Organic Letters
Letter
pubs.acs.org/OrgLett

Tandem O−H Insertion/[1,3]-Alkyl Shift of Rhodium Azavinyl Carbenoids with Benzylic Alcohols: A Route To Convert C−OH Bonds into C−C Bonds

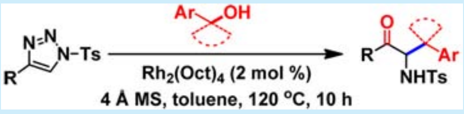
Pengbing Mi,[†] Rapolu Kiran Kumar,[†] Peiqiu Liao,[†] and Xihe Bi*[,†,‡]

[†]Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

S Supporting Information

ABSTRACT: Alcohols are among the most abundant and commonly used organic feedstock in industrial processes and academic research. The first tandem O−H insertion/[1,3]-alkyl shift reaction reported is between benzylic alcohols and rhodium azavinyl carbenoids derived from *N*-sulfonyl-1,2,3-triazoles, which provides a strategically novel way of cleaving C−OH bonds and forming C−C bonds. The substrate scope is broad, capable of covering 1°-, 2°-, and 3°-benzylic alcohols. Moreover, it constitutes a new and powerful synthetic method for constructing α-aminoketones. Mechanistic studies suggest that a [1,3]-alkyl shift of oxonium ylides is responsible for cleavage of the C−OH bonds.



Carbon−carbon bond-forming reactions are prevalent and of fundamental significance in the field of synthetic chemistry.[1] The utility of the "green" alcohols as the starting materials for forming carbon−carbon bonds is attracting massive attention, because they are among the most abundant, inexpensive, and environmentally benign chemicals. Instead of the traditional carbocation strategy,[2] dependence on the transition-metal catalysis has significantly expanded the horizon of this area in the past few decades. Many impressive strategies have emerged, for example, the ruthenium-catalyzed dehydrative C−H functionalization of alcohols,[3] the TM-catalyzed arylation/alkylation of benzyl alcohols with Grignard or arylboronic reagents,[4] the TM-catalyzed *C*-alkylation of ketones and secondary alcohols with alcohols by the borrowing of a hydrogen process,[5] sequential O−H insertion/[3,3]- or [2,3]-sigmatropic rearrangement of rhodium carbenoids with alcohols,[6,7] and the palladium-catalyzed allylic alkylation of ketones with allylic alcohols.[8] While these studies provide variable routes to exploit alcohols in C−C bond-forming reactions, the limited scope of alcohol substrates still remains a major drawback in applying these methods in synthetic practice.[3−8] Consequently, development of new alcohol-based C−C bond-forming reactions, especially those expanding the repertoire of the alcohols that can be used, is still a long-standing research goal.

Rhodium carbenoid insertion into O−H bonds, followed by sigmatropic rearrangement, has received considerable attention as an effective method for the cleavage of C−OH bonds to form C−C bonds.[6,7,9] These reactions are believed to proceed, mechanistically, via tandem formation of an oxonium ylide and sigmatropic rearrangement. Both [3,3]- and [2,3]-sigmatropic rearrangements have been utilized in such a reaction sequence, especially with applications in natural product synthesis.[6a,b,10] The groups of Wood,[6a−d] Mukarami,[6e] Fokin,[6f] and Lee[6g] have made leading contributions to the development of methods for O−H insertion/[3,3]-sigmatropic rearrangement (Figure 1a), while the [2,3]-sigmatropic rearrangement has been mainly exploited by Jung,[7a] Wood,[7b] and Davies[7c−h] (Figure 1b). Apparently, the dependence of either allylic or propargylic alcohols is necessary in all of these reactions. Therefore, expansion of this elegant strategy to general alcohols remains a hard task. The thermal [1,3]-alkyl shift of vinyl ethers was known in 1896 in the seminal report of Claisen[11] and recently

