JOC Article

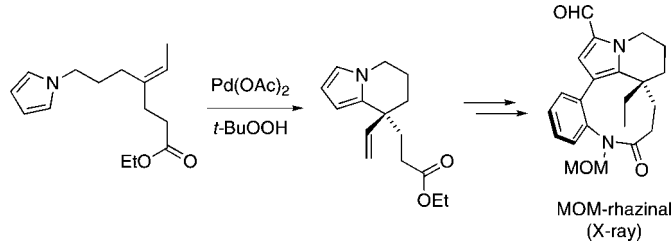
Total Synthesis of (±)-Rhazinal Using Novel Palladium-Catalyzed Cyclizations

Alfred L. Bowie, Jr. and Dirk Trauner*

Department of Chemistry, University of California, Berkeley, California 94720

trauner@berkeley.edu

Received August 29, 2008



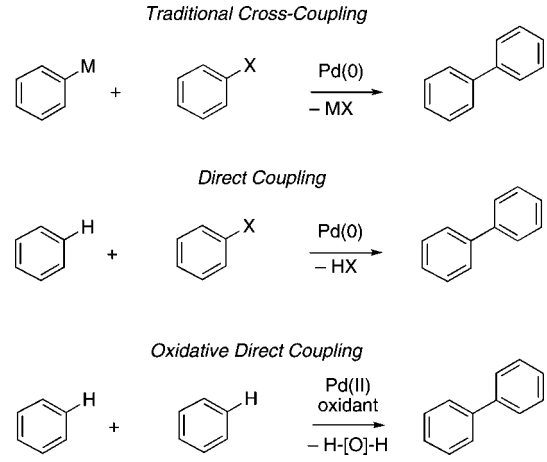
A concise synthesis of (±)-rhazinal that hinges on novel oxidative Heck cyclizations and palladium-catalyzed direct couplings is described. An X-ray structure of *N*-MOM-rhazinal, which provides insight into the conformation of the strained 9-membered lactam ring, is described.

Introduction

Transition-metal-catalyzed cross-coupling reactions have revolutionized the logic of chemical synthesis and have found innumerable applications in total synthesis.[1] Traditionally, both coupling partners must be properly functionalized prior to cross-coupling (Scheme 1). This usually requires installation of an organometallic moiety on one side to allow for transmetalation and a halide or triflate functional group on the other side to permit oxidative addition to a low-valent transition metal catalyst. The preparation of these precursors can involve several steps, and their reactions suffer from the formation of waste products (MX or HX), since neither of the two functional handles is incorporated into the final product.

Accordingly, there has been an increasing interest in the development of catalytic methods that allow the coupling of less functionalized components. Two palladium-catalyzed variants of these reactions have recently emerged, which gradually reduce the amount of prefunctionalization required (Scheme 1). The so-called "direct coupling" can be carried out with a Pd(0) catalyst due to the inbuilt oxidizing power of one of the reaction partners.[2] In terms of their atom-economy, however, "oxidative direct couplings", wherein both partners are unfunctionalized, are even more advantageous.[3] These reactions typically involve the electrophilic palladation of one reaction partner and require the addition of an external oxidant, ideally molecular oxygen, to close the catalytic cycle.[4]

SCHEME 1. Classical and Emerging Cross-Coupling Reactions

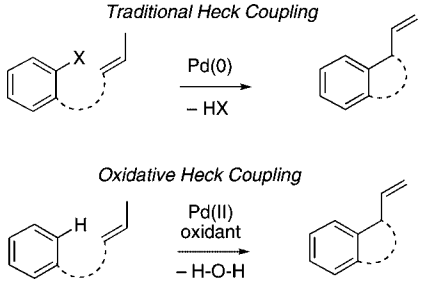


The Heck coupling has undergone a similar development toward decreased functionalization.[5] Like traditional cross-couplings, classical Heck reactions suffer from the stoichiometric production of HX, which needs to be intercepted with stoichiometric amounts of a base. To overcome this requirement, oxidative methodologies have been explored for the direct coupling of arenes with alkenes, though few reliable catalytic methods have emerged (Scheme 2).[6] Until recently, only a limited number of these catalytic processes had been applied

(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.

10.1021/jo801791j CCC: $40.75 © 2009 American Chemical Society
Published on Web 01/26/2009

SCHEME 2. Variants of the Heck Reaction



to the synthesis of complex products due to the harsh condition employed and difficulties with controlling the selectivity in these reactions.

In 2005, we have described the application of a palladium-catalyzed "direct coupling" in the total synthesis of the antitumor alkaloid rhazinilam **1** (Figure 1).[7] Herein, we demonstrate an extension of this strategy in the synthesis of the congener rhazinal (**2**). In addition, we wish to report on the development and application of an oxidative Heck coupling to furnish the tetrahydroindolizidine core of the natural products, which played a key role in our total synthesis of **2**.[8]

In 1998, Kam and co-workers reported the isolation of the alkaloid (−)-rhazinal (**2**) from the stem extracts of a Malayan *Kopsia* species.[9] Similar to Taxol and vincristine, rhazinal was found to interfere with tubulin polymerization dynamics, making it a promising starting point for the development of anticancer agents. Accordingly, compound **2** and its deformylated congener rhazinilam (**1**) have attracted considerable attention both in the biological and synthetic communities.[10]

