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Communication

Indoles

SPECIAL ISSUE

Mild and Practical Indole C2 Allylation by Allylboration of in situ Generated 3-Chloroindolenines

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Abstract: C2 allylation of indole derivatives is a challenging but important transformation given the biological relevance of the products. Herein we report a selective C2 allylation strategy that proceeds via allylboration of in situ-generated 3-chloroindolenines. The reaction is mild, practical, and compatible with a wide range of C3-substituted indoles. As allylboronates are readily accessible from commercial precursors, various substituted allyl moieties can be introduced using the same protocol. To showcase the utility of this method we applied it to the synthesis of the natural product, tryprostatin B.

Introduction

Indoles have been an important target in organic synthesis ever since Baeyer reported the first synthesis of the parent heterocycle in 1866.[1] In these early days of organic chemistry, many classical methods (e.g. the Fischer, Bischler, Reissert, and Madelung indole syntheses), were developed, several of which are still widely used today.[2] The interest in this "privileged scaffold" originates in part from the numerous naturally occurring bioactive indole alkaloids (Figure 1).[3]

Unfortunately, the state of the art in indole synthesis does not always allow construction of the indole ring system with the desired substitution pattern. Consequently, research in this area has shifted focus to selective functionalization of readily available indoles.[4] While functionalization at the C3 and N1 positions is typically straightforward owing to their nucleophilic properties (in the latter case after deprotonation), and substituents at the benzenoid ring are mostly introduced during construction of the indole core, selective functionalization of the C2 position is more challenging. Radicals have been reported to react preferentially at the indole C2 position.[5] Recently, Bach et al. reported a convenient C–H activation strategy that allows alkylation and arylation at the indole C2 position.[6]

During our studies on the reactivity of indole-functionalized isocyanides,[7] we became interested in the C2 allylation of indoles *en route* to natural product scaffolds. The importance of this transformation is underlined by the numerous examples in the literature.[8] Most strategies involve either directed lithiation (either by lithium–halogen exchange or by deprotonation) of the C2 position or C–H activation by a directing group (Scheme 1).

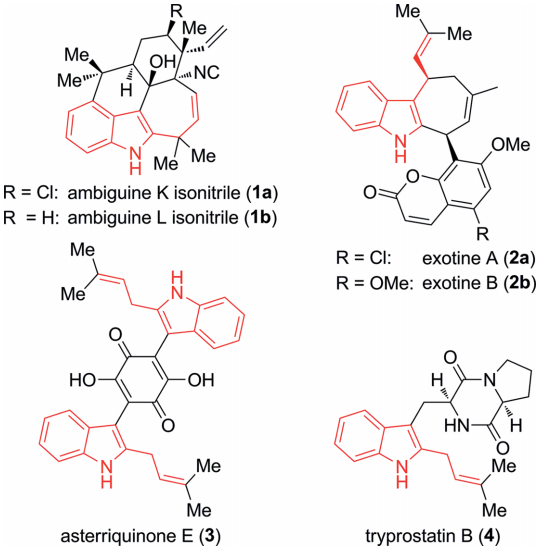

Figure 1. Selected naturally occurring indole alkaloids bearing an allyl moiety.

Although these strategies have great potential, they generally require a directing group at N1 which needs to be removed afterwards. In our pursuit of a more general and practical procedure for this selective conversion, we came across a method developed by Danishefsky et al. involving nucleophilic additions on in situ-generated 3-chloroindolenines.[9] After addition of a nucleophile to the imine, rearomatization by elimination of HCl gives back the indole. In our opinion, this method represents the most convenient strategy for the direct C2-allylation of indoles to date. However, the authors did not show the generality of the reaction with respect to allylating reagents and C3-substituted indoles. Moreover, the addition of nucleophiles (mostly toxic organotin reagents) required activation by BF_3·Et_2O, thus

