Organic LETTERS

Letter

pubs.acs.org/OrgLett

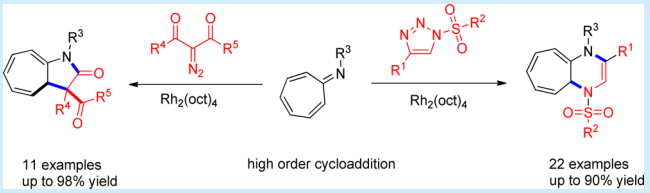
Rh(II) Catalyzed High Order Cycloadditions of 8-Azaheptafulvenes with *N*-Sulfonyl 1,2,3-Triazloes or α-Oxo Diazocompounds

Wei Chen, Ya-Li Bai, Yong-Chun Luo,* and Peng-Fei Xu*

State Key Laboratory of Applied Organic Chemistry, College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

Supporting Information

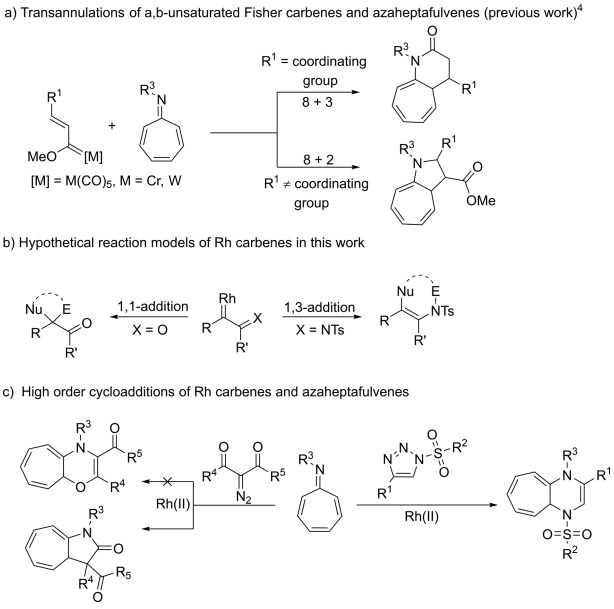
ABSTRACT: A novel strategy was developed for the application of Rh carbenes generated from readily accessible *N*-sulfonyl 1,2,3,-triazoles or diazocompouds in the high order cycloadditions, which offered an efficient route to a variety of N-containing medium-sized rings. The process provided a wide range of cyclohepta[*b*]pyrazine and cyclohepta[*b*]-pyrrolone derivatives with high yields.



The application of high-order cycloadditions in the synthesis of medium-sized cyclic compounds has been well-established.[1] Tropones are regarded as highly valuable partners that can be applied as 4π, 6π, or 8π components in various cycloadditions to afford the corresponding annulated products.[2] Comparatively, 8-azaheptafulvenes are mainly used as 8π components to undergo efficient [8 + *n*] cycloaddition reactions.[3] Typical application examples of 8-azaheptafulvenes in the field are the [8 + 2] cycloadditions with other electron-deficient π systems. However, the employment of 8-azaheptafulvenes in [8 + 3] cycloadditions is quite rare.[3] Tomás reported that the Fisher alkenyl carbenes could react with 8-azaheptafulvenes with regio- and stereoselectivities through completing [8 + 2] and [8 + 3] cyclization reactions (Scheme 1).[4] When the Cβ substituent of the alkenyl carbene complex was a coordinating moiety, the reactions would proceed completely via the [8 + 3] cyclization route. Otherwise, the [8 + 2] cyclization would take place smoothly. There exist some similarities between the Fisher alkenyl carbenes and metal carbenes derived from diazocompounds or *N*-sulfonyl 1,2,3-triazoles, and we anticipated that the Rh carbenes could react with 8-azaheptafulvenes in a catalytic reaction to afford diverse N-heterocyclics.

As mentioned above, the Rh carbenes are versatile intermediates in organic synthesis.[5] For instance, the azavinyl carbenes generated from *N*-sulfonyl 1,2,3-triazoles have been widely utilized for the synthesis of various N-containing compounds, especially aza-heterocycles.[6] Except for the common reactivity with α-oxo carbene species, these carbenes with a unique structure could serve as 1,3-dipoles to undergo cycloaddition reactions with dipolarphiles.[7] Representative works include their [3 + 2] cycloadditions with *N*-sulfonyl 1,2,3-trazoles to yield five-membered N-heterocyclics.[8] The related [3 + 3] and [4 + 3] cycloadditions involving *N*-sulfonyl 1,2,3-trazoles are relatively rare.[9] Several interesting studies were reported by Lacour and Murakami that applied the azavinyl carbenes in the synthesis of medium-sized cyclic compounds.[10] Despite their successful applications in cyclo-

