Organic LETTERS
Letter
pubs.acs.org/OrgLett

Rhodium(III)-Catalyzed Cross-Coupling of Alkenylboronic Acids and *N*-Pivaloyloxylamides

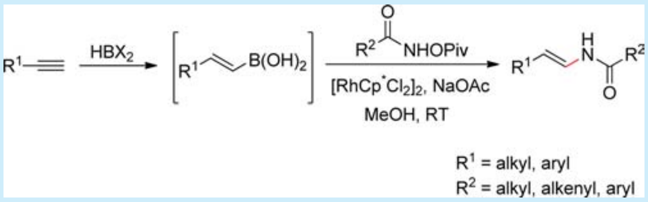
Chao Feng[†] and Teck-Peng Loh*[,†,‡]

[†]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

[‡]Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China

Supporting Information

ABSTRACT: Rh(III)-catalyzed umpolung amidation of alkenylboronic acids for the synthesis of enamides is reported. This reaction proceeds readily at room temperature and displays an extremely wide spectrum of functional group tolerance. With cooperation of hydroboration, it enables the formal anti-Markovnikov hydroamidation of terminal alkynes, stereospecifically affording the *trans*-enamides in excellent yields.



The umpolung C−N bond formation, which operates between electrophilic amino reagents and a diversity of nucleophiles, such as organomagnesium, zinc or boron derivatives, has been gaining increasing attention from the synthetic organic community in the past two decades.[1] By taking advantage of the electrophilic amination, it not only offers an alternative to the conventional C−N bond formation reactions, such as Buchwald-Hartwig amination,[2] but more importantly opens a new synthetic route for the retrosynthetic disconnection of these skeletons. In this context, transition-metal (TM)-catalyzed protocols prove to be particularly attractive because of their high efficiency, mild reaction conditions, and broad functional group tolerance. The elegant works by Narasaka,[3] Miura,[4] Lalic,[5] Jarvo,[6] Johnson,[7] Liebeskind,[8] and other groups nicely demonstrate the utility and potential of the TM-catalyzed umpolung amination in diverse C−N bond formation reactions.[9] In the realm of TM-catalyzed umpolung C−N bond formation, while much advancement has been attained with respect to the construction of aryl C−N and alkyl C−N bonds, relatively less attention has been paid toward the formation of alkenyl C−N analogues, such as those of enamides.

Enamides constitute a class of useful intermediate in synthetic organic chemistry and represent key structural motifs in various naturally occurring products, biologically active compounds, and pharmaceuticals (Figure 1).[10] Accordingly, much effort has been paid toward the discovery of new synthetic methods for the ease of realization of enamide construction.[11] Probably, the most widely applicable approach for the synthesis of such a motif relies on the copper-catalyzed cross-coupling between alkenyl halides and amides.[12] This method, while effective, often shows limited substrate scope; for example, halide functional groups could not be tolerated, owing to the harsh reaction conditions and low-valent copper catalyst employed. While substantial progress has been attained in developing TM-catalyzed enamide synthesis in the past decades, several shortcomings still remain, such as high stoichiometric amounts of coupling reagents used, intolerance of halogen functional groups, inapplicability to the formation of multisubstituted enamides. Therefore, it is still highly desirable to discover new synthetic methods of enamide formation that display broad functional group tolerance and high efficiency and, more importantly, are applicable in the late-stage transformation in natural products synthesis.

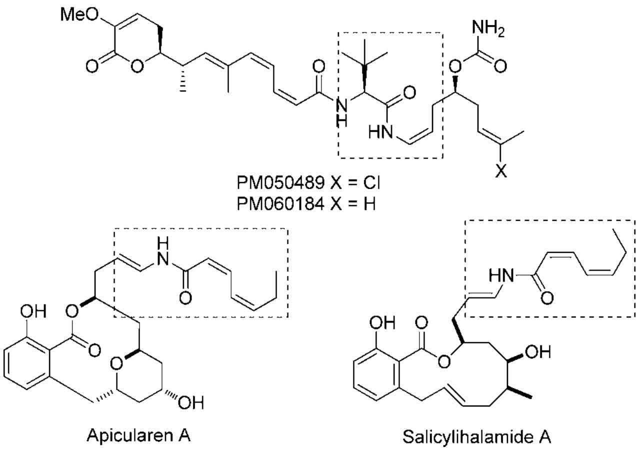


Figure 1. Biologically active natural products containing enamide structural motifs.

