Organic LETTERS

Letter

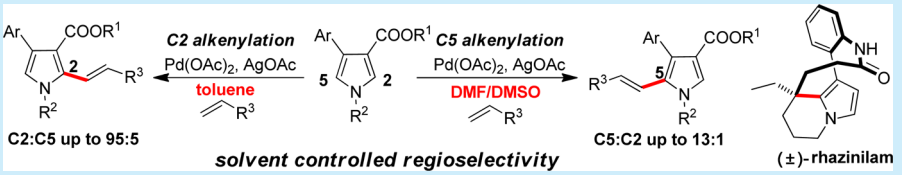
pubs.acs.org/OrgLett

Solvent-Controlled Switchable C−H Alkenylation of 4-Aryl-1*H*-pyrrole-3-carboxylates: Application to the Total Synthesis of (±)-Rhazinilam

Youla Su, Haipin Zhou, Jiaxuan Chen, Jinyi Xu, Xiaoming Wu, Aijun Lin,* and Hequan Yao*

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing, 210009, P. R. China

Supporting Information

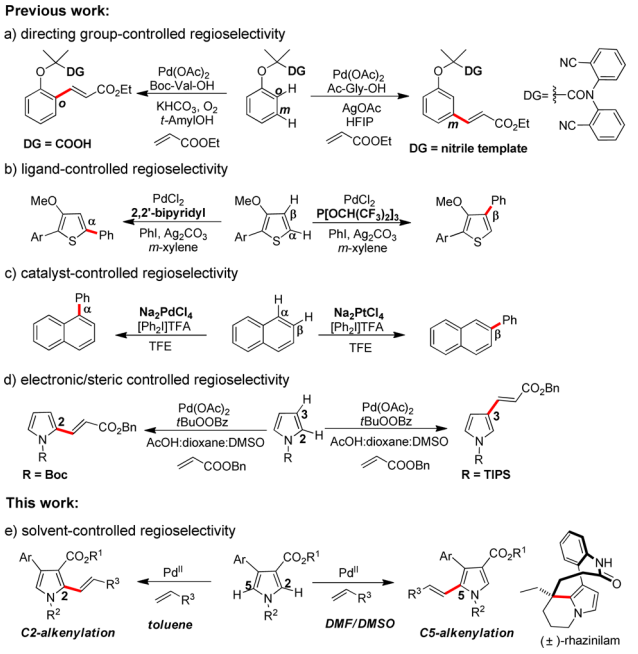


ABSTRACT: A solvent-controlled switchable C−H alkenylation of 4-aryl-1*H*-pyrrole-3-carboxylates via a $Pd(OAc)_2$ catalyzed oxidative Heck reaction was first realized. The corresponding C2 and C5 alkenylation products were obtained in good yields with high regioselectivities, respectively. The selective C5-alkenylation was successfully applied to the total synthesis of (±)-rhazinilam.

Over the past decades, transition-metal catalyzed direct C−H activation has emerged as a powerful and reliable tool in natural products synthesis, medicinal chemistry, and material sciences.[1] Despite the tremendous advances, the widespread application of C−H functionalization was still hampered by some long-standing challenges.[2] In particular, the control of regioselectivity is one of the most intriguing problems due to the multitude of C−H bonds existing in one molecule with subtle differences in intrinsic reactivity.[3,4] Common solutions for this problem involved directing groups,[5] ligands,[6] catalysts,[7] and electronic/steric[8] controlled regioselectivity. The Yu group[9] reported a highly efficient distal C−H bonds activation approach via an end-on nitrile template (Scheme 1a), which provided a groundbreaking route for *meta*-selectivity compared to the conventional *ortho*-directing mode. Itami et al. produced *β*-selective arylation of thiophenes using a phosphine ligand and *α*-selective arylation products with 2,2′-bipyridyl (Scheme 1b).[6d,e] In 2013, Sanford[7b] disclosed a complete reversal in selectivity of naphthalene arylation under the catalysis of Na_2PtCl_4 instead of Na_2PdCl_4 (Scheme 1c). In 2006, Gaunt developed a switchable 2 or 3 alkenylation of simple pyrroles via N-protecting groups differentiating in steric and electronic properties. N-Boc pyrroles offered 2-alkenylation products, while N-TIPS pyrroles gave 3-alkenylation products (Scheme 1d).[8a]

