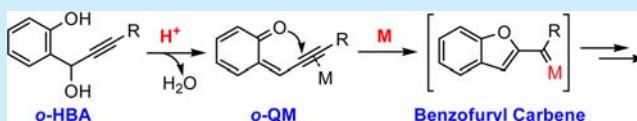


## Dual Catalysis: Proton/Metal-Catalyzed Tandem Benzofuran Annulation/Carbene Transfer Reaction

Jun Ma,<sup>†</sup> Kai Chen,<sup>†</sup> Hongguang Fu,<sup>‡</sup> Li Zhang,<sup>‡</sup> Wanqing Wu,<sup>†</sup> Huanfeng Jiang,<sup>†</sup> and Shifa Zhu<sup>\*,†</sup><sup>†</sup>School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, 510640, P. R. China<sup>‡</sup>School of Chemistry and Chemical Engineering, Sun Yat-sen University, Guangzhou, 510275, P. R. China

## S Supporting Information

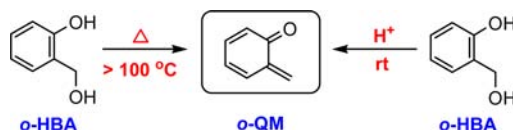
**ABSTRACT:** An efficient proton/metal-catalyzed tandem benzofuran annulation/carbene transfer reaction for the synthesis of various benzofuryl-substituted cyclopropanes and cycloheptatrienes has been developed. The reaction was proposed to proceed through two key intermediates, *o*-quinone methide (*o*-QM) and benzofuryl carbene. The DFT-based computational studies indicated that the reaction was initiated through the dehydration of *o*-HBA via a Brønsted acid mediated proton shuttle transition state, forming the key intermediate *o*-QM.



Dual catalysis is a powerful catalytic strategy in modern organic synthesis. It is particularly useful in the generation and trapping of those highly reactive transient species.<sup>1</sup>

*o*-Quinone methide (*o*-QM), a transient short-lived and highly reactive species, has attracted extensive interest from organic chemists for over 100 years.<sup>2</sup> Many of the synthetic techniques for producing *o*-QMs have been developed in the past decades, such as tautomerization, thermolysis, photolysis, and acid facilitation.<sup>3,4</sup> Among them, acid facilitation probably is one of the most useful strategies, and many tautomerization and thermal processes can be induced to occur at much lower temperature by addition of an acid catalyst. For example, in the presence of an acid catalyst, *o*-QM can be formed smoothly from the reaction of *o*-hydroxyl-benzyl alcohol (*o*-HBA) at room temperature,<sup>4</sup> whereas without the help of an acid catalyst, the reaction is largely decelerated and *o*-QM can be generated at much higher temperature (>100 °C)<sup>3</sup> (Scheme 1).

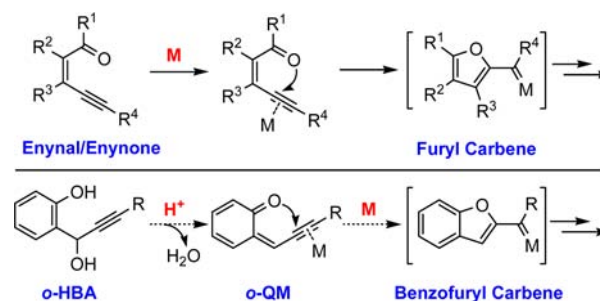
**Scheme 1. Generation of *o*-QM by Thermolysis or Acid Facilitation**



Recently, enynal/enynone has proved to be a new, safe, and practical carbenoid precursor.<sup>5</sup> We speculated that alkynyl-substituted *o*-HBA might be used as the benzofuryl carbene precursor under the dual catalysis of an acid and a transition metal via *o*-QM as the proposed intermediate (Scheme 2).<sup>6</sup>

With this in mind, *o*-HBA (1a) with a tethered enyne side chain was then chosen as the model substrate for this investigation, aiming at producing the cyclopropyl-fused pyrrolidine<sup>7</sup> (2a). As shown in Table 1, initial efforts were