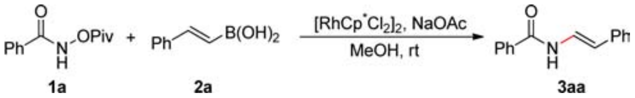
With our continuing interests in enamide chemistry and rhodium catalysis,[13,14] we report herein a highly efficient and reliable method for the synthesis of enamides via rhodium-catalyzed umpolung amidation between *O*-pivaloyl hydroxamic

Received: May 7, 2014
Published: June 17, 2014

acids and alkenylboronic acids, which could be easily accessed through hydroboration of alkynes. Thus, the total transformation could be regarded as a formal anti-Markovnikov hydroamidation of terminal alkynes.[15] It is also important to note that unlike most of the reported examples of TM-catalyzed umpolung amidation reactions employing low-valent (or in situ generated) metal catalysts, which enable the activation of electrophilic amino reagents through oxidative addition, this protocol relies on a high-valent rhodium catalyst and 1,2-alkenyl migration to accomplish the C−N bond formation.

At the very beginning, we endeavored to optimize the reaction conditions by cross-coupling of *N*-pivaloyloxyl benzamide **1a** and *trans*-2-phenylvinylboronic acid **2a** with copper as catalysts. However, after considerable attempts, no positive results were obtained. It was found that benzamide could be detected as the byproduct in many cases of copper catalysis, which results from the oxidative addition of **1a** to the copper catalyst followed by protiodemetalation. To prevent such an unproductive pathway, we turned our attention to the high-valent TM catalysts, envisioning that oxidative addition was much less favorable and the ensuing protiodemetalation would thus be inhibited in these cases. Much to our pleasure, when $[RhCp^*Cl_2]_2$ was used, the reaction proceeded smoothly even at room temperature to deliver the desired product **3aa** in quantitative yield (Table 1). Meanwhile, the formation of benzamide was totally suppressed. With such an exciting preliminary result in hand, a systematic screening of reaction solvents was carried out. Among all the solvents examined, methanol proved to be the best choice, affording the desired product in quantitative yield. While ethereal or chlorinated solvents, such as THF, DME and $ClCH_2CH_2Cl$, turned out to be inappropriate, toluene and acetonitrile were found to mediate the reaction with moderate to good efficiency. It is worth mentioning that when other TM catalysts, such as $[RuCl_2\text{-}p\text{-Cymene}]_2$, $Pd(OAc)_2$, $FeCl_3$, and $[Cp^*IrCl_2]_2$ were used in place of $[RhCp^*Cl_2]_2$, no desired product **3aa** could be detected. What needs to be further highlighted is that a Rh(I) catalyst, in sharp contrast with its Rh(III) analogue, did not display any catalytic reactivity in this reaction. Further examinations showed that both NaOAc and $[RhCp^*Cl_2]_2$ were indispensable, since no reaction occurred in the absence of either of these two species. Furthermore, 0.1 mol % of catalyst loading enabled the reaction to occur on gram scale to afford **3aa** in comparable yield.