Recently, the central theme in C−H bond functionalization is the development of a convenient method to install the reaction partner at a specific position and to achieve the target compounds from simple materials efficiently. However, the directing groups are not always desirable in the target molecules, thus the inevitable removal issue obviously limited their further synthetic utility. Moreover, the implication of relatively expensive catalysts or ligands does not meet the atom-economic and operationally simple request. Compared to Gaunt's work on pyrrole 2- or 3-alkenylation,[8a] differentiation between 2- and 5-positions should be more challenging. Herein, we will describe a direct solvent-controlled[10] switchable

Scheme 1. Strategies for Controlling Regioselectivity in C−H Bond Functionalizations



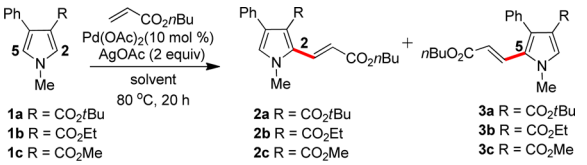
Received: August 12, 2014

   dx.doi.org/10.1021/ol5023933 | *Org. Lett.* XXXX, XXX, XXX−XXX

alkenylation of 3,4-substituted pyrroles and the application of C5-alkenylation to the total synthesis of (±)-rhazinilam (Scheme 1e).

We commenced our research by screening the reaction between *tert*-butyl *N*-methyl-4-phenyl-1*H*-pyrrole-3-carboxylate **1a** and *n*-butyl acrylate in the presence of 10 mol % of $Pd(OAc)_2$ and 2 equiv of AgOAc; the results are shown in Table 1. Reactions in acetone, dioxane, 1,2-dichloroethane, and

Table 1. Optimization of the Reaction Conditions[a]



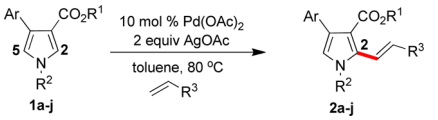
entry	R	solvent	total yield[b] (%)	ratio[b] (2:3)
1	COO*t*Bu	acetone	73	90:10
2	COO*t*Bu	1,4-dioxane	66	91:9
3	COO*t*Bu	DCE	74	94:6
4	COO*t*Bu	mesitylene	79	>95:5
5	**COO*t*Bu**	**toluene**	**92(89[c])**	**>95:5**
6	COO*t*Bu	DMF	53	4:1
7	COO*t*Bu	DMA	41	3:1
8	COO*t*Bu	NMP	50	3:1
9	COO*t*Bu	HMPA	41	1:1
10	COO*t*Bu	DMSO	68	1:5
11	COO*t*Bu	DMF/DMSO[d]	81(68[c])	1:6
12	COOEt	DMF/DMSO[d]	80(68[c])	1:7
13	**COOMe**	**DMF/DMSO[d]**	**85(73[c])**	**1:8**

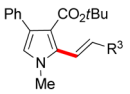
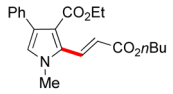
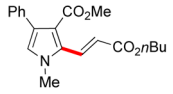
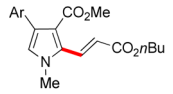
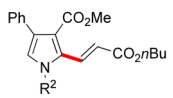
[a]Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), acrylate (1.0 mmol), and AgOAc (1.0 mmol) in solvent (2.0 mL), 80 °C, 20 h. [b]Yield and ratio were determined by ^{1}H NMR using dibromomethane as the internal standard. [c]Isolated yields of the major products. [d]DMF/DMSO (2.0 mL, v/v = 4:1).

mesitylene favorably produced the C2-alkenylated product **2a** with excellent regioselectivities (Table 1, entries 1−4), and toluene gave the best performance (entry 5). Further screening of solvents indicated that the C5-selectivity was slightly improved when aprotic polar solvents were employed (entries 6−9). Surprisingly, the regioselectivity was reversed when DMSO was employed as solvent, offering C5-alkenylated product **3a** (C5:C2 = 5:1) as the major product (entry 10). Subtle optimization revealed that the combination of DMF/DMSO (4:1) could slightly improve the C5-selectivity (C5:C2 = 6:1) (entry 11). Finally, we found that the ratio of C5 to C2 isomer could be further increased to 8:1 when **1c** was employed as the substrate (entry 13).

