JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Pd-Catalyzed Chemoselective Catellani *Ortho*-Arylation of Iodopyrroles: Rapid Total Synthesis of Rhazinal

Xianwei Sui,[†] Rui Zhu,[†] Gencheng Li, Xinna Ma, and Zhenhua Gu*

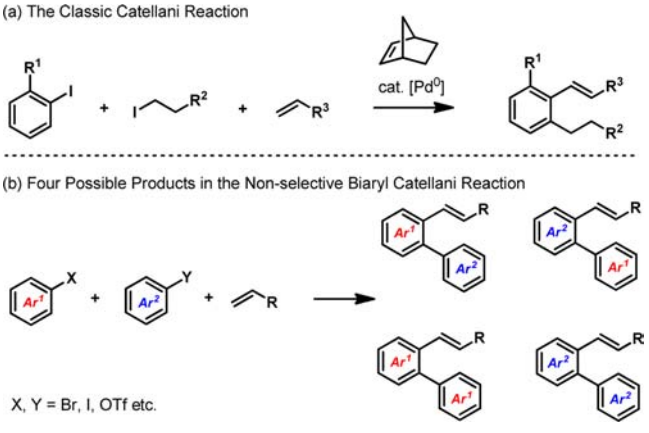
Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, China

Supporting Information

ABSTRACT: A Pd-catalyzed chemoselective Catellani reaction of iodopyrroles was developed. The rare chemoselectivity between two different aryl halides was realized by optimizing the kinetics of the different steps of this multicomponent process. The new developed method led to the rapid synthesis of rhazinal in a highly efficient manner.

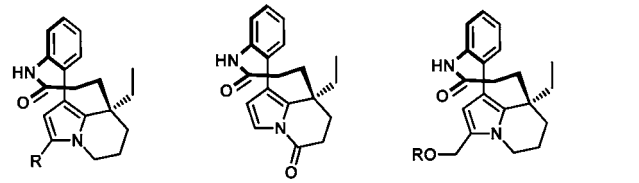
Transition-metal-catalyzed cross-coupling reactions have been proven to be highly beneficial transformations for organic synthesis and revolutionized synthesis planning in natural products total synthesis. Transition-metal-catalyzed domino or multicomponent reactions enable the assembly of complex molecules in a single step with a rapid buildup of complexity.[1] Among them, the Catellani reaction stands out as a powerful tool to construct polyfunctionalized aromatic rings.[2] Contributions from the groups of Catellani,[3] Lautens,[4] and others[5] expanded the utility of this transformation to various structurally divergent polyfunctionalized aromatic compounds. Typically, a combination of an aryl halide and an alkyl halide is necessary to circumvent chemoselectivity problems (Scheme 1a). The reaction with two different aryl halides has been rarely reported potentially due to poor chemoselectivity.[3a−c,4f] This point is illustrated in Scheme 1b, showing the formation of four theoretically possible biaryl products when two distinct aryl halides are used as substrates. Herein we report an application of an efficient chemoselective norbornene-mediated Catellani reaction in a concise total synthesis of rhazinal with two different aryl halides as the reaction components.

Scheme 1. Catellani Reaction



The rhazinilam family of natural products represents a class of compounds with interesting biological activity. (−)-Rhazinilam (**1**) was first isolated in 1965 from Mesodinus austrilia,[6] and later from *Rhazya stricta* Decaisne[7] and *Kopsia singapurensis* (Scheme 2).[8] (−)-Rhazinal (**2**),[9] (−)-rhazinicine (**3**),[10] and kopsiyunnanines (**4**−**6**)[11] were isolated in 1999, 2001, and 2009, respectively. It was found that (−)-rhazinilam (**1**), which mimics the effects of both vinblastine and Taxol, could induce an irreversible assembly of tubulin and inhibit cold-induced disassembly of microtubules.[12] It showed strong cytotoxicity toward various cancer cell lines in vitro, while having no activity in vivo, which led to several studies directed at its analogue synthesis and their biological evaluation.[13]

