The Utility of the Classical and Oxidative Heck Reactions in Natural Product Synthesis: Studies Directed toward the Total Synthesis of Dragmacidin F

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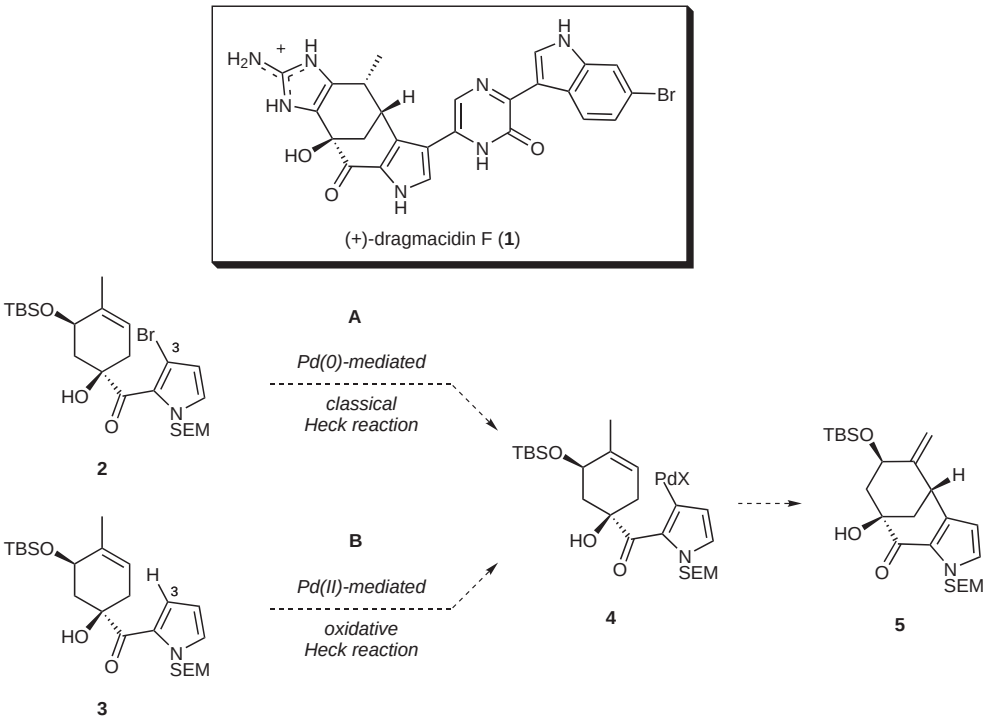
Dedicated to Professor Richard Heck for his outstanding contributions to organic synthesis

Abstract: The syntheses of complex pyrrole-fused [3.3.1] and [3.3.2] bicycles using classical and oxidative Heck cyclizations are described. While both [3.3.1] and [3.2.2] bicyclic products are formed in the classical Heck reaction, the oxidative Heck cyclization reaction furnishes solely the [3.3.1] bicycle. The [3.3.1] bicyclic product has been used as an intermediate to synthesize the complex marine alkaloid dragmacidin F.

Key words: Heck reaction, palladium, oxidative cyclization, bicyclic compounds, total synthesis

Over the past several decades, transition-metal-mediated cross-coupling reactions have emerged as powerful methods for the formation of carbon–carbon bonds.[1] Of the common Pd-mediated cross-coupling processes, the Heck reaction[2] is unique in its ability to construct sp^2–sp^3 bond linkages, thereby generating stereogenic centers.[3,4] Given its high synthetic utility, it is not surprising that the Heck reaction has been used extensively in the synthesis of complex natural products.[3a]

In planning our recent total synthesis of the bioactive marine alkaloid dragmacidin F (**1**, Scheme 1),[5] we envisioned two closely related Heck transformations for constructing the [3.3.1] bicyclic framework of the natural product. In the first scenario, a Pd(0)-mediated intramolecular Heck reaction of bromopyrrole **2** would be used to assemble bicycle **5**. In an alternative plan, Pd(II)-promoted cyclization of substrate **3**, which does not bear functionalization at C(3), would be used to prepare the identical bicyclic product (**5**). Both of these routes would presumably proceed via regioselective olefin insertion of palladium(II) intermediate **4**.[6] The latter of the proposed



