Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Rhodium-Catalyzed Transannulation of *N*-Sulfonyl-1,2,3-triazoles and Epoxides: Regioselective Synthesis of Substituted 3,4-Dihydro-2*H*-1,4-oxazines

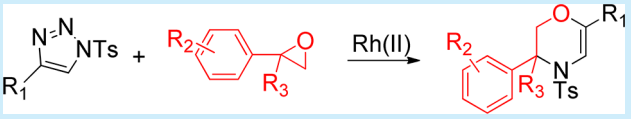
Xueji Ma,[†] Shanfei Pan,[†] Hangxiang Wang,*[,‡] and Wanzhi Chen*[,†]

[†]Department of Chemistry, Zhejiang University, Hangzhou 310028, People's Republic of China

[‡]First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, People's Republic of China

Supporting Information

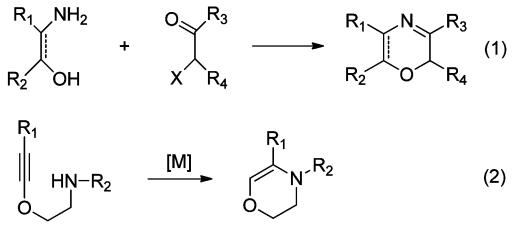
**ABSTRACT:** Rhodium-catalyzed transannulation of 1,2,3-triazoles and ring-opening reactions of epoxides is described. A number of 3,4-dihydro-2*H*-1,4-oxazines are obtained in moderate yields probably involving generation of $\alpha$-imino rhodium(II) carbene species.



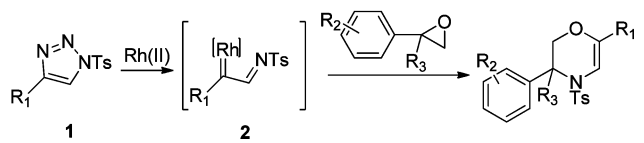

1,4-Oxazine derivatives show interesting photochromic properties[1] and are biologically active compounds as herbicides, fungicides, and other therapeutically useful drugs.[2] Aromatic ring-fused 1,4-oxazine derivatives are generally prepared via cyclocondensation of aminophenols with appropriate dihalo compounds,[3a] copper-catalyzed intramolecular *O*-arylation of $\beta$-amino alcohols,[3b] and silver-promoted sequential C−N and C−O formation reactions between 2,5-dihydroxybenzaldehyde and amino acid precursors.[3c] Nonfused 1,4-oxazines have been less studied. A typical approach to 1,4-oxazine derivatives involves the condensation of $\beta$-amino alcohols and $\alpha$-halo ketones (Scheme 1a). These methods suffered from tedious synthetic procedures and limited substrate scope. Recently, metal-catalyzed addition of alkene or alkyne with amines or alcohols emerged as an attractive alternative for 1,4-oxazine derivatives (Scheme 1a).[3d−f] However, only very limited examples were reported. Herein, we describe a novel approach to the synthesis of highly substituted 1,4-oxazine derivatives via a rhodium(II)-catalyzed intermolecular annulation of *N*-sulfonyl-1,2,3-triazoles with styrene oxide derivatives.

