Domino Cyclization

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A Palladium(II)-Catalyzed C–H Activation Cascade Sequence for Polyheterocycle Formation**

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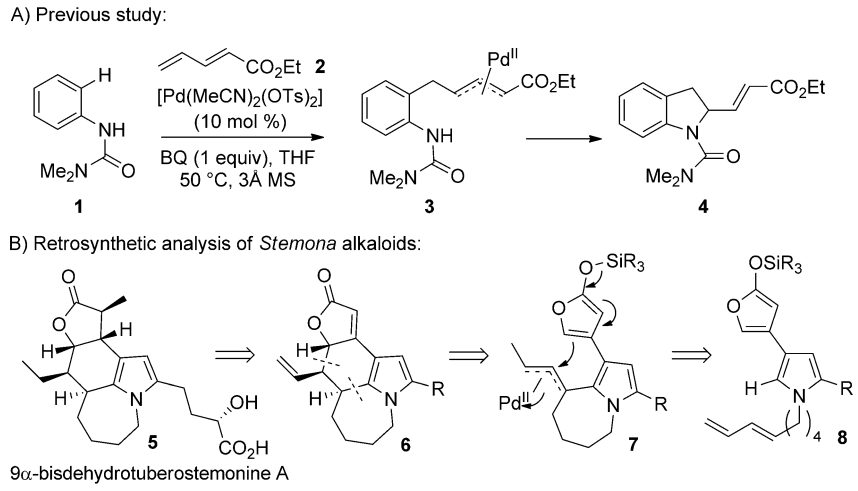
Abstract: *Polyheterocycles are found in many natural products and are useful moieties in functional materials and drug design. As part of a program towards the synthesis of Stemona alkaloids, a novel palladium(II)-catalyzed C–H activation strategy for the construction of such systems has been developed. Starting from simple 1,3-dienyl-substituted heterocycles, a large range of polycyclic systems containing pyrrole, indole, furan and thiophene moieties can be synthesized in a single step.*

Polyheterocycles are frequently found as the cores of both natural products[1] and drug molecules.[2] Furthermore, the extended heteroaromatic conjugated systems that these compounds can contain make them of interest as functional materials.[3] It is important therefore that new, efficient methodologies for their construction are developed. In recent decades, the selective coupling of unactivated C–H bonds under metal catalysis has been studied extensively owing to its potential to decrease the step count in syntheses and reduce the cost and waste of a process.[4] There has been great progress in the selective metal-catalyzed C–H activation of heterocycles and their subsequent use in arylation[5] and alkenylation[6] reactions. Alkenylation has mostly been carried out with simple alkenes in intermolecular reactions or through cyclizations. The potential for the heteroarylation of 1,3-dienes through novel difunctionalization reactions, however, remains relatively underexploited.

We previously reported the 1,2-carboamination of electron-deficient dienes with aryl ureas as both a directing group for *ortho* C–H activation and an internal nucleophile to trap the π-allyl system formed after carbopalladation (Scheme 1 A).[7] Extending this idea to heterocycle-containing substrates bearing a pendant diene, such as **8**, we identified a plausible and efficient route to the stenine group of *Stemona* alkaloids (Scheme 1 B).[8] In this envisioned route, palladium(II)-catalyzed C–H activation of the pyrrole ring in **8**, followed by diene cyclization to the π-allyl system **7** and subsequent nucleophilic capture by the internal siloxyfuran, would give access to the stenine ring system **6** in a single reaction from **8**. As the methodology required for such an efficient transformation is not currently available, we herein describe significant progress towards the synthesis of the stenine ring system through this cascade sequence by demonstrating a general and effective method for the synthesis of polyheterocycles.

We began our investigations by examining the cyclizations of the furyl–pyrrole systems **9a** and **9b** (Table 1). With a stoichiometric amount of $[Pd(MeCN)_2Cl_2]$, the desired cyclization did indeed take place in both cases to give the fully aromatic congeners **11a,b** in low yield (probably by the dehydrogenation of **10a,b** by Pd^{II}). The formation of the seven-membered ring in **11b** ($n=4$) was significantly less effective than the formation of the six-membered ring in **11a** ($n=3$; Table 1, entries 1 and 2). When 1,4-dioxane was used instead of THF as the solvent, the reaction could be carried out at the higher temperature of 90 °C, which led to a significant increase in the yield of **10a** and **11a** (Table 1, entry 3).