Scheme 1. Cycloadditions of Various Carbenes



addition reactions, the use of *N*-sulfonyl 1,2,3-triazoles in higher-order cycloaddition reactions has remained unexplored. We envisaged that a [8 + 3] reaction would take place between 8-azaheptafulvenes and azavinyl carbenes to construct the 7,6-fused heterocyclic compounds, and the reactions of 8-azaheptafulvenes with α-oxo carbenes would proceed in a different way. To our surprise, a class of 7,5-fused heterocyclic compounds were obtained by a rearrangement reaction when 8-azaheptafulvenes reacted with α-oxo diazocompounds. Here, we describe the rhodium-catalyzed reactions of 8-azaheptaful-

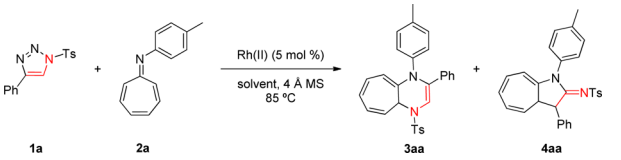
Received: November 28, 2016

DOI: 10.1021/acs.orglett.6b03542
Org. Lett. XXXX, XXX, XXX−XXX

venes with *N*-sulfonyl 1,2,3-triazloes and α-oxo diazocompounds, which proceed in a different way.

Our initial investigation started with 4-phenyl-*N*-tosyl-1,2,3-triazole **1a** and 1.2 equiv of 8-azaheptafulvene **2a** in the presence of 5 mol % of various Rh(II) catalysts and 4 Å MS in $CHCl_3$ at 85 °C (Table 1, entries 1−4).[11] It was found that

Table 1. Optimization of the Reaction Conditions[a]



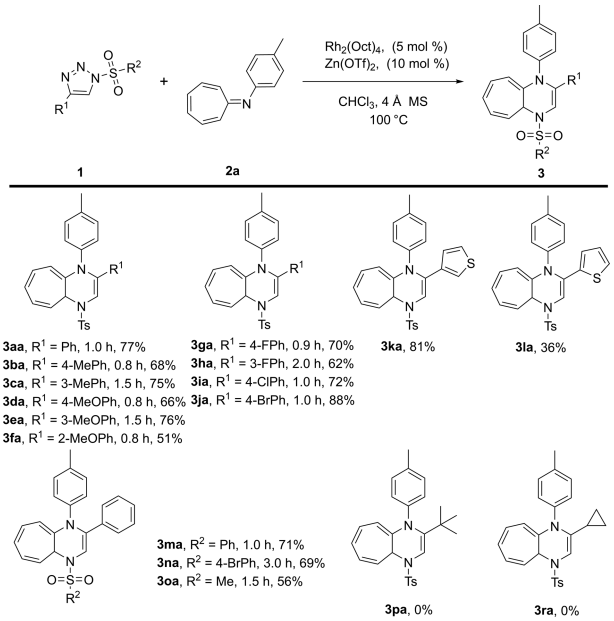
entry	catalyst	solvent	additive (0.1 equiv)	time (h)	yield[f] (%)
1	$Rh_2(OAc)_4$	$CHCl_3$	–	8.0	13
2	$Rh_2(esp)_4$	$CHCl_3$	–	5.0	30
3	$Rh_2(Oct)_4$	$CHCl_3$	–	3.0	56
4	Rh_2(R-DOSP)$_4$	$CHCl_3$	–	12.0	32
5[b]	$Rh_2(Oct)_4$	$CHCl_3$	–	1.5	47
6	$Rh_2(Oct)_4$	$CHCl_3$	$Sc(OTf)_3$	1.5	49
7	$Rh_2(Oct)_4$	$CHCl_3$	$Mg(OTf)_2$	1.5	52
8	$Rh_2(Oct)_4$	$CHCl_3$	$Cu(OTf)_2$	2.0	58
9	$Rh_2(Oct)_4$	$CHCl_3$	$Zn(OTf)_2$	1.5	75
10	$Rh_2(Oct)_4$	DCE	$Zn(OTf)_2$	1.5	60
11	$Rh_2(Oct)_4$	toluene	$Zn(OTf)_2$	1.5	62
12[c]	$Rh_2(Oct)_4$	$CHCl_3$	$Zn(OTf)_2$	1.0	75
13[d]	$Rh_2(Oct)_4$	$CHCl_3$	$Zn(OTf)_2$	0.5	26
14[e]	$Rh_2(Oct)_4$	$CHCl_3$	$Zn(OTf)_2$	1.0	77

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.24 mmol), Rh(II) (5 mol %), 4 Å MS (200 mg), and 4 mL of solvent were heated in a sealed tube until the consumption of **1a** was apparent by TLC. [b]2 mol % catalyst was used. [c]At 100 °C. [d]At 120 °C. [e]**1a** (0.20 mmol), **2a** (0.30 mmol), at 100 °C. [f]Isolated yields.