Scheme 1

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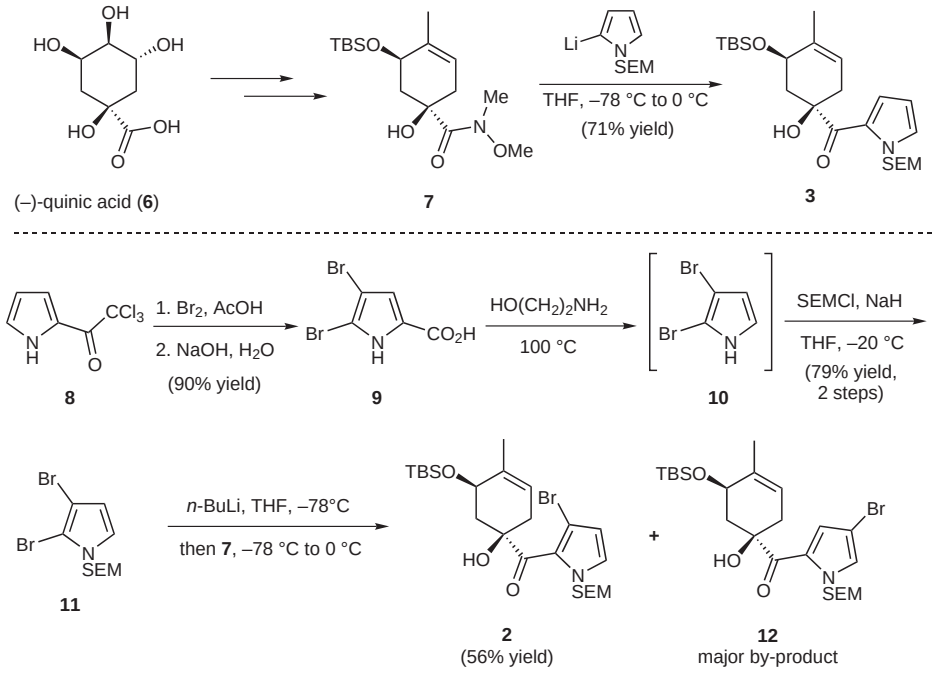
strategies, known as the 'oxidative Heck' cyclization,[7–9] was particularly attractive since it would not require the synthesis of a prefunctionalized pyrrole substrate (i.e., **2**) and furthermore, it would allow us to study reaction methodology that has been developed in our laboratories, in a highly complex chemical environment.[7] In this letter, we report our findings regarding the use of classical and oxidative Heck reactions as viable methods for the construction of complex bicycles.

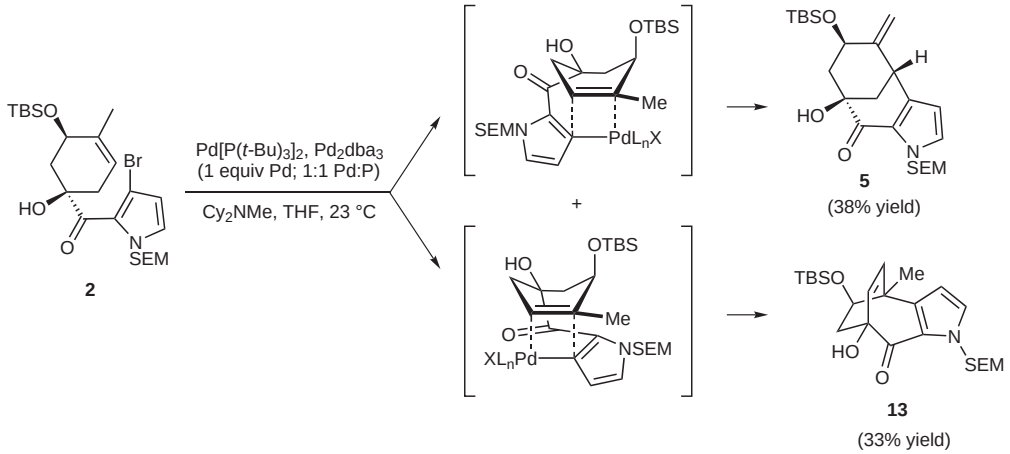
To initiate our studies, the key Heck cyclization substrates were prepared as depicted in Scheme 2. (–)-Quinic acid (**6**)[10] was first elaborated to Weinreb amide **7** using our previously reported protocol.[5] Subsequent displacement of Weinreb amide **7** with readily available 2-lithio-SEM-pyrrole[11] smoothly afforded oxidative Heck substrate **3** in 71% yield. Bromide **2** proved significantly more difficult to access as compared to its *des*-bromo counterpart; nonetheless, an efficient route was developed. Commercially available 2-trichloroacetyl pyrrole (**8**) was dibrominated and hydrolyzed following a literature procedure.[12] Heating dibromoacid **9** in ethanolamine at 100 °C facilitated decarboxylation to provide 2,3-dibromopyrrole (**10**), an unstable intermediate that could not be isolated.[13] Thus, the crude material (**10**) was treated with NaH and SEMCl to afford protected derivative **11**, which in contrast to **10**, could be chromatographed and stored for prolonged periods of time. Selective lithium–halogen exchange of dibromide **11**, followed by treatment with Weinreb amide **7**, furnished Heck substrate **2** in 56% yield. It should be noted that 4-bromopyrrole **12** was observed as a major by-product in the addition reaction. This by-product was presumably formed by anion scrambling after lithium–bromide exchange. This not only led to modest yields of Heck substrate **2**, but also complicated purification of the desired product.