Scheme 2. Rhazinilam Family of Natural Products



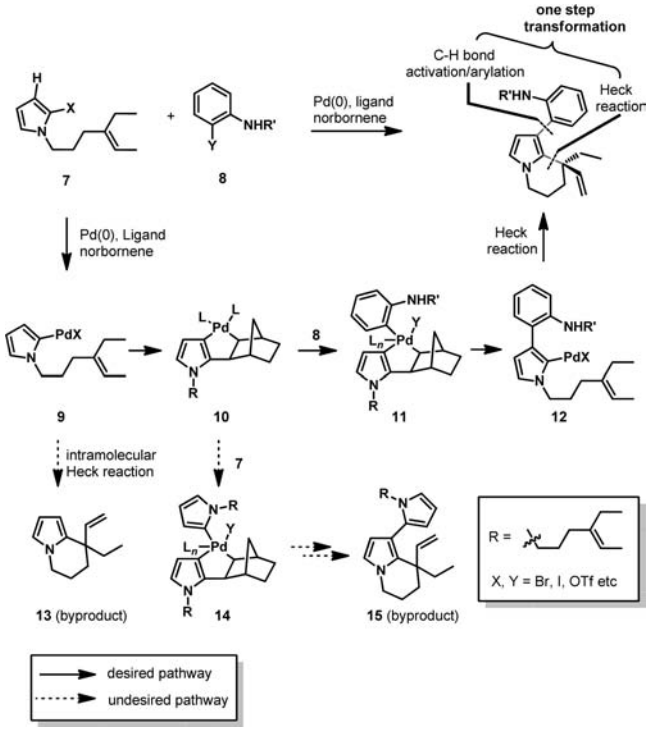
Structurally, compounds in the rhazinilam family share a tetracyclic framework which contains an axial chiral pyrrole aniline biaryl fragment and a strained nine-membered lactam bearing a quaternary carbon center. The unusual structure provided a popular platform for the development of new strategies and methods, and more than 10 syntheses in this area have been reported to date.[14] A C−H bond functionalization strategy was adopted by the groups of Sames, Trauner, and Gaunt,[15] while Nelson et al. constructed the quaternary carbon center via a gold-catalyzed allene cyclization.[16] During the synthesis of (−)-rhazinal, Banwell et al. constructed the tetrahydroindolizine fragment via asymmetric imminium-ion catalysis.[17] Zakarian's synthesis features a Heck-type transannular cyclization of a 13-membered lactam, where the six- and nine-membered rings as well as a quaternary carbon center were constructed in one step through axial-to-point chirality transfer.[18]

Received: May 6, 2013
Published: June 11, 2013

   dx.doi.org/10.1021/ja404494u | *J. Am. Chem. Soc.* 2013, 135, 9318−9321

The key features of our own synthetic plan are listed in Scheme 3. One phenyl−pyrrole bond and one six-membered

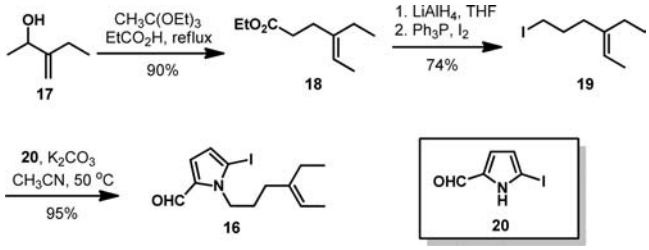
Scheme 3. Proposed Key Transformation in the Synthesis of Rhazinilam Family Natural Products



ring are projected to be formed in one step via the norbornene-mediated Catellani reaction. The pivotal issue is to match the reactivity of 2-halopyrrole and 2-haloaniline components. By tuning the nature of substituents and halogen atoms, as well as reaction conditions, we expect that (1) during the initial oxidative addition step, Pd(0) will react preferentially with aryl halide **7** rather than **8**; (2) pyrrolylpalladium species **9** would undergo the insertion reaction with norbornene faster than the intramolecular Heck reaction giving undesired product **13**;[19] and (3) once the carbopalladacycle formed, the Pd(II) species **10**[20] will selectively react with **8** rather than **7**, which will give the undesired bipyrrole compound **15**. Reductive elimination of **11**, followed by norbornene release, should deliver **12**, which is expected to undergo the intramolecular Heck reaction affording the fully assembled core structure.[21,22] Thus, a major goal of the study was to identify reaction components that would have optimal relative kinetics in the various steps of the multistep process, driving the reaction toward the desired cross-coupling/Heck product.

