Organic LETTERS

Letter

pubs.acs.org/OrgLett

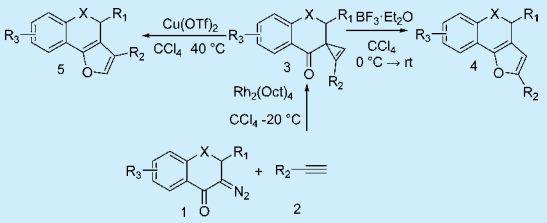
One-Pot Novel Regioselective Cycloisomerization Synthesis of 2-Substituted or 3-Substituted 4*H*-Furo[3,2-*c*]chromene through the Intermediate Cyclopropenes of 3-Diazochroman-4-one and Phenylacetylene

Jin Gong, Zhensheng Zhao, Fuming Zhang, Songyun Wu, Guangqi Yan, Yingjie Quan, and Baochun Ma*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

Supporting Information

ABSTRACT: A new class of cyclopropenes containing a chroman-4-one motif were synthesized using 3-diazochroman-4-one and phenylacetylene with rhodium(II) catalyst and followed by cycloisomerization to give 2-substituted or 3-substituted 4*H*-furo[3,2-*c*]chromene, respectively. Using $BF_3{\cdot}Et_2O$ as catalyst, 2-substituted 4*H*-furo[3,2-*c*]chromene was exclusively obtained in 70% yield. Using $Cu(OTf)_2$ as catalyst, 3-substituted 4*H*-furo[3,2-*c*]chromene was obtained in 95% yield with 98:2 regioselectivity. A one-pot cascade addition−cycloisomerization process was also developed with no need to isolate cyclopropenes of chroman-4-one intermediates.

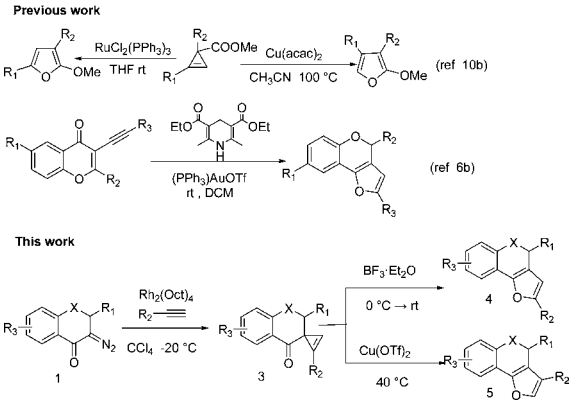


Cyclopropenes,[1] highly strained but readily accessible carbocyclic molecules, have been shown to possess useful reactivity in organic synthesis. Functionalized cyclopropenes as bioorthogonal chemical reporters can be used to target biomolecules in vitro and in live cells owing to their rigorous and highly strained structure. Although rhodium-catalyzed intermolecular cyclopropenation with donor−acceptor carbenoids is a well-established process,[2,3] there have been rare reports on the cyclopropeneation of 3-diazochroman-4-one and phenylacetylene.

As part of our ongoing efforts[4] toward the asymmetric synthesis of 3,3′-biflavanones, we have exclusively obtained cyclopropenes of 3-diazochroman-4-one in the presence of rhodium catalyst accompanied by no cycloisomerization products. Cyclopropenes containing the chroman-4-one motif have a unique structure with much more ring strain. After a cycloisomerization reaction catalyzed by $BF_3{\cdot}Et_2O$ or $Cu(OTf)_2$, 2-trisubstituted or 3-trisubstituted furo[3,2-*c*]chromene was obtained with good efficiency and regioselectivity. This class of cyclopropenes containing a chroman-4-one motif has not been employed as a substrate for cycloisomerizations to synthesize the 4*H*-furo[3,2-*c*]chromene skeleton.

The 4*H*-furo[3,2-*c*]chromene skeleton[5] can be found in many natural products and exhibits potential biological activity. Most synthetic methods have focused on the construction of a pterocarpan system which is the combination of benzofuran and chromene scaffold.[6−13] Herein, we report the synthesis of unique cyclopropenes containing a chroman-4-one motif using 3-diazochroman-4-one and phenylacetylene with rhodium(II) catalyst, followed by regioselectively cycloisomerization to give 2-substituted or 3-substituted 4*H*-furo[3,2-*c*]chromene, respectively. Using $BF_3{\cdot}Et_2O$ as catalyst, 2-substituted 4*H*-furo[3,2-*c*]chromene was exclusively obtained. Using $Cu(OTf)_2$ as catalyst, 3-substituted 4*H*-furo[3,2-*c*]chromene was obtained with 98:2 regioselectivity. We also developed a one-pot cascade addition−cycloisomerization process to synthesize 4*H*-furo[3,2-*c*]chromene with no need to isolate cyclopropenes of chroman-4-one intermediates (Scheme 1).

