

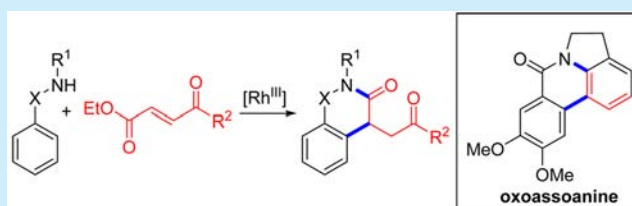
Convergent Synthesis of Diverse Nitrogen Heterocycles via Rh(III)-Catalyzed C–H Conjugate Addition/Cyclization Reactions

Adam B. Weinstein and Jonathan A. Ellman*

Department of Chemistry, Yale University, 225 Prospect Street, New Haven, Connecticut 06520-8107, United States

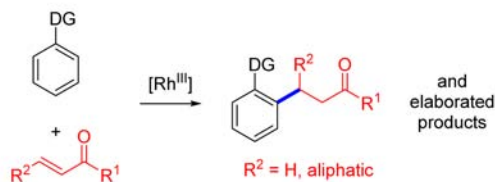
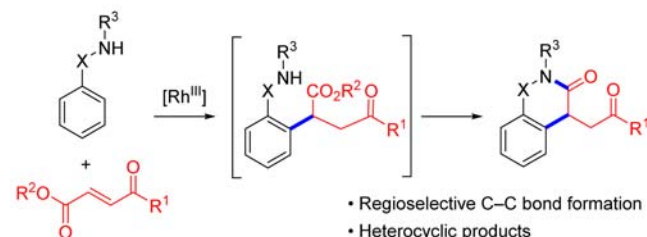
Supporting Information

ABSTRACT: The development of Rh(III)-catalyzed C–H conjugate addition/cyclization reactions that provide access to synthetically useful fused bi- and tricyclic nitrogen heterocycles is reported. A broad scope of C–H functionalization substrates and electrophilic olefin coupling partners is effective, and depending on the nature of the directing group, cyclic imide, amide, or heteroaromatic products are obtained. An efficient synthesis of a pyrrolophenanthridine alkaloid natural product, oxoassoanine, highlights the utility of this method.



Cyclopentadienyl-ligated Rh(III) complexes are proven catalysts for C–H functionalization reactions that enable rapid generation of molecular complexity from simple starting materials.¹ In particular, these catalysts have been employed in a range of reactions that couple sp^2 C–H bonds with olefin partners. Categories include Heck-type couplings,² hydroarylations,³ allylic substitutions,⁴ and cascade difunctionalizations.⁵ The regioselectivity of olefin functionalization in these transformations is sensitive to electronic, steric, and directing effects,^{6,7} and in the case of insertion into α,β -unsaturated carbonyl derivatives, the C–C bond typically forms distal to the carbonyl group with high fidelity (i.e., conjugate additions, Scheme 1a).

Scheme 1. Rhodium(III)-Catalyzed C–H Conjugate Addition Cascade Reactions

a) Prior work: β -addition to α,β -unsaturated carbonyl derivativeb) This work: α -addition to ester with cascade cyclization

Our interest in the synthetic utility of catalytic C–H conjugate addition reactions prompted us to explore new electrophilic olefin coupling partners.^{5w} Here, we show that addition to unsymmetrical 1,4-dicarbonyl derivatives leads to useful heterocyclic structures through an addition and cyclization cascade (Scheme 1b).⁸ This transformation requires that high regioselectivity be achieved for olefin addition based upon the electronic bias provided by the two carbonyl substituents. We further show that this cyclative cascade process can be applied to structurally diverse directing groups to provide different types of pharmaceutically relevant heterocycles. The utility of this method is showcased in a synthesis of the pyrrolophenanthridine alkaloid oxoassoanine.