$Rh_2(Oct)_4$ was a suitable catalyst to gain the desired product **3aa** in a moderate yield of 56% (entry 3). Decreasing the amount of the catalyst led to a lower yield (entry 5). In an effort to raise the yield, numerous Lewis acids were added to the reaction systems as additives (entries 6−9), which were expected to promote the dissociation of rhodium from the rhodium carbene complex to generate an intermediate of anionic enamine. The intermediate would subsequently undergo a cycloaddition reaction. From the results obtained, $Zn(OTf)_2$, a softer metal salt, was found to significantly increase the reaction yield (entry 9). The solvent, temperature, and molar ratio of two substrates were also optimized to give the best results (entry 14). During the optimization of the reaction conditions, a tiny amount of side-product **4aa** was obtained in a yield of 9% with moderate diastereoselectivity in favor of the *trans*-configuration (entry 14). Interestingly, the *N*-tosyl-1,2,3-triazole **1a** worked as a [2C]-component in the formation of **4aa**, and the structure of **4aa** was confirmed by single-crystal X-ray analysis.[12]

With the reaction conditions optimized, we focused on investigating the generality of this reaction. As summarized in Scheme 2, a wide range of substituted triazloes (**1a**−**1r**) were subjected to the reactions with **2a** to generate the functionalized cycloheptatriene-fused pyrazine derivatives. Instead of the electronic effect, steric hindrance had a greater influence on the reactivities of triazoles **1** bearing diverse aryl groups at the C4 position. Both electron-donating (**1b**−**1f**) and electron-

Scheme 2. Rhodium(II) Catalyzed Reaction of Triazoles (1) with 8-Azaheptafulvene (2a)[a,b]



[a]Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), $Rh_2(Oct)_4$ (5 mol %), $Zn(OTf)_2$ (10 mol %), 4 Å MS (200 mg), and $CHCl_3$ (4 mL) at 100 °C. [b]Isolated yields.

withdrawing group (**1g**−**1j**) substituted triazloes afforded the corresponding products in moderate to good yields. However, 2-methoxy substituted triazloe (**1f**) gave a slightly lower yield. The 3-thienyl substituent triazloe (**1k**) was also well tolerated, while the 2-thienyl substituted triazloe (**1l**) afforded a much lower yield due to the nucleophilicity of the 3-position at the thienyl group. Reactions with alkyl-substituted triazloes failed to take place. The ring-expansion and rearrangement reactions led to the decomposition of the rhodium carbene complex, as reported before (**1p**−**1r**).[13] The change of the 1-sulfonyl group at N1 of triazole (**1m**−**1o**) did not significantly affect the reaction efficiency, although the aliphatic sulfonyl group reduced the activity slightly compared with the aromatic moiety.

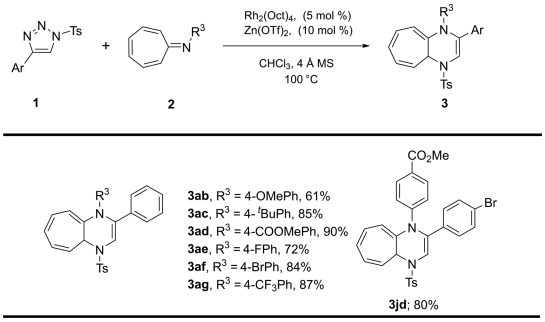
Further exploration of the novel reaction was conducted by evaluating the scope of the 8-azaheptafulvenes. These 8π components possessing various substituents including electron-donating (**2b**−**c**) and electron-withdrawing groups (**2d**−**g**) on the N-aryl group all provided the cyclization products in good yields (Scheme 3). Unfortunately, the effort to prepare *N*-alkyl substituted azaheptafulvenes failed.

