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Ruthenium-Catalyzed Transfer Oxygenative [2 + 2 + 1] Cycloaddition of Silyldiynes Using Nitrones as Adjustable Oxygen Atom Donors. Synthesis of Bicyclic 2-Silylfurans

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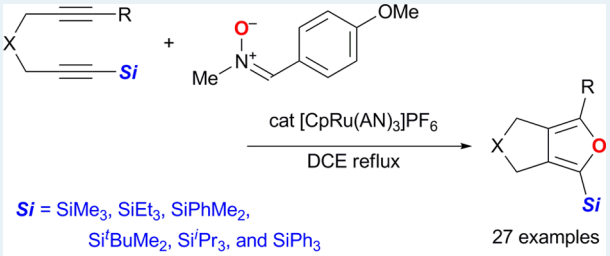
Supporting Information

ABSTRACT: The first example of the Ru-catalyzed transfer oxygenative [2 + 2 + 1] cycloaddition of silyldiynes to produce bicyclic 2-silylfurans is described. This cyclization process was realized using nitrones as readily available and adjustable oxygen atom donors. The bicyclic silylfuran products could be used as platforms for a diverse range of functionalized furans.



The first transfer oxygenative [2 + 2 + 1] cycloaddition of silyldiynes.

KEYWORDS: *cycloaddition, ruthenium, alkyne, furan, silane, nitrone*

2-Silylfurans are useful building blocks in synthetic chemistry because silyl groups are highly versatile synthetic handles owing to their low toxicity and high abundance of silicon. Accordingly, 2-silylfurans have been transformed into various furan derivatives via oxidation to furanones,[1] homo and cross-coupling reactions,[2] halodesilylation,[3] Friedel−Crafts type reactions,[4] and so on.[5] Moreover, 2-silylfuran motifs are commonly found in biologically active compounds and used in functional materials (Figure 1).[6,7]

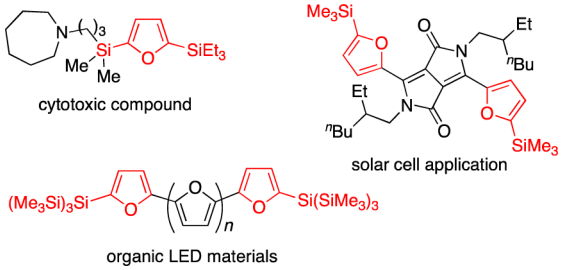


Figure 1. 2-Silylfuran motifs in functional molecules.

One of the simplest routes to 2-silylfurans is the silylation of furans via 2-furyllithium intermediates. However, this method has a limited functional group compatibility as strong bases are required for the lithiation of furans. Recently, several breakthrough studies have reported the direct C−H silylation of aromatic compounds using hydrosilanes.[8] Although direct silylation methods avoid the use of a strong base, their application has been confined to relatively simple furan substrates, and thus, the scope has not yet been fully established. The de novo synthesis of 2-silylfurans is highly important as complex 2-silylfuran frameworks can be assembled in an atom- and step-economical manner via the transition-metal-catalyzed cyclization of readily accessible acyclic precursors.[9] Therefore, we developed a novel synthetic approach to bicyclic 2-silylfurans via the ruthenium-catalyzed transfer oxygenative [2 + 2 + 1] cycloaddition of silyldiynes.

We previously reported the transfer oxygenative [2 + 2 + 1] cycloaddition of α,ω-diynes to afford bicyclic furans.[10,11] In this study, dimethyl sulfoxide (DMSO) and cationic ruthenium complexes, $[Cp'Ru(MeCN)_3]PF_6$ (**1a**: Cp′ = η^5-C_5H_5, **1b**: Cp′ = η^5-C_5Me_5), were used as the oxygen atom donor and catalysts, respectively (Figure 2). Although this process provided a straightforward route to bicyclic furans under neutral conditions, high reaction temperatures were required, and the terminal groups of the α,ω-diyne substrates were confined to aryl or alkyl groups. Therefore, we sought a more flexible approach to diverse bicyclic furan products under

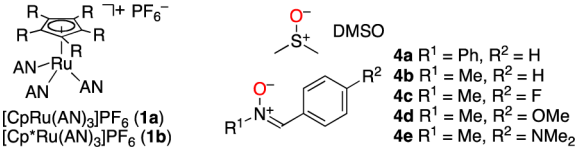


Figure 2. Ruthenium catalysts and oxygen atom donors used in this study.

