Organic LETTERS

Letter

pubs.acs.org/OrgLett

Copper-Catalyzed Formal Carbene Migratory Insertion into Internal Olefinic C═C Bonds with *N*-Tosylhydrazones To Access Iminofuran and 2(3*H*)-Furanone Derivatives

Fei Huang,[†,‡,∥] Zhuqing Liu,[†,‡,∥] Quannan Wang,[†,‡] Jiang Lou,[†,‡] and Zhengkun Yu*[,†,§]

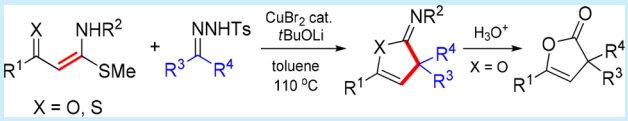
[†]Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

[‡]University of Chinese Academy of Sciences, Beijing 100049, China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

Supporting Information

ABSTRACT: Efficient copper-catalyzed formal carbene migratory insertion into the olefinic C═C bonds of internal olefins, that is, α-oxo ketene *N*,*S*-acetals, has been achieved by means of *N*-tosylhydrazones of ketones as the carbene precursors. Iminofuran derivatives were obtained and further transformed to the corresponding 2(3*H*)-furanones and 4-oxobutanoates (γ-ketoesters), respectively, under mild conditions. In a similar fashion, α-thioxo ketene *N*,*S*-acetals reacted with *N*-tosylhydrazones of ketones to afford iminothiophenes. It is suggested that formal carbene migratory insertion into the olefinic C═C bond is involved in the overall catalytic cycle, demonstrating a new type of carbene insertion reaction for five-membered heterocycle construction.



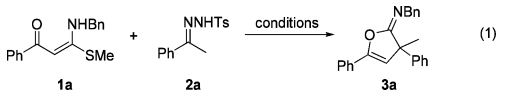
Carbene migratory insertion reactions have demonstrated versatile applications in the construction of various chemical bonds. Diazo compounds and *N*-tosylhydrazones have recently been paid much attention because they can be used as carbene precursors in diverse organic synthesis.[1] In this regard, carbene migratory insertion into X−H bonds (X = C,[2] N,[3] O,[4] S,[5] Si,[6] and B,[7] etc.) has been applied for the construction of C−X bonds. A few examples of carbene insertion into C−heteroatom bonds have also been documented.[8−11] Carbene migratory insertion into the C−C single bonds of cyclic ketones and alcohols were reported for ring expansion and synthesis of homologated ketones.[12] In 1885, Büchner et al. documented the seminal work on carbene insertion into arene C═C bonds in the reactions of diazo compounds with arenes,[13] which provide a unique approach to accessing cycloheptatriene derivatives[14] via intermolecular cyclopropanation. *N*-Tosylhydrazones have recently been utilized for the same purpose.[15] However, to the best of our knowledge, carbene migratory insertion into an olefinic C═C bond has not yet been reported. Despite being synthetically very useful and readily available, diazo compounds are usually associated with toxicity and explosion hazards, and methods for in situ preparation and use of their surrogates have been desired.[1] Thus, *N*-tosylhydrazones have recently been paid more and more attention for use as masked diazo compounds because they can be readily prepared.[1e,h] A transition metal is usually required to stabilize a diazo substrate or diazo intermediate and to moderate the reactivity of the in situ generated carbene species. In this respect, copper catalysts are preferably used to promote the reactions of diazo compounds or *N*-tosylhydrazones under relatively mild conditions.[1h]

α-Oxo ketene *N*,*S*-acetals feature an unusual internal olefin structure with three electron-withdrawing and donating functionalities, that is, carbonyl, alkylthio, and amino groups, which are attached to the two ends of the olefinic C═C bond, and can exhibit unusual reactivities.[16] During the ongoing investigation of C−H activation of internal olefins,[17] we reasonably envisioned carbene migratory insertion into the olefinic C(sp^2)−H bond of α-oxo ketene *N*,*S*-acetals with diazo compounds. Unexpectedly, in their reactions with ethyl 2-diazo-2-phenylacetate and analogues, no such carbene migratory insertion reactions were observed under copper catalysis, while carbene migratory insertion into the olefinic C═C bond occurred by using a copper salt as the catalyst and *N*-tosylhydrazones of ketones as the carbene precursors, affording iminofuran products. Iminofurans and related 2(3*H*)-furanones which can be readily converted from the corresponding iminofurans, are usually bioactive and abundant in many natural products and synthetic compounds.[18] Development of synthetic methods for such biologically active compounds has been strongly desired. Herein, we disclose the synthesis of iminofurans and related derivatives from the reactions of α-oxo (thioxo) ketene *N*,*S*-acetals with *N*-tosylhydrazones.