With the pyrrole-fused cyclohexene substrates in hand, we began investigating the classical Heck reaction of bromopyrrole **2**. Our initial attempts to effect intramolecular cyclization involved the use of standard protocols[3] where bromide **2** was heated in the presence of Pd(0), phosphine ligand, and base, in either acetonitrile or DMF, under an inert atmosphere. Although trace quantities of product were observed in a few rare cases, most experiments afforded recovered starting material accompanied by substantial decomposition. Likewise, exposure of bromide **2** to Jeffery's conditions[14] or Herrmann's catalyst[15] also returned starting material with significant loss of mass. Hypothesizing that the observed decomposition could partially be attributed to the thermal instability of substrate **2**, we turned to conditions recently developed by Fu, which are known to catalyze Heck reactions at room temperature.[16] Gratifyingly, the implementation of Fu's conditions, using one equivalent of Pd, led to the desired [3.3.1] bicycle (**5**), albeit in modest yield (Scheme 3). Unfortunately, the formation of [3.3.1] bicycle **5** was hampered by competitive production of [3.2.2] bicycle **13**.

A considerable effort was undertaken to optimize the intramolecular Heck cyclization for the production of desired bicycle **5**. To our dismay, varying parameters such as temperature, solvent, base, concentration, and Pd:phosphine ratio did not lead to more favorable product distributions. Unexpectedly, however, it was found that by increasing the quantity of palladium used in the Heck reaction, the ratio of the desired [3.3.1] bicycle (**5**) to the undesired [3.2.2] bicycle (**13**) improved (Table 1). In fact, the desired product (**5**) was favored in a 3:1 ratio when



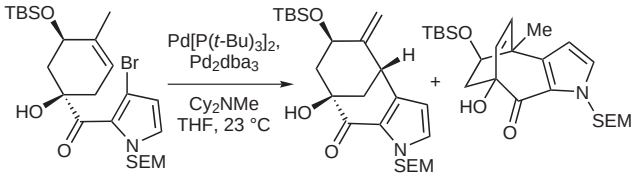
Scheme 2



Scheme 3

three equivalents of Pd were employed in the Heck reaction (77% isolated yield). In contrast, carrying out the reaction with 0.5 equivalent of palladium led to undesired bicycle **13** as the major product. In an attempt to gain a better understanding of these effects, a series of Heck reactions were carried out in THF-d_8 and monitored closely by ^{1}H NMR spectroscopy. Interestingly, the ratio of **5** to **13** decreased as the reaction progressed, suggesting that the active catalyst species varied during the course of the reaction or that selectivity changed as the concentration of $R_3NH^+Br^-$ increased. The latter of these hypotheses was probed by examining several inorganic and organic bases. While a few bases behaved comparably to Cy_2NMe (e.g., Et_3N and Hünig's base), most bases led to increased production of undesired bicycle **13**. Most notably, the use of pyridine led to the exclusive formation of [3.2.2] bicycle **13**.