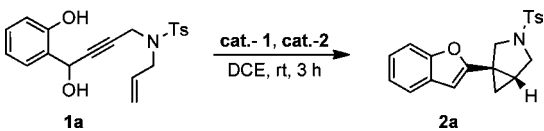
**Scheme 2. Formation of Furyl Carbene from Enynal/Enynone or *o*-HBA**



made to systematically investigate various catalytic reaction conditions for the tandem benzofuran annulation/cyclopropanation reaction. The metals used most commonly in carbene transformations, such as Cu, Ag, Au, and Rh, were then tested. It was found that the desired product 2a has not been detected when the metal catalysts were used alone, indicating that they are inefficient for this transformation (entries 1–4). We speculated that it might be the consequence of inefficiency of the formation of *o*-QM. The attempt to facilitate the generation of the *o*-QM intermediate by enhancing the temperature resulted in a complex system. The product 2a could be detected in 18% yield when 1 mol % Rh<sub>2</sub>(OPiv)<sub>4</sub> was used as the catalyst at 80 °C (entry 5). To examine whether the addition of acids could promote the formation of *o*-QM, the reactions in the presence of different acids as the cocatalyst of Rh<sub>2</sub>(OPiv)<sub>4</sub> have been carried out (entries 6–8). The addition of TsOH has no obvious positive effects (entry 6), whereas the yield of 2a was increased to 44% when PhCOOH was applied (entry 7). Gratifyingly, the yield was sharply enhanced to 88% when 50

Received: January 26, 2016

Published: March 7, 2016

Table 1. Optimization of the Reaction Conditions<sup>a</sup>


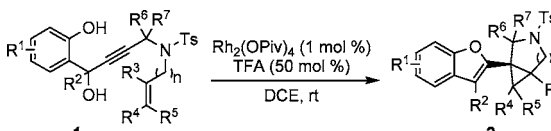
entry	cat.-1 (mol %)	cat.-2 (mol %)	yield (%) (2a)
1	CuCl <sub>2</sub> (5)	—	ND
2	AgNTf <sub>2</sub> (5)	—	ND
3	PPh <sub>3</sub> AuNTf <sub>2</sub> (5)	—	ND
4	Rh <sub>2</sub> (OPiv) <sub>4</sub> (1)	—	ND
5 <sup>b</sup>	Rh <sub>2</sub> (OPiv) <sub>4</sub> (1)	—	18
6	Rh <sub>2</sub> (OPiv) <sub>4</sub> (1)	TsOH (50)	20
7	Rh <sub>2</sub> (OPiv) <sub>4</sub> (1)	PhCOOH (50)	44
8	<b>Rh<sub>2</sub>(OPiv)<sub>4</sub> (1)</b>	<b>TFA (50)</b>	<b>88<sup>c</sup></b>
9	CuCl <sub>2</sub> (5)	TFA (50)	77
10	AgNTf <sub>2</sub> (5)	TFA (50)	trace
11	Rh <sub>2</sub> (OPiv) <sub>4</sub> (1)	TFA (20)	60
12	Rh <sub>2</sub> (OPiv) <sub>4</sub> (1)	TFA (100)	65
13	—	TFA (50)	ND

<sup>a</sup>The reaction was conducted with **1a** (0.2 mmol) in DCE (1 mL), rt, under N<sub>2</sub>, 3 h. The yield was determined by <sup>1</sup>H NMR analysis using CH<sub>3</sub>NO<sub>2</sub> as an internal standard; TFA: CF<sub>3</sub>COOH. <sup>b</sup>80 °C, 12 h. <sup>c</sup>Isolated yield.

mol % TFA was added instead (entry 8). The combination of CuCl<sub>2</sub>/TFA is another good choice for this transformation, albeit in a relatively lower yield (entry 9). However, only a trace amount of the desired product **2a** was detected when AgNTf<sub>2</sub>/TFA was employed (entry 10). Neither increasing nor decreasing the amounts of TFA in the rhodium-catalytic system can give better results (entries 11–12). TFA alone does not catalyze the formation of **2a** at all (entry 13).

With the optimized reaction conditions (Table 1, entry 8) in hand, the substrate scope was then examined (Table 2). It was found that the Rh<sub>2</sub>(OPiv)<sub>4</sub>/TFA catalytic system could be successfully applied to the reaction of a variety of *o*-HBA derivatives **1**. The aryl substituents R<sup>1</sup> have little effect on the yields (**2a–f**, 74–93%). In addition to the *o*-HBAs **1** with a simple terminal alkene, the substrates with a di- or trisubstituted alkene unit could also be effectively converted into the desired cyclopropane products in satisfied yields (**2g–k**, 64–87%), although the reactions were accomplished at elevated temperature (e.g., 80 °C). Furthermore, the reaction could be extended to the *o*-HBA with a tertiary alcohol (R<sup>2</sup> = Me), giving the product in excellent yield (**2l**, 88%). A bulky substrate (R<sup>6</sup> = R<sup>7</sup> = Me) transferred to the product in moderate yield (**2m**, 43%). Moreover, the *o*-HBAs with a longer side chain (*n* = 2, 3) could also be used as effective substrates, leading to the desired products **2n** and **2o** in 73% and 36% yields, respectively. For the latter case, a C–H insertion product **2o'** could be isolated in 40% yield as well, indicating that the reaction probably proceeded through the Rh-carbene intermediate (excluding the carbon cation mechanism<sup>7</sup>).<sup>8</sup> In all cases in Table 2, only one diastereoisomer was observed.