Initially, the reaction of (*E*)-3-(benzylamino)-3-(methylthio)-1-phenylprop-2-en-1-one (**1a**) with the *N*-tosylhydrazone of acetophenone (**2a**) was conducted to screen the reaction conditions (eq 1; see the Supporting Information for details). With 20 mol % of CuI as the catalyst and 2.5 equiv of K_2CO_3 as

Received: June 2, 2017
Published: June 14, 2017

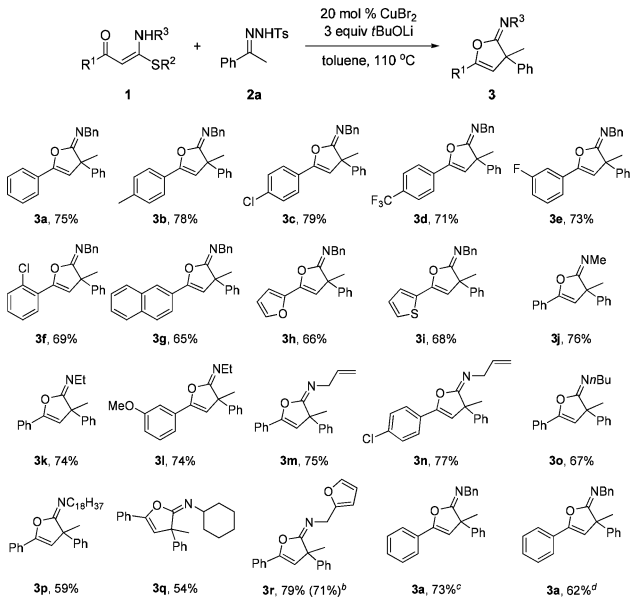
DOI: 10.1021/acs.orglett.7b01668
Org. Lett. 2017, 19, 3660−3663



the base, treatment of **1a** and **2a** in a 1.0:1.5 molar ratio in refluxing toluene for 12 h afforded the target iminofuran product **3a** in 35% yield. Among the screened bases, *t*BuONa did not promote the reaction, while *t*BuOLi acted most effectively. Increasing both the loadings of **2a** and *t*BuOLi to 3 equiv remarkably enhanced the yield to 72%. Lowering temperature to 90 °C or performing the reaction in 1,4-dioxane or 1,2-dichloroethane deteriorated the reaction efficiency. Copper(I) salts such as CuCl, CuBr, and CuOAc could not efficiently promote the reaction, whereas use of $CuBr_2$ gave the best yield (75%). A <20 mol % catalyst loading led to a lower product yield. Eventually, the reaction conditions were optimized to 20 mol % of $CuBr_2$ as the catalyst, use of 3 equiv of both **2a** and *t*BuOLi, toluene as the solvent, 110 °C, 12 h, under a nitrogen atmosphere.

Under the optimal conditions, the scope of α-oxo ketene *N*,*S*-acetals **1** was explored by reacting them with **2a** (Scheme 1). Substituted analogues of **1a**, that is, **1b**−**f**, behaved similarly

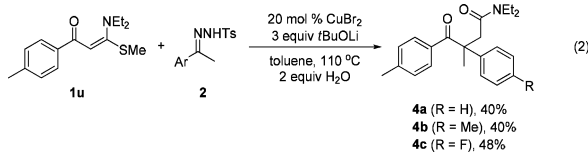
Scheme 1. Scope of α-Oxo Ketene *N*,*S*-Acetals 1[a]