Scheme 1. Synthesis of Multisubsituted Furan

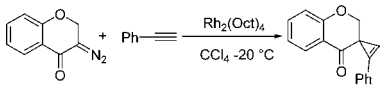


On the basis of the initial results, a number of different catalysts, solvents, and operating procedures were tested to optimize the cyclopropene reaction conditions (Table 1). When $Rh_2(OAc)_4$ was used as catalyst, a benchmark catalyst in metal carbenoid chemistry (Table 1, entry 1−4), the yield of the reaction was decreased greatly after completion of the reaction in 3 h as determined by TLC. $Rh_2(Oct)_4$ at −5 °C

Received: July 18, 2014
Published: October 23, 2014

   dx.doi.org/10.1021/ol502854y | *Org. Lett.* 2014, 16, 5524−5527

Table 1. Optimization for the Reaction Conditions[a,b]



1c 3c

entry	catalyst	solvent	temp (°C)	yield (%)
1	$Rh_2(OAc)_4$	CCl_4	rt	20
2	$Rh_2(OAc)_4$	CH_2Cl_2	rt	NR[c]
3	$Rh_2(OAc)_4$	CH_3CHCl_2	rt	NR
4	$Rh_2(OAc)_4$	*n*-hexane	rt	NR
5	$Rh_2(Oct)_4$	CCl_4	rt	26
6	$Ru(BYP)_3$	CCl_4	rt	NR
7	$(Ph_3P)_3RuCl_2$	CCl_4	rt	NR
8	$[(p\text{-cymene})Ru]_2Cl_4$	CCl_4	rt	NR
9	$Rh_2(Oct)_4$	CCl_4	−5	57
10	$Rh_2(Oct)_4$	CCl_4	−20	85

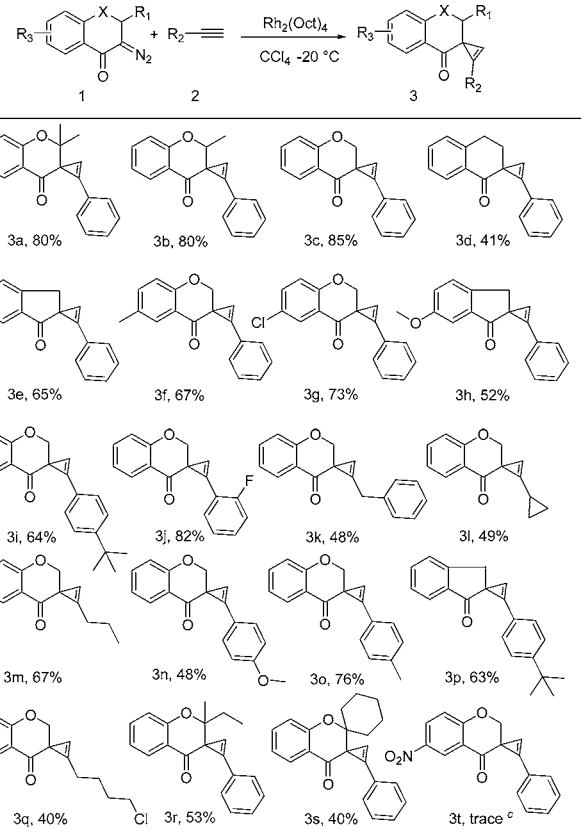
[a]Reaction conditions: The reaction was carried out using **1** (0.2 mmol), **2** (0.2 mmol), and catalyst (0.1 mol %) in the solvent (5 mL). [b]Isolated yields. [c]NR = not reaction.