Preliminary screening experiments with different substituted 2-halopyrroles revealed that 2-iodopyrrole with an electron-withdrawing substituent on the aromatic ring is necessary for successful cross-coupling (for details, see Supporting Information (SI)).[23] As a result, the easily available compound **16** was chosen as our model substrate, whose synthesis was listed in Scheme 4. Starting from the known alcohol **17**, which was synthesized from acetylacetone following Amri's procedure[24] (for details, see SI), the alkyl fragment **19** could be obtained via a routine three-step manipulation: Johnson−Claisen rearrangement,[25] reduction, and iodination reactions. Alkylation of the

Scheme 4. Synthesis of Model Compound 16



known iodopyrrole **20**[26] with iodide **19** delivered the model compound in excellent yield.

With **16** in hand, we conducted the nonsymmetric biaryl coupling/Heck reaction with various 2-haloaniline derivatives and their analogues (Figure 1). All the reactions of **16** with **8b**−**i** gave either the direct Heck-type product **22** or an uncharacterized dimer of **16**. Fortunately, heating the mixture **16** with 1-bromo-2-nitrobenzene **8a** in the presence of palladium dichloride, triphenylphosphine, and norbornene in acetonitrile gave the biaryl product **21** in 11% yield along with 10% of the direct Heck cyclization product **22** (Table 1, entry 1).[4o] The screening of the solvents found that the reaction in dioxane could give the desired product in 77% yield, with no significant amount of **22** being detected (entries 2−4). A similar yield (72%) was obtained when tri(2-furyl)phosphine

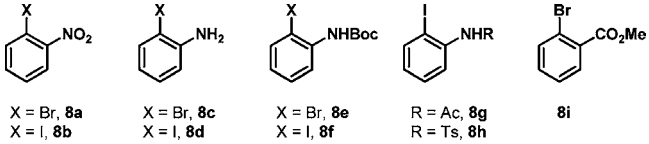
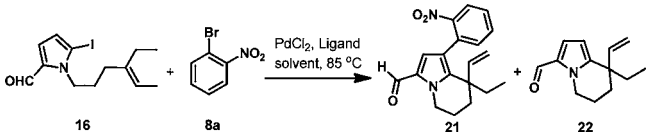


Figure 1. 2-Haloaniline derivatives and their analogues.

Table 1. Nonsymmetric Biaryl Coupling of 16 with 1-Bromo-2-nitrobenzene (8a)[a]



16 8a 21 22

entry	ligand	base (2.5 equiv)	solvent	yield of **21** (%)[b]
1	PPh_3	Cs_2CO_3	CH_3CN	11[c,d]
2	PPh_3	Cs_2CO_3	DMF	<2
3	PPh_3	Cs_2CO_3	toluene	67
4	PPh_3	Cs_2CO_3	dioxane	77
5	$P(2\text{-furyl})_3$	Cs_2CO_3	dioxane	72
6	*rac*-BINAP	Cs_2CO_3	dioxane	<2[e]
7	dppe	Cs_2CO_3	dioxane	35[d]
8	PPh_3	K_2CO_3	dioxane	51
9	PPh_3	KO*t*-Bu	dioxane	<2
10	PPh_3	2,6-lutidine	dioxane	<2[e]