Synthetically, rhazinal poses interesting challenges due to the presence of a strained nine-membered lactam ring incorporating a biaryl moiety and a quaternary stereocenter. Rhazinal, which can be prepared by Vilsmeier−Haack formylation of the closely

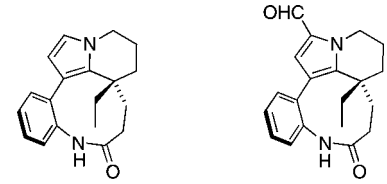
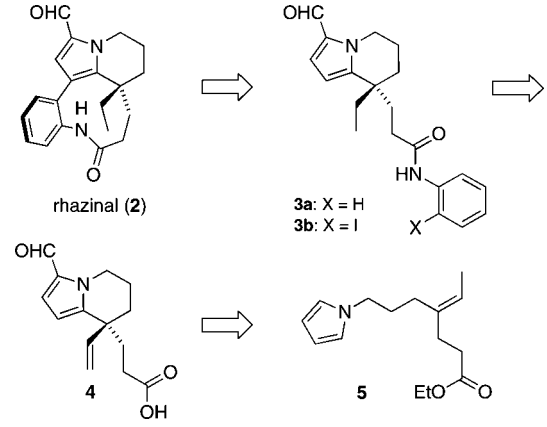


FIGURE 1. Antitumor alkaloids rhazinilam and rhazinal.

SCHEME 3. Retrosynthetic Analysis of Rhazinal



related alkaloid (−)-rhazinilam (**1**),[11] has been the subject of two successful total syntheses to date by Banwell.[10h] This elegant work relied on an organocatalytic intramolecular Michael addition of a pendant pyrrole onto a tethered enal to afford the tetrahydroindolizine scaffold.[10d] Another notable feature of this synthesis was the usage of an intermolecular Suzuki coupling to afford the key biaryl linkage.

We chose to take a very different route to demonstrate the usefulness of novel palladium-catalyzed couplings. Our retrosynthetic analysis hinges on a late-stage oxidative coupling (involving **3a**), or direct coupling (involving **3b**), to form the critical biaryl bond and close the strained 9-membered lactam ring of rhazinal (Scheme 3). The formyl group would serve as an inbuilt "protecting group" of the sensitive pyrrole nucleus in this step. Retrosynthetic cleavage of the amide bond and unsaturation would then afford alkene **4**, whose tetrahydroindolizine system would be formed through an intramolecular oxidative Heck reaction using a variant of pyrrole **5** as a substrate.

Results and Discussion

Oxidative Coupling Studies. In order to access the congested quaternary center, we first studied the feasibility of an oxidative Heck cyclization. Our initial synthetic route began with a Claisen rearrangement[12] of known allylic alcohol **6**[13] to afford the *E*-trisubstituted ester **7**. The ester was then reduced to the corresponding alcohol, which was then converted into tosylate **8** (Scheme 4). A nucleophilic substitution of the tosyl group by the potassium salt of pyrrole gave *N*-alkylated pyrrole **9**.

(2) For recent examples of direct couplings in synthesis, see: (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*, 918.

(3) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.

(4) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022.

(5) For a recent review of the Heck reaction, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (c) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranish, S *Tetrahedron Lett.* **1968**, *9*, 633.

(6) (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (b) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

(7) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207.

(8) For related stoichiometric oxidative Heck cyclizations, see: (a) Garg, N. K.; Capsi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552. (b) Garg, N. K.; Capsi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970. (c) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.

(9) Kam, T. S.; Tee, Y. M.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *12*, 307.

(10) (a) Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179. (b) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (c) Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647. (d) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296–305. (e) Liu, Z. S.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (f) Baudoin, O.; Guenard, D.; Gueritte, F. *Mini-Rev. Org. Chem.* **2004**, *1*, 333. (g) David, B.; Sevenet, T.; Morgat, M.; Guenard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motility Cytoskeleton* **1994**, *28*, 317. (h) Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, 163.

(11) David, B.; Sevenet, T.; Thoison, O.; Awang, K.; Pais, M.; Wright, M.; Guenard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155.

(12) Frauenrath, H. In *Methods of Organic Chemistry (Houben-Weyl), Stereoselective Synthesis, Vol. E21d*; Helmchen, G., Hoffman, R. W., Mulzer, J., Schaumann, R., Eds.; Thieme: Stuttgart, 1995; Vol. 330, pp 1−3756 and references cited therein.

(13) Marvel, M; Saunders, J. *J. Am. Chem. Soc.* **1948**, *70*, 1698.

SCHEME 4. Preparations of Unsaturated Pyrrole 9

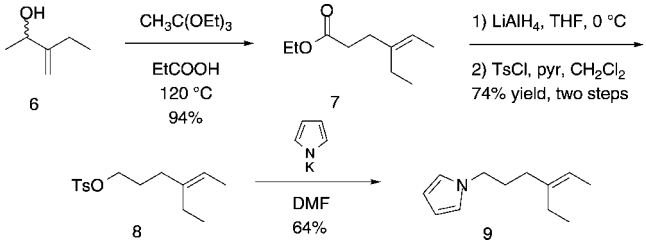
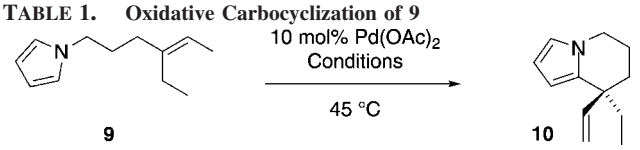