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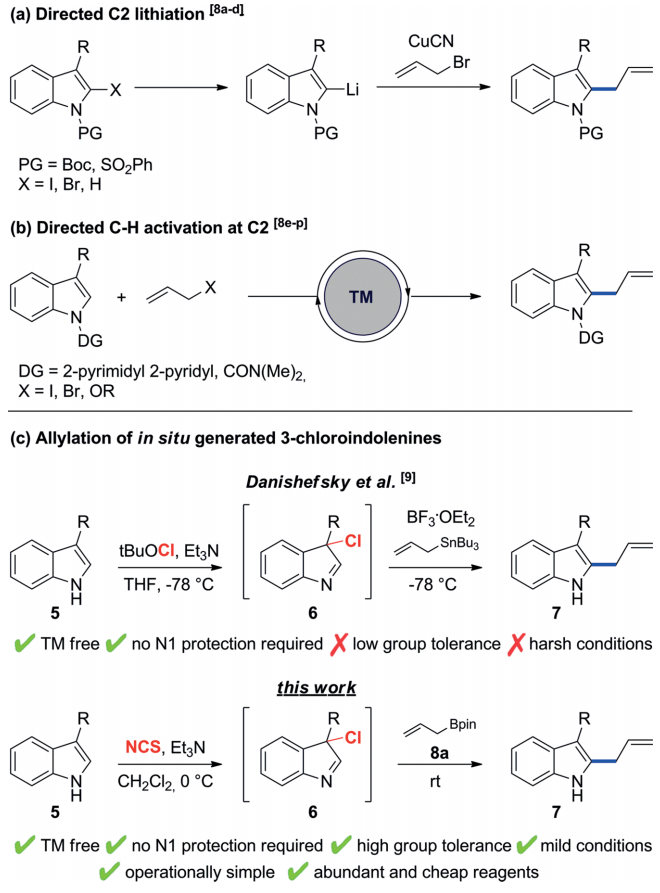


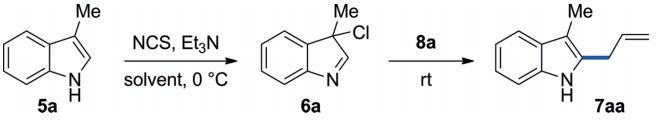
Scheme 1. C2 allylation strategies of indoles. (a) lithiation of the C2 position via either lithium–halogen exchange or deprotonation. (b) transition metal catalyzed C–H activation by use of a directing group. (c) two step chlorination of indoles followed by a allylation–rearomatization sequence.

limiting the functional group tolerance. In this communication, we present a milder and more general procedure for allylboration of 3-chloroindolenines.

Results and Discussion

In search of a mild and readily available nucleophilic allylation reagent, we arrived at allylboronic acid pinacol ester (allylBpin, **8a**). AllylBpin and related reagents effectively react with aldehydes and imines, and several convenient ways to synthesize substituted allylBpin derivatives from allylic alcohols and halides, 1,3-dienes, and allenes have been reported.[10] The reaction of 3-methylindole (**5a**) with NCS as the electrophilic chlorine reagent in the presence of triethylamine at 0 °C selectively generated 3-chloroindolenine **6a** in situ. After subsequent addition of **8a** and stirring this crude mixture for 1 h, we conveniently obtained 2-allylindole **7aa** in 44 % yield (Table 1, entry 1). We then showed that no reaction occurs in the absence of either Et_3N or NCS (entries 2 and 3).[11] Optimization of reagent stoichiometry (entries 4–7) allowed us to identify conditions affording **7aa** in 75 % isolated yield. Finally, we found that our initial choice for CH_2Cl_2 as the solvent was ideal for this reaction.

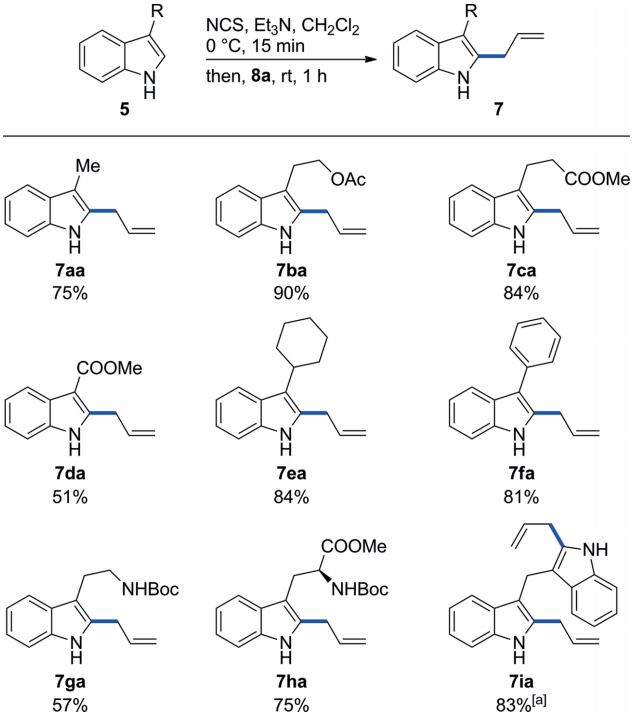
Table 1. Optimization of reaction conditions.