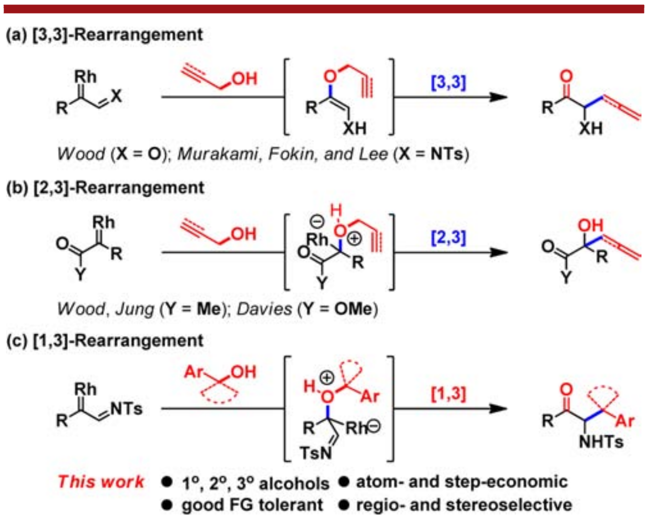


Figure 1. Tandem O−H insertion/sigmatropic rearrangement of rhodium carbenoids with alcohols.

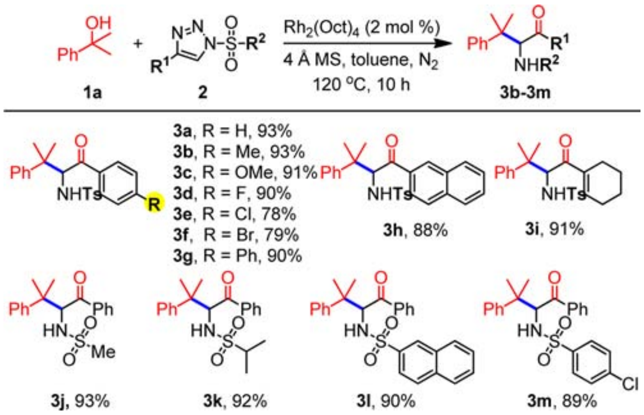
Received: August 17, 2016
Published: September 23, 2016

DOI: 10.1021/acs.orglett.6b02459
Org. Lett. 2016, 18, 4998−5001

further developed by means of transition metal catalysis[12] or Brønsted acid catalysis.[13] In comparison with [3,3]- and [2,3]-sigmatropic rearrangement, the [1,3]-alkyl migration is less developed.[9] Here, we for the first time have incorporated a [1,3]-alkyl shift into the C−OH bond cleavage of alcohols by a strategically novel O−H insertion/[1,3]-alkyl shift reaction of benzylic alcohols with rhodium azavinyl carbenoids which were derived from *N*-sulfonyl-1,2,3-triazoles (Figure 1c).[14] Notably, 1°-, 2°-, and 3°-alcohols are all suitable for this reaction. To the best of our knowledge, this is the first [1,3]-alkyl shift reaction developed directly starting from alcohols. In addition, this reaction constitutes a new and powerful synthetic method for the synthesis of *α*-aminoketones.[15]

After identifying the optimal conditions (for details, please see the Supporting Information), we then explored the reaction scope with regard to *N*-sulfonyl-1,2,3-triazoles (Scheme 1). *N*-Tosyl-1,2,3-triazoles substituted at C4 with a phenyl ring containing electron-donating or -withdrawing groups all afforded high yields of products (**3a**−**3g**, 78−93%). *N*-Tosyl-1,2,3-triazoles containing a fused aryl ring, such as naphthyl (**3h**, 88%), or an aliphatic cyclic system, such as cyclohexenyl (**3i**, 91%), also smoothly participated in the target reaction. Furthermore, variation of the sulfonyl units of 1,2,3-triazoles did not affect the reaction efficacy (**3j**−**3m**, 89−93% yields).