TABLE 1. Oxidative Carbocyclization of 9



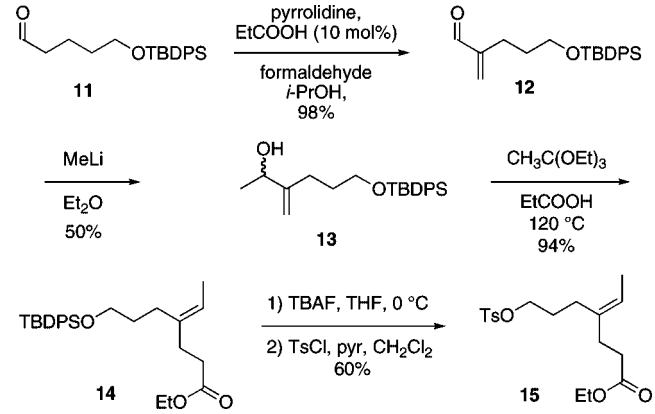
entry	oxidant	additive	solvent	yield (%)	time (h)
1	*t*-BuOOH	none	DCE/DMSO (9:1)	25	15
2	*t*-BuOOH	AgOAc	DCE/DMSO (9:1)	2	4
3	O_2	none	DCE/DMSO (9:1)	10	13
4	*t*-BuOOH	benzoic acid (0.6 equiv)	DCE/DMSO (9:1)	33	23
5	O_2	benzoic acid (1.5 equiv)	DCE/DMSO (9:1)	48	26
6	*t*-BuOOH	benzoic acid (1.5 equiv)	DCE/DMSO (9:1)	54	19
7	*t*-BuOOH	none	Diox/AcOH/DMSO (9:3:1)	62	3
8	O_2	none	Diox/AcOH/DMSO (9:3:1)	55	10

The stage was now set for the investigation of the key oxidative Heck cyclization. Table 1 depicts a representative list of conditions and oxidants that were investigated in effecting the key cyclization of **9**. To our delight, exposure of **9** to $Pd(OAc)_2$ under a variety of conditions led to the formation of **10**. The use of benzoic acid to help promote the oxidative cyclization of **9** is interesting because it obviates the use of acetic acid as a cosolvent (entry 6).[14] Carefully optimized conditions afforded the tetrahydroindolizidine **10** as a single regioisomer in 62% yield (entry 7). In our hands, the optimal oxidant appears to be *tert*-butyl hydroperoxide (*t*-BuOOH), and benzoic acid was not required as an additive. The use of molecular oxygen resulted in longer reaction times and slightly decreased yields. A similar protocol was described by Gaunt and co-workers and recently featured in a total synthesis of the related natural product rhazinicine.[15]

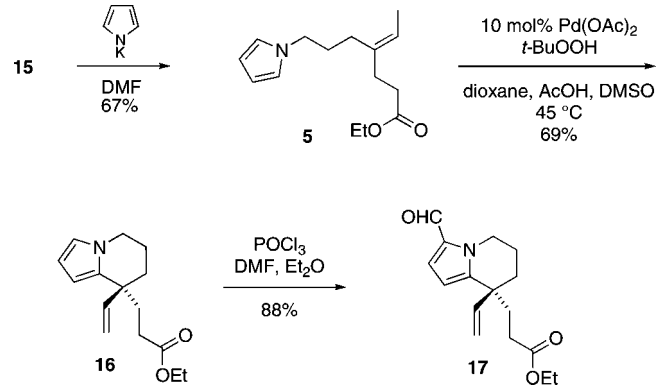
With this robust and concise route to heterocycle **10** in hand, attempts were made to convert **10** into the carboxylic acid **4** (Scheme 3). Unfortunately, the neopentylic vinyl group could not be functionalized effectively, presumably due to steric hindrance. Therefore, an alternative approach was developed.

Synthesis of Tetrahydroindolizine 17. Having worked out a viable method for the oxidative Heck cyclization, we proceeded to synthesize a more highly functionalized cyclization precursor (Scheme 5). Mild organocatalytic α-methylenation of known aldehyde **11**[16] provided enal **12** in excellent yield.[17] Treatment of **12** with methyllithium yielded allylic alcohol **13**, which smoothly underwent Claisen rearrangement to afford *E*-trisubstituted ester **14**. Deprotection and subsequent tosylation yielded tosylate **15** in modest yield.

SCHEME 5. Synthesis of Tosylate 15



SCHEME 6. Oxidative Cyclization of 16

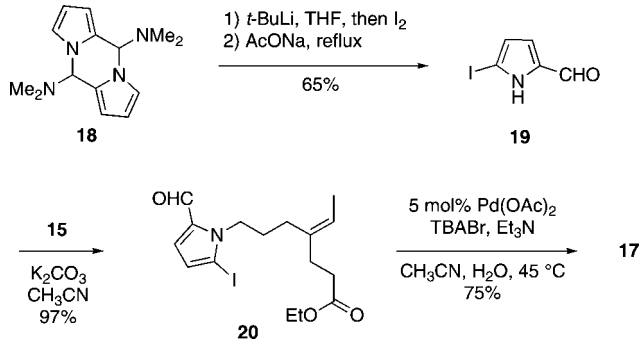


Nucleophilic substitution of the tosyate group with the potassium salt of pyrrole gave *N*-alkylated pyrrole **5**. With the requisite functional handle in place, the stage was now set for the implementation of the key oxidative cyclization (Scheme 6). Gratifyingly, using 10 mol % of $Pd(OAc)_2$ in the presence of a mixed solvent system and *t*-BuOOH resulted in the clean formation of tetrahydroindolizine **16** with the requisite quaternary stereocenter in 69% yield. Tetrahydroindolizine **16** was subjected to facile Vilsmeier−Haack formylation, affording aldehyde **17** as a single regioisomer.