In addition to the cyclopropanation reaction, another representative carbene-transfer reaction, a Buchner ring-expansion reaction, was also investigated for this dual catalysis.<sup>9</sup> For this purpose, various *N*-benzyl derived substrates *o*-HBA **3** were then tested. As shown in Table 3, the reaction has good substrate scope. A variety of different substituents R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> were well tolerated for this reaction system. The yields were

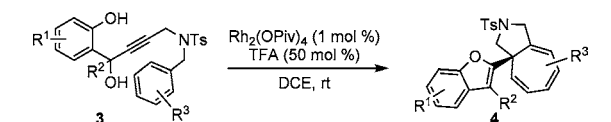
Table 2. Scope of Cyclopropanation Reaction<sup>a</sup>


product	yield (%) <sup>a</sup>	product	yield (%) <sup>a</sup>
<b>2a</b> : 88		<b>2b</b> : 93	
<b>2c</b> : 77		<b>2d</b> : 74 <sup>b</sup>	
<b>2e</b> : 90		<b>2f</b> : 93	
<b>2g</b> : 87		<b>2h</b> : 64	
<b>2i</b> : 80 <sup>b</sup>		<b>2j</b> : 71 <sup>b</sup>	
<b>2k</b> : 74 <sup>b</sup>		<b>2l</b> : 88	
<b>2m</b> : 43		<b>2n</b> : 73	
<b>2o</b> : 36		<b>2o'</b> : 40	

<sup>a</sup>Conditions: Rh<sub>2</sub>(OPiv)<sub>4</sub> (1 mol %), TFA (50 mol %), DCE (1 mL), **1** (0.2 mmol), rt, 3–12 h, isolated yield. <sup>b</sup>80 °C.

typically higher than 60%. For examples, both electron-rich and -deficient substituents of R<sup>1</sup> functioned well. It seems that electron-donating groups of R<sup>1</sup> (**4a–4c**) gave better results than electron-withdrawing ones (**4d**, **4f**). However, the electron-donating group methoxy (MeO–) led to product **4e** only in 44% yield, presumably due to the potential interaction between the electron-rich phenyl ring and the rhodium catalyst. The electronic effects of R<sup>2</sup> on the benzyl group had relatively little effect on this reaction, giving the desired products **4g–4k** in 41%–78% yields. Furthermore, the reaction could be extended to the *o*-HBA with a tertiary alcohol (R<sup>3</sup> = Me) as well, giving the product **4l** in 74% yield.

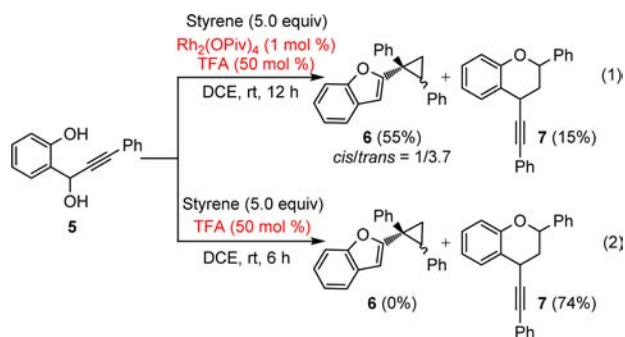
Besides the intramolecular reaction, the proton/Rh-catalyzed system could be extended to the intermolecular cyclopropanation as well. For instance, styrene could be cyclopropanated by the Rh<sub>2</sub>(OPiv)<sub>4</sub>/TFA in dichloroethane with *o*-HBA **5** as a carbene source at room temperature, affording the desired product **6** in 55% yield, accompanied by a 15% yield of chroman **7**. The latter should come from the [4 + 2] cycloaddition of the *in situ* generated *o*-QM with styrene [Scheme 3, eq 1].<sup>4</sup> Actually, chroman **7** could be produced solely in 74% yield when the reaction was promoted merely by TFA eq 2. Furthermore, when *o*-HBA **5** was subjected to