[a]Conditions: **1** (0.5 mmol), **2a** (1.5 mmol), $CuBr_2$ (0.1 mmol), *t*BuOLi (1.5 mmol), toluene (5 mL), 0.1 MPa N_2, 110 °C, 12 h. Yields refer to the isolated products. [b]Scale-up reaction conditions: **1r** (1.37 g, 5 mmol), **2a** (2.88 g, 10 mmol), $CuBr_2$ (1 mmol), *t*BuOLi (10 mmol), toluene (20 mL), 0.1 MPa N_2, 110 °C, 18 h. [c]From **1s** (R^2 = Et). [d]From **1t** (R^2 = Bn).

to yield iminofurans **3b**−**f** (69−79%). Bulky 2-naphthyl and heteroaryl-based *N*,*S*-acetals **1g**−**i** reacted with **2a** to give the corresponding products **3g**−**i** (65−68%), exhibiting moderate steric and electronic effects. Variation of the amino groups in **1** to methyl-, ethyl-, or allylamino led to **3j**−**n** in 74−77% yields. However, placement of a moderate to long-chain or cyclic aliphatic alkylamino group in **1** deteriorated the product yields to 54−67%. Furan-2-ylmethylamino-bearing ketene *N*,*S*-acetal **1r** reacted smoothly to yield **3r** (79%), and a 5 mmol scale reaction also efficiently afforded **3r** (71%). Replacement of the MeS group by EtS in **1** slightly reduced the yield to 73%, while the benzyl thioacetal substrate could not efficiently react to form **3a** (62%) due to an obvious steric effect. It is noted that the reactions of α-acetyl ketene *N*,*S*-acetals and α-oxo ketene *N*,*S*-acetals bearing an arylamino group (NHAr) with **2a** only gave inseparable mixtures.

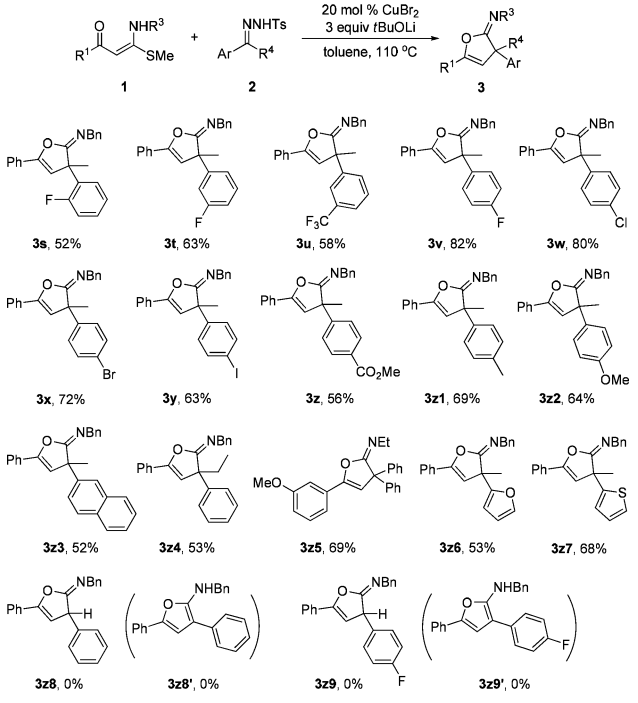
The scope of ketene *N*,*S*-acetals **1** was further explored by introducing a secondary alkylamino group, that is, diethylamino, to replace the primary amino moiety NHR in **1**. Thus, **1u** was applied to react with *N*-tosylhydrazone **2a** under the standard conditions. Unexpectedly, no carbene migratory insertion into the olefinic C═C bond could occur to form the product of type **3**, whereas the reaction underwent in the presence of 2 equiv of water to afford γ-ketoamide **4a** (40%). In a similar manner, **4b** (40%) and **4c** (48%) were also obtained (eq 2). The molecular structure of compound **4a** was



confirmed by its X-ray single-crystal structural analysis (see the SI). These results have revealed the occurrence of formal carbene migratory insertion into the C−C single bond between the carbonyl carbon and the vicinal olefinic carbon in **1**, which was reported in the cases of cyclic ketones and alcohols.[12]

