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Cross-Coupling Reactions of Indium Organometallics with 2,5-Dihalopyrimidines: Synthesis of Hyrtinadine A†

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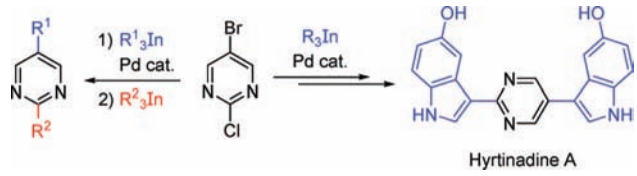
ABSTRACT



The palladium-catalyzed cross-coupling reaction of triorganoindium reagents (R_3In) with 5-bromo-2-chloropyrimidine proceeds chemoselectively, in good yields, to give 5-substituted-2-chloropyrimidines or 2,5-disubstituted pyrimidines using 40 or 100 mol % of R_3In, respectively. Sequential cross-couplings are also performed, in one pot, using two different R_3In. This method was used to achieve the first synthesis of the alkaloid hyrtinadine A. The key step was a two-fold cross-coupling reaction between a tri(3-indolyl)indium reagent and 5-bromo-2-chloropyrimidine.

The palladium-catalyzed cross-coupling reaction of indium organometallics with organic electrophiles is a useful reaction in organic synthesis.[1] In this reaction, triorganoindium compounds (R_3In, alkyl, alkenyl, aryl and alkynyl) can be efficiently coupled with aryl, benzyl, and alkenyl halides and triflates. The main features of these reactions are their high efficiency, versatility, and chemoselectivity, where all three organic groups bonded to indium are efficiently transferred to the electrophile. Additionally, organoindium reagents can be used in asymmetric cross-coupling reactions with racemic benzyl halides.[1h] Despite these appealing properties and the fact that the cross-coupling reaction is a fundamental tool in organic synthesis, the utility of indium organometallics in natural product synthesis has been demonstrated in only a limited number of examples.[2] In this communication we report the cross-coupling reactions of R_3In with 2,5-dihalopyrimidines and the application of this method to the synthesis of hyrtinadine A.

† Dedicated to Professor Antonio Mouriño on the occasion of his 60th birthday.

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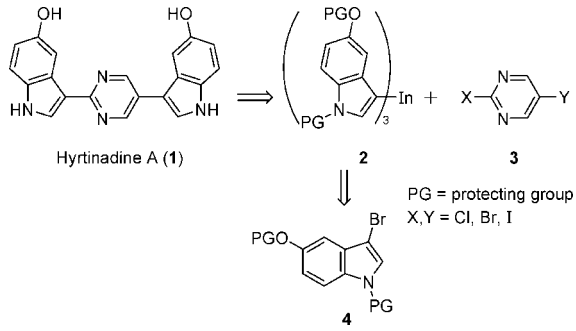
Scheme 1. Retrosynthetic Analysis for Hyrtinadine A

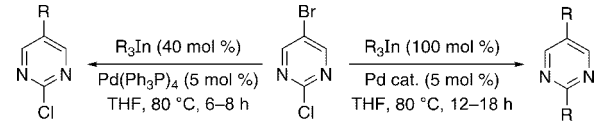


Hyrtinadine A (**1**, Scheme 1) is a novel bis-indole alkaloid with a 2,5-disubstituted pyrimidine nucleus, recently isolated from an Okinawan marine sponge of the *Hyrtios* genus.[3] This compound exhibits in vitro cytotoxic activity against murine leukemia L1210 cells (IC_{50} 1 μg/mL) and human epidermoid carcinoma KB cells (IC_{50} 3 μg/mL). Structurally related metabolites isolated from the *Hyrtios* genus are important biologically active compounds.[4]

The synthesis of hyrtinadine A was envisaged by a two-fold cross-coupling reaction between a 3-indolylindium derivative (**2**, Scheme 1) and a 2,5-dihalopyrimidine (**3**). The 3-indolylindium derivative **2** could be prepared from a 3-bromoindole (**4**). This method could also prove useful for the synthesis of other 2,5-disubstituted pyrimidines, which are attractive compounds that are of interest in materials science[5] and as intermediates in the synthesis of pharmaceuticals.[6]