Scheme 1. A) Palladium(II)-catalyzed 1,2-carboamination of dienes via a π-allyl intermediate.[7] B) Retrosynthetic analysis of 9α-bisdehydrotuberostemonine A on the basis of a C–H activation cascade sequence. BQ = benzoquinone, MS = molecular sieves, Ts = *p*-toluenesulfonyl.

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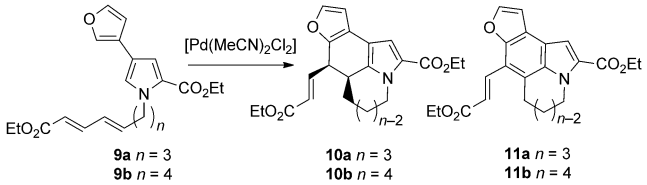
Table 1: Initial studies with stoichiometric $[Pd(MeCN)_2Cl_2]$.[a]



9a $n = 3$ **9b** $n = 4$ **10a** $n = 3$ **10b** $n = 4$ **11a** $n = 3$ **11b** $n = 4$

Entry	n	Solvent	T [°C]	t [h]	**10** [%]	**11** [%]
1[b]	3	THF	60	20	12	14
2[b]	4	THF	60	20	0	6
3[c]	3	1,4-dioxane	90	2.5	32	19

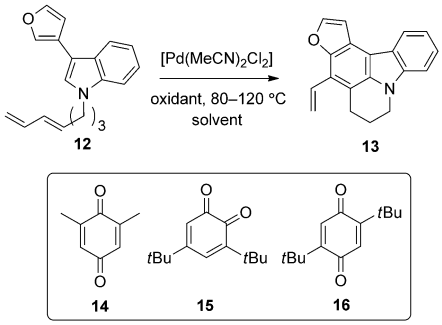
[a] Reaction conditions: **9** (210–250 μmol), $[Pd(MeCN)_2Cl_2]$, anhydrous solvent (2.5 mL), N_2 atmosphere. [b] $[Pd(MeCN)_2Cl_2]$ (1.1 equiv). [c] $[Pd(MeCN)_2Cl_2]$ (1.0 equiv).

Initial attempts to render this reaction catalytic with respect to palladium suffered from the susceptibility of the furan moiety to undergo conjugate addition to the benzoquinone (BQ) oxidant used. The use of non-quinone-based oxidants unfortunately did not lead to substantial product formation. A solution was found in the use of oxidants **14**–**16** featuring increased steric bulk around a quinone core.[9]

As the use of furylpyrrole-based starting materials led to mixtures of products, an alternative cyclization substrate was sought. In preliminary studies with the indole **12** (Table 2), only the fully oxidized product **13** was ever observed, thus indicating that the oxidation of the intermediate dihydro ring system (analogous to **10**) was more facile than in the case of pyrroles. 2,6-Dimethylbenzoquinone (**14**) and 3,5-di-*tert*-butyl-*o*-benzoquinone (**15**) were both found to effect catalytic turnover of palladium (Table 2, entries 1 and 2); however, during reactions with **14** a side product was observed that indicated addition of the furan moiety to the quinone was still taking place. As the initial cyclized product (analogous to **10**) was undergoing oxidation, it followed that two equivalents of **15** would be required for complete conversion. An increase in the amount of oxidant used to two equivalents increased the yield marginally from 17 to 27% but depleted the amount of starting material recovered (Table 2, entry 3). A further increase in the amount of oxidant used did not lead to an additional increase in product yield (Table 2, entry 4).

A substantial increase in productivity was observed when the solvent was switched to DMF (Table 2, entry 5) and the temperature was increased to 120°C (entry 6). Other quinones with sufficient bulk (e.g. **16**; Table 2, entry 8) gave the product in comparable yields. However, the key parameter to the success of the sequence was a short reaction time, typically under half an hour, at an elevated temperature. The most consistent results were obtained when the reaction flask containing substrate, catalyst, oxidant, and solvent was heated by rapid immersion in a preheated oil bath. Slow heating of the reaction mixture up to the required temperature resulted in poorer yields and mass recovery. The reaction concentration and catalyst loading were also significant, and optimization studies showed that a concentration of 0.02 M and a 5 mol% loading of the catalyst $[Pd(MeCN)_2Cl_2]$ led to consistently high-yielding reactions at the short contact

Table 2: Optimization studies.[a]



