C–H Activation

DOI: 10.1002/ange.200705005

Synthesis of Rhazinicine by a Metal-Catalyzed C–H Bond Functionalization Strategy**

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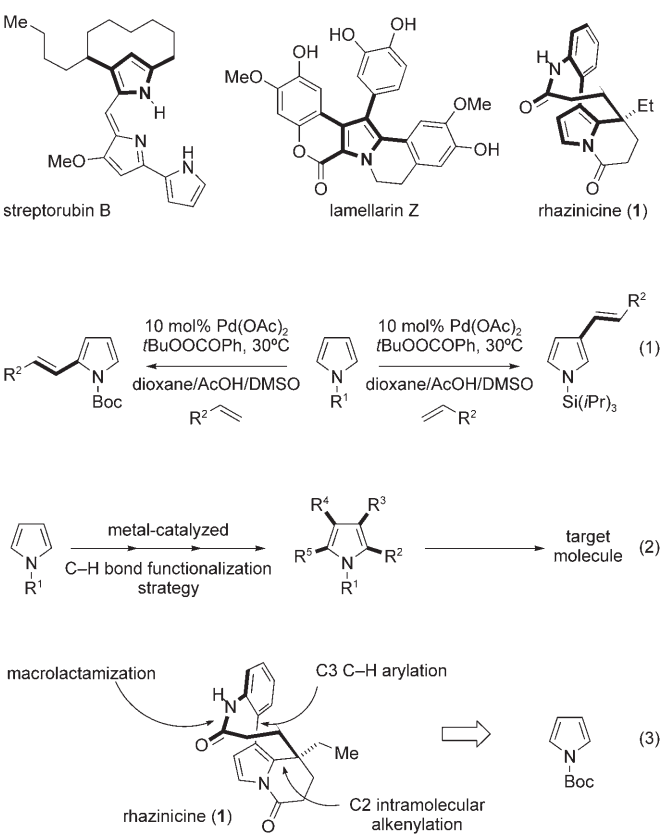
The chemical synthesis of natural products has been revolutionized by the development of metal-catalyzed coupling reactions. As part of these advances the successful assembly of complex molecules by cross-coupling tactics exploits the reactivity of strategically installed metal-active functional groups in the key bond-forming events.[1] The advance of metal-catalyzed C–H activation technology suggests that similar transformations are possible without the need to prefunctionalize the parent molecules.[2,3] There are many methodological advances that highlight the potential efficacy of these processes in synthesis. However, there are few examples of the application of such catalytic tactics in total synthesis, possibly because of complications with both the harsh reaction conditions and the selectivity and stability issues associated with the more complex substrates required for these purposes. However, direct C–H functionalization tactics could have an impact in streamlining natural product synthesis, so development in this area represents an important goal for synthetic chemists.[4] We report the first synthesis of the pyrrole alkaloid rhazinicine (**1**) by using a short synthetic strategy that demonstrates how iterative and regioselective metal-catalyzed C–H bond functionalizations can positively influence complex molecule assembly.

Molecules containing a diversely substituted pyrrole nuclei embedded within a complex architecture are common among structures found in nature (Scheme 1). Rhazinicine (**1**)[5a,b] is part of a family of natural products (rhazinilams) that mimic the cellular effects of pacitaxel.[5c] Although the total synthesis of rhazinicine is not known, the related rhazinilam structure has inspired a number of syntheses[4c–d,6] which showcased new methods for key bond constructions and enabled structure-activity studies into its biological properties.[5c,d] The striking feature of the rhazinilams is the embedded pyrrole unit that supports a tetrahydroindolizine ring system bearing a quaternary center, a heterobiaryl unit, and a nine-membered lactam. In addition, **1** displays a pyrrole amide motif that is likely to affect the reactivity and stability of the heteroarene core.



Scheme 1. Natural products with embedded pyrrole motifs and synthesis strategy of rhazinicine (**1**). R^1 = Boc or TIPS.

The synthesis of a highly substituted pyrrole motif is often beset by problems associated with regioselectivity, high reactivity, and oxidative instability in the transformations that will decorate the heteroarene nucleus. Towards this end, we recently reported an oxidative Pd^{II}-catalyzed C–H alkenylation of pyrroles,[7b] wherein we were able to control the regioselectivity depending on the characteristic of the protecting group on the N atom; the *tert*-butylcarboxy (Boc) group directed alkenylation to C2 and the triisopropylsilyl (TIPS) group directed alkenylation to C3 [Eq. (1)].