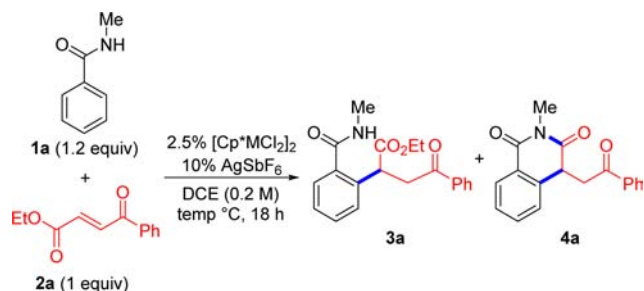
We began our studies by evaluating the reaction between *N*-methyl benzamide (1a) and ethyl-3-benzoyl acrylate (2a) under conditions for catalytic Cp*Rh(III) mediated C–H functionalization (Table 1). The cationic Cp*Rh(III) catalyst generated from [Cp*RhCl₂]₂ and AgSbF₆ in 1,2-dichloroethane (DCE) effected regioselective C–H addition of the benzamide substrate into the olefin at room temperature (entry 1). Addition product 3a, resulting from C–C bond formation α to the ester and β to the more electron-withdrawing acetophenone, was generated in moderate yield and with complete regioselectivity. Increasing the temperature of the reaction to 40 °C improved the yield of 3a (entry 2), and further increasing the temperature resulted in cascade cyclization to imide product 4a in good yield (entries 3–4). Notably, related Cp*Co(III) and Cp*Ir(III) catalyst precursors were not effective for this transformation under these conditions (entries 5–6).

Having identified viable catalytic conditions for selective C–H addition/cyclization of *N*-methyl benzamide and ethyl-3-benzoyl acrylate, we evaluated the scope of the reaction

Received: June 3, 2016

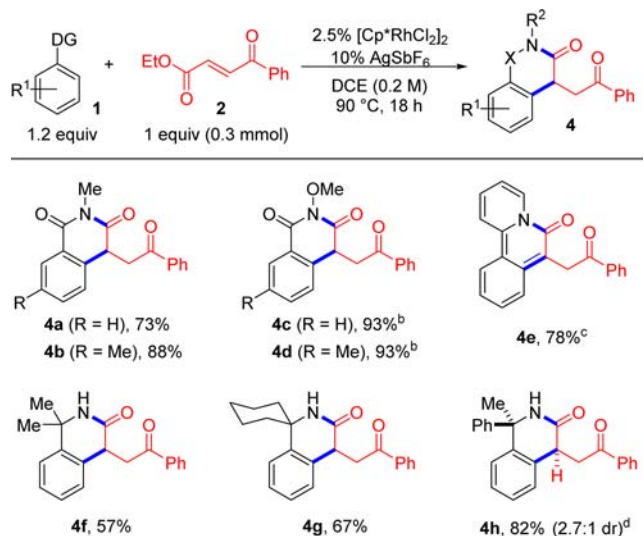
Published: June 23, 2016

Table 1. Reaction Discovery and Evaluation of Conditions



entry	[Cp* <i>M</i> Cl ₂] ₂	temp (°C)	% 3a ^a	% 4a ^a
1	[Cp*RhCl ₂] ₂	23	40	0
2	[Cp*RhCl ₂] ₂	40	61	2
3	[Cp*RhCl ₂] ₂	60	40	16
4	[Cp*RhCl ₂] ₂	90	0	75
5	[Cp*CoCl ₂] ₂	90	0	0
6	[Cp*IrCl ₂] ₂	90	2	9

^aYields determined by ¹H NMR spectroscopic analysis with phenyltrimethylsilane added as an internal standard.

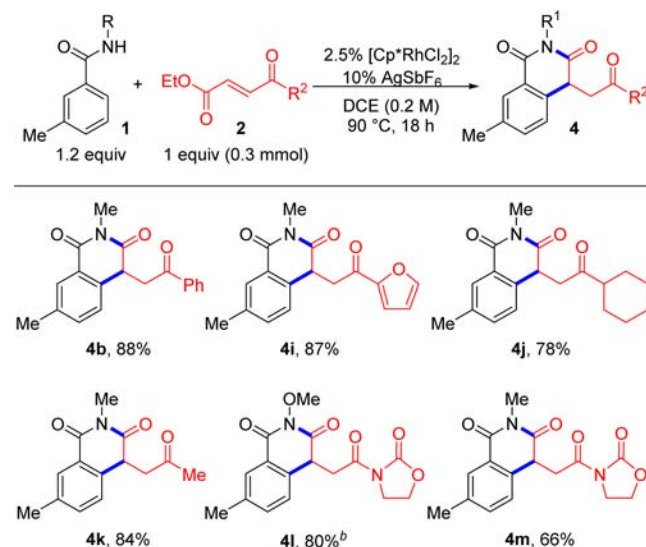
Scheme 2. Evaluation of Directing Group Substrate Scope^a