Table 1 Synthesis of Bicycles **5** and **13** with Various Quantities of Palladium



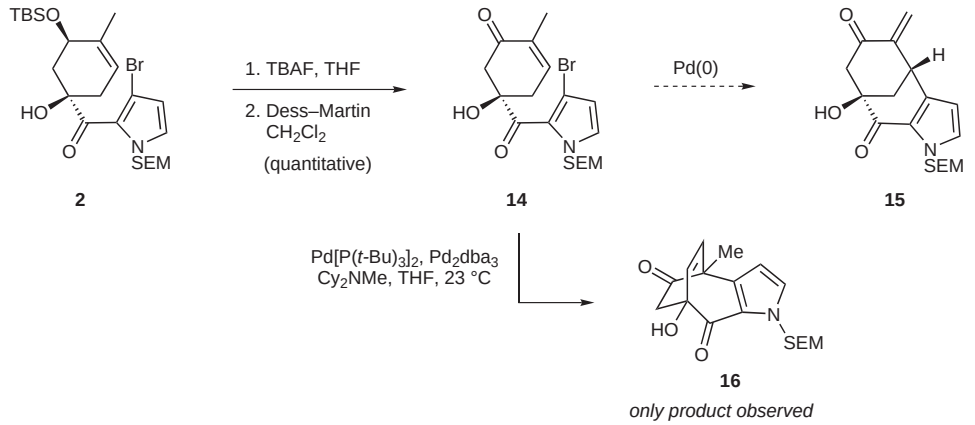
2 **5** **13**

Entry	Pd (equiv)	Ratio of **5**:**13**
1	3.0	3:1
2	2.0	1.5:1
3	1.0	1.1:1
4	1.2	1.2:1

In an effort to promote the formation of the desired [3.3.1] bicyclic framework, an alternate Heck substrate (**14**) was prepared via treatment of TBS ether **2** with TBAF, followed by Dess–Martin periodinane (Scheme 4). It was anticipated that the enone functionality of **14** would impose an electronic bias, thus favoring bicycle **15** in the intramolecular Heck cyclization.[3] To our surprise, however, [3.2.2] bicycle **16** was the only product generated from the Heck reaction of enone **14**.

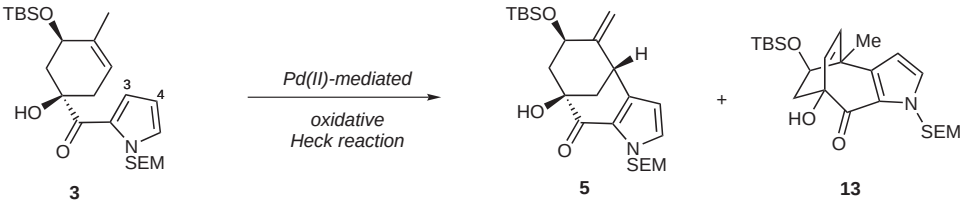
Although [3.2.2] bicycles **13** and **16** were not useful intermediates for the total synthesis at hand, the fact that these products are observed demonstrates the utility and power of the classical Heck reaction in assembling intricate molecular architectures. Moreover, the Heck reactions that afford **13** and **16** are particularly interesting since they create sterically congested quaternary carbon stereocenters, which are known to be synthetically challenging.[17] To the best of our knowledge, these results are the first use of Fu's Heck reaction conditions to construct molecules of such complexity.

Having assessed the classical Heck reaction as a means to prepare pyrrole-fused bicycles, we next explored the alternative Pd(II)-mediated oxidative Heck strategy involving cyclization of *des*-bromo substrate **3** (Scheme 1). Our initial experiments in this area employed conditions discovered in our laboratories for promoting related C–C bond-forming reactions.[7] Unfortunately, under these conditions [i.e., catalytic or stoichiometric $Pd(OAc)_2$, and pyridine-derived ligands], formation of either desired bicycle **5** or undesired bicycle **13** was not detected (Table 2, entry 1). However, by using DMSO as a ligand,[18] the desired cyclization product could be obtained in 56% yield (entry 2). Subsequent optimization of temperature and reaction time led to an ideal set of conditions whereby the desired [3.3.1] bicycle (**5**) was isolated as the sole product in 74% yield (entry 3).[19] This transformation is particularly noteworthy since it results in functionalization of the electronically deactivated and sterically congested C(3) position of acyl pyrrole **3**.[20,21] Importantly, the undesired [3.2.2] bicycle (**13**) seen as a by-product in the classical Heck reaction has never been observed as a product of the oxidative Heck cyclization of substrate **3**.