Table 1. Optimization of Reaction Conditions[a]

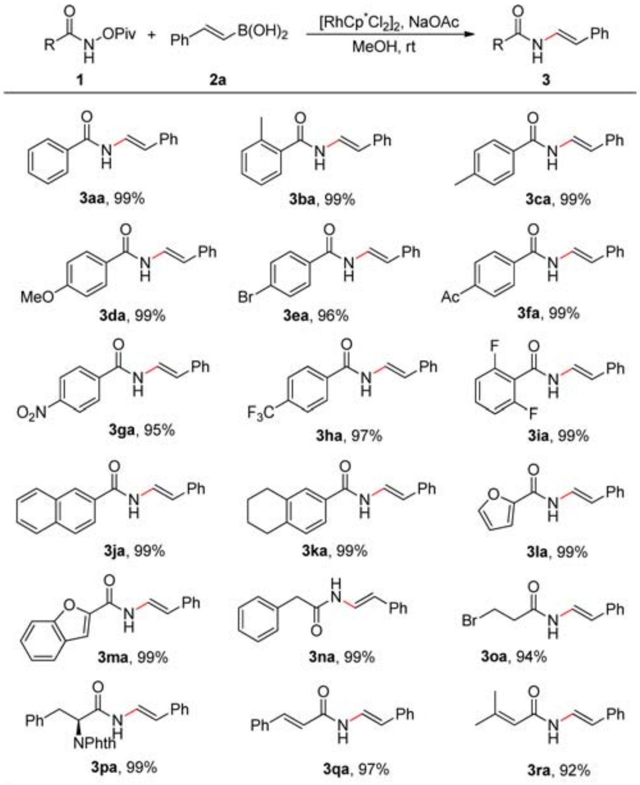


entry	catalyst	solvent	yield[b] (%)
1	$Cu(OAc)_2$	MeOH	
2	$CuCl_2$	MeOH	
3	$[Cp^*RhCl_2]_2$	MeOH	99
4	$[Cp^*RhCl_2]_2$	THF	trace
5	$[Cp^*RhCl_2]_2$	MeCN	82
6	$[Cp^*RhCl_2]_2$	toluene	76
7	$[Cp^*RhCl_2]_2$	$ClCH_2CH_2Cl$	24
8	$[Cp^*RhCl_2]_2$	DME	trace
9	$[Rh(cod)Cl]_2$	MeOH	
10	$[RuCl_2\text{−cymene}]_2$	MeOH	
11	$Pd(OAc)_2$	MeOH	
12	$FeCl_2$	MeOH	
13	$[Cp^*IrCl_2]_2$	MeOH	
14[c]	$[Cp^*RhCl_2]_2$	MeOH	
15		MeOH	NR

[a]Unless otherwise noted, the reactions were carried out at room temperature using **1a** (0.2 mmol), **2a** (0.3 mmol), and catalyst (0.0025 mmol) in solvent (1 mL) for 12 h. [b]Isolated yields. [c]NaOAc was omitted.

With the optimized reaction conditions in hand, we moved on to investigate the reaction scope of *N*-pivaloyloxylamides. As clearly shown in Scheme 1, this reaction tolerated a large variety of functional groups regardless of the electronic proprieties and substitution patterns, such as OMe, Ac, NO_2, and CF_3, and the products were formed in excellent to quantitative yield. Halogen substituents, such as Br and F, were nicely compatible with these reaction conditions. Notably, this reaction was also applicable to heterocyclic *N*-pivaloyloxyl amide, and when **1l** and **1m** were employed, the products **3la** and **3ma** were isolated in quantitative yield. With such excellent results using aromatic amide derivatives, we envisioned expanding the reaction scope further to nonaromatic substrates. Gratifyingly, both alkyl- and alkenyl-derived substrates worked smoothly to deliver the enamide products in excellent yield. In particular, when a 3-bromopropanamide derivative was subjected to the optimized reaction conditions, **3oa** was readily obtained in 94% yield, leaving the sp^3 C−Br bond untouched. Remarkably, the amino acid derived analogue **3pa** also successfully engaged in

Scheme 1. Substrate Scope of *N*-Pivaloyloxyl Amides[a]

