Organic LETTERS

Letter

pubs.acs.org/OrgLett

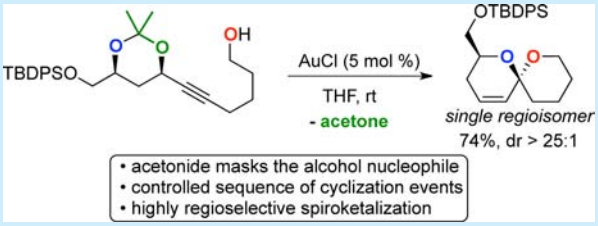
Controlling Regiochemistry in the Gold-Catalyzed Synthesis of Unsaturated Spiroketals

Paulo H. S. Paioti, John M. Ketcham, and Aaron Aponick*

Department of Chemistry, Center for Heterocyclic Compounds, University of Florida, Gainesville, Florida 32611, United States

Supporting Information

ABSTRACT: A novel gold-catalyzed synthesis of unsaturated spiroketals that addresses regioselectivity issues commonly reported in metal-catalyzed spiroketalization of alkynes is reported. The reaction sequence is regulated by an acetonide protecting group which undergoes extrusion of acetone to deliver the desired spiroketals in good yields and diastereoselectivities. The reaction, which is carried out under very mild conditions employing AuCl as the catalyst, should be widely applicable in the synthesis of a broad range of spiroketals.

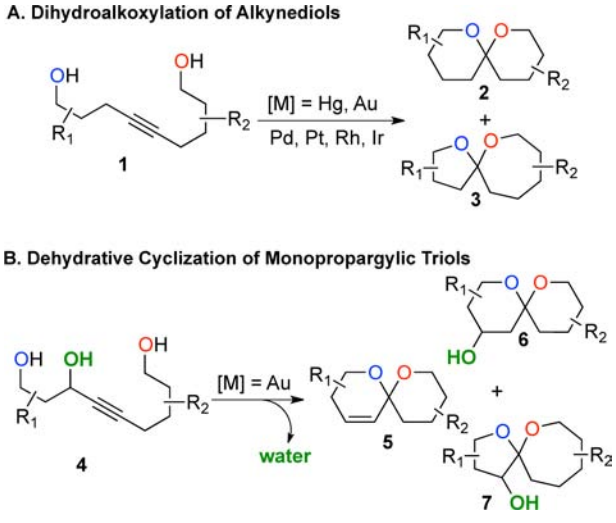


Spiroketals are an important class of compounds that appear in myriad biologically relevant molecules, most notably natural products and their analogues.[1] Within this class of compounds, monounsaturated spiroketals represent a structural motif with increasing significance and can be found in natural products such as okadaic acid,[2] salinomycin,[3] spirastrellolides,[4] phorbaketals,[5] alotaketals,[6] and others.[7] In addition to this natural occurrence, the presence of a double-bond moiety is synthetically useful, enabling complexity-building functionalization or simple reduction to generate saturated derivatives.[8]

Despite this importance, methods for synthesizing both saturated and unsaturated spiroketals rely mostly on the Brønsted-acid catalyzed dehydration of ketodiols, which has been demonstrated to be a reliable strategy for the synthesis of natural products.[1] While dehydration is effective, transition metal-catalyzed reactions have been developed to allow the use of triple bonds as carbonyl surrogates, and this strategy provides a popular alternative.[9] Utimoto's seminal report in this area demonstrated the spiroketalization of alkynediols **1** (Scheme 1A),[10] in a process now catalyzed by a wide range of metal complexes based on palladium,[11] gold,[12] mercury,[13] rhodium,[14] and iridium.[14] Although these reactions are generally functional group tolerant and high yielding, complex mixtures of spiroketals are often observed due to regioselectivity issues associated with hydroalkoxylation of internal alkynes.[15] The problem arises from the fact that regioselectivity is dictated by relative rates of cyclization when forming different ring sizes.[9−14] To address this problem, a platinum-catalyzed cyclization of monoprotected alkynediols was later reported.[16] However, controlling the separate cyclization and in situ deprotection events can be quite challenging.