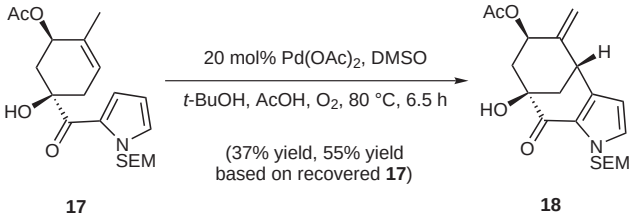
Scheme 4

Table 2 Synthesis of Bicycles **5** and **13** under Various Reaction Conditions



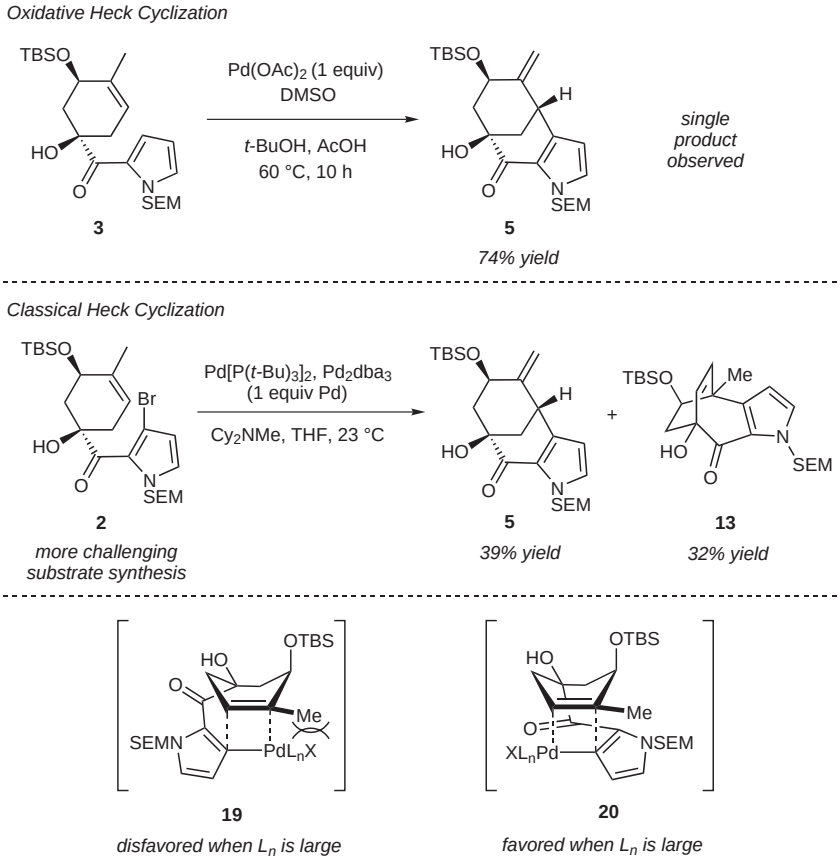
Entry	Conditions	Result	
1	$Pd(OAc)_2$ (stoichiometric or catalytic with O_2), pyridine or ethyl nicotinate, *t*-BuOH, AcOH, 80 °C	no reaction, starting material recovered	
2	$Pd(OAc)_2$ (1 equiv), DMSO, *t*-BuOH, AcOH, 80 °C, 2 h	**5** Yield: 56%	**13** not observed
3	$Pd(OAc)_2$ (1 equiv), DMSO, *t*-BuOH, AcOH, 60 °C, 10 h	**5** Yield: 74%	**13** not observed

Despite considerable experimentation, we were unable to render the conversion of acyl pyrrole **3** to bicycle **5** catalytic in Pd in the presence of a stoichiometric oxidant (e.g., O_2 or benzoquinone). This difficulty has been attributed to the extreme sensitivity of both the starting material and desired product to oxidative decomposition.[22,23] However, we have observed some catalysis in the cyclization of a closely related substrate, acetate **17** (Scheme 5). In this case, oxidative Heck cyclization using 20 mol% $Pd(OAc)_2$, under 1 atm of O_2, afforded [3.3.1] bicycle **18** in 37% yield (55% based on recovered **17**). As isolated yields and catalyst turnover for this process were low, and bicycle **18** was not directly useful for our total synthesis goals, we elected to utilize the stoichiometric Pd-mediated oxidative Heck reaction (Table 2, entry 3) as a means to advance material en route to dragmacidin F.