**Scheme 1. Synthesis of 1,4-Oxazine Derivatives**

a) Previous work




b) This work




Recently, the metal-catalyzed denitrogenative transannulation converting 1,2,3-triazoles to other heterocyclic compounds via $\alpha$-imino rhodium(II) carbene complexes received considerable attention.[4] Various interesting and useful cyclic compounds include cyclopropanes,[5] and heterocyclic compounds, pyrroles,[6] pyrroloindoline,[7] imidazoles,[8] oxazoles,[8a] indole,[9] imidazolones, and thiazoles[10] have been prepared through cycloaddtion of unsaturated compounds. The in situ generated $\alpha$-imino rhodium(II) carbene complexes are also able to react with 1,3-dioxolanes and 1,3-dioxanes, leading to eight- and nine-membered dioxazocine and dioxazonine adducts, respectively,[11] while the rhodium-catalyzed reactions of tetrahydrofuran and triazoles were also reported to give 1,4-oxazocines in poor yields.[9,11] Moreover, the ring expansion and rearrangement reactions of triazole derivatives under rhodium(II)-catalyzed conditions have been utilized to synthesize various enaminones.[12] Very recently, $\alpha$-ketone carbenes derived from triazoles were reported to be able to insert into epoxides to give 1,4-dioxene motifs with excellent stereochemistry.[13] The $\alpha$-imino rhodium(II) carbene species bear both an electrophilic carbenoid carbon and a nucleophilic $\alpha$-amino nitrogen; therefore, we envisioned that the nucleophilic oxygen of epoxides could interact with the carbenoid to generate oxonium species. After ring opening and the subsequent intramolecular attack of $\alpha$-imino nitrogen toward the epoxides, the oxonium species would afford substituted 3,4-dihydro-2*H*-1,4-oxazine derivatives. Here we describe the rhodium-catalyzed ring-opening reactions of triazoles and epoxide leading to 3,4-dihydro-2*H*-1,4-dioxazines.

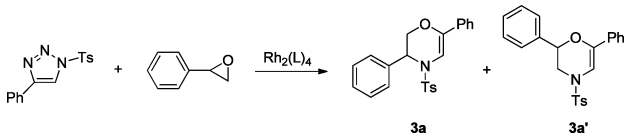
We initially attempted the reactions of *N*-tosyl-4-phenyl-1,2,3-triazoles with styrene oxide. Triazole **1a** was allowed to react with 1,2-epoxyethylbenzene in the presence of $Rh_2(OAc)_4$

**Received:** July 17, 2014

   dx.doi.org/10.1021/ol5021042 | *Org. Lett.* XXXX, XXX, XXX−XXX

(1.0 mol %) in dichloroethane (DCE) at 120 °C. After 1 h, triazole **1a** was completely consumed; however, the desired product **3a** was obtained in only 16% yield together with detosylated product 4-phenyl-1*H*-1,2,3-triazole (5−10%) and other unidentified mixtures (Table 1, entry 1). For comparison,

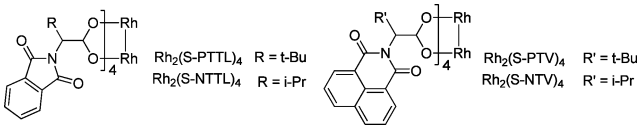
**Table 1. Optimization of Reaction Conditions**[a]




3a 3a'

| entry | $Rh_2L_4$ (mol %) | temp (°C) | solvent | yield[b] (%) |
|---|---|---|---|---|
| 1 | $Rh_2(OAc)_4$ (1) | 120 | DCE | 16 |
| 2 | $Rh_2(Oct)_4$ (1) | 120 | DCE | 19 |
| 3 | $Rh_2(Piv)_4$ (1) | 120 | DCE | 20 |
| 4 | $Rh_2$(S-PTV)$_4$ (1) | 120 | DCE | 38 |
| 5 | $Rh_2$(S-NTV)$_4$ (1) | 120 | DCE | 44 |
| 6 | $Rh_2$(S-PTTL)$_4$ (1) | 120 | DCE | 41 |
| 7 | $Rh_2$(S-NTTL)$_4$ (1) | 120 | DCE | 46 |
| 8 | $Rh_2$(S-NTTL)$_4$ (1.5) | 120 | DCE | 52 |
| 9 | $Rh_2$(S-NTTL)$_4$ (1.5) | 120 | $CHCl_3$ | 41 |
| 10 | $Rh_2$(S-NTTL)$_4$ (1.5) | 120 | toluene | 36 |
| 11 | $Rh_2$(S-NTTL)$_4$ (1.5) | 120 | PhF | 43 |
| 12 | $Rh_2$(S-NTTL)$_4$ (1.5) | 110 | DCE | 0 |
| 13 | $Rh_2$(S-NTTL)$_4$ (1.5) | 130 | DCE | 20 |

[a]Reaction were carried out with **1** (0.20 mmol) and styrene oxide (0.60 mmol) in DCE (0.5 mL). [b]All yields were determined by $^1$H NMR of the crude products.