As part of our program focused on dehydrative reactions,[17] we developed a highly regioselective cyclization of monopropargylic triols **4** to form monounsaturated spiroketals.[18] Reports using $Hg(OTf)_2$[19] and Au complexes in the presence of a surfactant in water[20] have since appeared. While most substrates generally work quite well, low regioselectivity was first observed by our group (Scheme 1B)[18] and later by the groups of Trost[21] and Forsyth[22] during total syntheses.

Scheme 1. Metal-Catalyzed Synthesis of Spiroketals

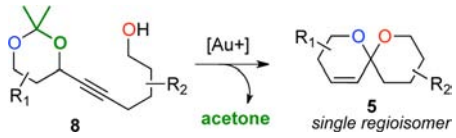


Although spiroketal syntheses from alkynediols and triols are well known, a general solution to the regioselectivity problem is lacking. To overcome these issues, we postulated that competing reactions could be precluded by a method where the rates of cyclization no longer dictate the product distribution. To this end, we decided to explore the feasibility of a gold-catalyzed reaction of acetonides **8** for the selective formation of [6,6]-monounsaturated spiroketals (Scheme 2). We reasoned that the acetonide moiety could mask the competing nucleophile and allow a stepwise spiroketalization that proceeds in a predictable manner. More specifically, with

Received: August 23, 2014
Published: October 1, 2014

   dx.doi.org/10.1021/ol5024954 | *Org. Lett.* 2014, 16, 5320−5323

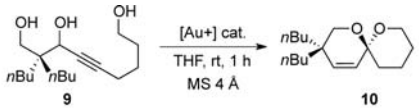
Scheme 2. Spiroketalization of Propargyl Acetonides



substrates such as **8**, we hypothesized that the free alcohol would cyclize prior to the extrusion of acetone, which would then reveal the second nucleophile, thus controlling any competition between the two hydroalkoxylation events. Herein we report our efforts in this area that reveal a straightforward approach to controlling the regiochemistry in the Au-catalyzed synthesis of monounsaturated spiroketals.

At the outset, a suitable substrate was required for initial studies. The triol **9**[23] was prepared, and it was found that under our previously reported conditions[18] the desired spiroketal **10** is formed in only 20−25% yield (Scheme 3). Although the

Scheme 3. Spiroketalization of Triol 9

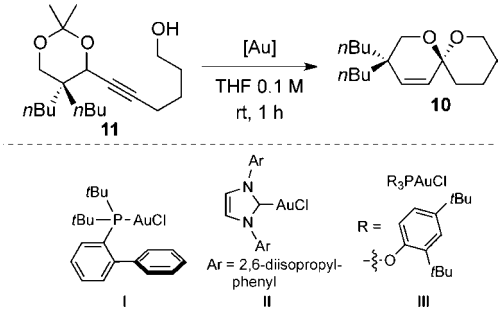


[Au+] cat.	yield of **10** (%)	
[P(*o*-biphenyl)(*t*-Bu)$_2$]AuCl/ AgOTf (5 mol %)	25%	+ complex mixture of saturated spiroketals
AuCl (10 mol %)	20%	+

yields for these reactions were very low, triol **9** was completely consumed in both cases, resulting in the formation of a complex mixture of saturated spiroketals, likely due to competing initial 5-exo and 6-endo-dig cyclization reactions.

With this result as a point of comparison, compound **9** was easily transformed into the acetonide **11** to probe our hypothesis.[23] Several gold(I) complexes, including phosphine, phosphite, NHC-carbene, and sulfide as ligands, were screened (Table 1, entries 1−4); however, employing AuCl as a catalyst gave the best yield and furnished the desired product in 48%

Table 1. Optimization Studies



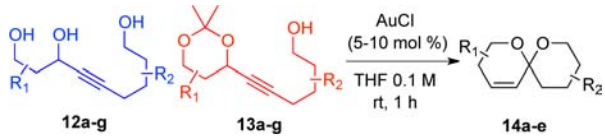
entry	catalyst	additive	loading (mol %)	yield (%)[a]
1	I	AgOTf	5	35
2	II	$AgBF_4$	5	25
3	III	AgOTf	5	25
4	DMS·AuCl		10	41
5	AuCl		5	48
6	AuCl		7	52
7	AuCl		10	67