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milder conditions. To this end, we selected nitrones as the oxygen atom donors because nitrones with optimal oxygen donor abilities could be readily prepared. Although the transition-metal-catalyzed cycloaddition of nitrones has been extensively studied,[12] the transition-metal-catalyzed reactions of α,ω-diynes with nitrones have rarely been investigated.[13] To the best of our knowledge, [2 + 2 + 1] cycloaddition using nitrone oxygen atom donors to produce furans has not been reported to date.

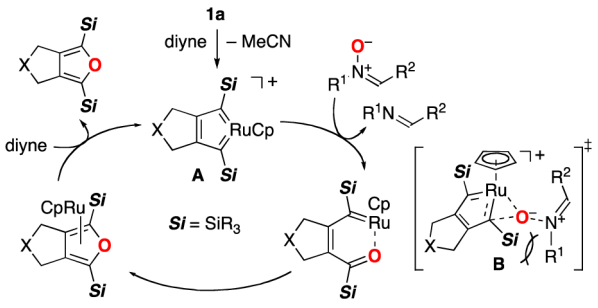
We began our proof-of-concept study on transfer oxygenative [2 + 2 + 1] cycloaddition with nitrones by revisiting the reaction of ether-tethered 1,6-diyne **2** bearing terminal phenyl groups (Scheme 1). Under previously optimized conditions

Scheme 1. Transfer Oxygenative [2 + 2 + 1] Cycloaddition of Diynes 2 and 5a with DMSO or Nitrone 4a as Oxygen Atom Donors

using DMSO (5 equiv),[10] diyne **2** was heated with 3 mol % **1a** in DMF at 140 °C for 4 h to afford the known furan **3** in 90% yield. The reaction was then conducted using nitrone **4a** (1.1 equiv) instead of DMSO, with the same catalyst loading of **1a**. Surprisingly, the reaction completed within 10 min at a lower temperature (60 °C) to afford **3** in 94% yield. These results demonstrate the exceptionally high oxygen donor ability of **4a**.

We next focused on the use of bis(trimethylsilyl)diynes as they would yield highly valuable bicyclic bissilylfurans. However, such silyldiynes have proved to be challenging substrates for transition-metal-catalyzed cycloaddition, and as such, catalytic cycloaddition of bissilyldiynes is underdeveloped compared to transformations using stoichiometric transition-metal templates.[14,15] In fact, several catalytic cycloadditions using bis(trimethylsilyl)diynes totally failed in the recent studies.[16] Our original protocol using DMSO as the oxygen atom donor and bis(trimethylsilyl)diyne **5a** as the substrate also did not yield the desired product after 3 h (Scheme 1). In a plausible mechanism outlined in Scheme 2, the α-anion stabilizing effect of the silyl groups dramatically reduces the reactivity of key ruthenacycle intermediate **A** by decreasing nucleophilicity of the α carbons. In addition, the sterically

Scheme 2. Plausible Catalytic Cycle of Transfer Oxygenative [2 + 2 + 1] Cycloaddition



demanding silyl terminal groups hamper the approach of the nitrone to the ruthenacycle in transition state **B**.