^aIsolated yields are reported. ^bReaction performed at 60 °C. ^c1.5 equiv of 2-phenylpyridine was employed. ^dThe diastereomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture, and the diastereomers were separated on isolation and the relative configurations were assigned by NOESY-1D spectroscopic analysis.

with respect to the identity of the directing group (Scheme 2). Full analysis of the reaction of *N*-methyl benzamide substrate **1a** revealed minor side products arising from difunctionalization of the arene. Installation of a blocking methyl group at the *meta* position thus improved the overall efficiency of the C–H addition/cyclization reaction (**4b**). Modification to an *N*-methoxy benzamide substrate provided a highly efficient reaction irrespective of the presence of a *meta* blocking group (**4c**, **4d**), probably due to rapid cyclization of the more acidic *N*-methoxy amide prior to a second C–H activation. The pyridyl directing group also participated in the C–H addition/cyclization cascade process, yielding fluorescent product **4e** following aromatization.^{8a} Additionally, α,α -disubstituted benzylamines led to the

corresponding dihydroisoquinolinone products (**4f**, **4g**, **4h**) in good yields. α -Methylbenzylamine and α -phenylbenzylamine were also evaluated as substrates but provided the desired cyclic products in <20% yield (data not shown).

We next evaluated the scope of the reaction with respect to the identity of the polarizing electron-withdrawing group β to the ester substituent on the olefin coupling partner (Scheme 3). In addition to the parent phenyl ketone (**4b**), furyl and

Scheme 3. Evaluation of Electrophilic Olefin Substrate Scope^a

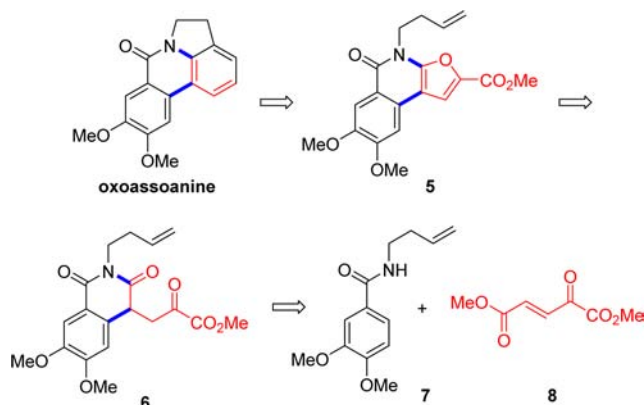
^aIsolated yields are reported. ^bReaction performed at 60 °C.

aliphatic ketones were well tolerated for regioselective insertion α to the ester (**4i**, **4j**, **4k**). Acyl oxazolidinone also proved effective in dictating efficient C–H addition (**4l**, **4m**).⁹