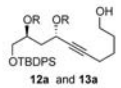
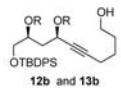
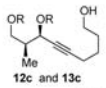
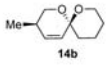
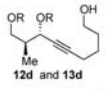
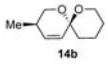
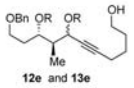
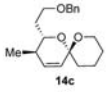
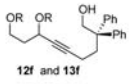
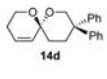
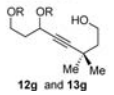
[a]Isolated yield.

yield with 5 mol % loading (entry 5). Increasing the catalyst loading to 10 mol % AuCl (entries 5−7) improved the yield to 67%, and these conditions were deemed optimal. This substrate appears to be fairly challenging, as it was later observed that 5 mol % loadings were often satisfactory (vide infra), but the improvement here over the triol is striking.

Having established the optimal conditions, the scope of the reaction was studied. For reference, it was important to compare results from the acetonides with the corresponding triols. The triols **12a** and **12b** were prepared and, based on previous examples, predicted to behave differently under these conditions.[18] As anticipated, a 95% yield of the desired spiroketal **14a** was isolated from the *anti* diol substrate **12a** and 30% yield from *syn* diol **12b**, and the remainder of the material was converted to undesired saturated spiroketals (Table 2, entries 1,2). Under the optimal conditions with 5 mol

Table 2. Reaction Scope[a]



entry	substrate	triol **12**[b] yield (%),[c] dr	acetonide **13** yield (%),[c] dr	product
1[d]	 **12a** and **13a**	95 dr > 25:1	72 dr > 25:1	 **14a**
2[d]	 **12b** and **13b**	30 dr > 25:1	74 dr > 25:1	 **14a**
3[e]	 **12c** and **13c**	15 dr = 2:1	77 dr = 2:1	 **14b**
4[e]	 **12d** and **13d**	15 dr = 2:1	67 dr = 2:1	 **14b**
5[f]	 **12e** and **13e**	10 dr = 16:1	52 dr = 16:1	 **14c**
6	 **12f** and **13f**	81	74	 **14d**
7[e,g]	 **12g** and **13g**	45	47	 **14e**

[a]See Supporting Information for determination of stereochemistry. [b]MS 4 Å used as an additive. [c]Isolated yield. [d]5 mol % AuCl. [e]Et_2O used as solvent. [f]1:1 mixture of diastereomers **12**/**13e** used as substrate. [g]Spiroketal **14e** detected as the exclusive product with reduced yield due to volatility.

% AuCl, both the 1,3-*trans* acetonide **13a** (entry 1) and the 1,3-*cis* acetonide **13b** (entry 2) provided the product **14a** as a single diastereomer in 72% and 74% yield, respectively, with no trace of saturated spiroketal byproducts. These results demonstrate that the relative stereochemistry of the triol is important. A rationale for this dependence was provided by Forsyth, which suggests that 5-exoalkoxyauration is disfavored in the successful diastereomer, thereby avoiding saturated spiroketal byproducts.[22] In contrast, with the acetonide, substrate stereochemistry appears to be inconsequential and a mixture of the