To establish a viable protocol for bissilylfuran formation, reaction parameters were optimized using various nitrones (Table 1 and Figure 2). In the presence of 3 mol % **1a**, diyne **5a**

Table 1. Reaction Optimization for Disilyldiyne 5a

entry	1, mol %	4	conditions	6a yield/%[a]
1	1a, 3	4a	DMF, 100 °C, 10 h	6
2	1a, 3	4b	DMF, 100 °C, 10 h	33
3	1a, 3	4b	DCE, reflux, 10 h	54
4	1a, 3	4c	DCE, reflux, 10 h	51
5	1a, 3	4d	DCE, reflux, 10 h	68 (64)
6	1a, 5	4d	DCE, reflux, 10 h	71 (69)
7	1a, 5	4e	DCE, reflux, 10 h	17
8[b]	1a, 5	4d	DCE, reflux, 8 h	81 (75)
9	1b, 5	4d	DCE, reflux, 17 h	0

[a]Yields were determined by ^{1}H NMR using an internal standard. Yields of isolated products are shown in parentheses. [b]1.1 equiv of **4d** was used.

and nitrone **4a** (1.7 equiv) were heated in DMF at 100 °C for 10 h (entry 1). As a result, small amounts of the desired product **6a** was detected by ^{1}H NMR analysis of the crude reaction mixture, although 50% of **5a** remained unreacted. The use of nitrone **4b** with an *N*-methyl substituent under the same conditions improved the conversion of **5a**, and the yield of **6a** increased to 33% (entry 2). The use of 1,2-dichloroethane (DCE) as the solvent led to a further increase in conversion (entry 3). Next, the electronic influence of the imine aryl group on the reaction efficacy was investigated using nitrones **4c** and **4d**, containing an electron-withdrawing *p*-fluorophenyl substituent or an electron-donating *p*-methoxyphenyl substituent, respectively. Although **4c** showed a negligible effect on the yield of **6a** (entry 4), the use of **4d** improved the yield (68%), but 11% of **5a** remained unreacted (entry 5). Increasing the catalyst loading of **1a** (5 mol %) gave a slightly higher yield (entry 6). In contrast, the product yield was considerably lowered using nitrone **4e** bearing a more electron-donating *p*-dimethylaminophenyl group. Finally, **5a** was completely consumed when the amount of **4d** was reduced to 1.1 equiv (entry 8). As a result, a maximum product yield of 81% was obtained, and **6a** was ultimately isolated in 75% yield by silica gel chromatography. The use of complex **1b** as the catalyst resulted in no reaction after 17 h (entry 9). Thus, the conditions shown in entry 8 are optimal.

Thus, various bis(trimethylsilyl)diynes were subjected to the optimal reaction conditions to demonstrate the general applicability of this process (Table 2). Diynes with oxa or aza tethers **5a–c** facilely underwent [2 + 2 + 1] cycloaddition to afford bicyclic bissilylfurans **6a–6c** in high yields. The reaction of amide-tethered diyne **5d** completed within 2.5 h, affording **6d** in a comparably high yield. In contrast, longer reaction times and/or increased catalyst loadings were required for bissilyldiynes containing all-carbon tethers. The formation of malonate derivative **6e** and 1,3-diketone derivative **6f** required prolonged reaction times of 24 and 20 h, respectively, although the yields were excellent. Moreover, the yields of barbituric acid