in the absence of rhodium catalyst no desired product was observed. To optimize the reaction, the influence of a few other dirhodium tetracarboxylate catalysts was examined. The results are summarized in Table 1. When 1 mol % of rhodium catalysts were employed, $Rh_2(Oct)_4$ and $Rh_2(Piv)_4$ were nearly identical for the annulation reaction to give **3a** in less than 20% yields (entries 2 and 3). We found that the yields could be significantly improved when Hashimoto-type catalysts were used. The yields of **3a** could be raised to more than 40% in the presence of $Rh_2$(S-NTV)$_4$, $Rh_2$(S-PTTL)$_4$, and $Rh_2$(S-NTTL)$_4$ (entries 5−7). $Rh_2$(S-NTTL)$_4$ was found to be the most efficient catalyst furnishing the product in 46% yield (entry 7). An increase in catalyst loading to 1.5 mol % can further improve the reaction yield to 52% (entry 8). The solvent optimization showed that among toluene, fluorobenzene, chloroform, and DCE tested (entries 9−11), DCE was the best solvent for this rhodium-catalyzed reaction. Temperature screening showed that the reaction was totally suppressed at 110 °C and only the starting material was recovered. Higher temperature was also found to be detrimental (entries 12 and 13). No product **3a′** was detected regardless of rhodium catalysts. X-ray crystallographic analysis confirmed the molecular structure of **3a**. The diffraction also shows that two enantiomers in equal amounts cocrystallize, and only one is shown in Figure 1.

The generality of the reaction was investigated with a diverse variety of triazoles under the optimized conditions. As illustrated in Scheme 2, the reactions of triazoles bearing an

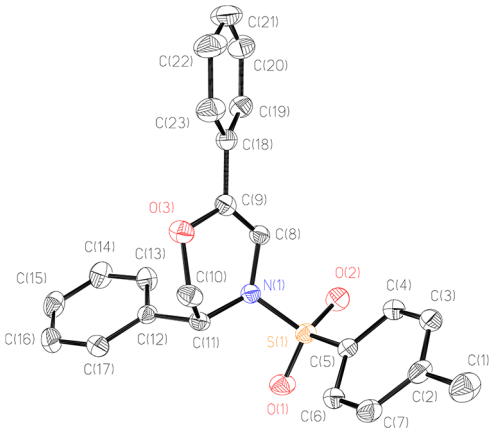
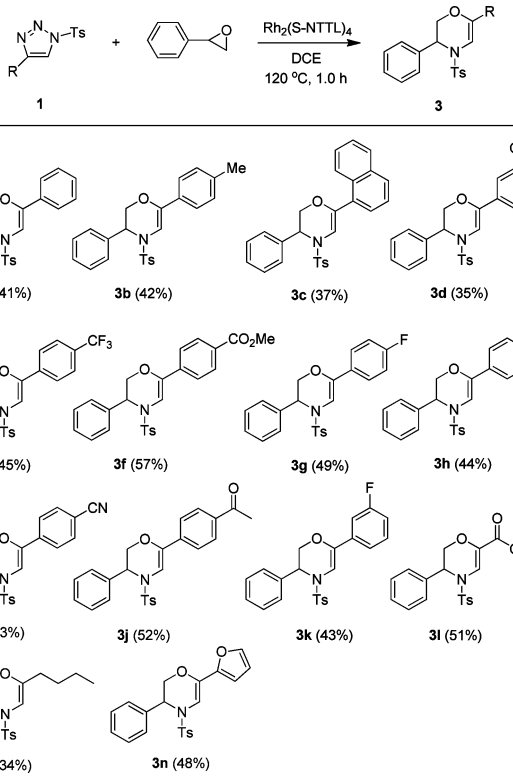



**Figure 1.** . Anisotropic displacement ellipsoids plot of **3a**.

**Scheme 2. Reactions of Styrene Oxide with Various Triazoles**[a]




[a]Reactions were carried out with **1** (0.20 mmol), $Rh_2$(S-NTTL)$_4$ (1.5 mol %), and styrene oxide (0.60 mmol) in DCE (0.5 mL); all are isolated yields.