Entry	Catalyst [mol%]	Oxidant (equiv)	Solvent	T [°C]	t	**13** [%]
1	10	**14** (1)	dioxane	90	5 h	16
2	10	**15** (1)	dioxane	90	25 h	17
3	10	**15** (2)	dioxane	90	18 h	27
4	10	**15** (4)	dioxane	90	22 h	23
5	10	**15** (2)	DMF	80	1 h	46
6	10	**15** (2)	DMF	120	20 min	60
7[b]	10	**15** (2)	DMF	120	20 min	54
8	10	**16** (2)	DMF	120	25 min	61
9[c]	1	**15** (2)	DMF	120	1.5 h	60
10[c,d]	10	**15** (2)	DMF	120	30 min	82
11[c,e]	5	**15** (2)	DMF	120	25 min	81

[a] Reaction conditions, unless otherwise specified: **12** (125 μmol, 0.1 M), anhydrous solvent, N_2 atmosphere. [b] The reaction was carried out in an open flask with reagent-grade dimethylformamide (DMF). [c] The reaction was carried out with 1 mmol of **12**. [d] The reaction was carried out at a 0.01 M concentration of **12**. [e] The reaction was carried out at a 0.02 M concentration of **12**.

times required at 120°C (Table 2, entry 11). It was pleasing to note that unlike in our previous carboamination studies, electron-withdrawing substituents were not necessary for diene functionalization.

Initial exploration of the scope of the reaction under these optimized conditions focused on varying the substituent on the indole ring (Table 3, entries 1–9). In general, electron-rich and electron-neutral systems performed better than electron-poor systems. The reaction is tolerant of halogen substituents (Table 3, entries 4 and 5) as well as esters, nitriles, and aldehydes (entries 6–8). The vinyl-substituted substrate **31** gave the desired product in moderate yield (Table 3, entry 9). Extension of the alkyl chain to four CH_2 units severely affected the cyclization, which gave only very small quantities of the *Stemona* alkaloid related product **34** (Table 3, entry 10). The application of this methodology to seven-membered-ring formation is a limitation that is currently under investigation. Chain branching in the alkyl tether is tolerated (Table 3, entry 11), although a *gem*-dimethyl group adjacent to the reactive diene center greatly impeded reactivity (entry 12).

Pleasingly, this reaction proved general in terms of the heterocycles present in the substrate, thus enabling rapid access to a range of novel structures. Thiophene- and pyrrole-containing products were readily obtained in good yield (Table 3, entries 13 and 14), and both furan and indole moieties can be replaced by pyrrole units, as in **43** (entry 15). One limitation appears to be the use of phenyl rings as the π-

Table 3: Scope of the reaction.[a]

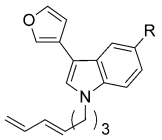
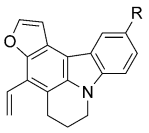
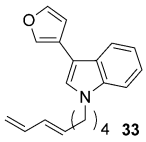
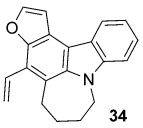
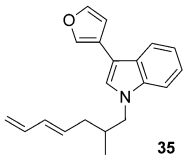
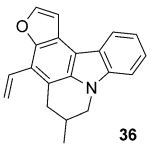
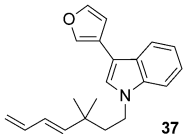
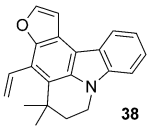
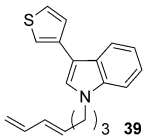
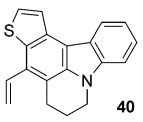
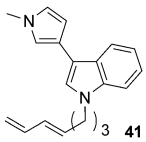
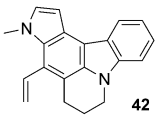
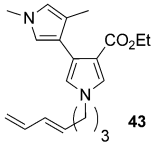
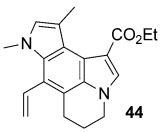
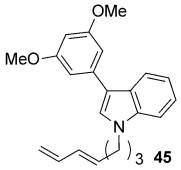
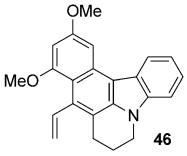
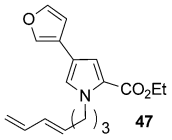
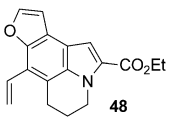
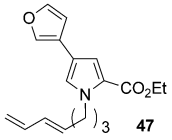
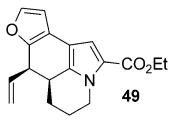
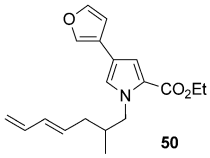
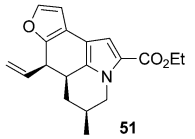
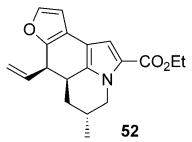
Entry	Starting material	Product(s)	Yield [%]
			