Entry	Solvent	Et_3N	NCS	8a	Yield
		[equiv]	[equiv]	[equiv]	[%][a]
1	CH_2Cl_2	1.5	1.1	1.5	43
2	CH_2Cl_2	0.0	1.3	1.5	0
3	CH_2Cl_2	1.5	0.0	1.5	0
4	CH_2Cl_2	1.5	1.3	1.1	72
5	CH_2Cl_2	1.5	1.3	1.3	73
6	CH_2Cl_2	1.5	1.3	1.5	75[b]
7	THF	1.5	1.3	1.5	0[c]
8	Toluene	1.5	1.3	1.5	15 %
9	MeCN	1.5	1.3	1.5	12 %

[a]) Yield determined by ^1H NMR analysis with 2,5-dimethylfuran as internal standard. [b] Isolated yield on 1.0 mmol scale. [c] The 3-chloroindolenine intermediate was not formed.

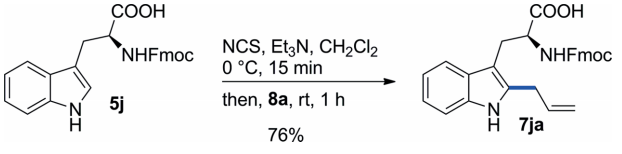
With the optimized conditions in hand, we started to evaluate the scope with regard to indoles **5**. We initially checked if unsubstituted indole would provide the desired allylated species. Unfortunately, the 3-chloroindolenine intermediate rapidly rearomatized to form 3-chloroindole. The reaction of 1,3-dimethylindole only led to decomposition under the reaction conditions. We therefore limited our selection to 3-substituted indoles (Scheme 2). As hypothesized, the mild reaction conditions tolerated a variety of functional groups. For example, the reactions of ester-functionalized substrates **5b** and **5c** afforded the corresponding allylation products **7ba** and **7ca** in very



Scheme 2. Scope of indoles **5**. Reaction conditions: indole **5** (1 mmol), Et_3N (1.5 mmol), NCS (1.3 mmol) in CH_2Cl_2 (4 mL, 0.25 M) at 0 °C; then **8a** (1.5 mmol) at r.t. [a] reagent stoichiometry adapted to bisindole **5i**.

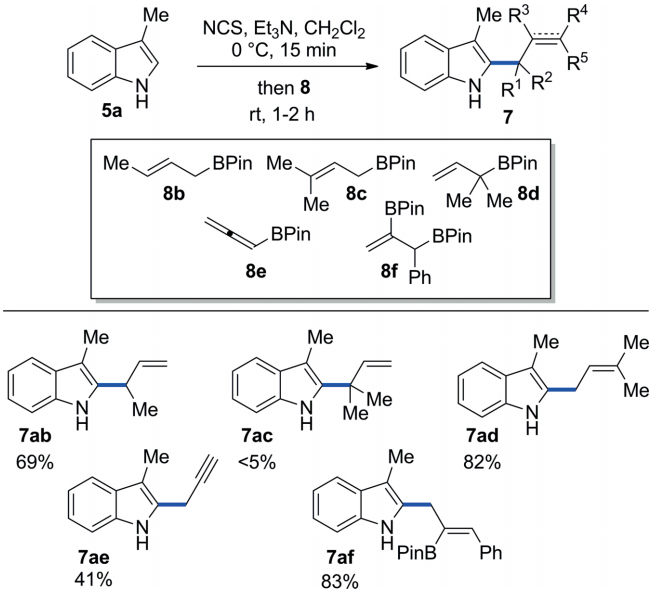
good yield. In contrast, the reaction of methyl indole-3-carboxylate (**5d**) gave product **7da** in lower efficiency. This can be rationalized by the instability of the 3-chloroindolenine intermediate, which is destabilized by the electron-withdrawing properties of the ester. On the other hand, cyclohexyl- and phenyl-substituted products **7ea** and **7fa** were obtained in good yield. We were pleased to see that also *N*-Boc-tryptamine and Boc-Trp-OMe (**5g** and **5h**) were well accepted. Finally, we successfully achieved double allylation with bis(indolyl)methane (**5i**) which was converted to bisallyl species **7ia** in high yield (83 %). Monoallylation of **5i** was also possible, however, this gave a statistical mixture of starting material, monoallylation and bisallylation products.