In considering rhazinicine as our target molecule, we questioned whether a metal-catalyzed C–H bond functional-

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[**] We gratefully acknowledge GSK and EPSRC for studentships (E.M.B.), the Royal Society for a University Research Fellowship (M.J.G.), Philip & Patricia Brown for a Next Generation Fellowship (M.J.G.), and the EPSRC Mass Spectrometry service (University of Swansea). We are also grateful to Prof. Steven Ley for valuable support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

InterScience
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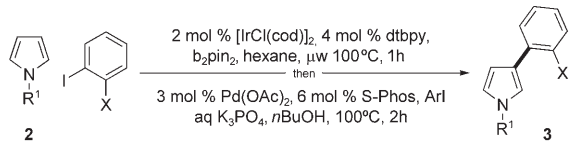
ization strategy could expedite the assembly of natural products that contain a highly substituted pyrrole core [Eq. (2)]. We envisioned that the key structural architecture of **1** could be directly installed from a simple pyrrole nucleus by a metal-catalyzed C–H bond arylation to produce the heterobiaryl framework, and subsequent oxidative Pd^{II}-catalyzed pyrrole C–H bond cyclization to form the indolizinone structure [Eq. (3)]. This strategy would facilitate the elaboration of the pyrrole nucleus in comparison to the conventional metal-catalyzed cross-coupling reactions, and reinforce the utility of catalytic C–H bond functionalization as a powerful tactic in natural product synthesis.

For the synthesis of **1** [Eq. (2)], we were confident that we could use our approach to control the site of arylation, although it was not clear whether subsequent C–H bond functionalizations could be similarly directed. Therefore, our initial investigation focused on the development of a C–H bond arylation reaction analogous to our previous alkenylation studies;[7b] however, despite our best attempts we were unable to effect such a process suitable for rhazinicine (**1**). Instead, we adopted the Ir^{I}-catalyzed C–H borylation, developed by the groups of Smith–Malezcka and Hartwig–Miyuara,[8] to furnish the desired pyrrole nucleus and then performed a Suzuki coupling. When testing this strategy with the Hartwig–Miyaura conditions[8b,c] (Table 1) we found that a

Table 1: Investigation of a regioselective one-pot C–H arylation process.[a]

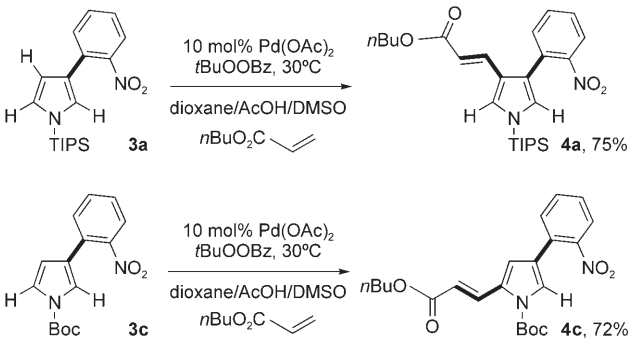


Entry	R^1	X	C3:C2	Product	Yield [%]
1	iPr_3Si	NO_2	>99:1	**3a**	82
2	iPr_3Si	H	>99:1	**3b**	68
3	Boc	NO_2	>99:1	**3c**	78

[a] B_2pin_2 = bis(pinacolato)diboron; cod = cycloocta-1,5-diene; dtbpy = 2,6-di-*tert*-butyl-4-methylpyridine; S-Phos = 2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl; μw = microwave.

range of N-protected pyrroles underwent microwave-assisted Ir^{I}-catalyzed C–H borylation, which was exclusively selective for the C3 position of the pyrrole ring in the presence of both *N*-Boc and *N*-TIPS groups. Moreover, the Suzuki coupling[9] was performed as part of the same transformation by directly adding the required components to the reaction mixture, thus enabling the isolation of **3a–c** in a single step from **2a–c** in excellent yield (Table 1).