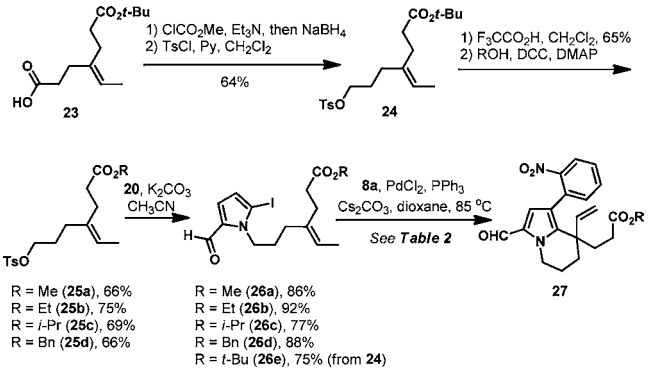
[a]The reaction was conducted with **16** (0.1 mmol), **8a** (6 equiv), $PdCl_2$ (10 mol %), ligand (20 mol %) (for *rac*-BINAP and dppe, 10 mol %), base (2.5 equiv), and norbornene (6 equiv) at 85 °C. [b]Isolated yields. [c]The reaction was conducted at 81 °C; **22** was isolated in 10% yield. [d]An unknown dimer of **16** was also isolated. [e]Crude ^1H NMR indicated most of SM unchanged. BINAP = 2,2′-bis-(diphenylphosphino)-1,1′-binaphthyl, dppe = 1,2-bis-(diphenylphosphino)ethane.

dx.doi.org/10.1021/ja404494u | J. Am. Chem. Soc. 2013, 135, 9318−9321

was used as a ligand (entry 5), while the reaction became sluggish when bidentate phosphine ligands such as BINAP or dppe were used (entries 6 and 7). Different bases were also screened, and it was found that K_2CO_3 is also an effective base (entry 8). The reaction with KO*t*-Bu as the base led to decomposition of iodopyrrole substrate **16** (entry 9), while with 2,6-lutidine it resulted in very poor conversion (entry 10).

Initially we tried to introduce the carboxyl group via the Ru-catalyzed alkene cross-metathesis with acrylates. However, presumably due to steric hindrance of the neopentylic vinyl group under various conditions with Grubbs second generation or Hoveyda-Grubbs second catalysts, alkene **21** is either unstable or inert. After unsuccessful functionalization of the terminal C=C double bond by various methods including hydroboration,[27] hydrozirconation,[28] and hydrocarbonylation,[29] we redesigned our approach to include the desired carboxy group in the precursor to the key cascade metal-catalyzed process. Thus, a group of substrates **26a**–**e** were synthesized (Scheme 5), which could be accessed from the known acid **23** via three- to five-step manipulation.

Scheme 5. Synthesis of Compound 27



Selective reduction of the known acid **23**[18] to alcohol, followed by tosylation, gave **24** in 64% yield. Deprotection of *tert*-butyl ester with trifluoroacetic acid, subsequent esterification, and alkylation would give the desired key precursors **26** (Scheme 5). To our disappointment, under identical conditions for the cascade metal-catalyzed process, the methyl ester substrate **26a** gave only a trace amount of the desired product with poor conversion (~50%) (Table 2, entry 1). However, a 40% yield of the cross-coupling/Heck product **27b** was obtained when ethyl ester **26b** was used (entry 2). In order to obtain more information about this remote substituent effect, three additional substrates **26c**–**e** were prepared in the same manner. Interestingly the reaction of isopropyl (**26c**) or benzyl ester (**26d**) afforded the cyclization products in 66% and 33% yields, respectively (entries 3 and 4). The best results were obtained when *tert*-butyl ester **26e** was used. Under our standard conditions, the reaction delivered the desired product **27e** in 85% yield (entry 5). Currently, the origin of this unusual substituent effect is unclear.

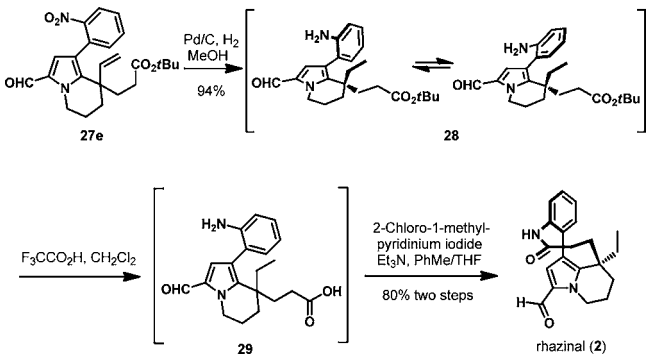
Table 2. Remote Substituent Effect of Nonsymmetric Biaryl Coupling of 26 with 1-Bromo-2-nitrobenzene[a]

entry	R (**26**)	yield of **27** (%)[b]
1	Me (**26a**)	<5 (**27a**)[c]
2	Et (**26b**)	40 (**27b**)
3	*i*-Pr (**26c**)	66 (**27c**)
4	Bn (**26d**)	33 (**27d**)
5	*t*-Bu (**26e**)	85 (**27e**)

[a]The reaction was conducted at 0.28–0.33 mmol scale; for details, see SI. [b]Isolated yields. [c]The reaction resulted in 50% conversion on analysis of crude mixture.