Next, the generality of *N*-tosylhydrazones **2** was investigated (Scheme 2). The *N*-tosylhydrazones of fluoro- and trifluoromethyl-substituted acetophenones reacted with **1a** to form **3s**−**v** (52−82%), respectively, exhibiting obvious steric effects from the substituents on the aryl moieties of the *N*-tosylhydrazones. By means of the *N*-tosylhydrazones of 4-

Scheme 2. Scope of *N*-Tosylhydrazones 2[a]



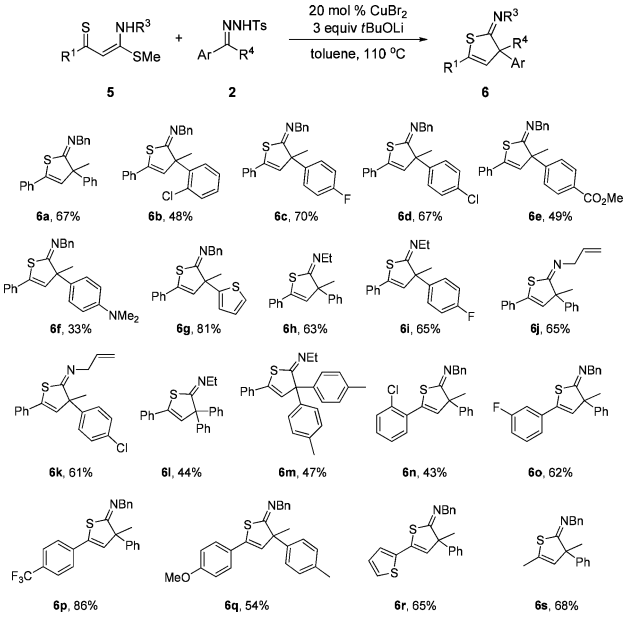
[a]Conditions: **1** (0.5 mmol), **2** (1.5 mmol), $CuBr_2$ (0.1 mmol), *t*BuOLi (1.5 mmol), toluene (5 mL), 0.1 MPa N_2, 110 °C, 12 h. Yields refer to the isolated products.

DOI: 10.1021/acs.orglett.7b01668
Org. Lett. 2017, 19, 3660−3663

substituted acetophenones, products **3w**–**z2** were obtained in 56–80% yields, showing electronic effects from the 4-substituents. A negative steric effect was present in the cases of using the *N*-tosylhydrazones of acetonaphthone, propiophenone, and benzophenone, leading to **3z3** (52%), **3z4** (53%), and **3z5** (69%), respectively. *N*-Tosylhydrazones of 2-acetylfuran and thiophene also underwent the reactions with **1a** to afford the corresponding iminofuran products **3z6** (53%) and **3z7** (68%). It is noteworthy that the *N*-tosylhydrazones derived from aromatic aldehydes such as benzaldehyde and 4-fluorobenzaldehyde were also used to react with **1a**. However, no desired reactions occurred to form the target iminofurans **3z8** and **3z9** or their furan isomers **3z8′** and **3z9′**. In these cases, most of the starting *α*-oxo ketene *N*,*S*-acetals were recovered. The molecular structures of products **3** were further confirmed by the X-ray single-crystal structural determination of **3z5** (see the SI).

In order to extend the substrate scope, *α*-thioxo ketene *N*,*S*-acetals of type **5** were employed to react with *N*-tosylhydrazones of ketones **2** under the standard conditions. To our delight, the structural analogues of iminofurans **3**, that is, iminothiophenes **6**, were conveniently obtained in 33–86% yields (Scheme 3). As compared to the corresponding *α*-oxo

Scheme 3. Scope of *α*-Thioxo Ketene *N*,*S*-Acetals 5[a]