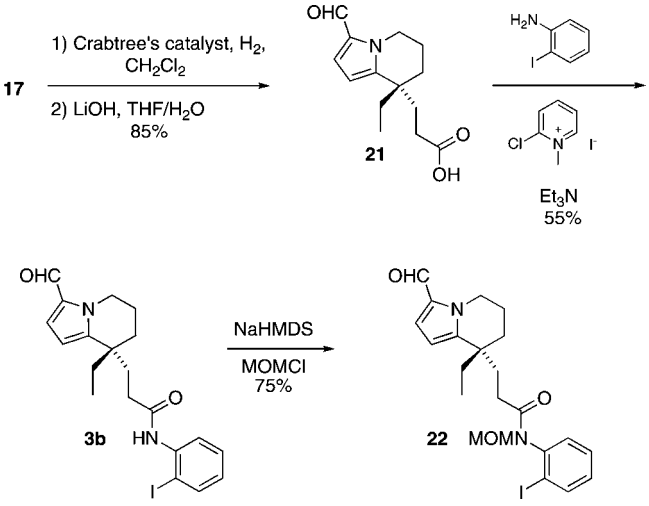
In parallel to investigating the oxidative Heck approach to the tetrahydroindolizinyl core of rhazinal, we also pursued a classical Heck route involving iodopyrole **19** (Scheme 5). This would open an opportunity to investigate asymmetric Heck cyclizations, which were found to be elusive under oxidative conditions. Although **19** is a known compound,[18] the published procedure for its synthesis gave low yields of the desired product in our hands (∼30%). Gratifyingly, we found that the known azafulvene **18** could be C-metalated with *tert*-butyllithium and quenched with molecular iodine. The corresponding 5-iodo-2-pyrrole carbaldehyde **19** was isolated via hydrolysis of the azafulvene with sodium acetate in refluxing THF. A high-yielding nucleophilic substitution of the tosylate **15** by the potassium salt of pyrrole **19** then gave *N*-alkylated pyrrole **20**. Heck reaction of **20** under modified Jeffery conditions yielded the annulated pyrrole **17** in good yield, which was identical in all respects to the **17** made from the formylation of **16** (Scheme 7).[19] Unfortunately, all attempts to develop an asymmetric

(14) Dams, M.; De Vos, D.; Celen, S.; Jacobs, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512.
(15) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.
(16) Kim, D.; Freeman, F. *J. Org. Chem.* **1992**, *57*, 1727.
(17) Erkkila, A.; Pihko, P. *J. Org. Chem.* **2006**, *71*, 2538.
(18) Denat, F.; Gaspard-Iloughmane, H.; Dubac, J. *J. Organomet. Chem.* **1992**, *423*, 173.
(19) Gradl, S.; Kennedy-Smith, J.; Kim, J; Trauner, D. *Synlett* **2002**, 1437.

SCHEME 7. Heck Reaction of 20



SCHEME 8. Preparation of Precursor 22



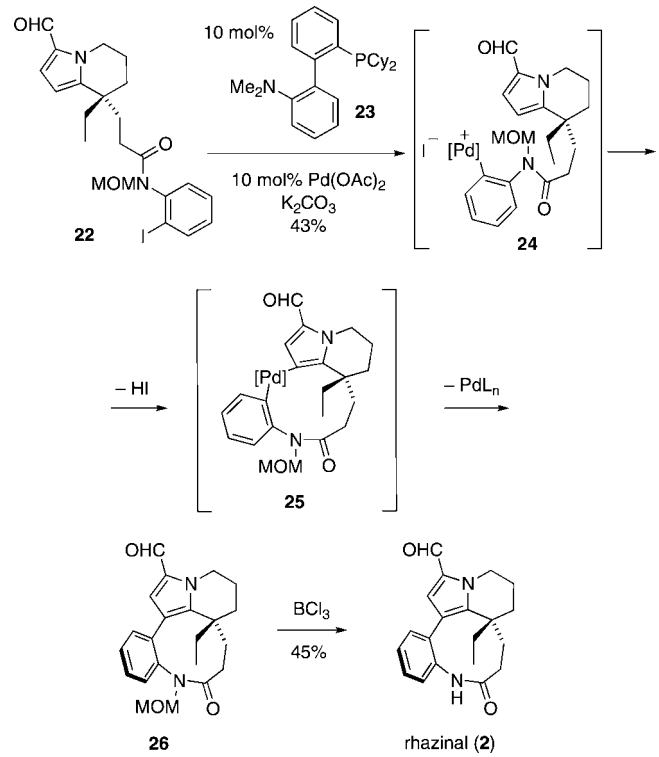
version of this reaction using chiral phosphine ligands gave low yields and disappointing ee's.