With the fully functionalized core structure **27e** in hand, the synthesis of rhazinal (**2**) could be completed in three steps (Scheme 6). In the presence of Pd/C at 3 atm of pressure of hydrogen, both the nitro group and the double bond could be reduced to deliver **28** in high yield. Compound **28** showed a pair of atropisomers (~1:1) due to the slow rotation of the pyrrole–phenyl bond at rt in $CDCl_3$; however, this did not affect the final cyclization reaction. Removal of the *tert*-butyl group under standard acidic conditions afforded amino acid **29**, which could be smoothly cyclized to afford macrolactam rhazinal (**2**) with 2-chloro-1-methylpyridinium iodide (Mukaiyama reagent)[30] in a diluted solution. The ^1H and ^{13}C NMR data of synthetic **2** are identical to those of the natural or previous synthesized rhazinal.

Scheme 6. Complete the Synthesis of Rhazinal (2)



In summary, a concise and efficient synthesis of rhazinal was developed. The synthesis features the tandem Catellani-type *ortho*-arylation/intramolecular Heck reaction which enables access to the core structure in a rapid and modular fashion. In this case, a rare chemoselectivity between two different aryl halides was realized by optimizing the kinetics of the different steps of this multicomponent process. This observation provides additional insight for extending the utility of the Catellani reaction in complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

zhgu@ustc.edu.cn

Author Contributions

†X.S. and R.Z. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by National Natural Science Foundation of China (21272221) and the Recruitment Program of Global Experts.

■ REFERENCES

(1) (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reaction in Organic Synthesis*; WILEY-VCH: Weinheim, 2006. (b) *Multicomponent Reactions*, Zhu, J., Bienayrmé, H., Eds.; WILEY-VCH; Weinheim, 2005.

(2) (a) Catellani, M.; Ferioli, L. *Synthesis* **1996**, 769. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119.

(3) For a review, see: Catellani, M. *Synlett* **2003**, 298. (a) Motti, E.; Della Ca, N.; Ferraccioli, R.; Catellani, M. *Synthesis* **2008**, 995. (b) Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. *Org. Lett.* **2006**, *8*, 3967. (c) Faccini, F.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2004**, *126*, 78. (d) Ferraccioli, R.; Carenzi, D.; Rombolà, O.; Catellani, M. *Org. Lett.* **2004**, *6*, 4759. (e) Ferraccioli, R.; Carenzi, D.; Catellani, M. *Tetrahedron Lett.* **2004**, *45*, 6903. (f) Motti, E.; Rossetti, M.; Bocelli, G.; Catellani, M. *J. Organomet. Chem.* **2004**, *689*, 3741. (g) Motti, E.; Mignozzi, A.; Catellani, M. *J. Mol. Catal. A: Chem.* **2003**, 115. (h) Cetallani, M.; Motti, E.; Baratta, S. *Org. Lett.* **2001**, *3*, 3611. (i) Catellani, M.; Motti, E.; Minari, M. *Chem. Commun.* **2000**, 157.

(4) (a) Weinstabl, H.; Suhartono, M.; Qureshi, Z.; Lautens, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5305. (b) Liu, H.; El-Salfiti, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9846. (c) Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 3312. (d) Gericke, K. M.; Chai, D. I.; Bieler, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1447. (e) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 5095. (f) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (g) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (h) Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett.* **2007**, *9*, 5255. (i) Hulcoop, D. G.; Lautens, M. *Org. Lett.* **2007**, *9*, 1761. (j) Martins, A.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 4827. (k) Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Marianmpillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939. (l) Jafarpour, F.; Lautens, M. *Org. Lett.* **2006**, *8*, 3601. (m) Mariampillai, B.; Alberico, D.; Bidau, V.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 14436. (n) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053. (o) Pache, S.; Lautens, M. *Org. Lett.* **2003**, *5*, 4827.

