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Concise Synthesis of (±)-Rhazinilam through Direct Coupling

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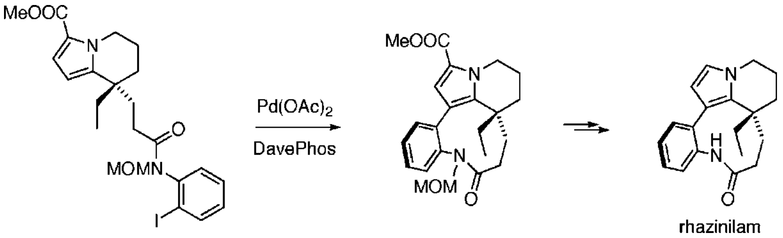
ABSTRACT



A concise synthesis of rhazinilam through direct, palladium-catalyzed, intramolecular coupling is described.

Transition-metal-catalyzed cross-couplings have emerged as one of the most powerful tools in synthesis.[1] Common logic holds that one coupling partner bears a functional group permitting oxidative addition, whereas the other component engages in transmetalation, e.g., as a stannane, borate, organocopper, organomagnesium, or organozinc species.

However, over recent years it has transpired that certain nucleophilic arenes can engage in cross-couplings without the need for prior functionalization as an organometallic species. Although these formal Heck couplings to arenes have been occasionally described,[2] the generality of this concept has not been widely recognized. With the advent of new catalysts and the systematic exploration of conditions this perception has changed, and numerous inter- and intramolecular examples for this reactivity have been recently reported.[3]

In 2002, we described the application of "direct" palladium-catalyzed biaryl coupling in the total synthesis of a natural product, the IL-8 inhibitor frondosin B (**3**) (Scheme 1).[4] Intramolecular coupling of benzofuranyl triflate **1** gave tetracycle **2**, which was converted to the natural product in a few steps. Recently, Fagnou reported an approach to allocolchicine (**6**) based on the direct intramolecular coupling of aryl chloride **4** to afford biphenyl derivative **5**.[5]

We now wish to report an exceptionally concise synthesis of (±)-rhazinilam (Figure 1) that further demonstrates the synthetic power of direct couplings to nucleophilic (hetero)-arenes.

Rhazinilam (**7**)[6a,b] and its congener rhazinal (**8**)[6c] have attracted considerable attention in both the biological and synthetic communities.[7] Similar to taxol and vincristine, rhazinilam was found to interfere with tubulin polymerization dynamics, making it a promising starting point for the development of anticancer agents.

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[1] For reviews on this topic, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 2004. (b) Hassa, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

[2] (a) Kozikowski, A. P.; Ma, D. *Tetrahedron Lett.* **1991**, *32*, 3317. (b) Burwood, M.; Davies, B.; Diaz, I.; Grigg, R.; Molina, P.; Sridharan, V.; Hughes, M. *Tetrahedron Lett.* **1995**, *36*, 9053.

[3] (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467. (b) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (c) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274. (d) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (e) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (f) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186.

[4] (a) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1569 (erratum: *Angew. Chem., Int. Ed.* **2002**, *41*, 2227). (b) Hughes, C. C.; Trauner, D. *Tetrahedron* **2004**, *60*, 9675.

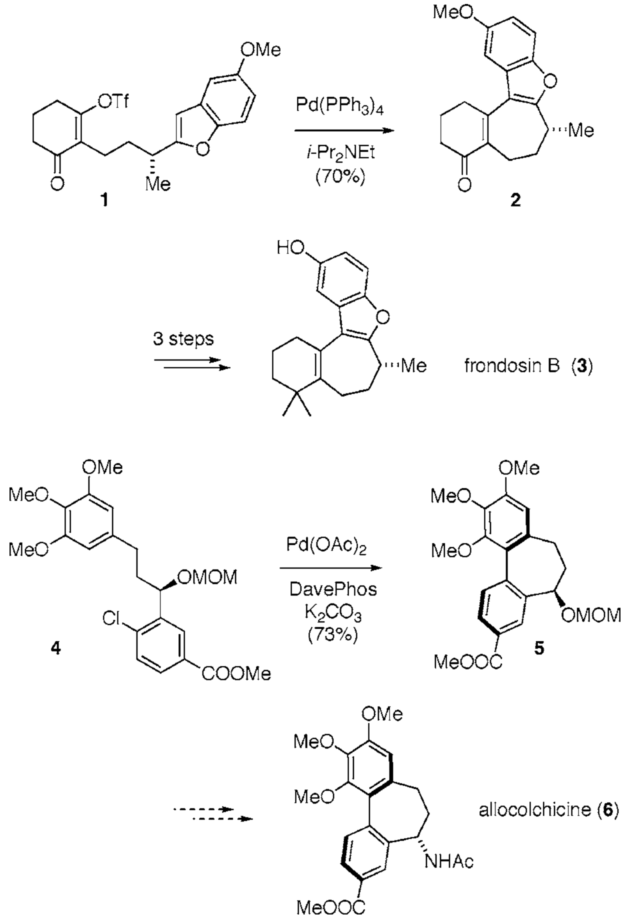
[5] LeBlanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849.