Table 3. Scope of Buchner Reaction<sup>a</sup>


product	yield (%) <sup>a</sup>	product	yield (%) <sup>a</sup>
	4a: 90		4b: 86
	4c: 90		4d: 70 <sup>b</sup>
	4e: 44		4f: 60
	4g: 78		4h: 76
	4i: 67 <sup>c</sup>		4j: 64
	4k: 41		4l: 74

<sup>a</sup>Conditions: Rh<sub>2</sub>(OPiv)<sub>4</sub> (1 mol %), TFA (50 mol %), DCE (1 mL), 3 (0.2 mmol), rt, 3–12 h, isolated yield. <sup>b</sup>72 h. <sup>c</sup>80 °C, without TFA.

Scheme 3. Intermolecular Reaction

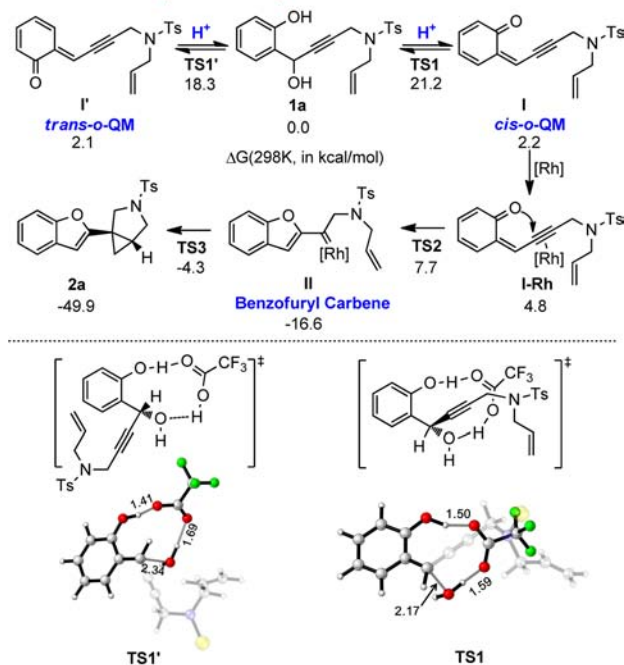


Rh<sub>2</sub>(OPiv)<sub>4</sub> without the addition of TFA, neither 7 nor 5 could be detected.<sup>10</sup>

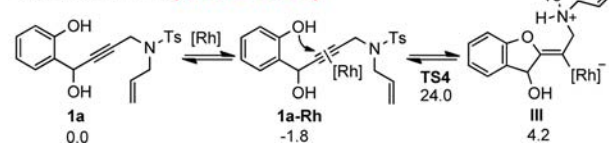
A possible reaction mechanism was proposed based on the reaction results and was also rationalized by DFT-based methods.<sup>11</sup> Taking the cyclopropanation reaction as example, the reaction starts with the dehydration of *o*-HBA 1a via a Brønsted acid mediated proton shuttle transition state,<sup>12</sup> forming the key intermediate *o*-QM (Scheme 4, Mechanism I). Under the catalysis of CF<sub>3</sub>COOH, both *cis*-*o*-QM I and *trans*-*o*-QM I' could be easily generated, with the energy barriers of 21.2 and 18.3 kcal/mol, respectively (Scheme 4). However, only *cis*-*o*-QM could be consumed through the rhodium-catalyzed benzofuran annulation/cyclopropanation tandem reaction, which drives the reaction to the right direction. The energy barrier for benzofuran annulation step is about 2.9 kcal/mol, which is almost negligible compared to

Scheme 4. Proposed Reaction Mechanism<sup>15</sup>

## Mechanism-I (favorable)



## Mechanism-II (unfavorable)



the dehydration process. Similar to Chen and co-workers' theoretical study,<sup>13</sup> the following cyclopropanation step is concerted but asynchronous. This step requires an activation free energy of 12.3 kcal/mol, while its reverse requires 45.6 kcal/mol, which indicates an irreversible process. Furthermore, the direct attack of phenolic oxygen to the Rh-alkyne complex pathway<sup>14</sup> was also considered (Mechanism II), but not as favorable as the acid assisted dehydration pathway. The energy barrier for the nucleophilic attack of the phenolic oxygen (sp<sup>2</sup> hybridization) to the Rh-alkyne complex is about 25.8 kcal/mol in Gibbs free energy, which is higher than that of the acid assisted dehydration process (21.2 kcal/mol). It is notable that the energy barrier for the nucleophilic attack of the *o*-QM oxygen (sp<sup>2</sup> hybridization) to the Rh-alkyne complex (2.9 kcal/mol) is much lower than the phenolic oxygen attack process (25.8 kcal/mol). (See Supporting Information for the details of the calculation.)