electron-donating methyl group at the *para*-position on the phenyl ring gave product **3b** in moderate yields. In the case of 1-sulfonyl-4-(2-methylphenyl)-1,2,3-triazole only a trace amount of the product was obtained, suggesting the significant steric encumbrance of the ortho substituent. However, 1-sulfonyl-4-naphthyl-1,2,3-triazole reacted smoothly with styrene oxide affording **3c** in a comparable yield as **3a**. The reaction of the triazole bearing a *m*-methoxy group on the phenyl ring reacted with styrene oxide affording **3d** in moderate yield. Unfortunately, the triazole bearing a *p*-methoxy group on the phenyl ring is nearly inactive, and the corresponding product was isolated in less than 5% yield, probably due to the


dx.doi.org/10.1021/ol5021042 | Org. Lett. XXXX, XXX, XXX−XXX

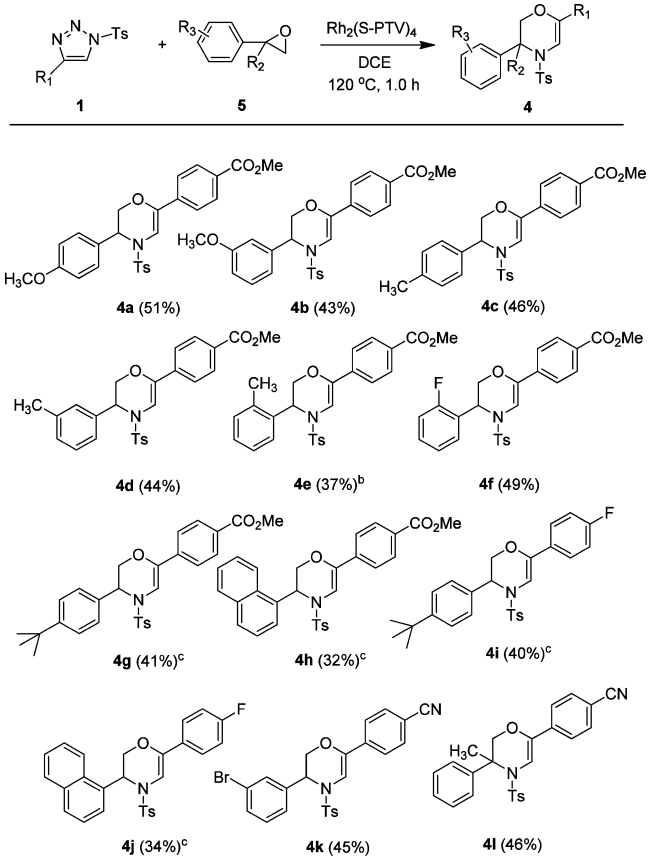
decreased electrophilicity of the α-imino rhodium carbenoid carbon center. It was expected that the electron-deficient triazoles would be more active for the annulation reaction. Indeed, the reactions of triazoles having electron-withdrawing substitutents such as fluoride, chloride, acetyl, cyanide, and carboxylate gave the corresponding products **3e−j** in enhanced yields. The triazoles derived from alphatic alkynes were also compatible under the optimized reaction conditions, producing **3l** and **3m** in yields of 51% and 34%, respectively. Furan-substituted triazole could also be transformed to 1,4-oxazine product **3n** in a comparable yield compared to other aromatic triazoles.

The scope of epoxides for the reaction was also explored, and the results are listed in Scheme 3. The transannulation, however, proceeded sluggishly in the presence of $Rh_2$(S-NTTL)$_4$. In contrast, the reactions of *N*-tosyl-4-acetylphenyl-1,2,3-triazole and styrene oxide having substituents such as methoxy, methyl, *tert*-butyl, and fluoride proceeded smoothly in the presence of less sterically demanding $Rh_2$(S-PTV)$_4$ complex to generate products **4a−g** in 37−51% yields. The variation of substituents did not show any significant influence on the reactivity of epoxides. Product **4e** was obtained in a slightly lower yield even the reaction time was prolonged to 2 h, which may be due to the steric hindrance of the *ortho* substituent. As a comparison, 2-fluorophenylethylene oxide did not show any steric effect giving the F-containing product **4f** in 47% yield within 1 h. These results clearly demonstrated the important role of steric effect in the cycloaddition reaction. 4-*tert*-Butylphenyl ethylene oxide and 1-naphthyl ethylene oxide also gave desired products **4g** and **4h** successfully when the reaction temperature was raised to 130 °C. 1-Tosyl-4-fluorophenyl-1,2,3-triazoles gave an identical result. 1-Methyl-1-phenyl-ethylene oxide was also compatible to the reaction, giving **4l** in 46% yield. Unfortunately, nonaromatic epoxides such as cyclohexene oxide and propylene oxide are not effective probably because the ring-opening to intermediate **6** is more difficult, and only decomposed mixtures were observed. *trans*-Stilbene oxide was also examined. Unfortunately, no desired product was detected, probably due to larger steric hindrance.