could promote the reaction efficiency to afford **3a** in 57% yield (Table 1, entry 9), while at room temperature, the yield dropped to 26% (Table 1, entry 5). Among other transition-metal catalysts, $Ru(BYP)_3$, $(Ph_3P)_3RuCl_2$, and $[(p\text{-cymene})Ru]_2Cl_4$ could not proceed the reaction (Table 1, entry 6,7,8). After screening commonly used solvents, CCl_4 was superior to CH_2Cl_2, CH_3CHCl_2, and *n*-hexane. After numerous screenings, we found that the reaction of **1** and **2** applying $Rh_2(Oct)_4$ (0.1 mol %) in CCl_4 (5 mL) at −20 °C to give the expected products **3a** in 85% yield (Table 1, entry 10). Attempts to add in more Rh^{II} catalyst failed to generate cycloisomerization product 4*H*-furo[3,2-*c*]chromene, this may be due to the specific structure of chroman-4-one precursor.[8h,i]

With the optimal reaction conditions in hand (Table 1, entry 10), we then tested the functional group tolerance of the newly developed [2 + 1] cycloaddition reactions of 2,2-dimethyl-3-diazochroman-4-one **1** and phenylacetylene. Some typical examples for this regioselective transformation are summarized in Scheme 2.

Obviously, the R^2 group with electronic and steric variation on the acetylene moiety afforded the corresponding cyclopropene product in good to moderate yields. The effect of R^1 group was investigated. The result showed the steric effect on the reaction obviously. When R^1 was methyl or ethyl group, the reaction was finished as reasonable yield (Table 2, such as **3a**, **3b**, and **3c**). The sterically hindered group decreased the yield (Scheme 2, such as **3r** and **3s**). Compared with electronic effects on aromatic substitution of chroman-4-one, the electronics of 3-diazo-2-substituted chroman-4-one should be similar; this dramatic difference in reactivity can be rationalized on the basis of steric interference. R^3 with an electron-donating group (Scheme 2, such as **3f**, **3h**) or electron-withdrawing group (Scheme 2, such as **3g** and **3t**) showed no significant electronic effect; this difference in reactivity can be rationalized on the basis of steric interference. Because of the slight steric effects of R^2, **3p** was obtained in 63% yield. Significantly, the cyclopropene reaction is compatible with various benzocyclic systems (Scheme 2, such as **3d**, **3e**, **3h**, and **3p**). Benzocyclopentanone and benzocyclohexanone can also be compatible. Cyclopropene bearing a chroman-4-one motif was slowly decomposed on standing at room temperature over a

Scheme 2. Substrate Scope for the Formation of 3[a,b]



[a]All reactions were performed by addition of the **1** (0.2 mmol) in 3 mL of CCl_4 over 3 h to a stirred solution of **2** (0.2 mmol) and $Rh_2(Oct)_4$ (0.1 mol %) in CCl_4 (2 mL) at −20 °C. [b]Isolated yields. [c]Low solubility of substrate **2t** in CCl_4

period of months and should be stored at −20 °C to avoid decomposition.

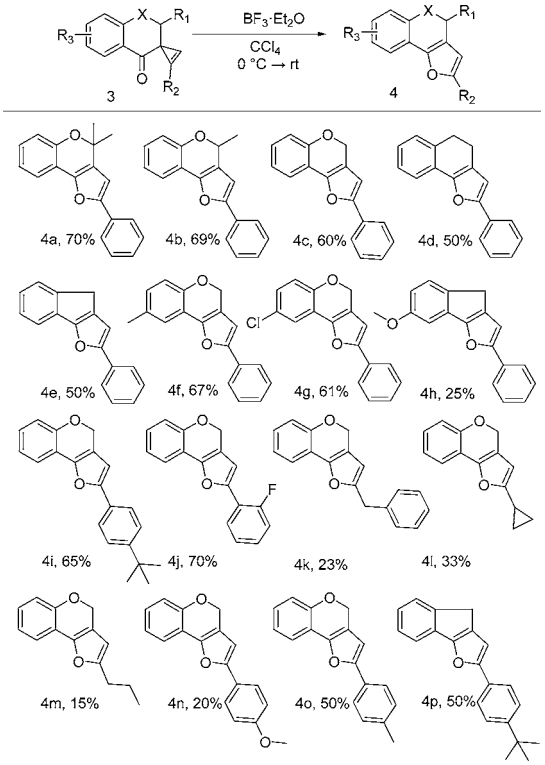
With the cyclopropenes of chroman-4-one in hand, the generality of the reaction and different substituent effects were subsequently investigated. With 1 mol % of $BF_3{\cdot}Et_2O$ as the catalyst, we developed a novel Lewis acid catalyzed cycloisomerization of cyclopropenes of chroman-4-one, and some of the typical results are summarized in Scheme 3. When the substrate **3a** derived from 2,2-dimethyl-3-diazochroman-4-one and acetylene was employed, the anticipated chroman-4-one derivative **4a** was obtained in 70% yield (Scheme 3). All cyclopropenes (Scheme 3, **3a**−**p**) could exclusively cycloisomerize to corresponding 2-substituted-4*H*-furo[3,2-*c*]-chromene in tolerance with R^1 as an alkyl benzyl, aryl, or vinyl group, while cyclopropane, 5-benzyl, and 5-phenyl groups gave low yield due to some portion of unidentified products.