The substrate scope and generality of C2-alkenylation was investigated under the optimized conditions as illustrated in Table 2. *tert*-Butyl, ethyl, and methyl acrylates reacted with **1a** smoothly to form **2aa**−**2ac** in 75−86% yields with excellent regioselectivities (C2:C5 > 95:5). Acrylamides and acrylonitrile gave **2ad**−**2ag** in moderate yields under a prolonged reaction time and higher temperature. For substrates bearing *tert*-butyl, ethyl, and methyl ester at the C3 position (**1a**−**1c**), the reactions afforded the corresponding products **2a**−**2c** in 89%, 70%, and 83% yield. In addition, substitutions at the C4-phenyl ring with electron-donating and -withdrawing groups were all compatible with this process. For example, 4-OMe substituted **1f** provided **2f** in 75% yield, and the 4-Cl substituted **1d** and 4-CF_3 substituted **1g** furnished **2d** and **2g** in 74% and 71% yield.

Table 2. Substrate Scope of C2-Alkenylation[a]



C2-alkenylation products		yield[b] and ratio[c] (C2:C5)	
	**2a**	R3 = CO2*n*Bu	89% (95:5)
	2aa	R3 = CO2*t*Bu	75% (>95:5)
	2ab	R3 = CO2Et	86% (>95:5)
	2ac	R3 = CO2Me	84% (>95:5)
	2ad	R3 = CONMe2	53% (91:9)[d]
	2ae	R3 = CONEt2	60% (92:8)
	2af	R3 = CONHBn	61% (90:10)[e]
	2ag	R3 = CN	64% (>95:5)[f]
	**2b**		70% (>95:5)
	**2c**		83% (93:7)
	**2d**	Ar = 4-Cl-C6H4	74% (>95:5)
	2e	Ar = 4-*t*Bu-C6H4	71% (>95:5)[g]
	2f	Ar = 4-OMe-C6H4	75% (95:5)
	2g	Ar = 4-CF3-C6H4	71% (>95:5)
	2h	Ar = 2-NO2-C6H4	62% (>95:5)
	**2i**	R2 = Et	75% (>95:5)
	2j	R2 = Bn	53% (91:9)[h]

[a]Unless otherwise mentioned, all reactions were carried out using **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.0 mmol), and alkenes (1.0 mmol) in toluene (2.0 mL), 80 °C, 20 h. [b]Isolated yields of major products. [c]Ratio and *E*/*Z* were determined by ^{1}H NMR. [d]120 °C, 36 h. [e]100 °C. [f]120 °C, *E*/*Z* = 1.6:1. [g]*E*/*Z* = 14:1. [h]*E*/*Z* = 8:1.

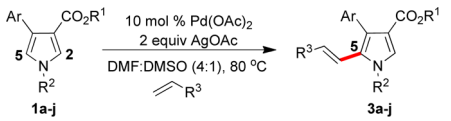
Further studies revealed that **1h** with the NO_2 group on the phenyl ring could also convert into the desired product **2h** in 62% yield with excellent regioselectivity (C2:C5 > 95:5). When *N*-ethyl and *N*-benzyl substituted **1i** and **1j** were tested, **2i** and **2j** were achieved in 75% and 53% yield.