In summary, we have developed an efficient proton/metal-catalyzed tandem benzofuran annulation/cyclopropanation and Buchner reaction for the synthesis of various benzofuryl-substituted cyclopropanes and cycloheptatrienes. The reaction was proposed to proceed through two key intermediates, *o*-QM and benzofuryl carbene. Full analysis of the reaction mechanistic pathway by DFT-based computational methods revealed that the reaction was initiated through the dehydration of *o*-HBA via a Brønsted acid mediated proton shuttle transition state, forming the key intermediate *o*-QM. Such a Brønsted acid mediated proton shuttle model may provide useful insight in understanding the reaction process and designing new reactions. Investigations on the asymmetric



version and additional applications of this reaction are underway 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.6b00260.

Typical experimental procedure and characterization for all products (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\* E-mail: zhushf@scut.edu.cn

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We appreciate financial support from the NSFC (21372086 and 21422204), Guangdong NSF (2014A030313229), SRF for ROCS, State Education Ministry, The Fundamental Research Funds for the Central Universities, SCUT, and China Postdoctoral Science Foundation (Grant No. 2015M582378).

## ■ REFERENCES

- (1) (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Hopkinson, M. N.; Sahoo, B.; Li, J.-L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874.
- (2) (a) Fries, K. *Liebigs Ann. Chem.* **1907**, 353, 335. (b) Gardner, P. D.; Sarrafzadeh, R. H.; Brandon, R. L. *J. Am. Chem. Soc.* **1959**, *81*, 5515.
- (3) (a) Dorrestijn, E.; Epema, O. J.; van Scheppingen, W. B.; Mulder, P. J. *Chem. Soc., Perkin Trans. 2* **1998**, 1173. (b) Dorrestijn, E.; Kranenburg, M.; Ciriano, M. V.; Mulder, P. J. *Org. Chem.* **1999**, *64*, 3012. (c) Dorrestijn, E.; Pugin, R.; Nogales, M. V. C.; Mulder, P. J. *Org. Chem.* **1997**, *62*, 4804. (d) Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Williams, A. J.; Watkin, D. J. *Org. Lett.* **1999**, *1*, 1937.
- (4) (a) Van de Water, R. W.; Pettus, T. R. *Tetrahedron* **2002**, *58*, 5367. (b) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2001**, *123*, 8089. (c) Chiang, Y.; Kresge, A. J.; Zhu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 717. (d) Chiang, Y.; Kresge, A. J.; Zhu, Y. *Photochem. Photobiol. Sci.* **2002**, *1*, 67. (e) Chiang, Y.; Kresge, A. J.; Zhu, Y. *Phys. Chem. Chem. Phys.* **2003**, *5*, 1039. (f) Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv.* **2014**, *4*, 55924. (g) Nakatani, K.; Higashida, N.; Saito, I. *Tetrahedron Lett.* **1997**, *38*, 5005. (h) Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *Chem. Commun.* **1999**, 691.
- (5) (a) Gonzalez, J.; Gonzalez, J.; Perez-Calleja, C.; Lopez, L. A.; Vicente, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 5853. (b) Vicente, R.; Gonzalez, J.; Riesgo, L.; Gonzalez, J.; Lopez, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8063. (c) Cao, H.; Zhan, H.; Cen, J.; Lin, J.; Lin, Y.; Zhu, Q.; Fu, M.; Jiang, H. *Org. Lett.* **2013**, *15*, 1080. (d) Clark, J. S.; Boyer, A.; Aimon, A.; Engel Garcia, P.; Lindsay, D. M.; Symington, A. D.; Danoy, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 12128. (e) Xia, Y.; Qu, S.; Xiao, Q.; Wang, Z. X.; Qu, P.; Chen, L.; Liu, Z.; Tian, L.; Huang, Z.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 13502. (f) Ma, J.; Jiang, H. F.; Zhu, S. *Org. Lett.* **2014**, *16*, 4472. (g) Liang, R.; Ma, T.; Zhu, S. *Org. Lett.* **2014**, *16*, 4412. (h) Zhu, S.; Zhang, Z.; Huang, X.; Jiang, H.; Guo, Z. *Chem. - Eur. J.* **2013**, *19*, 4695. (i) Ma, J.; Zhu, S. *Curr. Org. Chem.* **2016**, *20*, 102.
- (6) (a) Khasanova, T.; Sheridan, R. S. *J. Am. Chem. Soc.* **2000**, *122*, 8585. (b) Nikitina, A.; Sheridan, R. S. *J. Am. Chem. Soc.* **2002**, *124*, 7670. (c) Nikitina, A. F.; Sheridan, R. S. *Org. Lett.* **2005**, *7*, 4467. (d) Wang, J.; Sheridan, R. S. *Org. Lett.* **2007**, *9*, 3177. (e) Shirtcliff, L.