Scheme 5

In the context of our total synthesis objective, the oxidative Heck reaction strategy is advantageous compared to the classical Heck route for preparing [3.3.1] bicycle **5** on the basis of several factors (Scheme 6): a) the oxidative Heck approach does not require the synthesis of a halogenated starting material (i.e., **2**), which can sometimes be significantly challenging; b) using identical palladium loadings, the oxidative Heck cyclization provides bicycle **5** in nearly twice the chemical yield as the classical Heck reaction; c) the oxidative Heck reaction furnishes bicycle **5** as a single product, whereas the classical Heck reaction requires a more tedious chromatographic separation of the undesired [3.2.2] bicycle (**13**). Although more detailed mechanistic studies are pending, we partially attribute the differences in product distribution between the two strategies to the effects of ligands. More specifically, the use of bulky $P(t\text{-}Bu)_3$ ligands in the classical Heck cyclization could favor olefin insertion transition state **20** over **19**, as it would place the large PdL_nX away from the more substituted position of the olefin undergoing insertion.



Scheme 6

In conclusion, we have found that both the classical and oxidative Heck cyclization reactions are powerful methods for the construction of complex bicyclic molecules. The classical Heck reaction can be used to assemble either [3.3.1] bicycles or [3.2.2] bicycles, the latter of which contain sterically congested all-carbon quaternary stereocenters. In contrast, the oxidative Heck reaction was critical in its ability to deliver [3.3.1] bicycles with excellent selectivity. Ultimately, the [3.3.1] bicycles prepared by these reactions were used as intermediates in the total synthesis of dragmacidin F.[5]

Representative Procedure for the Heck Reaction of 2 (Table 1, 1.0 Equiv Pd)

Bromo acyl pyrrole **2** (52.0 mg, 0.0955 mmol), Pd_2dba_3 (21.9 mg, 0.0239 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (24.4 mg, 0.0477 mmol), THF (1.2 mL), and Cy_2NMe (24.3 μL, 0.115 mmol) were combined under a glovebox atmosphere and stirred at 23 °C for 10 h. The reaction vessel was removed from the glovebox, diluted with hexanes–EtOAc (3:1, 2 mL), and filtered over a plug of silica gel topped with Celite® (hexanes–EtOAc, 3:1). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2, then hexanes–EtOAc, 3:1). The crude product was further purified by flash chromatography (hexanes–EtOAc, 6:1) to afford [3.3.1] bicycle **5** (16.7 mg, 38% yield) and [3.2.2] bicycle **13** (14.4 mg, 33% yield), both as pale yellow oils.

Representative Procedure for the Oxidative Heck Reaction of 3 (Table 2, Entry 3)

To acyl pyrrole **3** (106.0 mg, 0.227 mmol) was added $Pd(OAc)_2$ (51.1 mg, 0.227 mmol), DMSO (32.3 μL, 0.455 mmol), *t*-BuOH (18.2 mL), and AcOH (4.5 mL). The mixture was heated to 60 °C for 10 h, cooled to 23 °C, and filtered over a plug of silica gel (hexanes–EtOAc, 3:1). The solvent was evaporated, and the residue was again filtered over a plug of silica gel (hexanes–EtOAc, 3:1). After removal of solvent in vacuo, the product was purified by flash chromatography on silica gel (hexanes–EtOAc, 6:1) to afford [3.3.1] bicycle **5** (78.4 mg, 74% yield) as a pale yellow oil.