dx.doi.org/10.1021/ol5024954 | *Org. Lett.* 2014, 16, 5320−5323

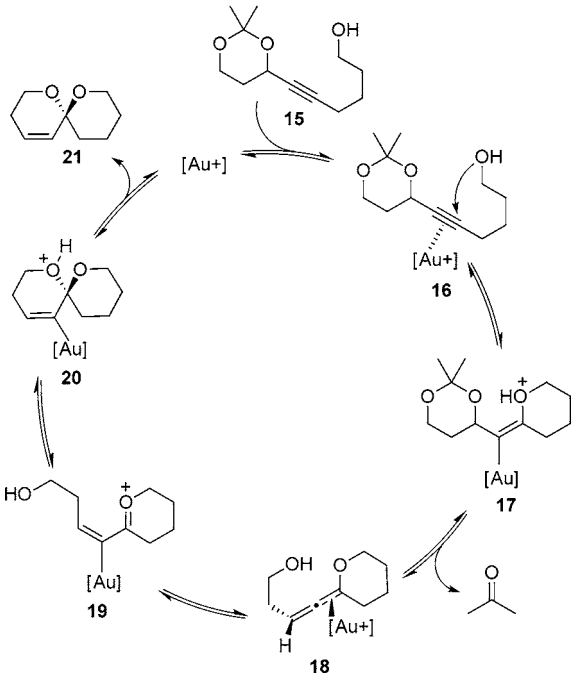
diastereomeric acetonides **13a** and **13b** could be successfully utilized. By removing the requirement for a specific diastereomer, a significant advantage is achieved, allowing substrate preparation by very basic methods.[24]

As substrate stereochemistry can affect the spiroketalization, additional substitution patterns were explored. Triols **12c** and **12d**, as well as the corresponding acetonides **13c** and **13d**, were prepared and exposed to the reaction conditions. With these substrates, the difference between the triols and the acetonides was even more pronounced. The cyclization of the triols **12c** and **12d** furnished the desired spiroketal **14b** in only 15% yield, whereas the cyclization of the 1,2-*cis* acetonide **13c** and the 1,2-*trans* acetonide **13d** gave the desired unsaturated spiroketal **14b** in 77% and 67% yields, respectively (entries 3−4). Substrates **12**/**13e**, containing the stereochemistry found in the spirastrellolides,[4] were also tested (entry 5). Cyclization of the triol **12e** proved to be difficult, and the spiroketal **14c** could be isolated in only 10% yield, in clear contrast to the cyclization of the acetonide **13e**, which delivered **14c** in 52% yield. Both reactions resulted in a 16:1 dr, suggesting that the reaction is under thermodynamic control.

One additional set of experiments was conducted to determine if the acetonide adversely affected substrates that work reasonably well as the triols (entries 6,7). When exposed to the reaction conditions, substrates **12**/**13f** both delivered spiroketal **14d** in satisfactory yields and **12**/**13g** also both similarly provided **14e**. These reactions proceeded smoothly, and no alternate, saturated spiroketals were observed. In these examples, the geminal diphenyl- and dimethyl-groups likely accelerate the rate of cyclization of the distal alcohol to the point where controlling the order of cyclization events by employing the acetonide is unnecessary.

Mechanistically, it is postulated that the gold catalyst activates the triple bond in **15** for nucleophilic attack of the pendant hydroxyl[25] to generate the vinyl gold intermediate **17** via a 6-exo-dig cyclization (Scheme 4). The free hydroxyl

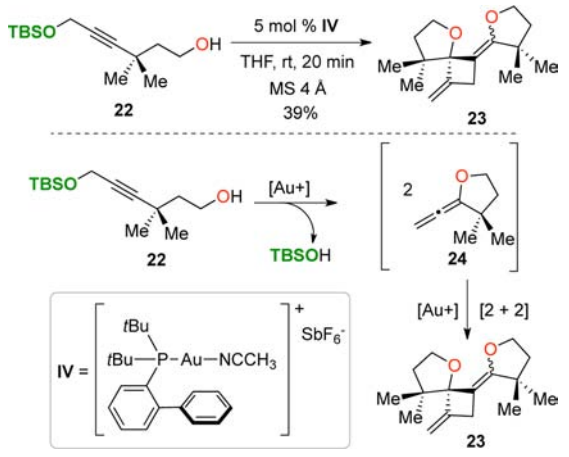
Scheme 4. Proposed Catalytic Cycle



present in **16** will exclusively act as the nucleophile because the competing nucleophile is masked in the form of an acetonide. The vinyl gold intermediate **17** then likely undergoes elimination of gold and extrusion of acetone to form the allenyl ether **18**, concomitantly revealing the second hydroxyl group. π-Complex **18** may then isomerize to the vinylgold oxocarbenium ion **19** and cyclize to form **20** or undergo addition to form **20** directly. Protodeauration then turns over the catalyst to yield spiroketal **21**. Alternatively, the free allene analogous to **18** may undergo Brønsted acid catalyzed cyclization to furnish the spiroketal **21**.[26]