The next step in the model studies for an iterative functionalization approach to rhazinicine (**1**), was to assess the selectivity of the subsequent Pd^{II}-catalyzed C–H alkenylation. The reaction with TIPS-protected pyrrole **3a** led to C–H bond alkenylation at the C4 position to give **4a**, in accordance with our hypothesis (Scheme 2).[7b] Boc-protected pyrrole **3c** could potentially react at either the C2 or the C5 position under these reaction conditions. When we tested the

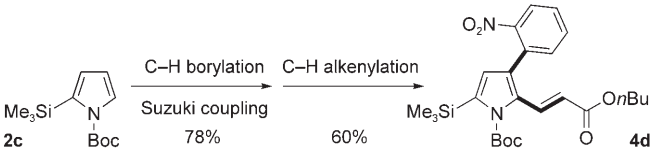


Scheme 2. Second step of the iterative pyrrole C–H bond functionalization strategy. Bz = benzoyl.

Pd^{II}-catalyzed C–H alkenylation on **3c**, it reacted predominantly at the C5 position to form **4c** (9:1 C5:C2) presumably because the C2 position is more sterically congested. Notably, the nature of the aryl group at C3 did not influence the selectivity (2-NO_2Ph, Ph, and 4-NO_2Ph gave the same C5 alkenylation products). Whereas this tactic provided a straightforward method for a directed synthesis of 3,4- and 3,5-disubstituted pyrrole derivatives, it would not be amenable for the assembly of the 2,3-disubstituted pyrrole motif of **1**.

We therefore considered the installation of a temporary blocking group for the C5 position. Upon closer examination of other rhazinilam syntheses we noticed that in all cases the route required the addition of a group to shield the C5 position of the pyrrole ring. Although not explicitly explained, we propose that this step prevents competing oxidative pyrrole dimerization reactions, which is in line with our own observations regarding the behavior of these heteroarenes. We installed a $SiMe_3$ (TMS) group at C5 to prevent the potential side reactions and to provide a handle for controlling the selectivity of the reaction.

The TMS-protected pyrrole **2c** underwent a one-pot Ir^{I}-catalyzed borylation and Suzuki coupling to form the desired pyrrole isomer with arylation at C3 (Scheme 3). Presumably,



Scheme 3. Iterative C–H bond functionalization to 2,3-difunctionalized pyrroles.

the $SiMe_3$ group at C5 and the *N*-Boc motif cooperatively directed borylation to C3, and hence, arylation to the C3 position. In turn, C–H bond alkenylation is forced to the C2 position; it proceeded in good yield to form **4c**, although the reaction required higher temperatures because of the more hindered nature of this position. This model iterative coupling strategy now enables the formation of the 2,3-disubstituted pyrrole isomer required for **1**.

Therefore, confident that we could control the functionalization of pyrrole rings, we applied this tactic to our

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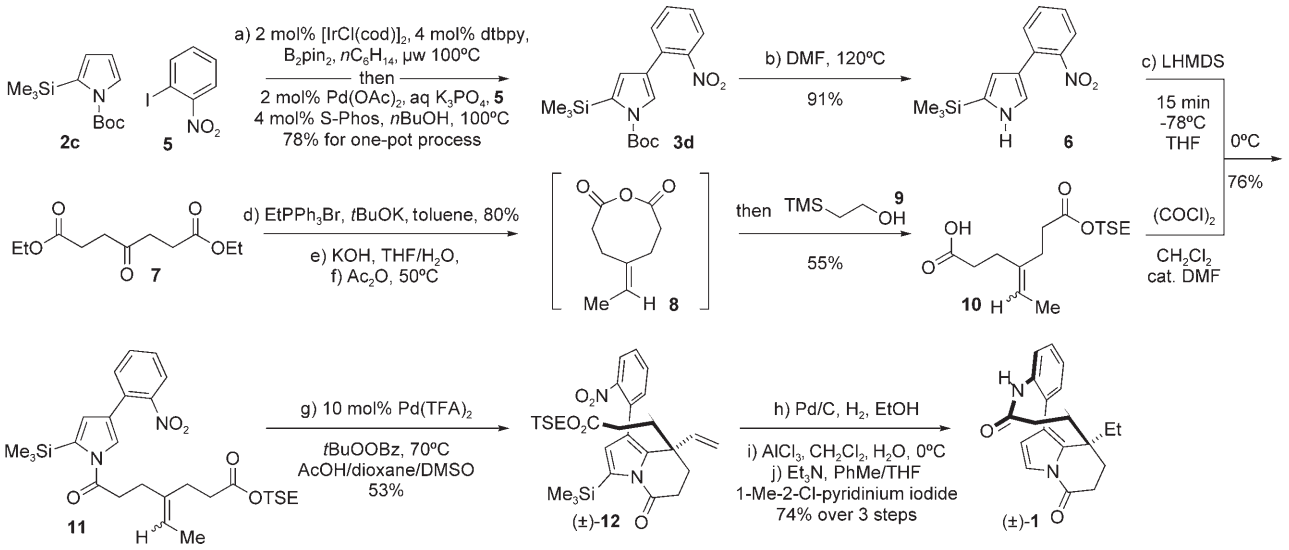