(5) (a) Jiao, L.; Bach, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 6080. (b) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (c) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990. (d) Larraufie, M.-H.; Maestri, G.; Beaume, A.; Derat, É.; Ollivier, C.; Fensterbank, L.; Courillon, C.; Lacôte, E.; Catellani, M.; Malacria, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12253.

(6) Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822.

(7) Banerji, A.; Majumder, P. L.; Chatterjee, A. G. *Phytochemistry* **1970**, *9*, 1491.

(8) Thoison, O.; Guénard, D.; Sévenet, T.; Kan-Fan, C.; Quirion, J.-C.; Husson, H.-P.; Deverre, J.-R.; Chan, K. C.; Potier, P. C. R. *Acad. Sci. Pair II* **1987**, *304*, 157.

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

(10) Gerasimenko, I.; Sheludko, Y.; Stöckigt, J. *J. Nat. Prod.* **2001**, *64*, 114.

(11) Wu, Y.; Suehiro, M.; Kitajima, M.; Matsuzaki, T.; Hashimoto, S.; Nagaoka, M.; Zhang, R.; Takayama, H. *J. Nat. Prod.* **2009**, *72*, 204.

(12) David, B.; Sévent, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thioson, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317.

(13) (a) Baudoin, O.; Claveau, F.; Thoret, S.; Herrbach, A.; Guénard, D.; Guéritte, F. *Bioorg. Med. Chem.* **2002**, *10*, 3395. (b) Dupont, C.; Guénard, D.; Thal, C.; Thoret, S.; Guéritte, F. *Tetrahedron Lett.* **2000**, *41*, 5853. (c) Dupont, C.; Guénard, D.; Tchertanov, L.; Thoret, S.; Guéritte, F. *Bioorg. Med. Chem.* **1999**, *7*, 2961.

(14) The first total synthesis of rhazinilam was reported by Smith and co-workers; see: Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179. For other synthesis, see: Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647.

(15) (a) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321. (b) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (c) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207. (d) Bowie, A. L.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581. (e) Beck, E. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9288. (f) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.

(16) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352.

(17) (a) Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, 163. (b) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem.* **2003**, *1*, 296.

(18) Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224.

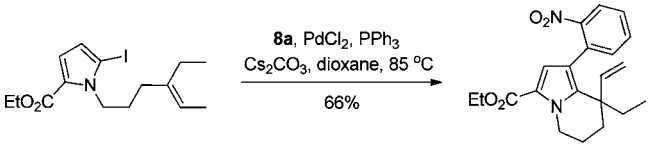
(19) For reviews of the application of the Heck reaction in natural products synthesis, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1.

(20) For the studies of isolation and reactivity of a norbornene carbopalladacycle, see: Catellani, M.; Mann, B. E. *J. Organomet. Chem.* **1990**, *390*, 251.

(21) A transmetallation mechanism from two Pd(II) species was also proposed; see: Cardenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033.

(22) The first example of using an intramolecular Heck reaction as a termination step in the Catellani reaction, see: Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045.

(23) During the preliminary screening, it was found that ethyl 2-iodopyrrole-5-carboxylate derived compound was also an effective substrate. The reaction gave a 66% yield of the cross-coupling/cyclization product under identical conditions.



(24) Ayed, T. B.; Amri, H. *Synth. Commun.* **1995**, *25*, 3813.

(25) Langlois, Y. In *The Claisen Rearrangement*; Hiersemann, M., Nubbemeyer, U., Eds; WILEY-VCH: Weinheim, 2007.

(26) (a) Denat, F.; Gaspard-Houghmane, H.; Dubac, J. *J. Organomet. Chem.* **1992**, *423*, 173. (b) Muchowski, J. M.; Hess, P. *Tetrahedron Lett.* **1988**, *29*, 777.

(27) Brown, H. C. *Tetrahedron* **1961**, *12*, 117.

(28) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.

(29) (a) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (b) Ko, S.; Na, Y.; Shang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750.

(30) Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045.