With the cyclopropenes of chroman-4-one in hand, the feasibility of Cu(II)-catalyzed cycloisomerization to 4*H*-furo-[3,2-*c*]chromene was also investigated (Scheme 4). This method furnished a straightforward route to 3-substituted 4*H*-furo[3,2-*c*]chromene and with Pd(II) or Cu(I) catalysts 2-substituted 4*H*-furo[3,2-*c*]chromene could be obtained.[9b,10b] The regioselectivity difference should be attributed to our unique chroman-4-one skeleton.

We chose **3c** as the model substrate to test Cu-catalyzed cycloisomerization. The reactions did occur smoothly under these catalytic conditions, and 3-substituted 4*H*-furo[3,2-*c*]chromene **5c** could be obtained in 95% yield with 98:2

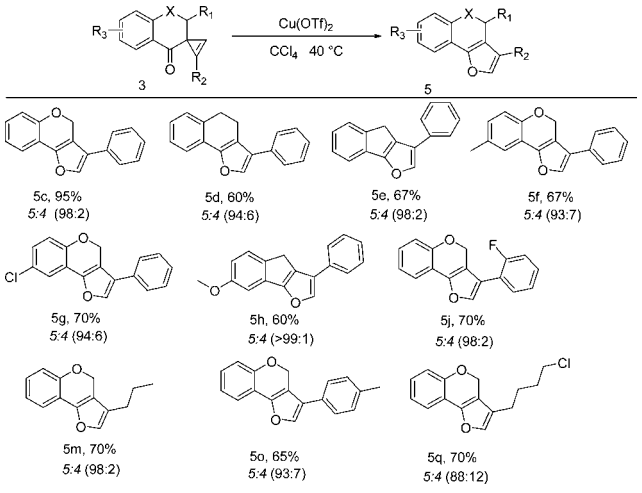
dx.doi.org/10.1021/ol502854y | Org. Lett. 2014, 16, 5524−5527

Scheme 3. Substrate Scope for the Formation of 4[a,b]



[a]All reactions were performed by addition of the $BF_3{\cdot}Et_2O$ (1 mol %) to a stirred solution of **3** (0.2 mmol) in dry CCl_4 (3 mL) at 0 °C. The reaction mixture naturally warmed to room temperature. [b]Isolated yields.

Scheme 4. Substrate Scope for the Formation of 5[a–d]

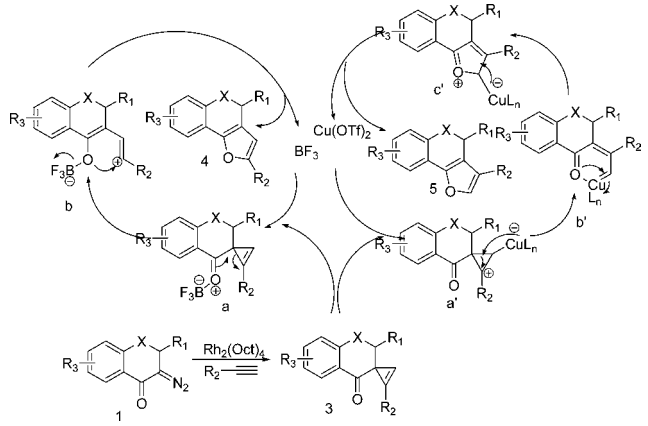


[a]All reactions were performed by a solution of **3** (0.2 mmol) and $Cu(OTf)_2$ (5 mol %) in dry CCl_4 (3 mL), stirred at 40 °C. The reaction mixture naturally warmed to room temperature. [b]Isolated yields. [c]Unless otherwise specified, isolated yields of two isomers. [d]The ratio was determined by ^1H NMR analysis of the crude reaction mixture.

regioselectivity with 5 mol % of $Cu(OTf)_2$ as the catalyst. We tried more typical substrates such as **3c**, **3d**, **3g**, **3h**, **3j**, **3m**, and **3o** to test copper(II)-catalyzed cycloisomerization and obtained the desired 3-substituted 4*H*-furo[3,2-*c*]chromene **5c**, **5d**, **5g**, **5h**, **5j**, **5m**, and **5o** with high regioselectivity.