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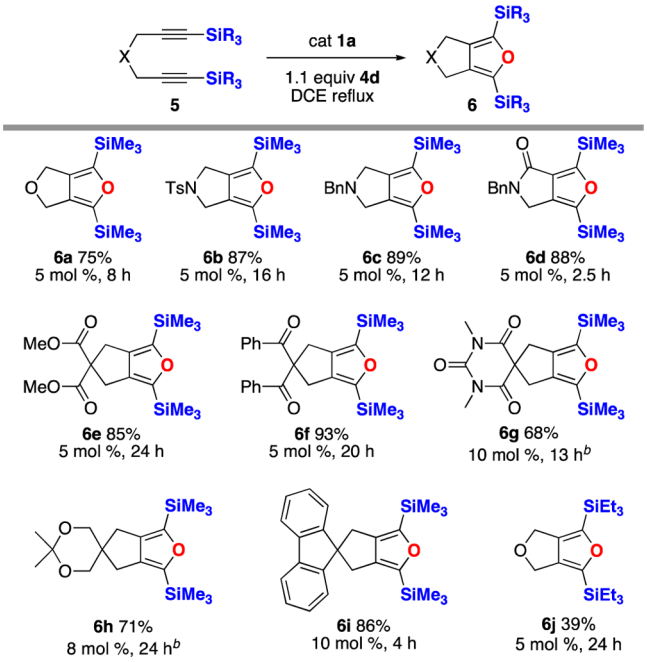
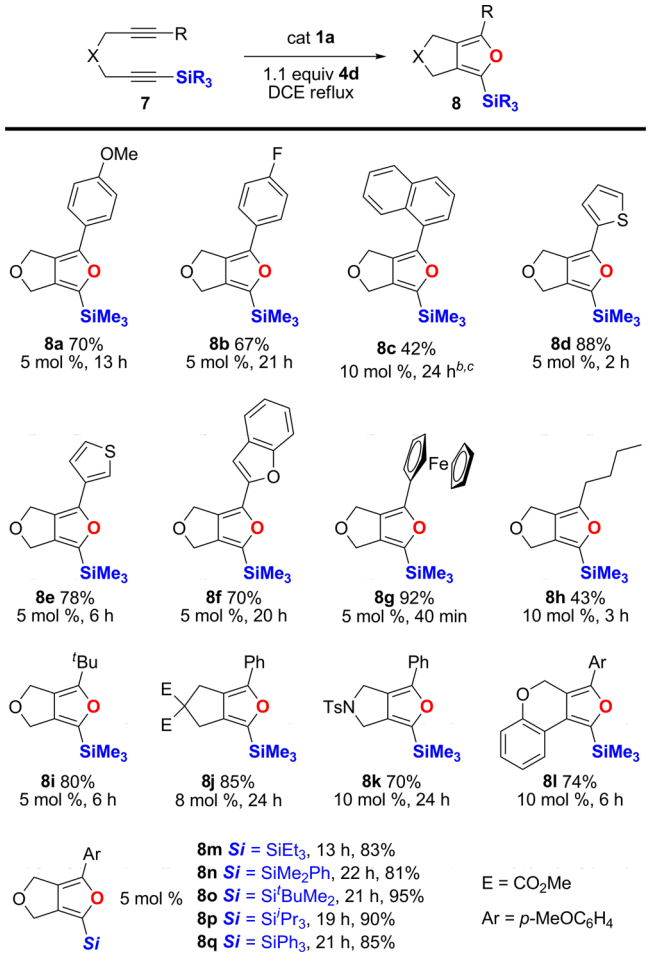
Table 2. Scope of Bissilyldiyne Substrates[a]



[a]Standard conditions: **1a** as the catalyst and nitrone **4d** (1.1 equiv) in DCE under reflux. Yields of isolated products were indicated. [b]A solution of **4d** (1.1 equiv) in DCE (1 mL) was added dropwise over 3 h.

Table 3. Scope of Monosilyldiyne Substrates[a]



[a]Standard conditions: **1a** as the catalyst and nitrone **4d** (1.1 equiv) in DCE under reflux. Yields of isolated products were indicated. [b]A solution of **4d** (1.1 equiv) in DCE (1 mL) was added dropwise over 3 h. [c]**7c** was recovered (35%).

derivative **6g** and acetal **6h** were poor, despite increasing the catalyst loading to 8−10 mol %. In these cases, the ruthenium catalyst was deactivated by the nitrone during very sluggish reactions.[17] Therefore, a solution of nitrone **4d** in DCE was added to the reaction mixture over a period of 3 h via a syringe pump, to prevent catalyst deactivation. As a result, **6g** and **6h** were successfully obtained in 68% and 71% yields, respectively. On the other hand, fluorene derivative **6i** was obtained in 86% yield without recourse to the slow addition technique. The present method was found to be ineffective for intermolecular reaction of phenyl(trimethylsilyl)acetylene. In addition to the trimethylsilyl group, other silyl groups were examined as the terminal groups on the diyne substrates. However, replacement of the trimethylsilyl groups of **5a** with bulkier triethylsilyl groups (**5j**) dramatically decreased the yield of the corresponding product **6j** (39%).