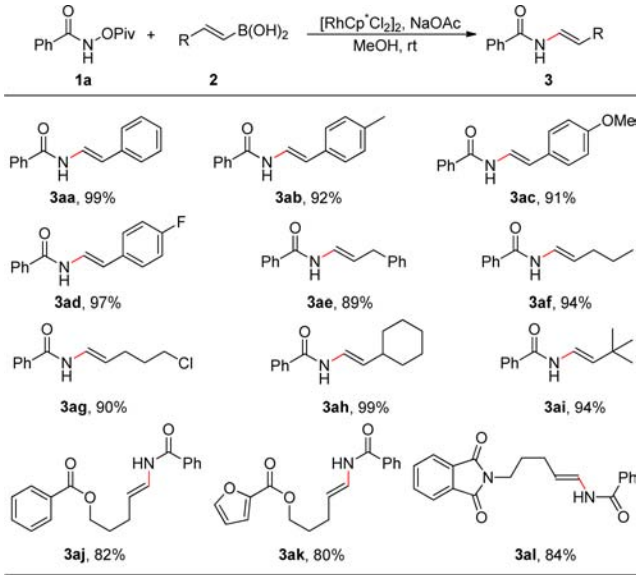


[a]Unless otherwise noted, the reactions were carried out at room temperature using **1** (0.2 mmol), **2a** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.0025 mmol), and NaOAc (0.3 mmol) in MeOH (1 mL) for 12 h. [b]Isolated yields.

such a transformation, which further demonstrates the potential and utility of this reaction in the elaboration of amino acid derivatives. Furthermore, when *α,β*-unsaturated hydroxamic acid derivatives **1q** and **1r** were employed, the reactions proceeded smoothly to afford the desired products in 97% and 92% yield, respectively. It also needs to be pointed out that in these two cases products arising from 1,4-addition were not detected.

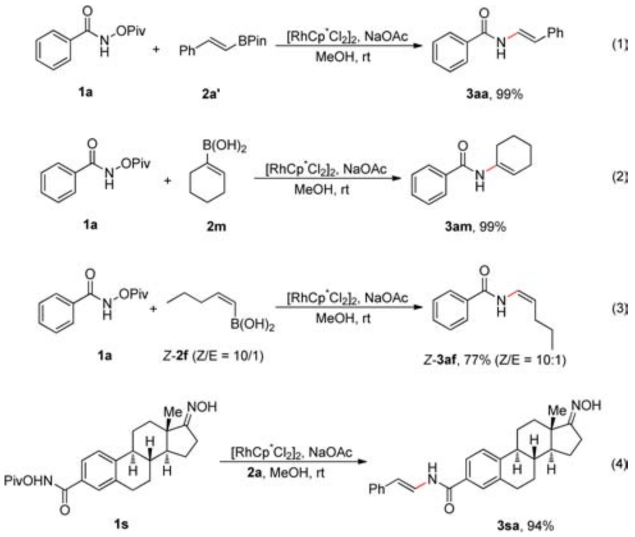
The reaction generality with respect to alkenylboronic acids was subsequently probed, and the results were summarized in Scheme 2. Initial examinations with *β*-aryl-substituted vinylboronic acids showed that the electronic nature of aryl substituents had little influence on the reaction efficiency with both electron-donating and electron-withdrawing ones, affording the desired products in excellent yields. Pleasingly, this reaction was also applicable to *β*-alkyl-substituted vinylboronic acids without any complication, and the desired enamides were obtained in excellent yield. In the case of **2g**, the desired product **3ag** was isolated in 90% yield, with the chlorine substituent being left untouched. This reaction also worked nicely with sterically more bulky alkenylboronic acids, for example, when using *β*-cyclohexyl and *β*-*tert*-butyl vinylboronic acids, the coupling products were formed in 99% and 94%, respectively. To investigate the reaction scope further and shed some light on the applicability of this method to natural products synthesis, several more complex alkenylboronic acids were synthesized and subjected to the optimized reaction conditions. It turned out to be rather noteworthy that reactions with alkenylboronic acids containing ester, heterocycle based ester as well as phthaloyl protected amino functional groups proceeded well without any difficulty, thus producing the corresponding functionalized enamides in high yield. What also needs to be pointed out is that in all these reactions examined in Scheme 2 only *trans*-enamides were formed.