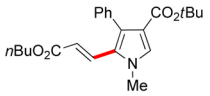
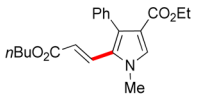
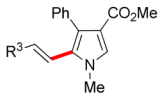
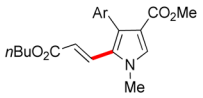
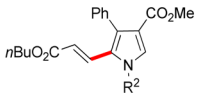
Next, we turned our attention to the investigation of C5-alkenylation (Table 3). Similar to the C2-alkenylation procedure, a series of alkenes worked well and C5-alkenylation products **3ca**−**3cg** were obtained in 57−74% yields. It was noteworthy that the regioselectivities of the reactions with acrylamides (i.e., **3cd** in 13:1 and **3ce** in 13:1) were higher than those with acrylates (i.e., **3ca** in 9:1 and **3cb** in 8:1). Moreover, a variety of substituents on the phenyl ring, regardless of the electron-deficient to -rich nature, all successfully produced C5-alkenylated products **3d**−**3h** in 64−75% yields with good regioselectivities (6:1−9:1). *N*-Ethyl and *N*-benzyl substituted substrates **1i** and **1j** offered the corresponding **3i** and **3j** in 65% and 71% yields.

To better understand the reaction, we proposed a plausible mechanism for our regioselective alkenylation process, which is shown in Scheme 2. The palladation could preferentially occur at the C2 position via a carboxylate assisted chelation[11] to form intermediate **I** in toluene. A subsequent Heck-type reaction offers the C2-alkenylation pyrroles **2**. However, a strong coordinating solvent (DMSO)[12,10b] overrides the chelation effect of the carboxylate group, promoting the palladation at the more electron-rich C5 position through an electrophilic C−H

dx.doi.org/10.1021/ol5023933 | *Org. Lett.* XXXX, XXX, XXX−XXX

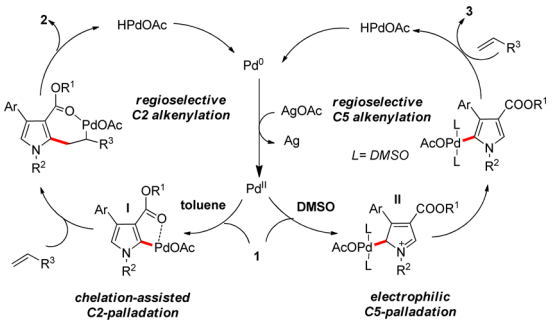
Table 3. Substrate Scope of C5-Alkenylation[a]



C5-alkenylation products		yield[b] and ratio[c] (C_5:C_2)
	**3a**	68% (6:1)
	**3b**	68% (7:1)
	**3c**	$R^3 = CO_2nBu$ 73% (8:1)
	3ca	$R^3 = CO_2tBu$ 68% (9:1)
	3cb	$R^3 = CO_2Et$ 72% (8:1)
	3cc	$R^3 = CO_2Me$ 70% (8:1)
	3cd	$R^3 = CONMe_2$ 70% (13:1)
	3ce	$R^3 = CONEt_2$ 74% (13:1)
	3cf	$R^3 = CONHBn$ 64% (7:1)[d]
	3cg	$R^3 = CN$ 57% (3:1)[e]
	**3d**	Ar = 4-Cl-C_6H_4 75% (9:1)
	3e	Ar = 4-*t*Bu-C_6H_4 64% (6:1)
	3f	Ar = 4-OMe-C_6H_4 70% (9:1)
	3g	Ar = 4-CF_3-C_6H_4 72% (9:1)
	3h	Ar = 2-NO_2-C_6H_4 71% (9:1)
	**3i**	R^2 = Et 65% (5: 1)
	3j	R^2 = Bn 71% (8: 1)

[a]Unless otherwise mentioned, all reactions were carried out using **1** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (1.0 mmol), and alkenes (1.0 mmol) in DMF/DMSO (2.0 mL, v/v = 4:1), 80 °C, 20 h. [b]Isolated yields of major products. [c]Ratio was determined by ^{1}H NMR. [d]100 °C. [e]*E*/*Z* = 1.6:1.