1	**12** R = H	**13** R = H	81
2	**17** R = OMe	**18** R = OMe	79
3	**19** R = Me	**20** R = Me	71
4	**21** R = F	**22** R = F	55
5	**23** R = Cl	**24** R = Cl	52
6	**25** R = CO_2Me	**26** R = CO_2Me	32
7	**27** R = CN	**28** R = CN	30
8	**29** R = CHO	**30** R = CHO	49
9	**31** R = $CH{=}CH_2$	**32** R = $CH{=}CH_2$	26
10	 **33**	 **34**	1
11	 **35**	 **36**	82
12	 **37**	 **38**	12
13	 **39**	 **40**	57
14	 **41**	 **42**	49
15	 **43**	 **44**	39
16	 **45**	 **46**	4
17	 **47**	 **48**	19

Table 3: (Continued)

Entry	Starting material	Product(s)	Yield [%]
18[b]	 **47**	 **49**	84
19[b]	 **50**	 **51**  **52**	77 (d.r. 3:2)

[a] Reaction conditions: starting material (100 μmol–1.46 mmol, 0.02 M), $[Pd(MeCN)_2Cl_2]$ (5 mol%), **15** (2 equiv), anhydrous DMF, N_2, 120°C. Reactions proceeded to completion as observed by TLC. See the Supporting Information for scale and reaction times. [b] Oxidant **16** (1.1 equiv) was used in place of **15**.

allyl-trapping partner; even the electron-rich system **45** gave the product in only 4% yield (Table 3, entry 16).

We next revisited the pyrrole–furan substrates. Disappointingly, these substrates performed less well than expected under the optimized conditions. For example, in Table 3, entry 17, the cyclized system **48** was obtained in only 19% yield. Upon examination of this reaction mixture, the unusual side product **53** (Figure 1) was identified. This compound is

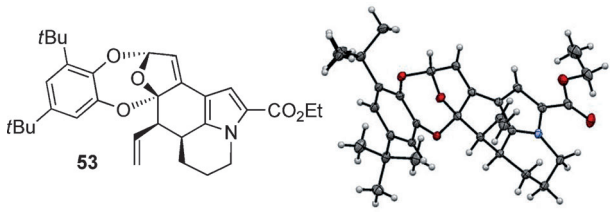


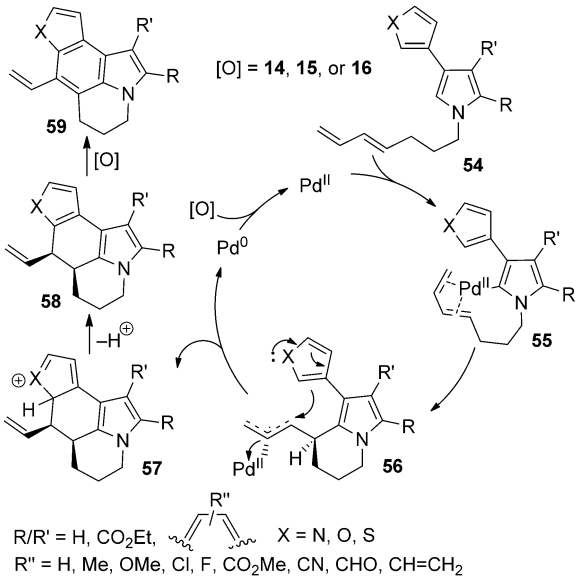
Figure 1. X-ray crystal structure of side product **53**.

seemingly formed by the interception of a reaction intermediate by a molecule of the *ortho*-benzoquinone **15**, and its formation is still not well understood.[10] Similar side products incorporating *o*-BQ **15** were not identified in other low-yielding cyclizations.