[6] (a) Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822. (b) Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13*, 909. (c) Kam, T.-S.; Tee, Y.-M.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *12*, 307.

[7] Baudoin, O.; Guénard, D.; Guéritte, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 333.

10.1021/ol052033v CCC: $30.25

Scheme 1. Direct Couplings in Total Synthesis



Synthetically, the molecule poses interesting challenges due to the presence of a strained nine-membered lactam ring incorporating a biaryl moiety and a quaternary stereocenter. Following a “classical” synthesis by Smith more than 30 years ago,[8] rhazinilam has recently gained prominence as a playground for the development of new synthetic methodology. Sames reported an asymmetric approach based on intramolecular platinum(II)-mediated C−H activation,[9] whereas Magnus used the conversion of a lactam to a pyrrole via a thiophenyl imine as a key step.[10] The synthesis of rhazinal[11a] and biologically active analogues of rhazinilam[11b] based on intermolecular Suzuki couplings have also been reported.

Our synthesis starts with the easily accessible, racemic γ-lactone **9**, which was featured before in the first total synthesis of rhazinilam by Smith (Scheme 2).[8] A high-yielding nucleophilic substitution of the tosyl group by the sodium salt of 2-carbomethoxy pyrrole (**10**) gave *N*-alkylated pyrrole **11**. Upon treatment with aluminum chloride, **11** underwent intramolecular Friedel−Crafts alkylation to afford indolizine carboxylic acid **12**, bearing the quaternary stereocenter. Coupling of **12** with 2-iodoaniline (**13**) under Mukaiyama’s conditions[12] afforded amide **14**, the X-ray structure of which is displayed in Supporting Information. Protection of the amide as a methoxymethyl (MOM) derivative then gave key intermediate **15**.

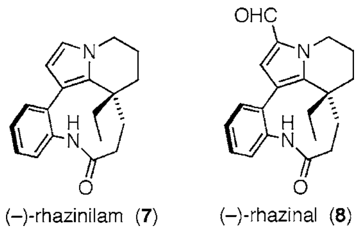
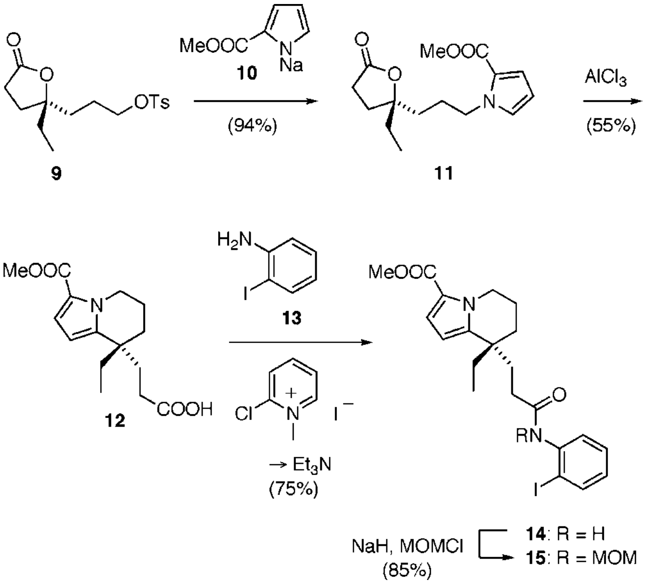


Figure 1.

Scheme 2. Preparation of Compound **15**



The stage was now set for the implementation of the direct coupling (Scheme 3). After extensive screening of ligands and metal sources, we found the conditions recently described by Fagnou[3f] to be superior to all other methods. Heating of **15** with 10 mol % of Buchwald’s “DavePhos” ligand (**16**)[13] and Pd(OAc)$_2$ in the presence of a base resulted in the clean formation of the strained, nine-membered lactam **19** in 47% yield. Other conditions gave little or no intended product and usually resulted in simple deiodination of the aryl ring.