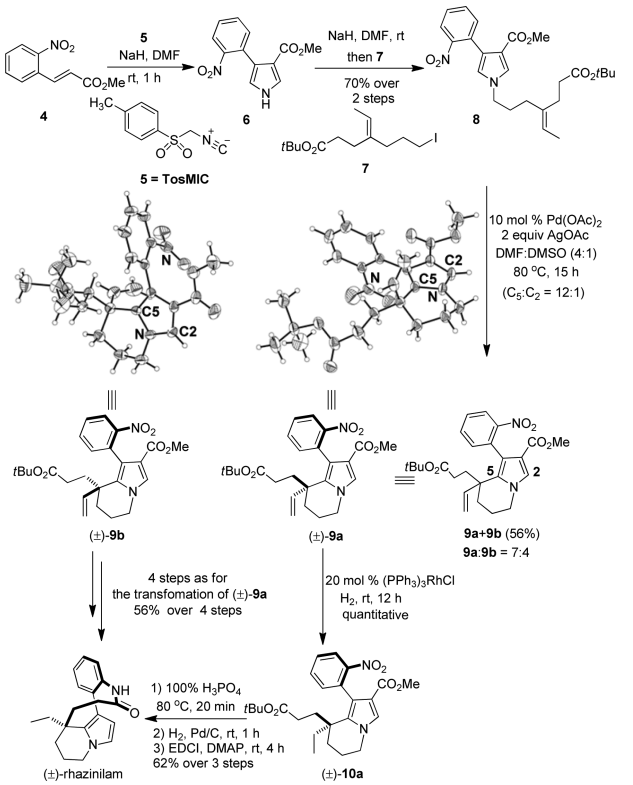
Scheme 2. Proposed Mechanism of the Regioselective C−H Alkenylations



activation pathway to produce intermediate **II**, followed by rearomatization and a Heck-type reaction to afford the C5-alkenylated products **3**. In additional studies,[13] we realized that the ratios of **3c** are closely related to the equivalents of DMSO; 40 mol % of DMSO could reverse the ratio (**2c**:**3c**) from 1.5:1 to 1:1.5. Further research showed that methyl 2-(4-(methylthio)phenyl) acetate, which contains a methylthio group, could also offer **3c** in good yield and regioselectivity.

Since pyrrole structural motifs were present in diverse pharmaceutical agents and bioactive natural products,[14] we then focused on the application of our method to the total synthesis of (±)-rhazinilam,[15] which showed moderate antitumor activity. As illustrated in Scheme 3, pyrrole **6** was first

Scheme 3. Total Synthesis of (±)-Rhazinilam



synthesized from phenyl acrylate **4** and TosMIC **5** through a van Leusen reaction.[16] Treatment of **6** and iodoolefin **7**[15e] with NaH in DMF provided alkyl pyrrole **8**. With the full carbon skeleton in hand, we set out to attempt the key intramolecular oxidative Heck reaction to build the architecture of (±)-rhazinilam. Gratifyingly, when **8** was subjected to the regioselective C5-alkenylation conditions, the desired product **9** was achieved in 56% yield (C5:C2 = 12:1). Notably, due to the existence of the C3-carboxylate group, compound **9** contains two pairs of separable stereoisomers (**9a**:**9b** = 7:4). The relative configurations of **9a** and **9b** were determined by X-ray structural analysis.[17] Hydrogenation of **9a** with Wilkinson's catalyst[18] gave intermediate **10a** in quantitative yield. Subsequent decarboxylation, hydrogenation, and macrolactamization fulfilled the total synthesis of (±)-rhazinilam. Fortunately, we found that **9b** was also able to transform to (±)-rhazinilam through the same sequential reactions as **9a**, since the biaryl axis can rotate after decarboxylation.[15h]

In conclusion, we have developed a solvent-controlled switchable alkenylation of 3,4-disubstituted pyrroles in moderate to good yields with excellent regioselectivities for the first time. Toluene favored the selective C2-alkenylations, while DMSO led to the C5-alkenylation products. Furthermore, the application of selective C5-alkenylation to the total synthesis of (±)-rhazinilam highlighted the potential utility of our method in complex natural products synthesis. Research on a detailed reaction mechanism and application to other natural products synthesis are underway in our laboratory.

dx.doi.org/10.1021/ol5023933 | *Org. Lett.* XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and ^{1}H 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 Authors

*E-mail: hyao@cpu.edu.cn.
*E-mail: ajlin@cpu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the generous financial support by the NSFC (21272276), the SKLNM (JKGZ201110, ZZJQ201306), and the Ministry of Education of China (PSCIRT-1193). We also thank Wei Cong in this group for reproducing the results for **2ac** in Table 2 and **3cd** in Table 3.