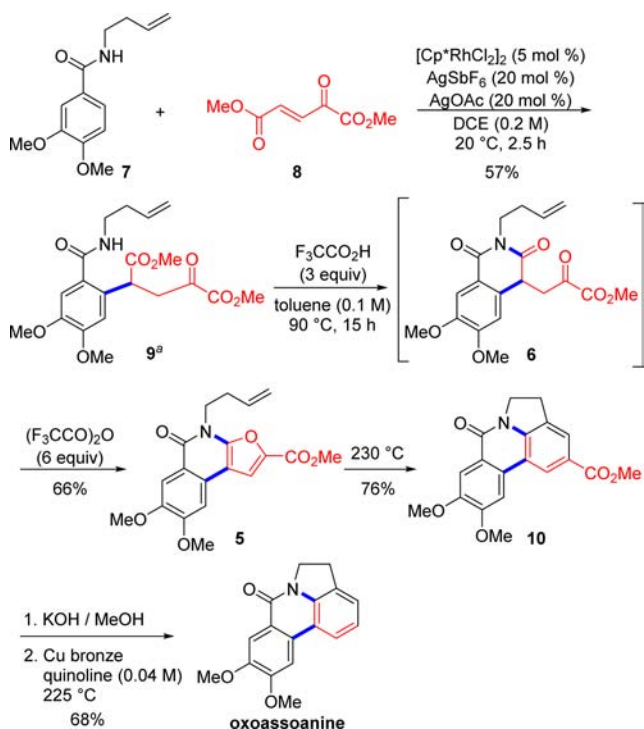
A key aspect of the catalytic reactions described here is the ability to install synthetically useful heterocyclic 1,4-dicarbonyl functionality in a convergent manner. We showcase the utility of this feature with a facile synthesis of oxoasoanine, a member of the lycorine alkaloid family of natural products.¹⁰ Studies by Padwa¹¹ and Boger¹² demonstrated the reactivity of 2-amidofurans in Diels–Alder reactions and the application of these transformations in the synthesis of lycorine alkaloids.¹³ Inspired by these works, we envisioned our conjugate addition/cyclization process could provide rapid access to amidofuran **5**, which could be converted to the desired pyrrolophenanthridinone alkaloid framework by an intramolecular Diels–Alder reaction (Scheme 4). Amidofuran **5** could be obtained by Paal–Knorr cyclization of imide **6**, which in turn could be generated from C–H addition/cyclization of *N*-homoallyl benzamide **7** with α,β -unsaturated ketoester **8**.

Our initial attempt to employ *N*-homoallyl benzamide substrate **7** in the C–H functionalization reaction gave a low yield of the desired conjugate addition product. Analysis of the reaction mixture revealed side reactivity derived from allylic C–H activation of the homoallyl group.¹⁴ Lowering of the temperature and addition of AgOAc to the catalyst system enabled conjugate addition product **9** to be obtained in moderate yield, though cyclization to imide **6** did not occur under these conditions (Scheme 5). Fortunately, treatment of intermediate **9** with trifluoroacetic acid gave clean conversion

Scheme 4. Retrosynthetic Analysis of Oxoassoanine



Scheme 5. Synthesis of Oxoassoanine



^aIsolated as a 9:1 mixture of terminal/internal alkene isomers.

to imide **6**, and subsequent addition of trifluoroacetic anhydride mediated Paal–Knorr cyclization to amidofuran **5** in one pot. Implementation of previously established conditions for intramolecular Diels–Alder reaction of the amidofuran, followed by decarboxylation, afforded oxoassoanine in an efficient five step sequence from *N*-homoallyl benzamide **7**. This convergent synthetic strategy, which takes advantage of the Diels–Alder reactivity of the amidofuran intermediate, could be amenable to the synthesis of diverse phenanthridine structures.

In summary, we have reported the development of an efficient Cp^{*}Rh(III) catalyzed aryl C–H addition/cyclization process that takes advantage of selective insertion into unsymmetrical 1,4-dicarbonyl coupling partners. The straightforward procedure is effective with structurally diverse directing groups, enabling the synthesis of an array of biologically relevant nitrogen heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01611.

Full experimental details and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jonathan.ellman@yale.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (F32-GM112454 to A.B.W. and R01-GM069559 to J.A.E.). The authors thank Haya Jamali (Yale University) for assistance with the acquisition of high-resolution mass spectrometric data.