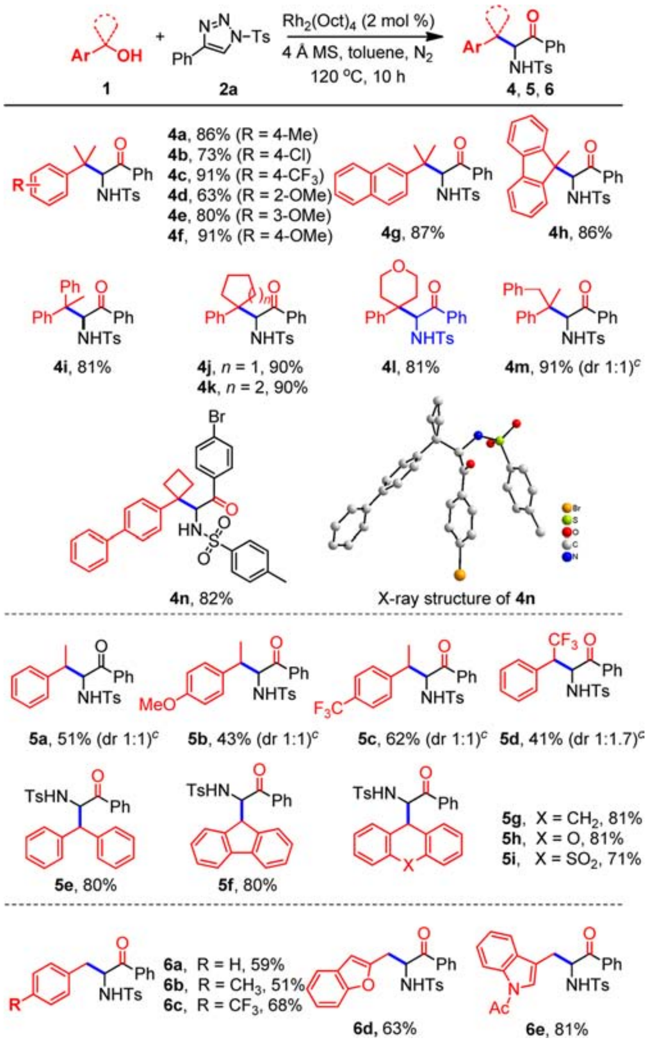
Scheme 1. Scope of *N*-Sulfonyl-1,2,3-triazoles[a,b]



[a]Conditions: **1** (0.75 mmol), **2** (0.5 mmol), $Rh_2(Oct)_4$ (2 mol %), 4 Å MS (100 mg), toluene (3 mL), 120 °C, under N_2, 10 h. [b]Isolated yields.

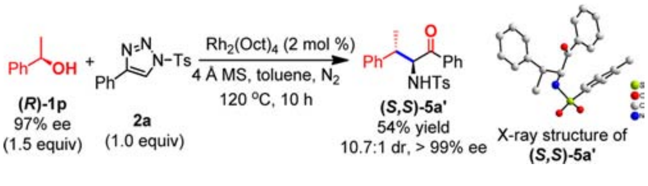
We next explored the scope of alcohols. As illustrated in Scheme 2, 3°-benzylic alcohols with electron-withdrawing (**4b** and **4c**) and electron-donating groups at the *o*/*m*/*p* positions were well tolerated (**4a**, **4d**−**4f**, 63−91%). Bulky tertiary alcohols, such as naphthyl (**4g**), fluorenyl (**4h**), and 1,1-diphenylethanol (**4i**), also smoothly underwent the target reaction to offer excellent product yields (81−92%). Furthermore, benzylic alcohols bearing aliphatic rings, such as cyclopentane (**4j**), cyclohexane (**4k**), and cyclobutane (**4n**), proved to be suitable. The structure of **4n** was further confirmed by single-crystal X-ray analysis. Similarly, a range of 2°-benzylic alcohols were reactive and resulted in the corresponding products in moderate-to-high yields (**5a**−**5i**, 41−81%). Next, the reaction scope was expanded to 1°-benzylic alcohols, which delivered the desired products (**6a**−**6c**), albeit in slightly decreased yields (51−68%). Alcohols derived from benzofuran (**6d**, 63%) and indole (**6e**, 81%) were also suitable for the target reaction.

Scheme 2. Scope of Alcohols[a]



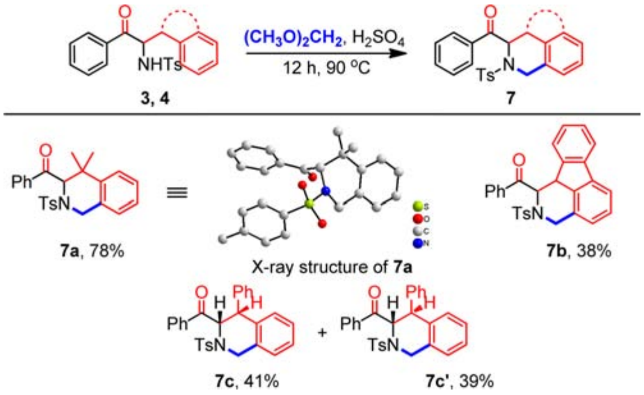
[a]Conditions: **1** (0.75 mmol), **2** (0.5 mmol), $Rh_2(Oct)_4$ (2 mol %), 4 Å MS (100 mg), toluene (3 mL), 120 °C, under N_2, 10 h. [b]Isolated yields. [c]The dr values were identified by HPLC analysis.