A possible mechanism is proposed in Scheme 4. Reaction of triazole **1** with dirhodium tetracarboxylate would generate α-imino rhodium(II) carbene species **2** upon reaction with rhodium catalyst by extrusion of one molecule of dinitrogen. The nucleophilic attack of epoxide oxygen to the electrophilic carbenoid carbon center would lead to the formation of oxonium species **6**. Driven by the electrophilic activation and ring strain of epoxide, the C−O cleavage would occur to give carbocationic intermediate 7 and 7′. The intermediate 7 is highly preferred due to the stabilizing effect of phenyl ring. The nucleophilic attack of the imino group toward the carbocation would result in the formation of the final product along with the releasing of the dirhodium complex. The bulky rhodium catalysts favor the reaction probably because the steric repulsion would accelerate the elimination of rhodium species. The electronic effect of the catalysts should also be responsible for the reaction since electronic deficient rhodium center would promote the formation of oxonium species **6** and facilitate the ring-opening of epoxides.

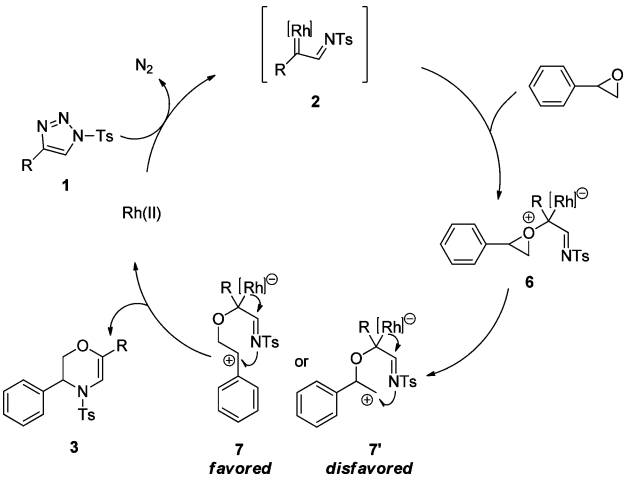
In summary, we have described a novel and efficient protocol for the preparation of a library of substituted 3,4-dihydro-2*H*-1,4-oxazine derivatives via the reaction of epoxides and triazoles. A number of 3,4-dihydro-2*H*-1,4-oxazines with diverse substituents were obtained in moderate yields. The proposed mechanism involves generation of α-imino rhodium(II) carbene species through denitrogenative transannulation of triazoles and ring-opening of epoxides. Although the efficiency needs to be improved, the present reaction offers an option for the preparation of 3,4-dihydro-2*H*-1,4-oxazines which are not easily available from the known synthetic routes.

**Scheme 3. Synthesis of 1,4-Oxazines with Various Styrene Oxides**[a]




[a]Reactions were carried out with **1** (0.20 mmol), **5** (0.60 mmol), $Rh_2$(S-PTV)4 (1.5 mol %), and DCE (0.5 mL, 0.4 M); all are isolated yields. [b]2 h. [c]130 °C.

**Scheme 4. Proposed Mechanism**





dx.doi.org/10.1021/ol5021042 | Org. Lett. XXXX, XXX, XXX−XXX

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Authors

*E-mail: wanghx@zju.edu.cn.
*E-mail: chenwzz@zju.edu.cn.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank the National Science Foundation of China for financial support (Nos. 21352002 and 21202147).