A possible mechanism for this regioselectivity cycloisomerization was depicted in Scheme 5 on the basis of previous

Scheme 5. Proposed Reaction Mechanism



work[14] and our experimental results. 3-Diazochroman-4-one was reacted with acetylene under rhodium(II) catalyst to form cyclopropene chroman-4-one. In the presence of the Cu(II) catalyst, the copper cation attacks the less substituted sp^2 carbon atom of cyclopropenone compounds, undergoing a ring-opening reaction to afford copper carbene intermediate, and then the carbonyl oxygen atom attacks the metal carbene carbon atom to afford the corresponding 3-substituted 4*H*-furo[3,2-*c*]chromene product. With $BF_3{\cdot}Et_2O$ as catalyst, $BF_3{\cdot}Et_2O$ chelated to the carbonyl group as a driving force to induce cyclopropene ring opening and a reclosure process, resulting in 2-substituted 4*H*-furo[3,2-*c*]chromene product.

With the optimized cycloisomerization reaction conditions in hand, we attempted to test a one-pot cascade addition–cycloisomerization reaction between 3-diazochroman-4-one and acetylene without isolating the intermediate cyclopropene chroman-4-one. Compound **1a** was treated with phenylacetylene under 0.1% equiv of rhodium catalysts in CCl_4 at −20 °C for 3 h, and then 1% equiv of $BF_3{\cdot}Et_2O$ was added to the reaction mixture at 0 °C. After the reaction mixture was stirred for 2 h at room temperature, the desired 2-substituted 4*H*-furo[3,2-*c*]chromene **4a** was obtained in 60% yield.

We also attempted a $Cu(OTf)_2$ catalyzed one-pot cascade addition–cycloisomerization; compound **1c** was treated with phenylacetylene under 0.1% equiv of rhodium catalyst in CCl_4 at −20 °C for 3 h, 5% equiv of $Cu(OTf)_2$ was added to the reaction mixture at 0 °C, the reaction was stirred at 40 °C, and the desired 3-substituted-4*H*-furo[3,2-*c*]chromene **5c** was obtained in 83% yield.

In summary, we have developed a novel one-pot cascade addition–cycloisomerization of 3-diazochroman-4-one and phenylacetylene for the regioselective synthesis of 2-substituted 4*H*-furo[3,2-*c*]chromene or 3-substituted 4*H*-furo[3,2-*c*]-chromene by using the catalyst $BF_3{\cdot}Et_2O$ or $Cu(OTf)_2$, respectively. The method is efficient (up to 95% yield and 98:2 regioselectivity), and there is no need to isolate the cyclopropenes of chroman-4-one. The reaction could be applied to the synthesis of various natural product skeletons. Further studies into the scope, mechanism, and synthetic applications of this transformation are being carried out in our laboratory.

dx.doi.org/10.1021/ol502854y | *Org. Lett.* 2014, 16, 5524–5527

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of new products, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mabaochun@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation of China (grant no 21172098, 21173105), the Fundamental Research Funds for the Central Universities (lzujbky-2013-50, lzujbky-2013-ct02), and the 111 Project of Chinese Ministry of Education.

■ REFERENCES

(1) (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2006**, *128*, 4598. (c) Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103. (d) Fattahi, A.; McCarthy, R. E.; Ahmad, M. R.; Kass, S. R. *J. Am. Chem. Soc.* **2003**, *125*, 11746. (e) Marek, I.; Simaan, S.; Masawara, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364.

(2) (a) Doyle, M. P.; Winchester, W. R.; Hoorn, J. A. A.; Lynch, V.; Simonsen, S. H.; Ghosht, R. *J. Am. Chem. Soc.* **1993**, *115*, 9968. (b) Doyle, M. P.; Protopopova, M.; Müller, P.; Erie, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492. (c) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (d) Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916. (e) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233. (f) Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22. (g) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211. (h) Goto, T.; Takeda, K.; Shimada, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6803.

(3) (a) Park, E. J.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 17268. (b) Uehara, M.; Suematsu, H.; Yasutomi, Y.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 170. (c) Cui, X.; Xu, X.; Lu, H.; Zhu, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 3304. (d) Briones, J. F.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 3984. (e) Briones, J. F.; Davies, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 11916.