Encouraged by the high functional group tolerance of our method in comparison to other literature precedents for this transformation, in particular by the compatibility of Boc-Trp-OMe (to give **7ha**), we wondered whether we could even use an *N*-protected amino acid. This would be highly interesting for peptide chemistry, as the resulting C2-allylated tryptophan could be readily incorporated in a peptide sequence by standard solid-phase peptide synthesis. To our delight, the reaction of Fmoc-Trp-OH (**5j**) afforded **7ja** in 76 % yield (Scheme 3).



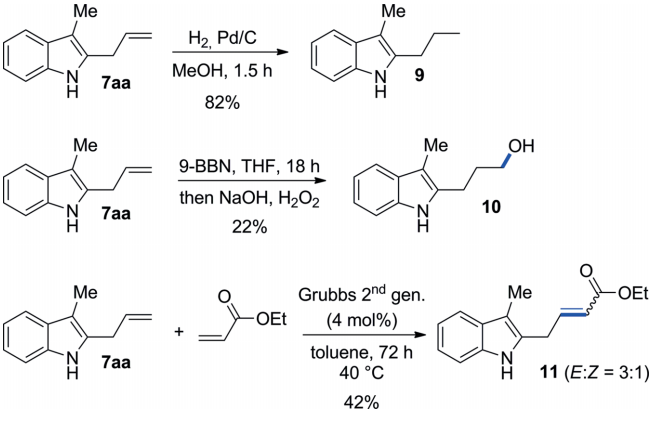
Scheme 3. C2 allylation of Fmoc-Trp-OH (**5j**).

Allylboronates are generally readily accessible from simple starting materials in one or two reaction steps. In addition, some simple allylboronates are commercially available. Moreover, they are non-toxic and easy to handle (i.e., air and temperature stable). We sought to exploit these advantages by evaluating the compatibility of a set of readily available allylboronates with our reaction manifold (Scheme 4). The reaction of **5a** with commercially available *trans*-crotylboronic acid pinacol ester (**8b**) cleanly afforded reverse crotylation product **7ab** in 69 % yield, nicely comparable to **7aa**. Encouraged by this result, we then tested prenylBpin (**8c**), however, only traces of reverse prenylation product **7ac** were obtained.[12] Possibly, the sterically encumbered γ-position is not sufficiently nucleophilic to attack the in situ-generated 3-chloroindolenine under these conditions. In contrast, C2 prenylation using **8d** proved highly compatible with our method, as we could obtain product **7ad** in 83 % yield. Unlike all other 2-allylindoles, **7ad** needed to be handled with care, as the product readily decomposed during chromatography if the silica gel was not pretreated with a base.[13] Next, we could even demonstrate the possibility to introduce a propargyl substituent at the C2 position by using commercially available allenylBpin (**8e**).[14] This significantly broadens the scope for post-modification as alkynes are versatile reagents in robust chemistry (e.g. azide-alkyne cycloaddition, Sonagashira coupling, Favorskii reaction, A3 coupling). We then successfully performed the allylation with 1,2-diboryl reagent **8f** which was conveniently prepared by diborylation of phenylallene. (β-Boryl)cinnamyl indole **7af** is again interesting for post-modification as vinylboronates are suitable reactants for Suzuki cross-coupling, Petasis reaction, or oxidation to the corresponding ketone.



Scheme 4. Scope with regard to allylic boronates **8**. Reaction conditions: indole **5a** (1 mmol), Et_3N (1.5 mmol), NCS (1.3 mmol) in CH_2Cl_2 (4 mL, 0.25 M) at 0 °C; then **8a** (1.5 mmol) at r.t. [a] 2.5 equiv of **8d** was added. [b] reaction was performed on 0.2 mmol scale.