Total Synthesis of Rhazinal via Direct Coupling. With two viable syntheses of racemic tetrahydroindolizidine **17** in hand, we proceeded to investigate the formation of the 9-membered lactam ring in the final stages of the synthesis. Chemoselective reduction of alkene **17** using Crabtree's catalyst afforded the corresponding saturated ester, which was subsequently saponified with lithium hydroxide to reveal the key acid **21** in excellent yield. Other more common catalysts such as Wilkinson's and Pd/C led to partial reduction of the formyl group. Coupling of **21** with 2-iodoaniline under Mukaiyama's conditions[20] then afforded amide **3b**. Subsequent protection of the amide as a methoxymethyl (MOM) derivative then gave **22**, our key intermediate for the direct coupling (Scheme 8).

After extensive screening of various ligands and metal sources, we found that the optimal conditions identified in our previous synthesis of rhazinilam,[7] namely heating **22** with 10 mol % of Buchwald's "DavePhos" ligand (**23**) and $Pd(OAc)_2$ in the presence of a potassium carbonate, were also most effective for the formation of the strained 9-membered ring in *N*-MOM rhazinal **26** (43% yield). Under a variety of other conditions we found little or no intended product and usually observed simple deiodination of the aryl ring.

Mechanistically, this key cyclization reaction could proceed through intramolecular nucleophilic attack of the pyrrole moiety onto the Pd(II) center in **24**, followed by deprotonation. Subsequent reductive elimination of Pd(0) from complex **25** then

SCHEME 9. Completion of Rhazinal



results in formation of the biaryl bond and the strained 9-membered lactam ring. The electron-rich Buchwald ligand **23** may not only facilitate oxidative addition but also the formation of a more reactive cationic palladium(II) species by dissociation of the halide. As noted before in our synthesis of rhazinilam, the MOM group proved crucial for the success of this cyclization, as the free amide resulted exclusively in protodeiodination and no cyclized product could be observed. This could be due to formation of a very stable six-membered oxapalladacyle or the altered conformational preferences of secondary vs tertiary amides. The structure of *N*-MOM rhazinal **26** was confirmed by X-ray crystallography proving our structural assignment and providing a detailed view of the 9-membered ring (for clarity the unnatural series is displayed; see the Supporting Information). As previously observed in the X-ray structure of rhazinal, the amide adopts an unusual cisoid conformation.[10]

The MOM protecting group could be removed by treatment of **26** with a large excess of boron trichloride at low temperature.[21] This afforded racemic rhazinal (**2**), which was identical in all respects to the natural product with the exception of its optical activity (Scheme 9).[9]

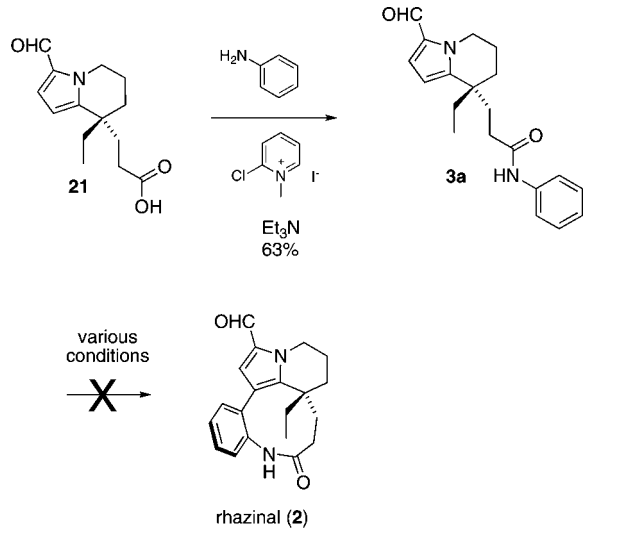
Attempted Oxidative Direct Coupling. Having worked out a viable synthesis of rhazinal that involves both an oxidative Heck reaction and a direct coupling, we finally turned our attention toward the direct oxidative coupling involving precursor **3a** (Scheme 10). We had some hope that such an ambitious plan would be met with success since the electrophilic *ortho*-palladation of acyl anilines is well-known and the resulting palladium(II) complexes have been shown to engage in Heck couplings.[22] Unfortunately, despite many attempts under a

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

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

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

SCHEME 10. Attempted Oxidative Direct Coupling



variety of conditions, the desired transformation could not achieved and the total synthesis of rhazinal through oxidative direct coupling remains an elusive goal.

Conclusion. In summary, we have developed a highly efficient and concise synthesis of rhazinal. Notable features of this synthesis include the development of several oxidative protocols for the construction of the tetrahydroindolizinyl moiety present in both rhazinal and rhazinilam. Future work will focus on the development of oxidative *ortho*-palladation/direct-coupling strategies for the synthesis of these natural products and related biologically active molecules. We are also working on asymmetric versions of our aerobic cyclization en route to tetrahydroindolizines.

