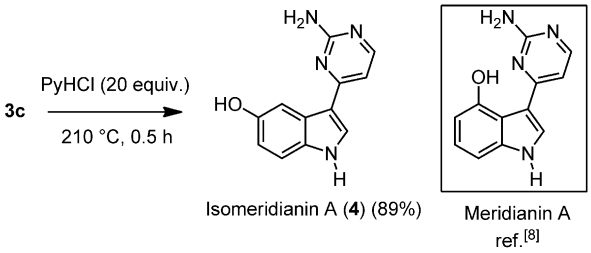
blocks of many biologically active compounds with significant relevance in medicinal chemistry.[15]

Our retrosynthetic analysis of hyrtinadine A suggests the Masuda borylation–Suzuki coupling as a key transform (Scheme 1), which is projected as a one-pot reaction in the sense of a sequentially palladium-catalyzed process.[16] Moreover, the Boc protecting group is concomitantly cleaved under the terminal Suzuki conditions, accounting for the efficiency of the sequence. As a consequence, *N*-Boc-3-iodo-5-methoxyindole and 5-bromo-2-iodopyrimidine are the electrophilic coupling partners; the former is readily available from commercially available starting materials.[17]

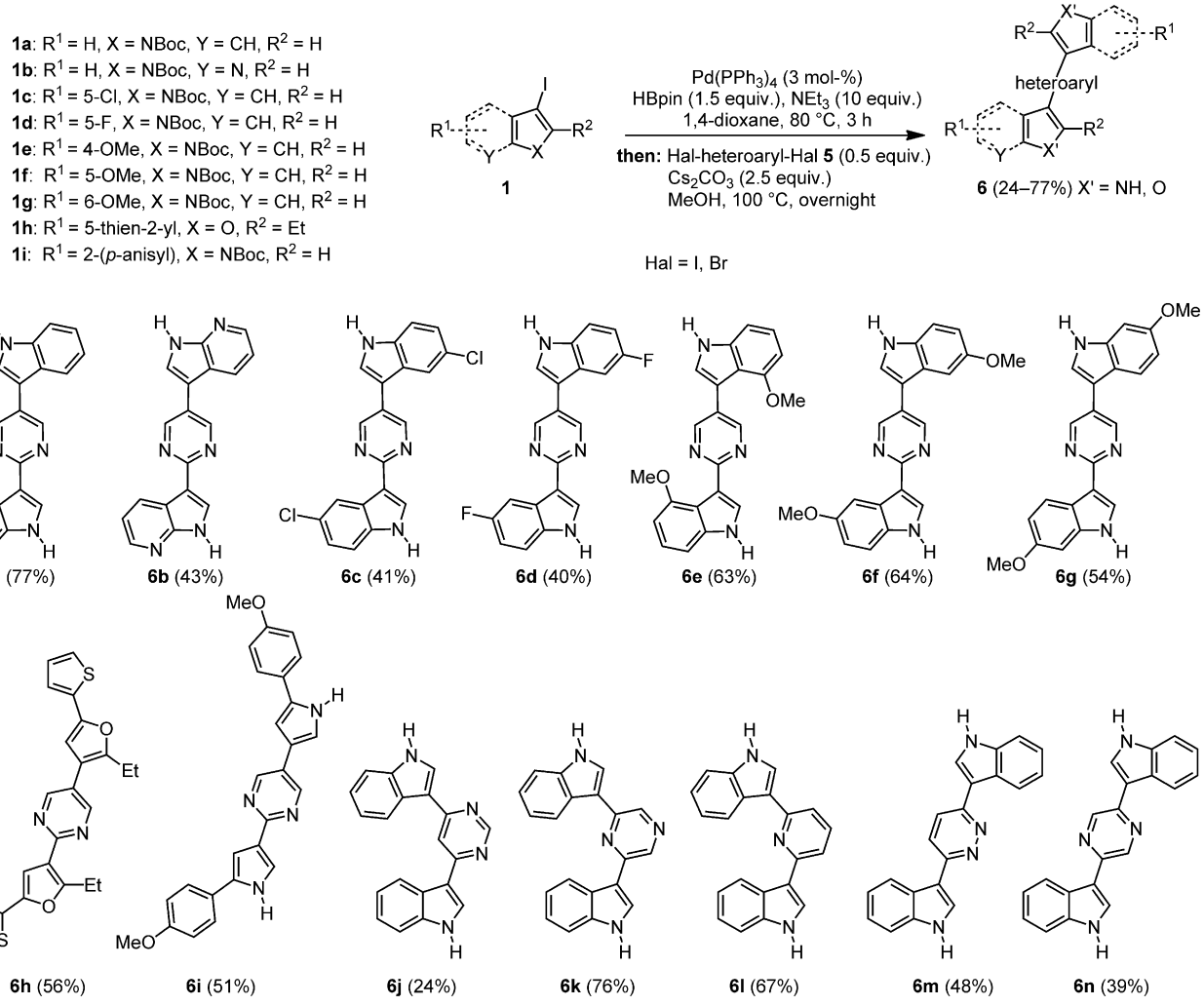
According to this strategy, we first scouted the applicability of the sequence to the synthesis of structural subunits **3a**–**c**, using the standard conditions[8] for the sequence (Scheme 2).