Characterization Data for Bicycles 5 and 13

[3.3.1] Bicycle (**5**): R_f = 0.20 (hexanes–EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 2.7 Hz, 1 H), 6.05 (d, *J* = 2.7 Hz, 1 H), 5.71 (d, *J* = 9.9 Hz, 1 H), 5.58 (d, *J* = 9.9 Hz, 1 H), 5.09–5.05 (m, 2 H), 4.00 (s, 1 H), 3.99–3.90 (m, 1 H), 3.84 (app. t, *J* = 3.0 Hz, 1 H), 3.55–3.47 (m, 2 H), 2.39 (app. dt, *J* = 7.4, 3.8 Hz, 1 H), 2.13–2.03 (comp. m, 2 H), 1.73 (app. t, *J* = 11.8 Hz, 1 H), 0.98–0.76 (comp. m, 11 H), –0.04 (s, 9 H), –0.11 (s, 6 H). ^{1}H NMR (300 MHz, C_6D_6): δ = 6.53 (d, *J* = 2.5 Hz, 1 H), 5.77 (d, *J* = 2.8 Hz, 1 H), 5.55 (d, *J* = 10.2 Hz, 1 H), 5.32 (app. t, *J* = 1.9 Hz, 1 H), 5.26 (d, *J* = 10.2 Hz, 1 H), 5.01–4.97 (m, 1 H), 4.29 (s, 1 H), 4.27–4.19 (m, 1 H), 3.59–3.47 (comp. m, 3 H), 2.45–2.31 (comp. m, 2 H), 2.16 (dd, *J* = 12.1, 3.0 Hz, 1 H), 2.07 (app. t, *J* = 11.8 Hz, 1 H), 0.92–0.89 (comp. m, 11 H), 0.01 (s, 9 H), –0.06 (s, 3 H), –0.07 (s, 3 H). ^{13}C NMR (75 MHz, C_6D_6): δ = 191.5, 149.4, 141.8, 132.0, 125.5, 108.5, 107.4, 76.8, 75.8, 68.4, 66.3, 48.9, 45.5, 40.7, 26.3 (3 C), 18.8, 18.2, –0.8 (3 C), –4.4, –4.7. IR (film): 3480, 2953, 2858, 1651, 1420, 1318, 1251, 1100, 1077 cm^{-1}. HRMS-FAB: *m/z* $[M]^+$ calcd for $C_{24}H_{41}NO_4Si_2$: 463.2574; found: 463.2577. $[\alpha]_D^{23}$ –275.07° (*c* 1.0, $CHCl_3$).

[3.2.2] Bicycle (**13**): R_f = 0.42 (hexanes–EtOAc, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, *J* = 2.7 Hz, 1 H), 6.15 (d, *J* = 2.7 Hz, 1 H), 6.02 (d, *J* = 9.3 Hz, 1 H), 5.98 (d, *J* = 8.8 Hz, 1 H), 5.69 (d, *J* = 9.9 Hz, 1 H), 5.62 (d, *J* = 9.9 Hz, 1 H), 4.93 (s, 1 H), 3.81 (d, *J* = 7.7 Hz, 1 H), 3.50 (t, *J* = 8.0 Hz, 2 H), 2.36 (dd, *J* = 14.3, 7.7 Hz, 1 H), 1.94 (dd, *J* = 14.3, 1.6 Hz, 1 H), 1.55 (s, 3 H), 0.91–0.83 (comp. m, 11 H), 0.02 (s, 3 H), 0.01 (s, 3 H), –0.07 (s, 9 H). ^{1}H NMR (300 MHz, C_6D_6): δ = 6.55 (d, *J* = 2.7 Hz, 1 H), 6.23 (d, *J* = 8.8 Hz, 1 H), 5.96 (d, *J* = 3.3 Hz, 1 H), 5.94 (d, *J* = 9.2 Hz, 1 H), 5.59 (d, *J* = 10.4 Hz, 1 H), 5.40 (d, *J* = 9.9 Hz, 1 H), 5.32 (s, 1 H), 3.82–3.75 (m, 1 H), 3.46 (t, *J* = 7.7 Hz, 2 H), 2.46 (dd, *J* = 13.7, 7.7 Hz, 1 H), 2.25 (dd, *J* = 13.7, 1.6 Hz, 1 H), 1.52 (s, 3 H), 0.92 (s, 9 H), 0.82 (t, *J* = 8.0 Hz, 2 H), –0.03 (s, 3 H), –0.08 (s, 3 H), –0.09 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.7, 144.1, 139.4, 134.5, 129.1, 121.8, 107.7, 78.2, 77.8, 73.3, 66.4, 45.7, 45.0, 26.0 (3 C), 22.2, 18.2, 18.0, –1.25 (3 C), –4.1, –4.6. IR (film): 3432, 2955, 2858, 1645, 1250, 1081 cm^{-1}. HRMS (EI): *m/z* $[M + H]^+$ calcd for $C_{24}H_{42}NO_4Si_2$: 464.2652; found: 464.2665. $[\alpha]_D^{19}$ +19.22° (*c* 1.0, C_6H_6).