As the production of **53** depended upon the *o*-BQ **15**, the reaction was carried out again with just 1.1 equivalents of *p*-BQ **16**. This quinone had been found to operate similarly in the previous screening (Table 2, entry 8). Pleasingly, the *non-oxidized* product **49** was obtained almost exclusively and isolated in 84% yield; only a trace amount (ca. 1%) of the fully oxidized analogue was observed (Table 3, entry 18). It

had already been observed that mixtures of oxidized and non-oxidized products could be obtained with similar systems (**9a**, for example), but this was the first time that clean conversion into the non-oxidized product, containing two adjacent stereocenters, had been observed. Furthermore, the cyclization appears to be highly diastereoselective during the central-ring-forming process (no other diastereomer of **49** was detected). It was found that a loading of quinone **16** at just 1.1 equivalents gave optimal yield and reproducibility. The methyl-branched diene **50** was also shown to cyclize efficiently (Table 3, entry 19). Although once again the stereoselectivity in the formation of the central ring was excellent, the methyl group unfortunately afforded little diastereoselectivity during the initial pyrrole/diene cyclization step.

A plausible mechanism for this cascade sequence is proposed in Scheme 2. The heterocycles **54** undergo C–H



Scheme 2. Proposed mechanism for the palladium(II)-catalyzed cyclization of **54**. Ligands have been omitted for clarity.

insertion, possibly assisted by prior coordination of the Pd^{II} center to the diene, to give a Pd^{II} species **55**. Cyclization by *syn*-carbometalation of the diene to form the π-allyl system **56** is followed by attack of the second heterocyclic ring onto this electrophilic complex to give **57** with the release of Pd^0. Loss of a proton from **57** then leads to rearomatization of the heterocyclic ring and the formation of **58**.

Depending on the nature of the substrate, or the oxidant used, **58** can either be isolated or react further. In the majority of cases, further oxidation of the central ring in **58** is facile, and the fully aromatized systems **59** are isolated. This oxidation is clearly a rapid process, as decreasing the amount of added quinone did not result in the isolation of significant amounts of **58**: merely incomplete reactions and lower yields of **59** were observed.

In conclusion, we have developed novel methodology for the rapid construction of a large range of polyheterocycles from simple starting materials by a palladium(II)-catalyzed C–H activation/cascade sequence. Present studies are concerned with improvement of the yields for seven-membered-ring formation and the application of this transformation in the synthesis of *Stemona* alkaloids.

Keywords: C–H activation · domino reactions · heterocycles · homogeneous catalysis · palladium

[1] See, for example: a) T. F. Molinski, *Chem. Rev.* **1993**, *93*, 1825 – 1838; b) R. A. Pilli, M. C. F. de Oliveira, *Nat. Prod. Rep.* **2000**, *17*, 117 – 127; c) A. Kornienko, A. Evidente, *Chem. Rev.* **2008**, *108*, 1982 – 2014; d) H. Fan, J. Peng, M. T. Hamann, J.-F. Hu, *Chem. Rev.* **2008**, *108*, 264 – 287; e) S. R. Walker, E. J. Carter, B. C. Huff, J. C. Morris, *Chem. Rev.* **2009**, *109*, 3080 – 3098; f) R. A. Pilli, G. B. Rosso, M. C. F. de Oliveira, *Nat. Prod. Rep.* **2010**, *27*, 1908 – 1937; g) V. Sridharan, P. A. Suryavanshi, J. C. Menéndez, *Chem. Rev.* **2011**, *111*, 7157 – 7259; h) J.-F. Hu, H. Fan, J. Xiong, S.-B. Wu, *Chem. Rev.* **2011**, *111*, 5465 – 5491.

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Communications

Domino Cyclization

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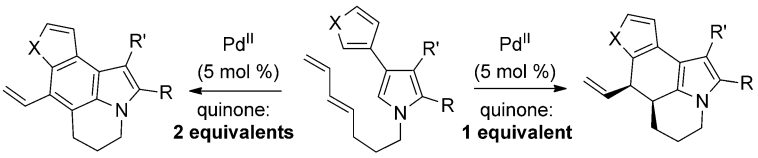
A Palladium(II)-Catalyzed C–H Activation Cascade Sequence for Polyheterocycle Formation



Don't overdo it: A palladium(II)-catalyzed C–H activation cascade sequence for the synthesis of polyheterocycles is reported. Aromatization of the initially formed dihydro species occurred with a quinone oxidant. In some cases the use of one equivalent of the oxidant enabled isolation of the dihydro species as a single isomer (see scheme; X = NMe, O, S).