To provide insight into the mechanism, we evaluated the likelihood of forming the allenyl ether intermediate **18**. It is probable that **18** undergoes rapid cyclization, so an alternative substrate was envisioned to preclude this possibility. To this end, **22** was prepared and a silyl ether was incorporated as a leaving group to reduce the chance of gold-catalyzed Meyer−Schuster rearrangement with a propargyl alcohol,[27] and also to reduce the ability of the group eliminated to act as a nucleophile in Au-catalyzed hydroalkoxylation[28] or hydration reactions.[25b,29] When compound **22** was submitted to Au catalysis conditions,[30] the formation of a new compound was observed in 20 min (Scheme 5). While the reaction product

Scheme 5. Mechanistic Studies



was not the allene but instead **23**, the result was intriguing as **23** was likely formed from a gold-catalyzed formal [2 + 2]-cycloaddition of two molecules of the allenyl ether **24**.[31] Shi and co-workers recently reported a similar [2 + 2] process that generates allenes by rearrangement of propargyl acetates,[32] but this type of reactivity is unknown for propargyl alcohols and ethers.

In summary, the chemistry outlined here demonstrates that it is possible to overcome the problematic regiochemical issues in the metal-catalyzed spiroketalization of alkynes. The method utilizes an acetonide to function as a regioselectivity regulator in the production of monounsaturated spiroketals. It is fortuitous that this common protecting group serves this purpose and that either saturated or functionalized spiroketals can easily be prepared from these compounds. For these reasons, we believe that this method will have broad applicability for the preparation of a wide range of spiroketals. Application of this method in the synthesis of natural products is ongoing in our laboratories and will be reported in due course.

dx.doi.org/10.1021/ol5024954 | *Org. Lett.* 2014, 16, 5320−5323

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: aponick@chem.ufl.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Herman Frasch Foundation (647-HF07) and the James and Ester King Biomedical Research Program (09KN-01) for their generous support of our programs.

■ REFERENCES

(1) (a) Brimble, M. A.; Stubbing, L. A. *Top. Heterocycl. Chem.* **2014**, *35*, 189. (b) Raju, B. R.; Saikia, A. K. *Molecules* **2008**, *13*, 1942. (c) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (d) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

(2) Tachibana, K.; Scheuer, P. J.; Tsukitani, Y.; Kikuchi, H.; Van Engen, D.; Clardy, J.; Gopichand, Y.; Schmitz, F. J. *J. Am. Chem. Soc.* **1981**, *103*, 2469.

(3) Kinashi, H.; Otake, N.; Yonehara, H.; Sato, S.; Saito, Y. *Tetrahedron Lett.* **1973**, *14*, 4955.

(4) Williams, D. E.; Roberge, M.; Van Soest, R.; Andersen, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 5296.

(5) Rho, J.-R.; Hwang, B. S.; Sim, C. J.; Joung, S.; Lee, H.-Y.; Kim, H.-J. *Org. Lett.* **2009**, *11*, 5590.

(6) Forestieri, R.; Merchant, C. E.; de Voogd, N. J.; Matainaho, T.; Kieffer, T. J.; Andersen, R. J. *Org. Lett.* **2009**, *11*, 5166.

(7) (a) Ma, L. Y.; Liu, W. Z.; Shen, L.; Huang, Y. L.; Rong, X. G.; Xu, Y. Y.; Gao, X. D. *Tetrahedron* **2012**, *68*, 2276. (b) Igarashi, Y.; Iida, T.; Yoshida, R.; Furumai, T. *J. Antibiot.* **2002**, *55*, 764. (c) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.