Experimental Section

3-(3-Formyl-8-vinyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic Acid Ethyl Ester 17. To a cooled solution (0 °C) of the pyrrole **16** (144 mg, 0.60 mmol) and DMF (0.58 mL) in Et_2O (6.5 mL) was added phosphorus oxychloride (98.6 mg, 0.64 mmol). After 0.5 h, the ice bath was removed and the mixture was stirred at room temperature for 3 h before the addition of Et_2O (26 mL) and Na_2CO_3 (26 mL of a 2 M aqueous solution). Stirring was continued for 10 min before the phases were separated, and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo to give a dark yellow oil. The product was subsequently purified by column chromatography (10% EtOAc in hexanes) to afford 146 mg (88%) of **17** as a foamy solid: IR (film) 1727, 1655 cm^{-1}; ^1H NMR δ 9.30 (s, 1H), 6.77 (d, J = 4.0 Hz, 1H), 5.97 (d, J = 4.0 Hz, 1H), 5.69 (q, J = 7.0 Hz, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 17.0 Hz, 2H), 3.97 (m, 3H), 2.22−2.09 (m, 2H), 1.95 (m, 2H), 1.88 (m, 2H), 1.65 (m, 2H) 1.15 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 178.4, 173.0, 143.7, 143.3, 130.8, 124.1, 114.8, 108.1 60.1, 45.4, 42.1, 35.1, 29.4, 29.1, 18.9, 14.1; HRMS (EI+) m/z ($M + H^+$) calcd for $C_{16}H_{21}NO_3$ 276.1599, found 276.1598.

5-Iodopyrrole-2-carbaldehyde 19. To a cooled (−15 °C) solution of azafulvene **18** (1.2 g, 4.92 mmol) in 50 mL of anhydrous THF was added 11.68 mmol of ^{t}BuLi (1.6 M in pentane). The mixture was stirred for 15 min at −15 °C then for 30 min at 0 °C and 1 h at room temperature. The violet solution thus formed was cooled to −75 °C, iodine (2.9 g, 11.68 mmol) was added slowly, and the mixture was stirred for 2 h at room temperature, becoming dark blue-green to black. Hydrolysis with a 1:1 solution of water and saturated bicarbonate at reflux for 5 h was followed by extraction with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo to give a dark brown solid. The product was purified by column chromatography (25% EtOAc in hexanes) to afford 1.4 g (65%) of **19** as an off-white solid: IR (film) 1730 cm^{-1}; ^1H NMR δ 10.7 (br s, 1H), 9.32 (s, 1H), 6.84 (d, J = 4.0 Hz, 1H), 6.50 (d, J = 4.0 Hz, 1H), ^{13}C NMR δ 177.7, 136.9, 123.2, 120.9, 78.2; HRMS (EI+) m/z (M^+) calcd for C_5H_4INO 220.9338, found 220.9332.

4-Eth-(*Z*)-ylidene-7-(2-formyl-5-iodopyrrol-1-yl)heptanoic Acid Ethyl Ester 20. To **19** (265 mg, 2.79 mmol) in acetonitrile (7 mL) was added potassium carbonate (1.15 g, 8.4 mmol). The tosylate **15** was then added to the mixture, and the reaction was stirred at 45 °C for 8 h. The reaction was allowed to cool to room temperature and then poured into water (30 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (15% EtOAc in hexanes) to afford 1.09 g (97%) of **20** as a colorless oil: IR (film) 1728, 1664, 1265 cm^{-1}; ^1H NMR δ 9.10 (s, 1H), 6.76 (d, J = 4.0 Hz, 1H), 6.34 (d, J = 4.0 Hz, 1H), 5.15 (q, J = 6.8 Hz, 1H), 4.22 (t, J = 8.0 Hz, 2H), 4.00 (t, J = 6.8 Hz, 2H), 2.29 (m, 4H), 2.00 (t, J = 8.0 Hz, 2H), 1.66 (m, 2H), 1.47 (d, J = 6.8 Hz, 3H), 1.14 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 177.3, 173.2, 137.0, 134.3, 125.9, 120.1, 119.9, 87.5, 60.1, 49.4, 33.0, 31.7, 29.1, 26.6, 14.2, 13.2; HRMS (EI+) m/z ($M + Na^+$) calcd for $C_{16}H_{22}INO_3$ 426.0542, found 426.0534.

3-(3-Formyl-8-vinyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic Acid Ethyl Ester 17. To iodopyrrole **20** (1.90 g, 4.7 mmol) were added H_2O (1.99 mL, 2.4 M), MeCN (24.3 mL, 0.2 M), Et_3N (1.96 mL, 14.0 mmol), tetrabutylammonium bromide (4.53 g, 14.0 mmol), and finally $Pd(OAc)_2$ (52.5 mg, 0.23 mmol). The reaction vessel was sparged with N_2 atmosphere three times prior to heating. The solution was heated to 75 °C for 15 h, cooled to room temperature, and filtered over a plug of silica gel (10% EtOAc in hexanes). After removal of solvent in vacuo, the product was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford 0.944 mg (73%) of annulated pyrrole **17**: IR (film) 1727, 1655 cm^{-1}; ^1H NMR δ 9.30 (s, 1H), 6.77 (d, J = 4.0 Hz, 1H), 5.97 (d, J = 4.0 Hz, 1H), 5.69 (q, J = 7.0 Hz, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 17.0 Hz, 2H), 3.97 (m, 3H), 2.22−2.09 (m, 2H), 1.95 (m, 2H), 1.88 (m, 2H), 1.65 (m, 2H) 1.15 (t, J = 6.8 Hz, 3H); ^{13}C NMR δ 178.4, 173.0, 143.7, 143.3, 130.8, 124.1, 114.8, 108.1 60.1, 45.4, 42.1, 35.1, 29.4, 29.1, 18.9, 14.1; HRMS (EI+) m/z ($M + H^+$) calcd for $C_{16}H_{21}NO_3$ 276.1599, found 276.1593.