To develop an asymmetric version of this reaction, we tested a series of chiral rhodium catalysts, including $Rh_2(S\text{-BNP})_4$,[16] $Rh_2(S\text{-DOSP})_4$,[17] and $Rh_2(S\text{-nttl})_4$,[18] but no satisfying results were obtained. Therefore, we considered achieving high stereoselectivity by chiral induction using a chiral alcohol. Pleasingly, the alcohol (*R*)-**1p** (97% ee) produced the product **5a′** with high dr and ee values (dr = 10.7:1, ee >99%).



All *α*-aminoketone products structurally contained a benzylic motif at the *α*-carbon, thus providing a handle for further synthetic derivation. We investigated the cyclization under various conditions and eventually achieved the conversion of these *α*-aminoketones into tetrahydroisoquinolines **7** via reaction with dimethoxymethane in the presence of H_2SO_4 at 90 °C (Scheme 3).[19] The isoquinoline structure was

Scheme 3. Synthetic Utility of the Products[a,b]

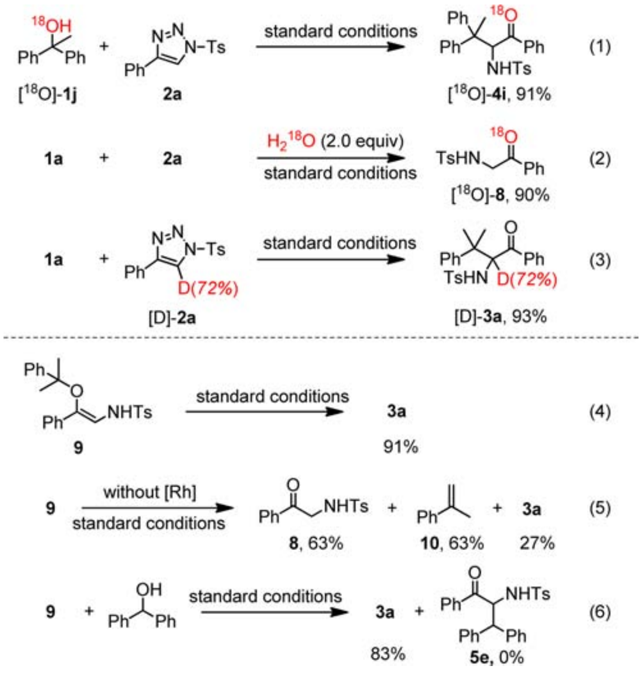


[a] Reaction conditions: **3** (0.5 mmol), dimethoxymethane (0.5 mL), H_2SO_4 (0.5 mL) at 90 °C. [b] Isolated yields.

unambiguously confirmed by single-crystal X-ray analysis of product **7a**. Notably, 1,2,3,4-tetrahydroisoquinoline is a privileged structure in many biological and medicinal compounds such as Solifenacin, a commercial antimuscarinic drug.[20]