■ REFERENCES

(1) For recent reviews on application of C−H activation in the total synthesis of natural products, medicinal chemistry, and material sciences, see: (a) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (b) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177. (c) Chen, D. Y. K.; Youn, S. W. *Chem.—Eur. J.* **2012**, *18*, 9452. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (e) Mercier, L. G.; Leclerc, M. *Acc. Chem. Res.* **2013**, *46*, 1597.

(2) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439.

(3) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.

(4) For selected examples of Pd-catalyzed regioselective functionalizations, see: (a) Tang, D.-T. D.; Collins, K. D.; Ernst, J. B.; Glorius, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1809. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (c) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387. (d) Tani, S.; Uehara, T. N.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2014**, *5*, 123. (e) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (f) Jiao, L.; Bach, T. *J. Am. Chem. Soc.* **2011**, *133*, 12990. (g) Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109.

(5) For recent reviews on directing group controlled regioselectivity, see: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145. (c) Zhu, C.; Wang, R.; Falck, J. R. *Chem.—Asian J.* **2012**, *7*, 1502.

(6) Selected examples of ligand controlled regioselectivity, see: (a) Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642. (b) Sanhueza, I. A.; Wagner, A. M.; Sanford, M. S.; Schoenebeck, F. *Chem. Sci.* **2013**, *4*, 2767. (c) Lyons, T. W.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 4455. (d) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (e) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946. (f) Xu, K.; Thieme, N.; Breit, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 7268.

(7) (a) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (b) Wagner, A. M.; Hickman, A. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 15710. (c) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (d) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112. (e) Lanke, V.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 2818. (f) Yeung, C. S.; Zhao, X.; Borduas, N.; Dong, V. M. *Chem. Sci.* **2010**, *1*, 331. (g) Duong, H. A.; Gilligan, R. E.; Cooke, M. L.; Phipps, R. J.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 463.

(8) For selected examples of electronic/steric controlled regioselectivity, see: (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (b) Cook, A. K.; Emmert, M. H.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 5428. (c) Chen, C.; Hartwig, J. F. *Science* **2014**, *343*, 853.

(9) (a) Tang, R.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215. (b) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344. (c) Wan, L.; Dastbaravardeh, N.; Li, G.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 18056. (d) Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518. (e) Dai, H.-X.; Li, G.; Zhang, X.-G.; Stepan, A. F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 7567.

(10) For selected examples of solvent-controlled regioselectivity, see: (a) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301. (b) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

(11) For carboxylate assisted C−H functionalization, see: Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440 and references therein.

(12) For selected examples on using DMSO as a coordinating ligand, see: (a) Diao, T.; White, P.; Guzei, I.; Stahl, S. S. *Inorg. Chem.* **2012**, *51*, 11898. (b) McDonald, R. I.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5529. (c) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346.

(13) See Table S3 in the Supporting Information for details.

(14) (a) Chong, P. H.; Seeger, J. D. *Pharmacotherapy* **1997**, *17*, 1157. (b) Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem.* **1995**, *38*, 3895. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (d) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

(15) For first isolation of rhazinilam, see: (a) Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822. For selected examples of total synthesis of rhazinilam, see: (b) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (c) Bowie, A. L., Jr.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207. (d) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352. (e) Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224. (f) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7168. For related total synthesis of rhazinal and rhazinicine, see: (g) Sui, X.; Zhu, R.; Li, G.; Ma, X.; Gu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 9318. (h) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.

(16) van Leusen, D.; van Echten, E.; van Leusen, A. M. *J. Org. Chem.* **1992**, *57*, 2245.

(17) CCDC960492 (**9a**) and CCDC960493 (**9b**) contain the supplementary crystallographic data for this paper.

(18) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. (A)* **1966**, 1711.

dx.doi.org/10.1021/ol5023933 | *Org. Lett.* XXXX, XXX, XXX−XXX