Scheme 4. The synthesis of rhazinicine. LHMDS = lithium hexamethyldisilazide; TSE = 2-trimethylsilylethyl; TFA = trifluoroacetate.

synthesis of **1** and began with a one-pot microwave-assisted Ir^{I}-catalyzed C–H borylation and Suzuki coupling on **2d**, which formed **3d** in 78% yield as a single isomer (Scheme 4). Removal of the Boc group under thermal conditions delivered **6** in excellent yield. With biaryl **6** in hand we turned our attention to the development of a concise synthesis of the remaining framework. The synthesis began with a Wittig ethenylation of diester **7** that proceeded in good yield. Ester hydrolysis (80% from **7**) and subsequent treatment of the crude diacid with Ac_2O formed the eight-membered ring anhydride **8** in situ. Subsequent reaction with **9** formed monoester **10** in 55% yield over two steps as an inseparable (but inconsequential) mixture of geometric alkene isomers. Fragment union to deliver **11** was affected by the acylation of the lithium pyrrolate anion of **6** with the acid chloride of **10** in 76% yield.

With the full carbon skeleton in place we were set for the key oxidative Pd^{II}-cyclization reaction that would assemble the architecture of **1**. By using conditions adapted from our intermolecular alkenylation studies we found that when **11** was treated with 10 mol% $Pd(TFA)_2$ catalyst and *t*BuOOBz as the oxidant, the reaction formed (±)-**12** in 53% yield, installing the tetrahydroindolizine ring system and all quaternary carbon centers as a single regioisomer at the desired C2 position of the pyrrole unit.[10] Interestingly, the reaction proceeded better with the more active $Pd(TFA)_2$ catalyst than with $Pd(OAc)_2$, which is perhaps a reflection of the lower reactivity of the sterically hindered C2 position of the pyrrole ring. Notably, despite the potential pitfalls associated with catalytic oxidative pyrrole reactions,[4g] the Pd^{II}-catalyzed cyclization on this system successfully formed the embedded heteroarene architecture in good yield for this delicate transformation. The final steps involved hydrogenation of the NO_2 and alkene groups in (±)-**12** and subsequent $AlCl_3$ mediated cleavage of the 2-trimethylsilylethyl and $SiMe_3$ groups to give the corresponding acid. When treated with Mukaiyama's reagent, the acid underwent macrolactamization to (±)-**1** to complete the synthesis of rhazinicine.

In summary, we have completed the first total synthesis of rhazinicine in 11 steps from commercial materials by using a short synthetic strategy that demonstrates how iterative metal-catalyzed C–H bond functionalizations can positively influence complex molecule assembly. The catalytic strategy forms the key part of our synthesis wherein we have utilized a one-pot Ir^{I}-catalyzed C–H borylation and Suzuki coupling sequence, and developed an oxidative Pd^{II}-catalyzed pyrrole C–H bond cyclization to rapidly deliver the natural product. We are currently exploring the utility of these transformations in other target syntheses and these results will be reported in due course.

Received: October 29, 2007
Revised: January 5, 2008
Published online: March 12, 2008

Please note minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.

Keywords: C–H activation · natural products · palladium

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[10] The product of the Pd^{II}-catalyzed cyclization, (±)-**12**, contains a new quaternary stereogenic center and a biaryl axis. The ^{1}H NMR spectra of (±)-**12** showed the presence of two interconverting rotamers that are maintained until macrocyclization, whereupon they are presumably dynamically resolved to form (±)-**1**.

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