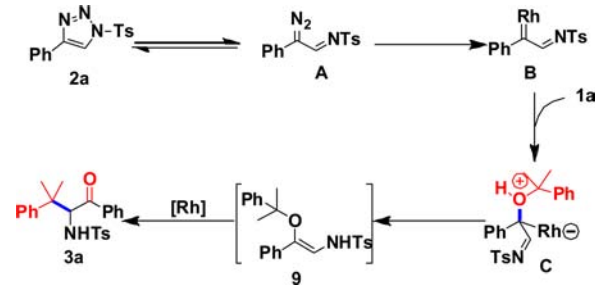
We performed extensive experiments to elucidate the reaction mechanism (Scheme 4). First, we sought to identify the source of the oxygen and hydrogen atoms in the products. A reaction using the oxygen isotope-labeled alcohol [^{18}O]-**1j** gives *β*-aminoketone [^{18}O]-**4i** (eq 1). Trace amount of water in the solvent was ruled out as the source of the oxygen atom through an experiment with $H_2{}^{18}O$, which afforded a H_2O-insertion product, [^{18}O]-**8**, as in Mukarami's report (eq 2).[21] These results suggest that the hydroxyl group of the alcohol is the source of the oxygen atom in the *β*-aminoketones. A reaction with deuterium-labeled triazole [D]-**2a** offered product [D]-**3a**, and equivalent quantities of deuterium were observed in both compounds (eq 3). Control experiments validated the involvement of the rhodium catalyst in the [1,3]-sigmatropic rearrangement step (eqs 4−6). The *β*-oxyenamine **9** was prepared separately and then subjected to the standard reaction conditions, which delivered **3a** in 91% yield, whereas the reaction without the rhodium catalyst afforded the thermal dissociation products **8** (63%) and **10** (63%), along with **3a** in small amounts (23%). Finally, a competition experiment was conducted by adding diphenylmethanol to the rearrangement reaction of **9**, which led to **3a** in 83% yield, without formation of the cross-reaction product **5e**. This result further suggests that the rhodium-catalyzed rearrangement of intermediate **9** occurs through an intramolecular process.

Scheme 4. Mechanistic Investigations



Based on these results and related precedents,[6,7,12] a plausible mechanism is proposed (Scheme 5). Initially, *N*-sulfonyl-1,2,3-triazole **2a** is converted to the *α*-diazo imine intermediate **A** via ring−chain tautomerization. This conversion is followed by reaction with the rhodium catalyst to afford *α*-imino rhodium carbenoid intermediate **B**, along with release of molecular nitrogen. Alcohol **1a** then adds to the electrophilic carbene center of **B** to generate zwitterionic intermediate **C**. Then, intermediate **C** released the rhodium to form the vinyl ether intermediate **9** which then undergoes a rhodium-induced [1,3]-alkyl shift to give product **3a**.[12]

Scheme 5. Plausible Mechanism



In conclusion, we have developed a practical, general method for the construction of C−C bonds using alcohols and rhodium carbenoids, generated in situ from *N*-sulfonyl-1,2,3-triazoles. In contrast to the [2,3]-alkyl shifts typically observed with conventional rhodium carbenoids derived from *α*-diazocarbonyl precursors, and the [3,3]-alkyl shifts observed for rhodium azavinyl carbenoids derived from *N*-sulfonyl-1,2,3-triazoles, these reactions proceed via an unusual formal [1,3]-alkyl migration pathway. In addition, this atom-economic reaction provides a useful tool for the synthesis of a range of densely functionalized *α*-aminoketones.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02459.

Experimental procedures and spectra copies (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bixh507@nenu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (21522202, 21502017, 21372038), the Ministry of Education of the People's Republic of China (NCET-13-0714), the Jilin Provincial Research Foundation for the Basic Research (20140519008JH), Fundamental Research Funds for Central Universities (2412015BJ005, 2412015KJ013, 2412016KJ040), and the Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis (No. 130028658).

■ REFERENCES

(1) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Meijere, A., Eds.; Wiley-VCH: Weinheim, 2004.

(2) Emer, E.; Sinisi, R.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, *2011*, 647.

(3) (a) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *Science* **2011**, *333*, 1613. (b) Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134*, 7325. (c) Walton, J. W.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12166.

(4) (a) Yu, D.-G.; Wang, X.; Zhu, R.-Y.; Luo, S.; Zhang, X.-B.; Wang, B.-Q.; Wang, L.; Shi, Z.-J. *J. Am. Chem. Soc.* **2012**, *134*, 14638. (b) Cao, Z.-C.; Yu, D.-G.; Zhu, R.-Y.; Wei, J.-B.; Shi, Z.-J. *Chem. Commun.* **2015**, *51*, 2683. (c) Cao, Z.-C.; Luo, F.-X.; Shi, W.-J.; Shi, Z.-J. *Org. Chem. Front.* **2015**, *2*, 1505.

(5) For a recent review, see: Huang, F.; Liu, Z.; Yu, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 862.