Next, monosilyldiynes containing an ether tether were investigated as substrates (Table 3). Diynes **7a** and **7b**, possessing *p*-methoxyphenyl or *p*-fluorophenyl terminal groups, underwent smooth reaction in the presence of 5 mol % **1a** and nitrone **4d** (1.1 equiv) to afford **8a** and **8b** in 70% and 67% yields, respectively. Notably, the reaction was faster with the electron-donating terminal group. In contrast, the reaction was sluggish for diyne **7c**, which contained a bulky 1-naphthyl group, and the expected product **8c** was obtained in a moderate yield via the slow addition technique with an increased catalyst loading. Smaller thienyl groups gave favorable effects; diynes **7d** and **7e** containing 2-thienyl or 3-thienyl terminal groups afforded **8d** and **8e** in 75% and 78% yields, respectively, with shorter reaction times. Diyne **7f**, which contained a bulkier 2-benzofuryl terminal group, required a prolonged reaction time (20 h), affording **8f** in 70% yield. On the other hand, the reaction of diyne **7g**, which possessed a ferrocenyl terminal group, was completed within 40 min to afford **8g** in an excellent yield, although the ferrocenyl group is assumed to sterically hinder the ruthenacycle intermediate.

In addition to aryl-substituted diynes, *n*-butyl- and *t*-butyl-substituted diynes **7h** and **7i** were also converted into **8h** and **8i** in 43% and 80% yields, respectively. The impact of the tether moiety was also briefly investigated for malonate derivative **8j** and tosylamide derivative **8k**, containing a phenyl terminal group, and were obtained in 85% and 70% yields, respectively, after reaction for 24 h with increased catalyst loadings of 8−10 mol %. Moreover, 4*H*-furo[3,4-*c*]chromene derivative **8l** was successfully synthesized in a good yield via six-membered-ring formation of 1,7-diyne **7l**.

In striking contrast to bissilyldiyne **5j**, monosilyldiyne **7m**, which contains triethylsilyl and *p*-methoxyphenyl terminal groups, was successfully converted into the corresponding furan **8m** in 83% yield. More sterically demanding diynes **7n** and **7o**, bearing dimethylphenylsilyl or *tert*-butyldimethylsilyl groups, also afforded **8n** and **8o** in high yields, albeit with longer reaction times. In the same manner, bicyclic furans **8p** and **8q**, bearing much more bulkier triisopropylsilyl and triphenylsilyl groups, were also obtained in high yields. These results corroborate the notion that oxygen atom transfer must occur on the carbene carbon opposite to the one bearing the silyl group.

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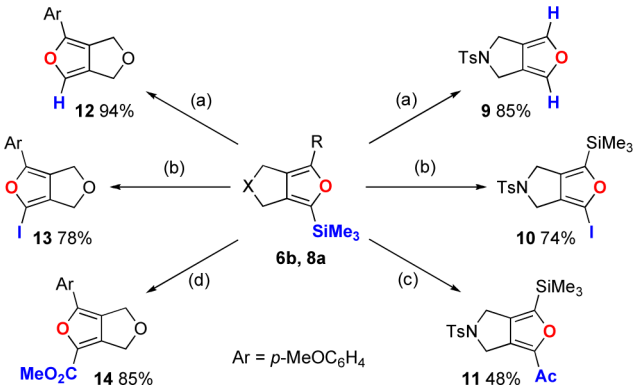
We further investigated the transformation of bicyclic bissilylfuran **6b** and monosilylfuran **8a** (Scheme 3). Upon treatment with TBAF at room temperature, **6b** and **8a** underwent complete protodesilylation within 5 min, affording the corresponding bicyclic furans **9** and **12** in high yields. As iodofurans are valuable building blocks for cross-coupling reactions, iododesilylation was attempted using NIS and KF in MeCN at 50 °C.[3b] Consequently, substitution of one of the two silyl groups selectively occurred in **6b** to afford iodosilylfuran **10** in 74% yield. In the same manner, iodofuran **13** was obtained in 78% yield from **8a**. Friedel–Crafts acylation of **6b** using acetyl chloride and $ZnCl_2$ in CH_2Cl_2 at 30 °C[4a] resulted in the formation of the mono acylation product **11** in 48% yield. Carboxylation of silylfuran **8a** was also carried out under a CO_2 atmosphere in the presence of CsF at 100 °C,[18] affording **14** in 85% yield after methylation of the carboxylate intermediate.