In order to demonstrate the synthetic application and its convenient operation of this reaction, a three-component one-pot protocol was developed. Initially, phenylacetylene **5** (0.30 mmol), tosyl azide **6** (0.30 mmol), **2a** (0.45 mmol), CuTC (10 mol %), 4 Å MS (200 mg), and $CHCl_3$ (2 mL) were mixed and stirred at room temperature for 16 h. After triazole **1a** was generated, $Rh_2(Oct)_4$ (5 mol %) and $Zn(OTf)_2$ (10 mol %) were added to the same vessel, and then the mixture was heated to 100 °C for 1 h. The product **3aa** was isolated with a yield of 47% (Scheme 4).

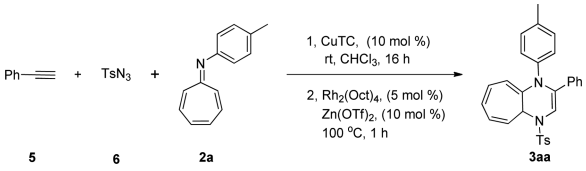
Finally, a plausible mechanism for this transannulation is proposed, which is shown in Scheme 5. Treated with a rhodium(II) catalyst, the α-imino rhodium carbene **A** is generated via a tandem triazole ring opening and nitrogen

DOI: 10.1021/acs.orglett.6b03542
Org. Lett. XXXX, XXX, XXX−XXX

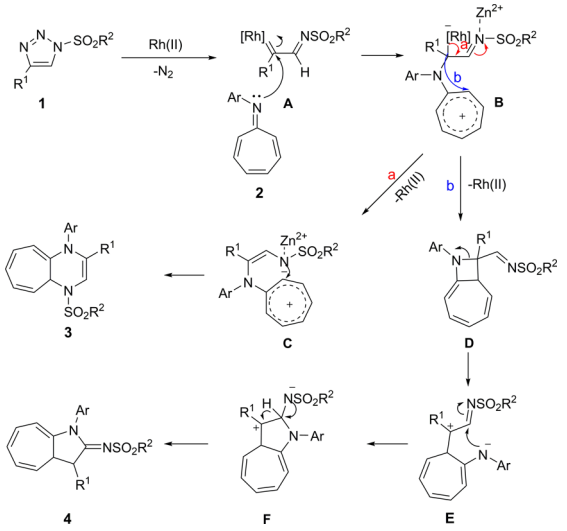
Scheme 3. Rhodium(II) Catalyzed Reactions of Various 8-Azaheptafulvenes



Scheme 4. One-Pot Synthesis of Cyclohepta[*b*]pyrazine 3aa



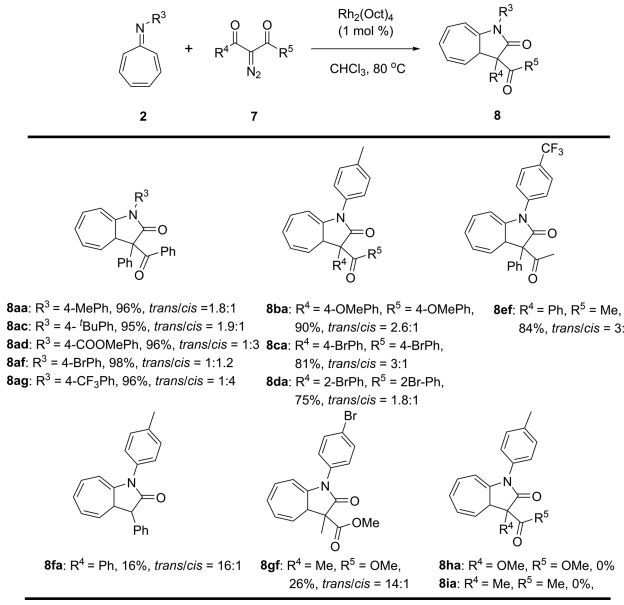
Scheme 5. Plausible Mechanism



extrusion. The active intermediate **A** is then attacked by the nitrogen atom of azaheptafulvene **2** on its carbene center to provide a key rhodium-bound zwitterionic intermediate **B** with the positive charge of the 8π component delocalized within the ring. At this point, there are two different pathways for the formation of different products. Intermediate **B** predominantly converts to intermediate **C** by an imine−enamine tautomerization (pathway a); subsequently, a ring closure occurs to yield adduct **3**. Coordination of a Lewis acid with the α-imine can promote this process to improve the yield of **3**. Meanwhile, the electron pair released by the resulting anionic rhodium may directly attack the C8 position to generate an unstable structure D (pathway b). Due to the great strain caused by the twisted seven-member ring, this active intermediate **D** will undergo an immediate rearrangement with the cleavage of the N−C bond to give intermediate **E**. Final product **4** is formed by a sequential ring closure and 1,2-H shift.