(4) Li, W. Z.; Ma, B. *Org. Lett.* **2005**, *7*, 271.

(5) (a) Khupse, R. S.; Erhardt, P. W. *J. Nat. Prod.* **2008**, *71*, 275. (b) Furstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760.

(6) (a) Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285. (b) Hu, F.; Chen, T.; Yan, J.; Cheng, M.; Huang, L.; Hu, Y. *RSC Adv.* **2012**, *2*, 11238.

(7) (a) Nakatani, K.; Adachi, K.; Tanabe, K.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 8221. (b) Mahaffy, P. G.; Visser, D.; Torres, M.; Bourdelande, J. L.; Strausz, O. P. *J. Org. Chem.* **1987**, *52*, 2680. (c) Halton, B.; Jones, C. S.; Margetic, D. *Tetrahedron* **2001**, *57*, 3529. (d) Padwa, A.; Akiba, M.; Chou, C. S.; Cohen, L. *J. Org. Chem.* **1982**, *47*, 183. (e) Zimmerman, H. E.; Wright, C. W. *J. Am. Chem. Soc.* **1992**, *114*, 6603.

(8) (a) Rosenfeld, M. J.; Shankar, B. K. R.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2699. (b) Padwa, A.; Chiacchio, U.; Garreau, Y.; Kassir, J. M.; Krumpe, K. E.; Schoffstall, A. M. *J. Org. Chem.* **1990**, *55*, 414. (c) Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820. (d) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971. (e) Padwa, A.; Kinder, F. R. *J. Org. Chem.* **1993**, *58*, 21. (f) Lee, Y. P.; Suk, J. P. *Tetrahedron Lett.* **2000**, *41*, 4795. (g) Müller, P.; Allenbach, Y. F.; Bernardinelli, G. *Helv. Chim. Acta* **2003**, *86*, 3164. (h) Briones, J. F.; Davies, H. M. L. *Tetrahedron* **2011**, *67*, 4313. (i) Pang, W.; Zhu, S.; Xin, Y.; Jiang, H.; Zhu, S. *Tetrahedron* **2010**, *66*, 1261. (j) Li, H.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 4462. (k) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1987**, *52*, 2631. (l) Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1997**, *62*, 1642.

(9) (a) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (b) Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, *125*, 12386. (c) Song, C.; Ju, L. *Chem.—Eur. J.* **2013**, *19*, 3584.

(10) (a) Peng, L.; Zhang, X.; Ma, M.; Wang, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1905. (b) Chen, J.; Ma, S. *Chem.—Asian J.* **2010**, *5*, 2415. (c) Xia, Y.; Xia, Y.; Ge, R.; Liu, Z.; Xiao, Q.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 3917. (d) Tsai, Y.; Das, U.; Syu, S.; Lee, C.; Lin, W. *Eur. J. Org. Chem.* **2013**, 4634. (e) Miao, M.; Xu, X.; Xu, L.; Ren, H. *Eur. J. Org. Chem.* **2014**, 5896. (f) Dong, Z.; Liu, C.; Wang, Y.; Lin, M.; Yu, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 14157. (g) Rauniyar, V.; Wang, Z.; Burks, H.; Toste, F. *J. Am. Chem. Soc.* **2011**, *133*, 8486. (h) Lenden, P.; Entwistle, D.; Willis, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10657.

(11) (a) Zhou, L.; Ma, J.; Zhang, Y.; Wang, J. *Tetrahedron Lett.* **2011**, *52*, 5484. (b) Swenson, A. K.; Higgins, K. E.; Brewer, M. G.; Brennessel, W. W.; Coleman, M. G. *Org. Biomol. Chem.* **2012**, *10*, 7483.

(12) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981.

(13) Phun, L. H.; Aponte-Guzman, J.; France, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3198.

(14) (a) Selvi, T.; Srinivasan, K. *J. Org. Chem.* **2014**, *79*, 3653. (b) Kokubo, K.; Koizumi, T.; Harada, K.; Mochizuki, E.; Oshima, T. *J. Org. Chem.* **2005**, *70*, 7776. (c) Chen, M.; Roush, R. W. *J. Am. Chem. Soc.* **2013**, *135*, 9512. (d) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944. (e) Yadav, K. V.; Sriramurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 16366. (f) Koizumi, T.; Harada, K.; Mochizuki, E.; Kokubo, K.; Oshima, T. *Org. Lett.* **2004**, *6*, 4081. (g) Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.