Scheme 2. One-pot Masuda borylation–Suzuki arylation synthesis of heteroaryl-substituted indoles **3**.



Scheme 3. Synthesis of isomeridianin A (**4**) by demethylation of **3c**.



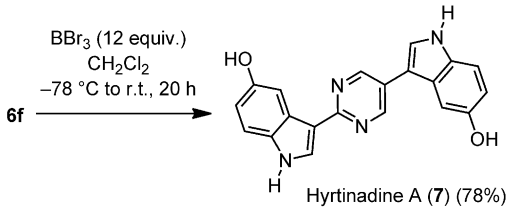
Scheme 4. One-pot Masuda borylation–Suzuki arylation synthesis of diazine-bridged bisheteroaryls **6**.

After generating the boronate intermediate by Masuda borylation of indoles **1** with pinacolborane, methanol, 2-bromopyrimidine (**2a**), 5-bromopyrimidine (**2b**), or 4-chloro-2-aminopyrimidine (**2c**), and cesium carbonate were subsequently added to the reaction mixture to give, after the Suzuki arylation step, 3-pyrimidyl-substituted indoles **3** in good to excellent isolated yields. For quenching the excess amount of pinacolborane, the addition of anhydrous methanol has proven to furnish highest yields in the two-step sequence. For demethylation of **3c**, heating in the melt of pyridinium chloride (PyHCl)[18] was applied to give the literature unknown isomeridianin A (**4**) in a very good yield (Scheme 3).

With this convenient sequential Masuda borylation–Suzuki arylation protocol in hand we set out to perform the sequence as a pseudo-three-component synthesis, that is, the ratio of the in situ generated heterocyclic pinacolester to the dihalodiazine was chosen as 2:1. Starting from 3-iodo-substituted heterocycles such as indoles **1a**, **1c**–**g**, 7-azaindole (**1b**), 2-ethyl-5-thien-2-yl-furane (**1h**),[19] and 5-(*p*-anisyl)pyrrole (**1i**),[20] after Masuda borylation with pinacolborane the Suzuki arylation step with various diiodo-, dibromo-, or bromoiodo-substituted diazines **5** furnishes bis(heteroaryl) substituted diazines **6** in a one-pot fashion in moderate to good yields (Scheme 4).

In particular, 2,5-bis(methoxyindol-3-yl)pyrimidines **6e**–**g** can be readily obtained by this one-pot procedure, with the literature unknown compound **6f** being *O*,*O*′-dimethyl hyrtinadine A, a precursor of the natural product. Thus, by virtue of the one-pot Masuda borylation–Suzuki arylation sequence as a key step, the total synthesis of hyrtinadine A can be conducted in a very concise fashion. Starting from commercially available 5-methoxy-1*H*-indole, after iodination, Boc protection, and Masuda borylation–Suzuki coupling sequence, dimethyl hyrtinadine A (**6f**) is accessible in good yield.

However, unexpectedly the final demethylation with PyHCl furnished hyrtinadine A (**7**) in only 39% yield. Therefore, we sought an alternative deprotection method.[21] Gratifyingly, demethylation of **6f** using BBr_3 gave hyrtinadine A in 78% yield (Scheme 5).



Scheme 5. Synthesis of hyrtinadine A (**7**) by demethylation of *O*,*O*′-dimethyl hyrtinadine A (**6f**).