Scheme 3. Transformations of 2-Silylfuran Products 6b and 8a[a]



[a]Reagents and conditions: (a) TBAF (1 M in THF, 2.0 equiv for **6b** or 1.0 equiv for **8a**), rt; (b) NIS (1.1 equiv), KF (1.1 equiv), MeCN, 50 °C; (c) AcCl (1.1 equiv), $ZnCl_2$ (1.1 equiv), CH_2Cl_2, 30 °C; (d) CO_2 (1 atm), CsF (2.0 equiv), DMF, 100 °C, then MeI (2.0 equiv), rt.

In summary, we have developed a new method for the synthesis of bicyclic 2-silylfurans from silyldiynes via ruthenium-catalyzed transfer oxygenative [2 + 2 + 1] cycloaddition. Readily available nitrones were used as the oxygen atom donors, and were found to be superior to DMSO. The reaction of unsymmetrical diynes containing one silyl terminal group can tolerate sterically demanding silyl groups, such as triethylsilyl, dimethylphenylsilyl, *tert*-butyldimethylsilyl, triisopropylsilyl, and triphenylsilyl groups. To demonstrate the synthetic potential of this method, bissilyl- and monosilylfurans were transformed into various bicyclic furans, which could not be obtained directly from the corresponding diyne precursors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b01855.

Experimental details, characterization data for all new compounds, and NMR charts (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505–3508. (b) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835–5838. (c) Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625–4628.

(2) (a) Denmark, S. E.; Baird, J. D. *Chem. - Eur. J.* **2006**, *12*, 4954–4963. (b) Matsuda, S.; Takahashi, M.; Monguchi, D.; Mori, A. *Synlett* **2009**, *2009*, 1941–1944.

(3) (a) Aquila, B. M. *Tetrahedron Lett.* **1997**, *38*, 2795–2798. (b) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, *2002*, 453–457. (c) Melzig, L.; Rauhut, C. B.; Knochel, P. *Chem. Commun.* **2009**, 3536–3538.

(4) (a) Sasaki, T.; Nakanishi, A.; Ohno, M. *J. Org. Chem.* **1982**, *47*, 3219–3224. (b) Gill, M. *Tetrahedron* **1984**, *40*, 621–626. (c) Aikawa, K.; Hioki, Y.; Mikami, K. *Chem. - Asian J.* **2010**, *5*, 2346–2350.

(5) (a) Devarie-Baez, N. O.; Kim, W.-S.; Smith, A. B., III; Xian, M. *Org. Lett.* **2009**, *11*, 1861–1864. (b) Das, M.; O'Shea, D. F. *J. Org. Chem.* **2014**, *79*, 5595–5607. (c) Das, M.; O'Shea, D. F. *Org. Lett.* **2015**, *17*, 1962–1965.

(6) (a) Lukevits, É.; Demicheva, L. *Chem. Heterocycl. Compd.* **1993**, *29*, 243–267. (b) Ignatovich, L.; Romanovs, V.; Shestakova, I.; Domrachova, I.; Popelis, J.; Lukevics, E. *Chem. Heterocycl. Compd.* **2009**, *45*, 1441–1448. (c) Ignatovich, L.; Muravenko, V.; Shestakova, I.; Domrachova, I.; Popelis, J.; Lukevics, E. *Appl. Organomet. Chem.* **2010**, *24*, 158–161.

(7) (a) Rim, C.; Son, D. Y. *Macromolecules* **2003**, *36*, 5580–5584. (b) Bendikov, M.; Gidron, O.; Sheynin, Y. PCT International Application No. 061019, 2014. (c) Tamano, M.; Chisaka, J.; Watanabe, M. Japan Patent Kokai No. 78702, 2014.

(8) (a) Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853–857. (b) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80–84. (c) Sharma, R.; Kumar, R.; Kumar, I.; Singh, B.; Sharma, U. *Synthesis* **2015**, *47*, 2347–2366.