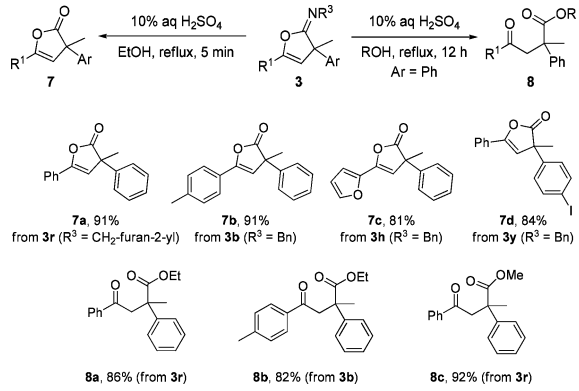


[a]Conditions: **5** (0.5 mmol), **2** (1.5 mmol), $CuBr_2$ (0.1 mmol), *t*BuOLi (1.5 mmol), toluene (5 mL), 0.1 MPa N_2, 12 h. Yields refer to the isolated products.

ketene *N*,*S*-acetals of type **1**, compounds **5** usually exhibited a lower reactivity. The steric effects from the *N*-tosylhydrazones were obvious, which deteriorated the reaction efficiencies. In contrast to the *α*-acetyl ketene *N*,*S*-acetal, *α*-thioxo ketene *N*,*S*-acetal **5s** (R^1 = Me, R^3 = Bn) could undergo the reaction with **2a**, yielding iminothiophene **6s** in 68% yield.

Derivation of iminofurans **3** was carried out in the presence of 10% aq H_2SO_4 in an alcohol solvent.[19] Compounds **3** were thus efficiently hydrolyzed to the corresponding 2(3*H*)-furanones **7** (81–91%) in refluxing ethanol within 5 min (Scheme 4). Extension of the reaction time to 12 h led to the ring-opening products 4-oxobutanoates, that is, *γ*-ketoesters **8**

Scheme 4. Hydrolysis of Iminofurans 3[a]

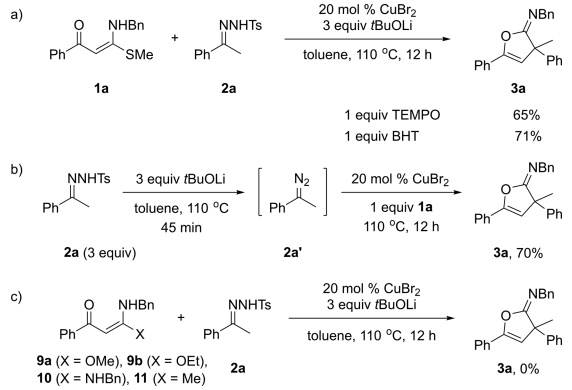


[a]Conditions: **3** (0.2 mmol), 10% aq H_2SO_4 (0.2 mL), ROH (2 mL), reflux, air. Yields refer to the isolated products.

(82–92%), revealing easy hydrolysis of 2(3*H*)-furanones **7** under the stated conditions. These results have demonstrated the potential application of the synthetic protocol in the synthesis of furanone derivatives.

The control experiments were then conducted to probe into the reaction mechanism (Scheme 5). Addition of a radical

Scheme 5. Control Experiments



scavenger, i.e., 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT), to the reaction of **1a** and **2a** only slightly reduced the yield of **3a**, suggesting that the reaction did not occur through a radical pathway (Scheme 5a). Treatment of **2a** with equimolar amount of *t*BuOLi base at 110 °C followed by reacting the resultant mixture with **1a** in the presence of $CuBr_2$ catalyst gave product **3a** in 70% yield (Scheme 5b), implicating that diazo compound **2a′** generated from **2a** is involved as the reaction intermediate in the overall catalytic cycle. However, the *α*-aroyl ketene *N*,*O*-acetals **9**, *N*,*N*-acetal **10**, and enamine **11** could not react with **2a** under the standard conditions to form the target product **3a** (Scheme 5c), which is presumably attributed to both the better leaving group capability of the alkylthio moiety compared to OMe, OEt, NHBn, and Me groups and the higher reactivity of the ketene *N*,*S*-acetals.[20] This work has demonstrated the first example of formal carbene migratory insertion into olefinic C=C bonds.[1,21] The reaction mechanism may involve initial cyclopropanation of the internal olefin substrate, that is, *α*-oxo ketene *N*,*S*-acetal, followed by a simple rearrangement of the push–pull cyclopropane intermediate.[14] However, no

DOI: 10.1021/acs.orglett.7b01668
Org. Lett. 2017, 19, 3660–3663

experimental evidence has been obtained to clarify the reaction pathway at this stage.