Mechanistically, the key cyclization reaction proceeds through intramolecular nucleophilic attack of the pyrrole moiety onto the Pd(II) center in **17**, followed by deprotonation, as first suggested by Miura.[3a] Reductive elimination of Pd(0) from complex **18** then results in formation of the biaryl bond. The electron-rich ligand **16** may facilitate not

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(8) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179.

(9) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900.

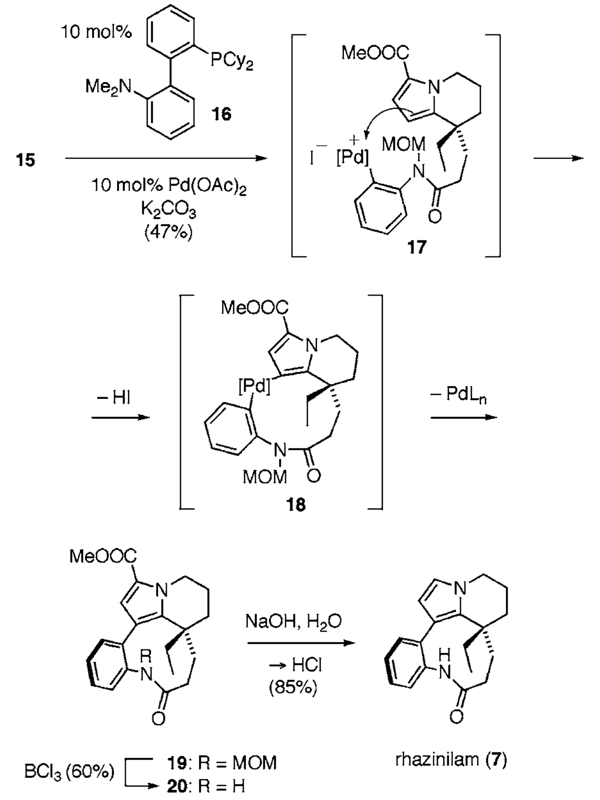
(10) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647.

(11) (a) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296. (b) Dupont, C.; Guénard, D.; Thal, C.; Thoret, S.; Guéritte, F. *Tetrahedron Lett.* **2000**, *41*, 5853.

(12) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707.

(13) Harris, M. C.; Geis, O.; Buckwald, S. L. *J. Org. Chem.* **1999**, *64*, 6019.

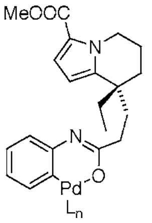
Scheme 3. Key Coupling and Total Synthesis of Rhazinilam



only oxidative addition but also the formation of a more reactive cationic palladium(II) species by dissociation of the halide.

Importantly, the MOM amide protecting group proved crucial for the success of this cyclization, since with the free amide we only observed deiodination. This could be due to reluctance of the palladium(II) complex **21**, which can be expected to form in the presence of a base, to undergo the coupling.

The removal of the MOM protecting group, however, proved to be a considerable challenge, presumably due to the sensitivity of the pyrrole moiety. After careful optimization, we found that this transformation could be achieved by treatment of **19** with a large excess of boron trichloride at low temperature.[14] This afforded ester **20**, which was identical in all respects to the immediate rhazinilam precursor obtained in a previous synthesis.[9] Accordingly, saponification of the ester moiety, followed by decarboxylation, gave the natural product **7** as a racemate.



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In conclusion, we have developed a highly efficient synthesis of rhazinilam that features the formation of a strained nine-membered ring through intramolecular coupling to an unactivated pyrrole.[15] Future work will focus on the asymmetric synthesis of **7** and **8** and the development of *ortho*-palladation/direct coupling strategies[16] for the synthesis of these natural products and related biologically active molecules.

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Supporting Information Available: Spectroscopic and analytical data for compounds **11**, **12**, **14** (including X-ray; CCDC 285045), **15**, **19**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Nicolaou, K. C.; Chen, David Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 12888.

(15) For another recent example of the participation of a pyrrole in palladium-catalyzed cyclizations, see: Garg, K. N.; Caspi, D. D.; Stoltz, B. M., *J. Am. Chem. Soc.* **2004**, *126*, 9552.

(16) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4046.