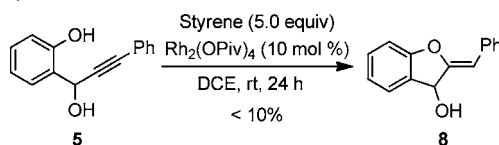
D.; McClintock, S. P.; Haley, M. M. *Chem. Soc. Rev.* **2008**, *37*, 343. (f) Sheridan, R. S. *Chem. Rev.* **2013**, *113*, 7179.

(7) For a calcium-catalyzed example (carbonation mechanism), see: Haven, T.; Kubik, G.; Haubenreisser, S.; Niggemann, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4016.

(8) An asymmetric version of this reaction with chiral dirhodium catalyst was also investigated. Preliminary results indicated that the ee value is up to 82% when  $\text{Rh}_2(\text{S-TFPTTL})_4$  was used as a chiral catalyst. See Supporting Information for detail.

(9) (a) Buchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2371. (b) Ye, T.; McKervy, M. A. *Chem. Rev.* **1994**, *94*, 1091. (c) Ford, A.; Miel, H.; Ring, A.; Slaterry, C. N.; Maguire, A. R.; McKervy, M. A. *Chem. Rev.* **2015**, *115*, 9981.

(10) When the reaction was conducted with 10 mol %  $\text{Rh}_2(\text{OPiv})_4$  as a catalyst at rt for 24 h, only alcohol **8** could be detected in less than 10% yield. For a similar catalytic process, see: (a) Harkat, H.; Blanc, A.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2008**, *73*, 1620. (b) Yu, M.; Lin, M.-D.; Han, C.-Y.; Zhu, L.; Li, C.-J.; Yao, X.-Q. *Tetrahedron Lett.* **2010**, *51*, 6722.



(11) All structures were optimized in Gaussian09 using a hybrid B3LYP functional in conjugation with the LANL2DZ basis set for rhodium, augmented with a 4f function and the 6-31g(d) basis set for the other atoms at 298 K. Frequency calculations were performed at the same theoretical level to obtain the thermal corrections.

(12) (a) Xu, B.; Li, M.-L.; Zuo, X.-D.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2015**, *137*, 8700. (b) Xu, B.; Zhu, S.-F.; Xie, X.-L.; Shen, J.-J.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11483. (c) Liang, Y.; Zhou, H.; Yu, Z.-X. *J. Am. Chem. Soc.* **2009**, *131*, 17783. (d) Xu, B.; Zhu, S.-F.; Zhang, Z.-C.; Yu, Z.-X.; Ma, Y.; Zhou, Q.-L. *Chem. Sci.* **2014**, *5*, 1442. (e) Xu, B.; Zhu, S.-F.; Zuo, X.-D.; Zhang, Z.-Z.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3913. (f) Kisan, H. K.; Sunoj, R. B. *Chem. Commun.* **2014**, *50*, 14639. (g) Kisan, H. K.; Sunoj, R. B. *J. Org. Chem.* **2015**, *80*, 2192.

(13) Xue, Y.-S.; Cai, Y. P.; Chen, Z.-X. *RSC Adv.* **2015**, *5*, 57781.

(14) (a) Rana, A.; Cinar, M. E.; Samanta, D.; Schmitt, M. *Org. Lett.* **2016**, *18*, 84. (b) Prechter, A.; Henrion, G.; Faudot dit Bel, P.; Gagosz, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 4959. (c) Qiu, Y.; Ma, D.; Kong, W.; Fu, C.; Ma, S. *Org. Chem. Front.* **2014**, *1*, 62.

(15) Optimized transition structures are illustrated using CYLView. Tosyl groups are simplified as S atoms, and some atoms are set to be transparent for clarity. Selected bond lengths are given in Å, and atoms of C, H, O, N, F, and S are colored in gray, light gray, red, blue, green, and yellow, respectively.