Scheme 2. Substrate Scope of Alkenylboronic Acids[a]



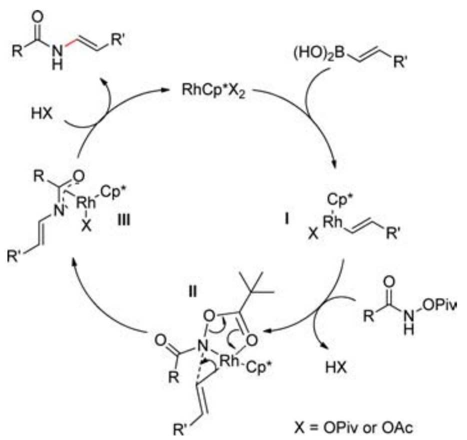
[a]Unless otherwise noted, the reactions were carried out at room temperature using **1a** (0.2 mmol), **2** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.0025 mmol), NaOAc (0.3 mmol) in MeOH (1 mL) for 12 h. [b]Isolated yields.

With the aim of extending the reaction scope further and evaluating the applicability of this method, the following experiments were conducted (eqs 1–4). It needs to be noted that not only boronic acids but also a pinacol boronate derivative could be successfully engaged in such transformations. Furthermore, it was demonstrated that this reaction was not limited to the terminal alkenylboronic acids, and when 1-cyclohexenylboronic acid **2m** was employed, the desired product **3am** was isolated in quantitative yield. Moreover, the reaction between **1a** and (*Z*)-pent-1-en-1-ylboronic acid (*Z*)-**2f** worked fairly well to produce the *cis*-enamide (*Z*)-**3af** in 77% yield. For a further showcase of the applicability of this method to the modification of naturally occurring or related compounds, estrone derived *N*-pivaloyloxyl amide **1s** was synthesized and subjected to the optimized reaction condition with **2a**, which worked nicely and afforded the desired enamide **3sa** in 94% yield.



Based on the documented precedents and results of our examination, the reaction mechanism is tentatively proposed as shown in Scheme 3. The reaction is initiated through the transmetalation between Rh(III) catalyst and vinylboronic acid to form intermediate **I**,[16] which further undergoes base-induced association with *N*-pivaloyloxyl amide to produce intermediate **II**. As an alternative pathway to reach intermediate **II**, the coordination of *N*-pivaloyloxyl amide to the Rh(III) catalyst

Scheme 3. Proposed Reaction Mechanism



may happen first followed by ensuing transmetalation with boronic acid. Once the intermediate **II** is formed, 1,2-migration of the vinyl group from rhodium to nitrogen, which is accompanied by the release of the pivaloyloxyl group, results in the C−N bond formation and affords the intermediate **III**.[17] Finally, intermediate **III** undergoes further protonation to release the desired enamide product and regenerate the active Rh(III) catalyst.

In conclusion, we have presented a novel and highly effective method for enamide synthesis using Rh(III)-catalyzed umpolung amidation between *N*-pivaloyloxyl amides and alkenylboronic acids. By taking advantage of hydroboration reaction, this protocol enables the formal anti-Markovnikov hydroamidation of terminal alkynes. The operational simplicity, mild reaction conditions, and broad functional group tolerance of this reaction makes it an appealing and complementary strategy to the traditional copper catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: teckpeng@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the USTC Research Fund, the Nanyang Technological University, and the Singapore Ministry of Education Academic Research Fund (ETRP 1002 111, MOE2010-T2-2-067, MOE 2011-T2-1-013) for the funding of this research.

■ REFERENCES

(1) (a) Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. (b) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449. (c) Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kurti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253. (d) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505. (e) Kitamura, M.; Suga, T.; Chiba, S.; Narasaka, K. *Org. Lett.* **2004**, *4*, 4619. (f) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 5683.

(2) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(3) (a) Tsutsui, H.; Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1997**, 317. (b) Tsutsui, H.; Ichikawa, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1869.

(4) (a) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3642. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11827. (c) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617. (e) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395. (f) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860. (g) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2013**, *15*, 172.

(5) (a) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *J. Am. Chem. Soc.* **2012**, *134*, 6571. (b) Rucker, R. P.; Whittaker, A. M.; Dang, H.; Lalic, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 3953.