3-(8-Ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic Acid Ethyl Ester. The alkene **17** (958 mg, 3.48 mmol) was dissolved in CH_2Cl_2 (25 mL), and then Crabtree's catalyst (208 mg, 0.35 mmol) was added. The vessel was sparged with an H_2 atmosphere three times prior to being charged with an H_2 balloon. The reaction was allowed to stir at room temperature for 18 h. After removal of solvent in vacuo, the product was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to afford 0.83 mg (86%) of 3-(8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic acid ethyl ester: IR (film) 2982, 1729, 1653, 1265 cm^{-1}; ^1H NMR δ 9.23 (s, 1H), 6.72 (d, J = 4.0 Hz, 1H), 5.88 (d, J = 4.0 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 3.93 (q, J = 6.0 Hz, 2H), 2.15−2.00 (m, 2H), 1.83−1.80 (m, 4H), 1.07 (t, J = 6.0 Hz, 3H), 0.69 (t, J = 6.0 Hz, 3H); ^{13}C NMR δ 178.1, 173.1, 145.7, 143.3, 130.6, 124.1, 107.2, 60.1, 45.1, 37.8, 34.5, 33.0, 29.5, 28.6, 19.3, 14.0, 8.3; HRMS (EI+) m/z ($M + H^+$) calcd for $C_{16}H_{23}NO_3$ 278.1756, found 278.1764.

3-(8-Ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic Acid 21. To 3-(8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propionic acid ethyl ester (963 mg, 3.48 mmol) in THF (17.4 mL) was added a solution of lithium hydroxide (291 mg, 12.2 mmol) in H_2O (8.7 mL). The reaction was allowed to stir for 16 h at room temperature. The mixture was diluted with H_2O (20 mL) and then extracted with EtOAc. The aqueous layer was then

acidified to pH 2 with 1 N hydrochloric acid and then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo to give a yellow oil. The product was subsequently purified by column chromatography (35% EtOAc in hexanes) to afford 859 mg (99%) of **21** as a foamy solid: IR (film) 3055, 2987, 1653 cm^{-1}; ^1H NMR δ 9.33 (s, 1H), 6.90 (d, $J = 5.0$ Hz, 1H), 6.04 (d, $J = 5.0$ Hz, 1H), 4.31 (m, 2H), 2.33−2.21 (m, 2H), 2.04−1.92 (m, 4H), 1.76 (m, 1H), 1.67 (m, 3H), 0.80 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR δ 179.1, 178.7, 146.3, 130.7, 125.1, 107.7, 45.4, 38.1, 34.5, 33.2, 29.6, 28.8, 26.6, 19.5, 8.5; HRMS (EI+) *m/z* (M + H^+) calcd for $C_{14}H_{19}NO_3$ 250.1443, found 250.1443.

3-(8-Ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)-*N*-(2-iodophenyl)propionamide 3b. To a solution of acid **21** (301 mg, 1.20 mmol) in CH_2Cl_2 (6 mL) were added 2-chloro-1-methylpyridinium iodide (371 mg, 1.45 mmol), 2-iodoaniline (317 mg, 1.45 mmol), and Et_3N (0.33 mL, 2.4 mmol). The mixture was heated at reflux for an additional 15 h, allowed to cool, poured into water (40 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried, filtered, and concentrated. The product was purified by column chromatography (25% EtOAc in hexanes) to furnish 299 mg (55%) of **3** as a foamy solid: IR (film) 3300, 2946, 1724, 1654 cm^{-1}; ^1H NMR δ 9.42 (m, 1 H), 8.13 (d, $J =$ 10.0 Hz, 1 H), 7.74 (d, $J = 5.0$ Hz, 1 H) 7.42 (br s, 1 H), 7.30 (t, $J = 5$ Hz, 1 H), 6.89 (d, $J = 5.0$ Hz, 1 H), 6.82 (t, $J = 5$ Hz, 1 H), 6.08 (d, $J = 5.0$ Hz, 1 H), 4.37 (m, 1H), 4.28 (m, 1H), 2.34 (m, 1 H), 2.23 (m, 1 H), 2.03 (m, 2 H), 1.97 (m, 2 H), 1.70 (m, 4 H), 0.86 (t, $J = 10$ Hz, 3H); ^{13}C NMR δ 178.6, 171.0, 146.1, 138.8, 138.1, 130.9, 129.3, 126.1, 124.7, 122.3, 107.5, 90.3, 45.5, 38.3, 35.3, 33.6, 33.2, 28.8, 19.6, 8.6; HRMS (EI+) *m/z* (M + H^+) calcd for $C_{20}H_{23}IN_2O_2$ 451.0883, found 451.0891.