(6) For selected examples, see: (a) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1995**, *117*, 10413. (b) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641. (c) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748. (d) Chen, J.-H.; Levine, S. R.; Buergler, J. F.; McMahon, T. C.; Medeiros, M. R.; Wood, J. L. *Org. Lett.* **2012**, *14*, 4531. (e) Miura, T.; Tanaka, T.; Biyajima, T.; Yada, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3883. (f) Chuprakov, S.; Worrell, B. T.; Selander, N.; Sit, R. K.; Fokin, V. V. *J. Am. Chem. Soc.* **2014**, *136*, 195. (g) Jung, D. J.; Jeon, H. J.; Lee, J. H.; Lee, S.-g. *Org. Lett.* **2015**, *17*, 3498.

(7) (a) Jung, M. E.; Pontillo, J. *Org. Lett.* **1999**, *1*, 367. (b) Moniz, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 5095. (c) Li, Z.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 396. (d) Parr, B. T.; Li, Z. J.; Davies, H. M. L. *Chem. Sci.* **2011**, *2*, 2378. (e) Li, Z. J.; Parr, B. T.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 10942. (f) Li, Z. J.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 15497. (g) Chepiga, K. M.; Feng, Y.; Brunelli, N. A.; Jones, C. W.; Davies, H. M. L. *Org. Lett.* **2013**, *15*, 6136. (h) Parr, B. T.; Davies, H. M. L. *Org. Lett.* **2015**, *17*, 794.

(8) Huo, X.; Yang, G.; Liu, D.; Liu, Y.; Gridnev, I. D.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 6776.

(9) For reviews, see: (a) Jones, A. C.; May, J. A.; Sarpong, R.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 2556. (b) West, T. H.; Spoehrle, S. S. M.; Kasten, K.; Taylor, J. E.; Smith, A. D. *ACS Catal.* **2015**, *5*, 7446.

(10) (a) Tamaki, K.; Shotwell, J. B.; White, R. D.; Drutu, I.; Petsch, D. T.; Nheu, T. V.; He, H.; Hirokawa, Y.; Maruta, H.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1689. (b) Drutu, I.; Krygowski, E. S.; Wood, J. L. *J. Org. Chem.* **2001**, *66*, 7025.

(11) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 2931.

(12) (a) Harada, N.-a.; Nishikata, T.; Nagashima, H. *Tetrahedron* **2012**, *68*, 3243. (b) Kona, C. N.; Patil, M. N.; Ramana, C. V. *Org. Chem. Front.* **2016**, *3*, 453. (c) Vidhani, D. V.; Cran, J. W.; Krafft, M. E.; Manoharan, M.; Alabugin, I. V. *J. Org. Chem.* **2013**, *78*, 2059. (d) Kona, C. N.; Ramana, C. V. *Chem. Commun.* **2014**, *50*, 2152. (e) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240.

(13) (a) Tayama, E.; Otoyama, S.; Isaka, W. *Chem. Commun.* **2008**, 4216. (b) De, C. K.; Mittal, N.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 16802. (c) Tayama, E.; Horikawa, K.; Iwamoto, H.; Hasegawa, E. *Tetrahedron* **2013**, *69*, 2745.

(14) For reviews, see: (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (c) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151. See also: (d) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (e) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746. (f) Jeon, H. J.; Jung, D. J.; Kim, J. H.; Kim, Y.; Bouffard, J.; Lee, S.-g. *J. Org. Chem.* **2014**, *79*, 9865. (g) Park, S.; Yong, W.-S.; Kim, S.; Lee, P. H. *Org. Lett.* **2014**, *16*, 4468. (h) Miura, T.; Nakamuro, T.; Hiraga, K.; Murakami, M. *Chem. Commun.* **2014**, *50*, 10474.

(15) DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904.

(16) McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P. *Tetrahedron Lett.* **1992**, *33*, 5983.

(17) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972.

(18) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034.

(19) Durola, F.; Sauvage, J. P.; Wenger, O. S. *Chem. Commun.* **2006**, 171.

(20) Ko, Y.; Malone, D. C.; Armstrong, E. P. *Pharmacotherapy* **2006**, *26*, 1694.

(21) Miura, T.; Biyajima, T.; Fujii, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 194.