(9) (a) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645–7655. (b) Cui, X.; Xu, X.; Wojtas, L.; Kim, M. M.; Zhang, X. P. *J. Am. Chem. Soc.* **2012**, *134*, 19981–19984. (d) Padwa, A.; Zou, Y. *J. Org. Chem.* **2015**, *80*, 1802–1808.

(10) Yamashita, K.; Yamamoto, Y.; Nishiyama, H. *J. Am. Chem. Soc.* **2012**, *134*, 7660–7663.

(11) Palladium-catalyzed [2 + 2 + 1] furan synthesis has been reported, see: (a) Wang, A.; Jiang, H.; Xu, Q. *Synlett* **2009**, *2009*, 929–932. (b) Wen, Y.; Zhu, S.; Jiang, H.; Wang, A.; Chen, Z. *Synlett* **2011**, *2011*, 1023–1027.

(12) For recent reviews, see: (a) Xiao, J.; Li, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226–7236. (b) Yang, J. *Synlett* **2012**, *23*, 2293–2297. (c) Stecko, S.; Furman, B.; Chmielewski, M. *Tetrahedron* **2014**, *70*, 7817–7844. (d) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2015**, *115*, 5366–5412. For selected recent examples, see: (e) Zhang, Z.-M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X.-L.; Zhang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 4350–4354. (f) Pagar, V. V.; Liu, L.-S. *Angew. Chem., Int. Ed.* **2015**, *54*, 4923–4926. (g) Dateer, R. B.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4908–4911. (h) Suneel Kumar, C. V. S.; Ramana, C. V. *Org. Lett.* **2015**, *17*, 2870–2873.

(13) (a) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040–7043. (b) Wang, C.; Wang, D.; Yan, H.; Wang, H.; Pan, B.; Xin, X.; Li, X.; Wu, F.; Wan, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 11940–11943.

DOI: 10.1021/acscatal.5b01855
ACS Catal. 2015, 5, 6468–6472

(14) For catalytic reactions, see: (a) Parnell, C. A.; Peter, K.; Vollhardt, C. *Tetrahedron* **1985**, *41*, 5791−5796. (b) Shibata, T.; Yamashita, K.; Ishida, H.; Takagi, K. *Org. Lett.* **2001**, *3*, 1217−1219. (c) Gutnov, A.; Abaev, V.; Redkin, D.; Fischer, C.; Bonrath, W.; Heller, B. *Synlett* **2005**, 1188−1190. (d) Goswami, A.; Ito, T.; Okamoto, S. *Adv. Synth. Catal.* **2007**, *349*, 2368−2374.

(15) For selected recent examples of stoichiometric reactions, see: (a) Knölker, H.-J.; Cämmerer, S. *Tetrahedron Lett.* **2000**, *41*, 5035−5038. (b) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7925−7926. (c) Wong, K.-T.; Chen, R.-T. *Tetrahedron Lett.* **2002**, *43*, 3313−3317. (d) Sung, M. J.; Pang, J.-H.; Park, S.-B.; Cha, J. K. *Org. Lett.* **2003**, *5*, 2137−2140.

(16) (a) Lane, T. K.; D'Souza, B. R.; Louie, J. *J. Org. Chem.* **2012**, *77*, 7555−7563. (b) Stolley, R. M.; Duong, H. A.; Louie, J. *Organometallics* **2013**, *32*, 4952−4960. (c) Tahara, Y.; Matsubara, R.; Shibata, T. *Heterocycles* **2015**, *90*, 1094−1110.

(17) In fact, the desired product **6a** was formed in a low yield when the catalyst **1a** was mixed with nitrones before adding substrate **5a**. Furthermore, the decomposition of **1a** in the presence of nitrone **4d** was observed by ^{1}H NMR spectroscopy.

(18) Mita, T.; Tanaka, H.; Michigami, K.; Sato, Y. *Synlett* **2014**, *25*, 1291−1294.

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ACS Catal. 2015, 5, 6468−6472