(8) (a) Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523. (b) Brimble, M. A.; Edmonds, M. K.; Williams, G. M. *Tetrahedron* **1992**, *48*, 6455. (c) Brimble, M. A.; Edmonds, M. K.; Williams, G. M. *Tetrahedron Lett.* **1990**, *51*, 7509. (d) Wu, Y.-B.; Tang, Y.; Luo, G.-Y.; Chen, Y.; Hsung, R. P. *Org. Lett.* **2014**, *16*, 4550.

(9) Palmes, J. A.; Aponick, A. *Synthesis* **2012**, *44*, 3699.

(10) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

(11) (a) Brenzovich, W. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 8933. (b) Ramana, C. V.; Suryawanshi, S. B.; Gonnade, R. G. *J. Org. Chem.* **2009**, *74*, 2842. (c) Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987. (d) Palmes, J. A.; Paioti, P. H. S.; de Souza, L. P.; Aponick, A. *Chem.—Eur. J.* **2013**, *19*, 11613.

(12) (a) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698. (b) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279.

(13) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420.

(14) (a) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97. (b) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, *78*, 385. (c) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031. (d) Ho, J. H. H.; Hodgson, R.; Wagler, J.; Messerle, B. A. *Dalton Trans.* **2010**, *39*, 4062.

(15) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Corma, A.; Leyva-Perez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.

(16) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907.

(17) (a) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669. (b) Aponick, A.; Biannic, B. *Synthesis* **2008**, 3356. (c) Aponick, A.; Li, C.-Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624. (d) Aponick, A.; Biannic, B.; Jong, M. R. *Chem. Comun.* **2010**, *46*, 6849. (e) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330. (f) Biannic, B.; Ghebreghiorgis, T.; Aponick, A. *Beilstein J. Org. Chem.* **2011**, *7*, 802. (g) Ghebreghiorgis, T.; Biannic, B.; Kirk, B. H.; Ess, D. H.; Aponick, A. *J. Am. Chem. Soc.* **2012**, *134*, 16307. (h) Ketcham, J. M.; Biannic, B.; Aponick, A. *Chem. Commun.* **2013**, *49*, 4157. (i) Ketcham, J. M.; Cardoso, F. S. P.; Biannic, B.; Piras, H.; Aponick, A. *Isr. J. Chem.* **2013**, *53*, 923.

(18) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2009**, *11*, 121.

(19) Ravindar, K.; Reddy, M. S.; Deslongchamps, P. *Org. Lett.* **2011**, *13*, 3178.

(20) Minkler, S. R. K.; Isley, N. A.; Lippincott, D. J.; Krause, N.; Lipshutz, B. H. *Org. Lett.* **2014**, *16*, 724.

(21) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061.

(22) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528.

(23) See Supporting Information for the synthesis of substrates and for the determination of the stereochemistry of substrates and products.

(24) Guillarme, S.; Ple, K.; Banchet, A.; Liard, A.; Haudrechy, A. *Chem. Rev.* **2006**, *106*, 2355.

(25) (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896.

(26) (a) Coric, I.; List, B. *Nature* **2012**, *483*, 315. (b) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074. (c) Takaoka, L. R.; Buckmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528. (d) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796.

(27) (a) Ramón, R. S.; Gaillard, S.; Slawin, A. M. Z.; Porta, A.; D'Alfonso, A.; Zanoni, G.; Nolan, S. P. *Organometallics* **2010**, *29*, 3665. (b) Engel, D. A.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027.

(28) (a) Li, Z.; Brouer, C.; He, C. *Chem. Rev.* **2008**, *108*, 32390. (b) Paton, R. S.; Maseras, F. *Org. Lett.* **2009**, *11*, 2237. (c) Hashmi, A. S. K.; Blanco, M. C.; Fischer, D.; Bats, J. W. *Eur. J. Org. Chem.* **2006**, 1387. (d) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066.

(29) Norman, R. O. C.; Parr, W. J. E.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1983.

(30) Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402.

(31) (a) Alonso, I.; Faustino, H.; López, F.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11496. (b) Gonzalez, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., III; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500. (c) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804.

(32) Su, Y.; Zhang, Y.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Org. Lett.* **2014**, *16*, 2478.