Reactions between 8-azaheptafulvene and carbonyl-containing diazo compounds proceed via a similar pathway of b (see Supporting Information). When azaheptafulvene **2a** and diazo compound **7a** were treated with a 1 mol % of $Rh_2(Oct)_4$ in $CHCl_3$ under 80 °C, the cycloheptatriene-fused pyrrolone derivative was obtained with an excellent yield of 96% (Scheme 6). However, a modest diastereoselectivity of **8aa**−**8da** was

Scheme 6. Reactions of Diazo Compounds with 8-Azaheptafulvenes



observed when the substituent R^4 and R^5 share similar steric bulk. By changing the R^5 to methyl, the **8ef** was gained with a yield of 84%. The active 2-diazo-1-phenylethanone **7f** gave **8fa** in a yield of 16% with good diastereoselectivity (16:1). While both R^4 and R^5 were altered from a phenyl group to a methyl or methoxyl group, we failed to gain the products **8ia** and **8ha**. When the R^5 was a methoxyl group and the R^4 was a methyl group, **8gf** was obtained with a low yield of 26%.

In conclusion, we have successfully applied *N*-tosyl 1,2,3-triazloes to a [8 + 3] high order cycloaddition with 8-azaheptafulvenes and developed a novel strategy for the synthesis of cyclohepta[*b*]pyrazine derivatives with readily available starting materials. Remarkably, the formation of **4aa** demonstrated the potential of α-imine carbene complexes as a [2C] component in cyclization reactions. The reactions of α-oxo diazocompounds and 8-azaheptafulvenes revealed an intriguing rearrangement process which afforded the cyclohepta[*b*]pyrrolone derivatives with excellent yields. Further investigations of the cycloaddition reactions of *N*-tosyl 1,2,3-triazloes are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03542.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)
X-ray data for **3af** (CIF)
X-ray data for *trans*-**4aa** (CIF)
X-ray data for *trans*-**8ca** (CIF)

DOI: 10.1021/acs.orglett.6b03542
Org. Lett. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Authors

*E-mail: xupf@lzu.edu.cn.
*E-mail: luoych@lzu.edu.cn.

ORCID

Yong-Chun Luo: 0000-0002-9567-7297
Peng-Fei Xu: 0000-0002-5746-758X

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the NSFC (21302075, 21372105, 21572087, and 21632003), the International S&T Cooperation Program of China (2013DFR70580), and the "111" program from the MOE of P. R. China for financial support.

REFERENCES

(1) For reviews of higher-order cycloadditions, see: (a) Ylijoki, K. E. O.; Stryker, J. M. *Chem. Rev.* **2013**, *113*, 2244. (b) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189. (c) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595.

(2) (a) Li, P.-F.; Yamamoto, H. *J. Am. Chem. Soc.* **2009**, *131*, 16628. (b) Asao, T.; Itô, S.; Murata, I. *Eur. J. Org. Chem.* **2004**, 899. (c) Teng, H.-L.; Yao, L.; Wang, C.-J. *J. Am. Chem. Soc.* **2014**, *136*, 4075. (d) Trost, B. M.; McDougall, P. J.; Hartmann, O.; Wathen, P. T. *J. Am. Chem. Soc.* **2008**, *130*, 14960. (e) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (f) Rigby, J. H.; Fleming, M. *Tetrahedron Lett.* **2002**, *43*, 8643. (g) Isakovic, L.; Ashenhurst, J. A.; Gleason, J. L. *Org. Lett.* **2001**, *3*, 4189.

(3) (a) Xie, M.-S.; Liu, X.-H.; Cai, Y.-F.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2013**, *52*, 5604. (b) Lage, M. L.; Fernández, I.; Sierra, M. A.; Torres, M. R. *Org. Lett.* **2011**, *13*, 2892. (c) Barluenga, J.; García-Rodríguez, J.; Suárez-Sobrino; Ángel, L.; Tomás, M. *Chem.-Eur. J.* **2009**, *15*, 8800. (d) Nair, V.; Abhilash, K. G. *Tetrahedron Lett.* **2006**, *47*, 8707. (e) Takaoka, K.; Aoyama, T.; Shioiri, T. *Heterocycles* **2001**, *54*, 209. (f) Yamamoto, K.; Kajigaeshi, S.; Kanemasa, S. *Chem. Lett.* **1977**, *6*, 85. (g) Ishizu, T.; Harano, K.; Yasuda, M.; Kanematsu, K. *J. Org. Chem.* **1981**, *46*, 3630.