(6) (a) Barker, T. J.; Jarvo, E. R. *Synthesis* **2011**, 3954. (b) Barker, T. J.; Jarvo, E. R. *J. Am. Chem. Soc.* **2009**, *131*, 15598. (c) Barker, T. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 8325.

(7) (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 364. (c) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (d) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521. (e) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799.

(8) (a) Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918. (b) Zhang, Z.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2008**, *10*, 3005. (c) Yu, Y.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2004**, *6*, 2631. (d) Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947.

(9) (a) He, C.; Chen, C.; Cheng, J.; Liu, C.; Liu, W.; Li, Q.; Lei, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 6414. (b) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676.

(10) (a) Tan, N.-H.; Zhu, J. *Chem. Rev.* **2006**, *106*, 840. (b) Joullie, M. M.; Richard, D. J. *Chem. Commun.* **2004**, 2011. (c) He, G.; Wang, J.; Ma, D. *Org. Lett.* **2007**, *9*, 1367. (d) Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040. (e) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425. (f) Furstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem.—Eur. J.* **2001**, *7*, 5286. (g) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701. (h) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (i) Tanoury, G. J.; Chen, M.; Dong, Y.; Forslund, R. E.; Magdziak, D. *Org. Lett.* **2008**, *10*, 185. (j) Smith, A. B., III; Duffey, M. O.; Basu, K.; Walsh, S. P.; Suennemann, H. W.; Frohn, M. *J. Am. Chem. Soc.* **2008**, *130*, 422. (k) Nicolaou, K. C.; Sun, Y.-P.; Guduru, R.; Banerji, B.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 3633. (l) Nicolaou, K. C.; Guduru, R.; Sun, Y.-P.; Banerji, B.; Chen, D. Y.-K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896. (m) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387. (n) Huang, X.; Shao, N.; Huryk, R.; Palani, A.; Aslanian, R.; Seidel-Dugan, C. *Org. Lett.* **2009**, *11*, 867. (o) Nicolaou, K. C.; Leung, G. Y. C.; Dethe, D. H.; Guduru, R.; Sun, Y.-P.; Lim, C. S.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 10019. (p) Palimkar, S. S.; Uenishi, J. *Org. Lett.* **2010**, *12*, 4160. (q) Palimkar, S. S.; Uenishi, J.; Ii, H. *J. Org. Chem.* **2012**, *77*, 388. (r) Florence, G. J.; Wlochal, J. *Chem.—Eur. J.* **2012**, *18*, 14250.

(11) (a) Snider, B. B.; Song, F. B. *Org. Lett.* **2000**, *2*, 407. (b) Furstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955. (c) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109. (d) Sergeyev, S.; Hesse, M. *Synlett* **2002**, 1313. (e) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927.

(12) (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Cesati, R. R., III; Dwyer, G.; Jones, R. C.; Hayes, M. P.; Yalamanchili, P.; Casebier, D. S. *Org. Lett.* **2007**, *9*, 5617. (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (d) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (e) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889.

(13) (a) Feng, C.; Loh, T.-P. *Chem. Sci.* **2012**, *3*, 3458. (b) Zhou, H.; Chung, W. J.; Xu, Y. H.; Loh, T.-P. *Chem. Commun.* **2009**, 3472. (c) Zhou, H.; Xu, Y. H.; Chung, W. J.; Loh, T. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 5355. (d) Pankajakshan, S.; Xu, Y. H.; Cheng, J. K.; Low, M. T.; Loh, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5701.

(14) (a) Feng, C.; Loh, T.-P. *Chem. Commun.* **2011**, *47*, 10458. (b) Feng, C.; Feng, D.; Loh, T.-P. *Org. Lett.* **2013**, *15*, 3670. (c) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722.

(15) (a) Yudha, S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609. (b) Gooßen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042. (c) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc. Chem. Commun.* **1995**, 413.

(16) (a) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876. (b) Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 2867.

(17) (a) Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 66. (b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449.