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References and Notes

(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, **1998**. (b) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, **1998**, Chap. 2.10, 158. (c) Tsuji, J. In *Transition Metal Reagents and Catalysts*; Wiley: Chichester, UK, **2000**, Chap. 3, 27.

(2) For seminal reports, see: (a) Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, *37*, 2320. (b) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (c) Tao, W.; Silverberg, L. J.; Rheingold, A. L.; Heck, R. F. *Organometallics* **1989**, *8*, 2550.

(3) For recent reviews of the Heck reaction, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (c) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254. (d) Braese, S.; de Meijere, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1; Negishi, E.-I., Ed.; Wiley: Hoboken, New Jersey, **2002**, 1223–1254. (e) Link, J. T. *Org. React.* **2002**, *60*, 157.

(4) The Ni-catalyzed Negishi couplings of secondary halides have also been used to create stereogenic centers. For a pertinent review, see: Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525.

(5) (a) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552. (b) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5970.

(6) In the case of the oxidative Heck route, an alternative Wacker-type mechanism involving nucleophilic attack of a Pd-activated olefin by the pyrrole species cannot be ruled out. It should be noted that in two extensively studied systems for oxidative Heck cyclization, both were shown to involve initial palladation of the aromatic system followed by olefin insertion and β-hydrogen elimination, see ref. 7.

(7) (a) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (c) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 6144.

(8) For catalytic intermolecular oxidative Heck arylations that employ main group organometallic arenes with a range of olefinic coupling partners and Pd(II) catalysis, see: (a) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212. (b) Farrington, E. J.; Brown, J. M.; Barnard, C. F. J.; Rowsell, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 169; and references cited therein.

(9) For related examples of Pd-mediated carbocyclizations in natural product synthesis, see: (a) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. (b) Williams, R. M.; Cao, J.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172.

(10) For reviews and examples regarding the use of (–)-quinic acid in natural product synthesis, see: (a) Barco, A.; Benetti, S.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron: Asymmetry* **1997**, *8*, 3515. (b) Huang, P.-Q. *Youji Huaxue* **1999**, *19*, 364. (c) Hanessian, S.; Pan, J.; Carnell, A.; Bouchard, H.; Lesage, L. *J. Org. Chem.* **1997**, *62*, 465. (d) Hanessian, S. In *Total Synthesis of Natural Products: The 'Chiron' Approach*; Baldwin, E. J., Ed.; Pergamon Press: Oxford, **1983**, 206–208.

(11) (a) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630. (b) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203. (c) Edwards, M. P.; Ley, S. V.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503. (d) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723.

(12) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300.

(13) (a) Tada, H.; Tozyo, T. *Chem. Lett.* **1988**, *5*, 803. (b) For a discussion regarding the instability of bromopyrroles, see: Audebert, P.; Bidan, G. *Synth. Met.* **1986**, *15*, 9.

(14) Jeffery, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751; see also references cited therein.

(15) (a) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844. (b) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Reirmeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, *3*, 1357. (c) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Mol. Catal. A: Chem.* **1995**, *103*, 133.

(16) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.

(17) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. (c) Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.

(18) DMSO has commonly been employed in oxidative Pd(II) chemistry. See: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (b) Van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357. (c) Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749. (d) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (e) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400, see also references cited therein.

(19) Recently, related oxidative cyclizations of pyrrole substrates have been reported. See: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Paladino, G. *Tetrahedron* **2005**, *61*, 1077. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.

(20) Gilow, H. M.; Hong, Y. H.; Millirons, P. L.; Snyder, R. C.; Casteel, W. J. Jr. *J. Heterocycl. Chem.* **1986**, *23*, 1475.
(21) Reactions conducted in the presence of CH_3COOD led to deuterium incorporation in the pyrrole ring of both the starting material (**3**) and the product (**5**), mostly at C(4).
(22) The instability of pyrroles to oxidants is well known. See: (a) Ciamician, G.; Silber, P. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 1842. (b) Bernheim, F.; Morgan, J. E. *Nature (London)* **1939**, *144*, 290. (c) Chierici, L.; Gardini, G. P. *Tetrahedron* **1966**, *22*, 53.
(23) The instability of the starting material and product to oxidation was confirmed by a series of control experiments where aliquots of reactions were carefully monitored by ^1H NMR analysis with an internal standard. In the presence of oxidants, substantial non-specific decomposition readily took place.