■ REFERENCES

- (1) For reviews, see: (a) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Patureau, F. W.; Wencel-Delord, J.; Glorius, F. *Aldrichimica Acta* **2012**, *45*, 31. (d) Song, G. Y.; Wang, F.; Li, X. W. *Chem. Soc. Rev.* **2012**, *41*, 3651. (e) Yang, L.; Huang, H. M. *Chem. Rev.* **2015**, *115*, 3468. (f) Ye, B. H.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.
- (2) (a) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (b) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (c) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (d) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (e) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540. (f) Schroder, N.; Besset, T.; Glorius, F. *Adv. Synth. Catal.* **2012**, *354*, 579. (g) Huang, L. B.; Wang, Q.; Qi, J.; Wu, X.; Huang, K. F.; Jiang, H. F. *Chem. Sci.* **2013**, *4*, 2665. (h) Shi, Z. Z.; Bouladakis-Arapinis, M.; Glorius, F. *Chem. Commun.* **2013**, *49*, 6489. (i) Bouladakis-Arapinis, M.; Hopkinson, M. N.; Glorius, F. *Org. Lett.* **2014**, *16*, 1630. (j) Davis, T. A.; Wang, C. Q.; Rovis, T. *Synlett* **2015**, *26*, 1520. (k) Han, S. H.; Choi, M.; Jeong, T.; Sharma, S.; Mishra, N. K.; Park, J.; Oh, J. S.; Kim, W. J.; Lee, J. S.; Kim, I. S. *J. Org. Chem.* **2015**, *80*, 11092. (l) Otley, K. D.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 1332. (m) Wen, J.; Wu, A.; Wang, M. Y.; Zhu, J. J. *J. Org. Chem.* **2015**, *80*, 10457. (n) Xu, L. T.; Zhang, C.; He, Y. P.; Tan, L. S.; Ma, D. W. *Angew. Chem., Int. Ed.* **2016**, *55*, 321. (o) Zheng, J.; Cui, W.-J.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2016**, *138*, 5242.
- (3) (a) Yang, L.; Correia, C. A.; Li, C. J. *Org. Biomol. Chem.* **2011**, *9*, 7176. (b) Yang, L.; Qian, B.; Huang, H. M. *Chem. - Eur. J.* **2012**, *18*, 9511. (c) Davis, T. A.; Hyster, T. K.; Rovis, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 14181. (d) Ye, B. H.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636. (e) Ye, B. H.; Donets, P. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 507. (f) Kim, J.; Park, S. W.; Baik, M. H.; Chang, S. J. *J. Am. Chem. Soc.* **2015**, *137*, 13448. (g) Jiang, Q. B.; Guo, T. L.; Wu, K. K.; Yu, Z. K. *Chem. Commun.* **2016**, *52*, 2913. (h) Sharma, S.; Han, S. H.; Oh, Y.; Mishra, N. K.; Lee, S. H.; Oh, J. S.; Kim, I. S. *Org. Lett.* **2016**, *18*, 2568.
- (4) (a) Wang, H. G.; Schroder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5386. (b) Zhang, S. S.; Wu, J. Q.; Lao, Y. X.; Liu, X. G.; Liu, Y.; Lv, W. X.; Tan, D. H.; Zeng, Y. F.; Wang, H. G. *Org. Lett.* **2014**, *16*, 6412. (c) Hara, Y.; Onodera, S.; Kochi, T.; Kakiuchi, F. *Org. Lett.* **2015**, *17*, 4850. (d) Park, J.; Mishra, N. K.; Sharma, S.; Han, S.; Shin, Y.; Jeong, T.; Oh, J. S.; Kwak, J. H.; Jung, Y. H.; Kim,

I. S. *J. Org. Chem.* **2015**, *80*, 1818. (e) Zhang, S. S.; Wu, J. Q.; Liu, X. G.; Wang, H. G. *ACS Catal.* **2015**, *5*, 210.