## ■ REFERENCES


(1) Minkin, V. I. *Chem. Rev.* **2004**, *104*, 2751−2776.

(2) (a) Jabeen, I.; Wetwitayaklung, P.; Klepsch, F.; Parveen, Z.; Chiba, P.; Ecker, G. F. *Chem. Commun.* **2011**, *47*, 2586−2588. (b) Li, W. P.; Duan, X. W.; Yan, H.; Xin, H. X. *Org. Biomol. Chem.* **2013**, *11*, 4546−4550. (c) Baraldi, P. G.; Saponaro, G.; Moorman, A. R.; Romagnoli, R.; Preti, D.; Baraldi, S.; Ruggiero, E.; Varani, K.; Targa, M.; Vincenzi, F.; Borea, P. A.; Tabrizi, M. A. *J. Med. Chem.* **2012**, *55*, 6608−6623. (d) Fox, B. M.; et al. *J. Med. Chem.* **2014**, *57*, 3464−3483. (e) Matralis, A. N.; Kourounakis, A. P. *J. Med. Chem.* **2014**, *57*, 2568−2581. (f) Kourounakis, A. P.; Charitos, C.; Rekka, E. A.; Kourounakis, P. N. *J. Med. Chem.* **2008**, *51*, 5861−5865.

(3) (a) Kuroita, T.; Sakamori, M.; Kawakita, T. *Chem. Pharm. Bull.* **1996**, *44*, 756−764. (b) Zhangqin Liu, Z.; Chen, Y. *Tetrahedron Lett.* **2009**, *50*, 3790−3793. (c) Iqbal, J.; Tangellamudi, N. D.; Dulla, B.; Balasubramanian, S. *Org. Lett.* **2012**, *14*, 552−555. (d) Lai, J. Y.; Shi, X. X.; Gong, Y. S.; Dai, L. X. *J. Org. Chem.* **1993**, *58*, 4775−4777. (e) Zulys, A.; Dochnahl, M.; Hollmann, D.; Lohnwitz, K.; Herrmann, J. S.; Roesky, P. W.; Blechert, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7794−7798. (f) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820−1821.

(4) For leading reviews, see: (a) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862−872. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371−1373. (c) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151−5162.

(5) (a) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034−18035. (b) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510−2511. (c) Alford, J. S.; Davies, H. M. L. *Org. Lett.* **2012**, *14*, 6020−6023. (d) Zibinsky, M.; Fokin, V. V. *Org. Lett.* **2011**, *13*, 4870−4872.

(6) (a) Parr, B. T.; Green, S. A.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 4716−4718. (b) Alford, J. S.; Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 11712−11715. (c) Kwok, S. W.; Zhang, L.; Grimster, N. P.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 3452−3456. (d) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746−3749. (e) Shi, Y.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 5394−5396. (f) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470−1471. (g) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.* **2013**, *15*, 3298−3301. (h) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696−4699. (i) Kim, C. E.; Park, S.; Eom, D.; Seo, B.; Lee, P. H. *Org. Lett.* **2014**, *16*, 1900−1903. (j) Ran, R. Q.; He, J.; Xiu, S. D.; Wang, K. B.; Li, C. Y. *Org. Lett.* **2014**, *16*, 3704−3707.

(7) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802−6805.

(8) (a) Zibinsky, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1507−1510. (b) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972−14974.

(9) Miura, T.; Funakoshi, Y.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 2272−2275.

(10) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 4652−4655.

(11) Medina, F.; Besnard, C.; Lacour, J. *Org. Lett.* **2014**, *16*, 3232−3235.

(12) (a) Selander, N.; Worrell, B. T.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 13054−13057. (b) Miura, T.; Funakoshi, Y.; Morimoto, M.; Biyajima, T.; Murakami, M. *J. Am. Chem. Soc.* **2012**, *134*, 17440−17443. (c) Liu, R. H.; Zhang, M.; Winston-McPherson, G.; Tang, W. P. *Chem. Commun.* **2013**, *49*, 4376−4378.

(13) Achard, T.; Tortoreto, C. T.; Lacour, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6140−6144.