(4) Barluenga, J.; García-Rodríguez, J.; Martínez, S.; Suárez-Sobrino, Á. L.; Tomás, M. *Chem. - Asian J.* **2008**, *3*, 767.

(5) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998.

(6) For recent reviews, see: (a) Davies, H. M. L.; Alford, J. S. *Chem. Soc. Rev.* **2014**, *43*, 5151. (b) Anbarasan, P.; Yadagiri, D.; Rajasekar, S. *Synthesis* **2014**, *46*, 3004. (c) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (d) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862.

(7) For seminal works, see: (a) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510. (b) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 1470. (c) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034.

(8) (a) Shi, Y.; Gevorgyan, V. *Org. Lett.* **2013**, *15*, 5394. (b) Chattopadhyay, B.; Gevorgyan, V. *Org. Lett.* **2011**, *13*, 3746. (c) Miura, T.; Hiraga, K.; Biyajima, T.; Nakamuro, T.; Murakami, M. *Org. Lett.* **2013**, *15*, 3298. (d) Schultz, E. E.; Sarpong, R. *J. Am. Chem. Soc.* **2013**, *135*, 4696. (e) Kim, C.-E.; Park, S.; Eom, D.; Seo, B.; Lee, P. H. *Org. Lett.* **2014**, *16*, 1900. (f) Rajasekar, S.; Anbarasan, P. *J. Org. Chem.* **2014**, *79*, 8428. (g) Ran, R.-Q.; He, J.; Xiu, S.-D.; Wang, K.-B.; Li, C.-Y. *Org. Lett.* **2014**, *16*, 3704. (h) Zibinsky, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1507. (i) Lee, D. J.; Shin, J.; Yoo, E. J. *Chem. Commun.* **2014**, *50*, 6620. (j) Miura, T.; Funakoshi, Y.; Tanaka, T.; Murakami, M. *Org. Lett.* **2014**, *16*, 2760. (k) Jung, D.-J.; Jeon, H. J.; Kim, J. H.; Kim, Y.; Lee, S.-G. *Org. Lett.* **2014**, *16*, 2208. (l) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (m) Spangler, J. E.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6802. (n) Chuprakov, S.; Kwok, S. W.; Fokin, V. V. *J. Am. Chem. Soc.* **2013**, *135*, 4652. (o) Miura, T.; Funakoshi, Y.; Fujimoto, Y.; Nakahashi, J.; Murakami, M. *Org. Lett.* **2015**, *17*, 2454. (p) Parr, B. T.; Green, S. A.; Davies, H. M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4716. (q) Miura, T.; Funakoshi, Y.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 2272.

(9) (a) Ma, X.-J.; Pan, S.-F.; Wang, H.-X.; Chen, W.-Z. *Org. Lett.* **2014**, *16*, 4554. (b) Ryu, T.; Baek, Y.; Lee, P. H. *J. Org. Chem.* **2015**, *80*, 2376. (c) Miura, T.; Tanaka, T.; Hiraga, K.; Stewart, S. G.; Murakami, M. *J. Am. Chem. Soc.* **2013**, *135*, 13652. (d) Shang, H.; Wang, Y.-H.; Tian, Y.; Feng, J.; Tang, Y.-F. *Angew. Chem., Int. Ed.* **2014**, *53*, 5662. (e) Zhao, Y.-Z.; Yang, H.-B.; Tang, X.-Y.; Shi, M. *Chem. - Eur. J.* **2015**, *21*, 3562. (f) Wang, Y.-H.; Lei, X.-Q.; Tang, Y.-F. *Chem. Commun.* **2015**, *51*, 4507.

(10) (a) Miura, T.; Fujimoto, Y.; Funakoshi, Y.; Murakami, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 9967. (b) Medina, F.; Besnard, C.; Lacour, J. *Org. Lett.* **2014**, *16*, 3232.

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

(12) Lei, X.-Q.; Li, L.-B.; He, Y.-P.; Tang, Y.-F. *Org. Lett.* **2015**, *17*, 5224.

(13) (a) Liu, R.-H.; Zhang, M.; Winston-Mcpherson, G.; Tang, W.-P. *Chem. Commun.* **2013**, *49*, 4376. (b) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371.

DOI: 10.1021/acs.orglett.6b03542
Org. Lett. XXXX, XXX, XXX−XXX