(5) For leading references, see: (a) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (b) Wang, F.; Song, G. Y.; Li, X. W. *Org. Lett.* **2010**, *12*, 5430. (c) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (d) Hyster, T. K.; Knorr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (e) Shi, Z. Z.; Schroder, N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8092. (f) Wang, H. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318. (g) Ye, B. H.; Cramer, N. *Science* **2012**, *338*, 504. (h) Zhu, C.; Falck, J. R. *Tetrahedron* **2012**, *68*, 9192. (i) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66. (j) Shi, X. Y.; Li, C. J. *Org. Lett.* **2013**, *15*, 1476. (k) Shi, Z. Z.; Grohmann, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5393. (l) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 2735. (m) Piou, T.; Rovis, T. *J. Am. Chem. Soc.* **2014**, *136*, 11292. (n) Shi, Z. Z.; Bouladakis-Arapinis, M.; Koester, D. C.; Glorius, F. *Chem. Commun.* **2014**, *50*, 2650. (o) Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718. (p) Wodrich, M. D.; Ye, B. H.; Gonthier, J. F.; Corminboeuf, C.; Cramer, N. *Chem. - Eur. J.* **2014**, *20*, 15409. (q) Zhao, D. B.; Lied, F.; Glorius, F. *Chem. Sci.* **2014**, *5*, 2869. (r) Hyster, T. K.; Dalton, D. M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254. (s) Piou, T.; Rovis, T. *Nature* **2015**, *527*, 86. (t) Romanov-Michailidis, F.; Sedillo, K. F.; Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 8892. (u) Wu, S. Z.; Zeng, R.; Fu, C. L.; Yu, Y. H.; Zhang, X.; Ma, S. M. *Chem. Sci.* **2015**, *6*, 2275. (v) Zhao, D. B.; Vasquez-Céspedes, S.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 1657. (w) Boerth, J. A.; Ellman, J. A. *Chem. Sci.* **2016**, *7*, 1474. (x) Wang, Q.; Li, Y. Z.; Qi, Z. S.; Xie, F.; Lan, Y.; Li, X. W. *ACS Catal.* **2016**, *6*, 1971. (y) Yang, W.; Wang, J. Y.; Wei, Z. L.; Zhang, Q.; Xu, X. X. *J. Org. Chem.* **2016**, *81*, 1675. (z) Hu, Z. Y.; Tong, X. F.; Liu, G. X. *Org. Lett.* **2016**, *18*, 1702.

(6) For examples and mechanistic discussion, see refs 2l, 5o, 5s, and: (a) Li, L.; Jiao, Y. Z.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2010**, *29*, 4593. (b) Brasse, M.; Campora, J.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 6427.

(7) For an example of catalyst controlled regioselectivity, see ref 5r.

(8) Cyclization of directing groups with pendant ester functionality has also been observed in reactions involving diazo compounds. For examples, see: (a) Zhao, D. B.; Kim, J. H.; Stegemann, L.; Strasser, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508. (b) Son, J. Y.; Kim, S.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2015**, *17*, 2518. (c) Shi, J. J.; Zhou, J.; Yan, Y. N.; Jia, J. L.; Liu, X. L.; Song, H. C.; Xu, H. E.; Yi, W. *Chem. Commun.* **2015**, *51*, 668.

(9) A 4-phenyl-substituted oxazolidinone derivative also led to the cyclic imide product, but did not provide control of diastereoselectivity (approximately 1:1 dr was observed).

(10) (a) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 79. (b) Lamoral-Theys, D.; Decaestecker, C.; Mathieu, V.; Dubois, J.; Kornienko, A.; Kiss, R.; Evidente, A.; Pottier, L. *Mini-Rev. Med. Chem.* **2010**, *10*, 41. (c) Van Goietsenoven, G.; Andolfi, A.; Lallemand, B.; Cimmino, A.; Lamoral-Theys, D.; Gras, T.; Abou-Donia, A.; Dubois, J.; Lefranc, F.; Mathieu, V.; Kornienko, A.; Kiss, R.; Evidente, A. *J. Nat. Prod.* **2010**, *73*, 1223.

(11) Padwa, A.; Dimitroff, M.; Waterson, A. G.; Wu, T. H. *J. Org. Chem.* **1998**, *63*, 3986.

(12) Wolkenberg, S. E.; Boger, D. L. *J. Org. Chem.* **2002**, *67*, 7361.

(13) For alternative synthetic approaches, see: (a) Perez, D.; Bures, G.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1996**, *61*, 1650. (b) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; SadaCosta, M. *Tetrahedron* **1997**, *53*, 299. (c) Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.

(14) For leading references, see: (a) Cochet, T.; Bellosta, V.; Roche, D.; Ortholand, J. Y.; Greiner, A.; Cossy, J. *Chem. Commun.* **2012**, *48*, 10745. (b) Archambeau, A.; Rovis, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 13337. (c) Shibata, Y.; Kudo, E.; Sugiyama, H.; Uekusa, H.; Tanaka, K. *Organometallics* **2016**, *35*, 1547.