Before undertaking the synthesis of hyrtinadine A, we studied the reactivity of R_3In in metal-catalyzed cross-coupling reactions with 2,5-dihalopyrimidines. In general, cross-coupling reactions with pyrimidines are quite rare.[5b–d,6,7] For this reason, we found it of particular interest to study the reactivity of R_3In with the commercially available 5-bromo-2-chloropyrimidine (**5**, Table 1). The different substitution on the pyrimidine ring should allow monosubstituted pyrimidines by single selective coupling reactions or 2,5-disubstituted pyrimidines by dicoupling reactions. Additionally, the high chemoselectivity of R_3In could also allow sequential cross-coupling reactions.[1c,f]

Table 1. Palladium-Catalyzed Cross-Coupling Reactions of Triorganoindium Reagents with 5-Bromo-2-chloropyrimidine (**5**)



entry	R	product	yield (%)[a]
1	Ph–	**6**	81
2	MeO–	**7**	83
3	S	**8**	78
4	N, OMe	**9**	62
5	Ph–≡–	**10**	70
6	Ph–	**11**	95[b]
7		**12**	80[c]
8	S	**13**	89[c]
9	N, OMe	**14**	60[c]
10	Ph–≡–	**15**	88[b]

[a] Isolated yields. [b] Reaction performed with $Pd(dppf)Cl_2$ (5 mol %) as catalyst. [c] Reaction performed with $Pd(Ph_3P)_4$ (5 mol %) as catalyst.

In our initial experiments we found that the palladium-catalyzed reaction of triphenylindium (40 mol %) with **5** using $Pd(Ph_3P)_4$ (5 mol %) under reflux for 6 h afforded 2-chloro-5-phenylpyrimidine (**6**) in 81% yield (Table 1, entry 1). This result shows that R_3In transfers the three groups to the pyrimidine ring and that the C-5 position is more reactive in cross-coupling reactions. During the catalyst screening, the best results were obtained using $Pd(Ph_3P)_4$ (5 mol %), although $Pd(dppf)Cl_2$ also gave satisfactory yields. Other aryl- and heteroarylindium reagents, such as thiophenyl-, pyridyl-, naphthyl-, and alkynylindium reagents, also reacted with 5-bromo-2-chloropyrimidine to afford the corresponding 2-chloro-5-

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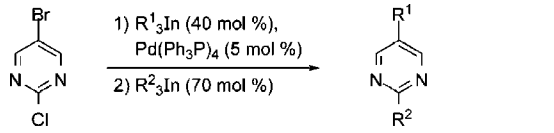
(8) The cross-coupling reaction using alkylindium reagents proceeded with lower yields and chemoselectivity, requiring longer reaction times.

substituted pyrimidines **7**−**10** in good yields (62−83%, Table 1, entries 2−5).[8]

The use of a slight excess of R_3In (100 mol %) and longer reaction times (12−18 h) led to the efficient double cross-coupling, and a variety of symmetrical 2,5-diaryl, diheteroaryl, and dialkynyl pyrimidines **11**−**15** were obtained in good yields (60−95%, Table 1, entries 6−10). It is remarkable that the two-fold cross-coupling takes place efficiently with the 2-chloro-substituted pyrimidine. Usually, cross-coupling reactions at the C-2 position of pyrimidines are performed using 2-bromo- or 2-iodo-substituted pyrimidines,[5b–d,6] compounds that are not readily available. In general, the cross-coupling reaction of 2-chloropyrimidines requires nonconventional catalysts, higher temperatures, or nonclassical methods.[7] On the other hand, the chemoselectivity shown by triorganoindium reagents is comparable to the other few organometallics reported.[6b,7a,d]

At this point we became fascinated by the possibility of performing chemoselective sequential (one-pot) cross-coupling reactions, a reaction type that is only known for Suzuki and indium couplings.[1c,f,9] The reaction of **5** with tri(4-methoxyphenyl)indium (40 mol %) in the presence of $Pd(Ph_3P)_4$ (5 mol %) for 6 h, followed by addition of triphenylindium (70 mol %), afforded after 12 h the cross-coupling product **16** in 70% yield (Scheme 2). When the