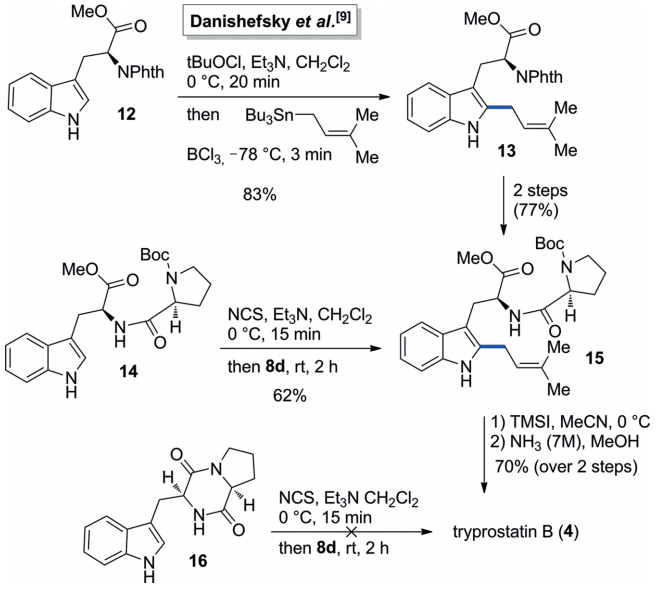
To demonstrate the versatility of the 2-allyl moiety we performed some follow-up transformations with **7aa** (Scheme 5). As expected, catalytic hydrogenation of the alkene readily furnished **9** in 82 % yield. Hydroboration with 9-BBN followed by H_2O_2 oxidation afforded anti-Markovnikov hydration product **10**, albeit in a rather modest yield. Finally, cross metathesis of **7aa** and ethyl acrylate in the presence of Grubbs' 2nd generation catalyst gave **11** in 42 % yield as a 3:1 *E*/*Z* mixture.



Scheme 5. Chemical transformations of **7aa**.

Having established the scope of this C2 allylation procedure of indoles, we wanted to demonstrate its utility in the synthesis of a natural product. We envisioned that we could efficiently access tryprostatin B (**4**) via this synthetic strategy. Danishefsky et al. already showed that their method could be applied to a five-step synthesis of this natural product starting from *N*-

phthalamide protected **12** (Scheme 6).[9] Our initial plan was to simply prenylate brevianamide F (**16**) to obtain **4** in a single step. Unfortunately, this route proved unsuccessful, not even producing a trace of **4**. We hypothesized that the diketopiperazine was not stable under the reaction conditions, resulting in a mixture of unidentified products. However, since we had shown that Boc-Trp-OMe was well tolerated in the allylation reaction, we anticipated that Boc-Pro-Trp-OMe (**14**) would be a suitable substrate for prenylation with boronate **8d**. To our delight, dipeptide **14** was smoothly converted to prenylated product **15** in 62 % yield without losing optical purity. Then, Boc deprotection by treatment with TMSI followed by base-mediated cyclization (NH_3/MeOH) as described previously by Danishefsky completed the total synthesis of tryprostatin B.



Scheme 6. Total synthesis of tryprostatin B by Danishefsky and our method.

Conclusions

In conclusion, we report a mild and practical C2 allylation strategy of 3-substituted indoles via allylboration of in situ-generated 3-chloroindolenines. The reaction is compatible with a range of functionalized indoles, providing the products in a short amount of time. We also demonstrated the compatibility with various allylic boronates, thus further expanding the range of accessible products. To show the potential of this method we synthesized tryprostatin B in a very efficient three-step sequence starting from dipeptide **13**. We believe that this method is the most efficient C2 allylation of 3-substituted indoles in terms of scope and practical use, which can be employed as either an early or a late stage modification strategy to generate valuable building blocks.

Experimental Section

To a solution of an indole **5** (1.0 equiv) in CH_2Cl_2 (0.25 M) was added triethylamine (1.5 equiv) and *N*-chlorosuccinimide (1.3 equiv) at 0 °C. After stirring for 15 minutes at this temperature allylboronate **8** (1.5 equiv) was added, followed by stirring for an additional hour at room temperature. The reaction was quenched by the addition of aq. NaOH solution (0.125 M) and stirred for an additional two hours. Then, the reaction mixture was extracted with EtOAc (3 ×), washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by silica gel column chromatography.

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Keywords: Indoles · Allylation · Boron reagents · Heterocycles · Synthetic methods

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