3-(8-Ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)-*N*-(2-iodophenyl)-*N*-methoxymethylpropionamide 22. To a solution of the amide **3b** (234 mg, 0.520 mmol) in THF (2.66 mL) at −78 °C was added a solution of sodium bis(trimethylsilyl)amide in THF (0.34 mL, 2.0 M, 0.68 mmol) dropwise via syringe. After 2 h at 0 °C, a solution of chloromethyl methyl ether in THF (1.0 mL, 0.70 M, 0.70 mmol) was added dropwise. After an additional 10 min, the mixture was allowed to warm to room temperature over 1 h, diluted with water (15 mL), and extracted with EtOAc (3 × 20 mL). The product was purified by column chromatography (30% EtOAc in hexanes) to yield 191 mg (75%) of **22** as a yellowish solid: IR (film) 3055, 2364, 1722, 1653 cm^{-1}; ^1H NMR δ 9.37 (s, 1 H), 7.93 (m, 1 H), 7.37 (t, $J = 8.0$ Hz, 1 H) 7.22 (d, $J = 8.0$ Hz, 0.5 H), 7.15 (d, $J = 8.0$ Hz, 0.5 H), 7.07 (t, $J = 8.0$ Hz, 1 H), 6.77 (m, 1 H), 5.80 (m, 1 H), 5.55 (m, 1H), 4.32 (m, 1H), 4.22−4.11 (m, 2 H), 3.42 (s, 3 H), 1.98−1.78 (m, 6 H), 1.61 (m, 1 H), 1.45 (m, 3 H), 0.86 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR δ 178.4, 173.7, 146.2, 143.2, 140.1, 130.8, 130.6, 130.2, 129.6, 124.5, 107.5, 100.5, 90.3, 78.1, 57.0, 45.3, 38.1, 38.0, 35.1, 34.9, 35.3, 33.1, 32.9, 30.1, 30.0, 28.9, 28.7, 19.5, 8.5; HRMS (EI+) *m/z* (M + Na^+) calcd for $C_{22}H_{27}IN_2O_3$ 517.0964, found 517.0960.

Lactam 26. Iodide **22** (53.5 mg, 0.11 mmol), potassium carbonate (29.9 mg, 0.22 mmol), 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl (4.3 mg, 0.11 mmol), and palladium acetate (2.5 mg, 0.11 mmol) were placed in a flame-dried vial. The vial was flushed with nitrogen, *N*,*N*-dimethylacetamide (DMA, 1.8 mL) was added, and the solution was heated to 135 °C. After 18 h, the solution was allowed to cool, and the solvent was removed by rotary evaporation under high vacuum. The resulting black residue was diluted with CH_2Cl_2 and passed through a plug of silica gel. The product was purified by column chromatography (25% EtOAc in hexanes) to afford 17.3 mg (43%) of **26** as a white solid: IR (film) 1653 cm $^{-1}$; ^1H NMR δ 9.37 (s, 1 H), 7.43 (m, 1 H), 7.35 (m, 3 H) 6.57 (s, 1 H), 5.17 (d, $J = 10.0$ Hz, 1 H), 4.75 (m, 1 H), 4.30 (d, $J = 10.0$ Hz, 1 H), 3.93 (m, 1 H), 3.26 (s, 3 H), 2.50 (m, 2 H), 2.17 (m, 2 H), 1.92 (m, 1 H), 1.73 (m, 1 H), 1.55 (m, 4 H), 0.86 (t, $J = 10.0$ Hz, 3H); ^{13}C NMR δ 178.6, 175.3, 142.5, 141.4, 136.9, 131.3, 129.9, 129.1, 127.5, 127.1, 125.6, 120.0, 78.9, 56.8, 46.3, 39.7, 36.8, 31.9, 29.8, 29.4, 18.5, 8.2; HRMS (EI+) *m/z* (M + Na^+) calcd for $C_{22}H_{26}N_2O_3$ 389.1841, found 389.1842.

Rhazinal 2. To a solution of lactam **26** (16 mg, 0.044 mmol) in CH_2Cl_2 (2.2 mL) at −78 °C was added boron trichloride (0.44 mL, 1.0 M, 0.44 mmol) dropwise via syringe over 2 min. After 2.5 h at −78 °C, the reaction was quenched with a saturated $NaHCO_3$ solution (5 mL), and the mixture was extracted with EtOAc (3 × 15 mL), dried, and concentrated down. The crude solid was dissolved in MeOH (2.2 mL) and Et_3N (0.14 mL) and the solution was heated at 50 °C for 2 h. The product was purified by column chromatography (30% EtOAc in hexanes) to give 8.0 mg (45%) of **1** as a white solid: mp 230−234 °C; IR (film) 3510, 1662 cm $^{-1}$; ^1H NMR δ 9.39 (s, 1 H), 7.41 (m, 1 H), 7.37 (m, 3 H) 6.74 (br s, 1 H), 6.55 (s, 1 H), 4.78 (m, 1 H), 3.98 (m, 1 H), 2.50 (m, 2 H), 2.19 (m, 1 H), 2.04 (m 1 H), 1.97 (m, 1 H), 1.79 (m, 1 H), 1.55 (m, 3 H), 1.24 (m, 1 H), 0.71 (t, $J = 7.5$ Hz, 3 H); ^{13}C NMR δ 178.6, 176.57, 141.4, 138.2, 137.5, 131.3, 130.1, 129.0, 127.8, 127.1, 125.6, 120.4, 46.3, 39.6, 36.6, 31.9, 29.8, 28.0, 18.5, 8.1; HRMS (EI+) *m/z* (M + H^+) calcd for $C_{20}H_{22}N_2O_2$ 323.1759, found 323.1755.

Acknowledgment. We acknowledge financial support from Novartis, Roche, and the National Institutes of Health (Minority Supplement). We thank Dr. Frederick J. Hollander and Dr. Allen G. Oliver for the crystal structure determination of compound **26**.

Supporting Information Available: Experimental procedures for the preparation of **5**, **7**−**16**, and **3a** and the X-ray structure of **26**. Copies of NMR spectra for all new compounds are available (including X-ray structure CCDC 697745). This material is available free of charge via the Internet at http://pubs.acs.org.

JO801791J