The biological activities of *O*-methyl isomeridianin A (**3c**), isomeridianin A (**4**), selected diazine-bridged bisheteroaryls **6**, and hyrtinadine A (**7**) were evaluated by screening against a broad panel of 102–121 kinases at the Division of Signal Transduction Therapy (DSTT), University of Dundee, UK, and by determining the IC_{50} values in viability assays with HCT116 (colon carcinoma) and A2780 (ovarian carcinoma) cell lines (Table 1).[22] Interestingly, *O*,*O*′-dimethyl hyrtinadine A (**6f**) as well as the chloro analogue (**6c**) show a low micromolar activity in viability assays, which however seems not to be correlated with kinase inhibitory activity. Fascinatingly, precursor **6f** was more active than the natural product in viability assays.

Table 1. Biological data of selected compounds **3**, **4**, **6**, and **7**.

	Number of kinases with >50% inhibition at 1 μM / Number of kinases tested	IC_{50} (HCT116) [μm][a]	IC_{50} (A2780) [μm][a]
3c	7/110	>10	>10
4	8/110	>10	>10
6a	0/102	>10	>10
6b	7/121	>10	>10
6c	1/121	5.3	0.9
6e	0/121	>10	>10
6f	0/110	3.7	4.5
6m	0/121	>10	3.3
7	3/121	>10	>10

[a] IC_{50}: concentration reducing cell proliferation by 50%.

Conclusions

In summary we have successfully adapted the one-pot Masuda borylation–Suzuki arylation sequence to a general synthesis of diazine-bridged bisheteroaryls in the sense of a one-pot pseudo-three-component reaction. The procedure is another showcase for sequential Pd-catalyzed processes, which can be easily performed without the need for exotic ligands or the excessive use of expensive reagents. Besides the concise total synthesis of the marine alkaloid hyrtinadine A, several bisheteroaryl analogues have been efficiently prepared in a straightforward fashion. Studies directed towards the syntheses of structurally more complex marine alkaloids, kinase inhibitors, and oligomeric heteroarenes using the Masuda borylation–Suzuki arylation are currently underway.

Experimental Section

Synthesis of 6f: Tetrakis(triphenylphosphane)palladium(0) (69 mg, 0.06 mmol, 3 mol-%) and *tert*-butyl 3-iodo-5-methoxy-1*H*-indole-1-carboxylate (**1f**; 746 mg, 2.00 mmol) were placed under an argon atmosphere in a dry screw-cap vessel with a septum. Then, dry 1,4-dioxane (10 mL) was added, and the mixture was degassed with argon (5 min). Dry triethylamine (1.0 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.45 mL, 3.00 mmol) were successively added to the mixture, which was then stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), dry methanol (10 mL), 5-bromo-2-iodopyrimidine (**5a**; 289 mg, 1.00 mmol), and cesium carbonate (1.63 g, 5.00 mmol) were successively added. The mixture was stirred at 100 °C overnight (preheated oil bath). Then, after cooling to room temperature, the solvents were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia) to give compound **6f** as a yellow solid (238 mg, 0.64 mmol, 64% yield). For full analytical details, see the Supporting Information.

Synthesis of 7 (Demethylation of Compound 6f; Synthesis of Hyrtinadine A): 3,3′-(Pyrimidine-2,5-diyl)bis(5-methoxy-1*H*-indole) (**6e**; 185 mg, 0.50 mmol) was placed in a dry screw-cap vessel under an argon atmosphere. Then, dry dichloromethane (15 mL) was added. The suspension was cooled to –78 °C (acetone/dry ice bath) and tribromoborane (0.58 mL, 6.00 mmol) was slowly added. The mixture was allowed to reach room temperature and continuously stirred for 20 h. The reaction progress was monitored by TLC. Then the mixture was cooled to 0 °C (water/ice bath), and water (3 mL) followed by saturated potassium carbonate solution (30 mL) were slowly added. The resulting yellow precipitate was filtered and purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia) to give hyrtinadine A (**7**) as a yellow solid [147 mg, 0.43 mmol, 78% yield (contained one molecule of MeOH)]. For full analytical details, see the Supporting Information.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data and copies of the NMR spectra of compounds **3**, **4**, **6**, and **7**.

Acknowledgments

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