Scheme 2. Sequential Palladium-Catalyzed Cross-Coupling Reaction with **5**



5

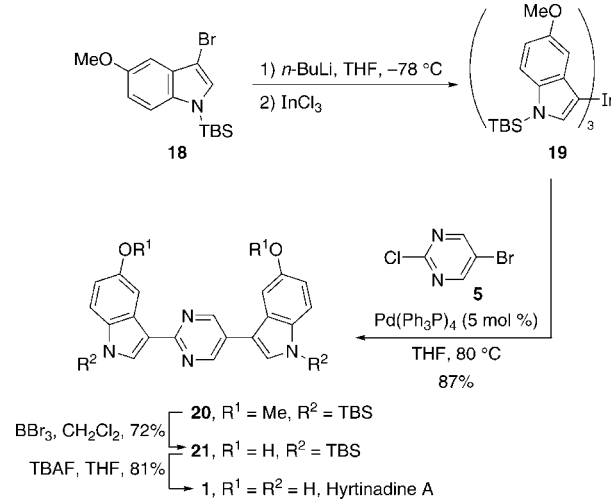
16, R^1 = 4-MeOC$_6$H$_4$, R^2 = Ph, 70%
17, R^1 = 2-thiophenyl, R^2 = PhC≡C, 57%

same sequence was performed with tri(2-thiophenyl)indium and tri(phenylethynyl)indium, compound **17** was obtained in a satisfactory 57% yield. These reactions are new examples of the very few reported precedents in sequential cross-coupling reactions and the first examples involving the use of R_3In with pyrimidines. The high chemoselectivity and the high atom efficiency shown by the indium reagents are remarkable and confirm the usefulness of these reagents for the preparation of a variety of substituted pyrimidines.

After discovering that R_3In are efficient reagents for single, double, and sequential cross-coupling reactions with 2,5-dihalopyrimidines such as **5**, we decided to apply our method to the synthesis of the natural alkaloid hyrtinadine A (**1**, Scheme 1). According to our synthetic strategy, the first step was the preparation of a functionalized 3-indolylindium reagent (**2**) from a 3-bromoindole (**4**). In this way, starting from the commercially available 5-methoxyindole, N-silylation with TBSCl followed by bromination with NBS at low temperature afforded the desired 3-bromoindole **18** in a one-pot procedure in 90% yield.[10]

The lithium−halogen exchange reaction of **18** with *n*-BuLi at low temperature, followed by addition of $InCl_3$, afforded the indolylindium reagent **19** in solution (Scheme 3). The reaction of **19** (100 mol %), with 5-bromo-2-

Scheme 3. Synthesis of Hyrtinadine A (**1**)



chloropyrimidine (100 mol %) in the presence of $Pd(Ph_3P)_4$ (5 mol %), gave after heating under reflux in THF for 18 h the 2,5-bis(indolyl)pyrimidine **20** in excellent yield (87%).[11]

With *N*,*N*′-di-*tert*-butyldimethylsilyl-5,5′-dimethylhyrtinadine A (**20**) in hand, the deprotection was assessed using two alternative routes: removal of the silyl groups followed by cleavage of the methyl ethers or vice versa. The initial cleavage of the silyl group with TBAF afforded an insoluble material that proved difficult to handle. Alternatively, treatment of **20** with BBr_3 at low temperature afforded the dihydroxyindole **21** (72% yield), which was converted into hyrtinadine A by treatment with TBAF in 81% yield.

The spectroscopic and analytical data for synthetic hyrtinadine A were almost identical to those reported by Kobayashi et al.[3] The ^{1}H NMR spectrum is fully consistent, but the ^{13}C NMR spectrum differs in the 112.0−112.6 ppm region, where we observed four peaks instead of the three signals (4 carbons) reported. This difference can probably be attributed to the NMR aquisition method or due to the small amount of the natural product isolated (1 mg).

In summary, we have shown that indium organometallics are useful reagents for chemoselective cross-coupling reactions with

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(11) The use of lower amounts of the tri(3-indolyl)indium reagent or shorter reaction times provided the monocoupling product at the C-5 position in good yields (75−85%). For further details, see Supporting Information.

halo(chloro and bromo)pyrimidines. This method was applied to the first synthesis of the natural product hyrtinadine A using the palladium-catalyzed cross-coupling reaction of indium organometallics. The synthesis, which is short and efficient, was developed in four steps (46% overall yield) from commercially available 5-methoxyindole. Further applications of this method in the synthesis of natural products are now under investigation.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for compounds prepared, and copies of NMR spectra for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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