In conclusion, copper-catalyzed synthesis of iminofurans and iminothiophenes has been efficiently realized by means of the reactions of α-oxo (thioxo) ketene *N*,*S*-acetals with *N*-tosylhydrazones of ketones. This is the first report on the formal carbene migratory insertion into olefinic C=C bonds. The iminofurans can be readily transformed to potentially bioactive 2(3*H*)-furanones and γ-ketoesters. The synthetic protocol provides a concise route to iminofurans, iminothiophenes, and 2(3*H*)-furanones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01668.

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis (PDF)

X-ray crystallographic data for compounds **4a** and **3z5** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zkyu@dicp.ac.cn.

ORCID

Fei Huang: 0000-0002-5290-2490
Zhuqing Liu: 0000-0002-5225-1771
Quannan Wang: 0000-0002-4136-0016
Jiang Lou: 0000-0002-5653-1359
Zhengkun Yu: 0000-0002-9908-0017

Author Contributions

‖F.H. and Z.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21472185) and the National Basic Research Program of China (2015CB856600) for support of this research.

■ REFERENCES

(1) (a) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486. (b) Zhang, Y.; Wang, J. B. *Eur. J. Org. Chem.* **2011**, *2011*, 1015. (c) Shao, Z. H.; Zhang, H. B. *Chem. Soc. Rev.* **2012**, *41*, 560. (d) Xiao, Q.; Zhang, Y.; Wang, J. B. *Acc. Chem. Res.* **2013**, *46*, 236. (e) Hu, F. D.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. B. *Chem. Commun.* **2015**, *51*, 7986. (f) Liu, L.; Zhang, J. L. *Chem. Soc. Rev.* **2016**, *45*, 506. (g) Candeias, N. R.; Paterna, R.; Gois, P. M. P. *Chem. Rev.* **2016**, *116*, 2937. (h) Wang, B.; Qiu, D.; Zhang, Y.; Wang, J. B. *Beilstein J. Org. Chem.* **2016**, *12*, 796.

(2) For selected recent reports on carbene insertion into C−H bonds, see: (a) Caballero, A.; Despagnet-Ayoub, E.; Díaz-Requejo, M. M.; Díaz-Rodríguez, A.; González-Núñez, M. E.; Mello, R.; Muñoz, B. K.; Ojo, W.-S.; Asensio, G.; Etienne, M.; Pérez, P. J. *Science* **2011**, *332*, 835. (b) Qin, C. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792. (c) Key, H. M.; Dydio, P.; Clark, D. S.; Hartwig, J. F. *Nature* **2016**, *534*, 534. (d) Yu, Z. Z.; Ma, B.; Chen, M. J.; Wu, H.-H.; Liu, L.; Zhang, J. L. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (e) Gutiérrez-Bonet, Á.; Juliá-Hernández, F.; Luis, B. D.; Martin, R. *J. Am. Chem. Soc.* **2016**, *138*, 6384. (f) Conde, A.; Sabenya, G.; Rodríguez, M.; Postils, V.; Luis, J. M.; Díaz-Requejo, M. M.; Costas, M.; Pérez, P. J. *Angew. Chem., Int. Ed.* **2016**, *55*, 6530. (g) Yu, Z. Z.; Li, Y. F.; Shi, J. M.; Ma, B.; Liu, L.; Zhang, J. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 14807. (h) Ye, F.; Ma, X. S.; Xiao, Q.; Li, H.; Zhang, Y.; Wang, J. B. *J. Am. Chem. Soc.* **2012**, *134*, 5742. (i) Peña-López, M.; Beller, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 46.

(3) (a) Moerdyk, J. P.; Blake, G. A.; Chase, D. T.; Bielawski, C. W. *J. Am. Chem. Soc.* **2013**, *135*, 18798. (b) Ma, X. C.; Jiang, J.; Lv, S. Y.; Yao, W. F.; Yang, Y.; Liu, S. Y.; Xia, F.; Hu, W. H. *Angew. Chem., Int. Ed.* **2014**, *53*, 13136.

(4) Goudedranche, S.; Besnard, C.; Egger, L.; Lacour, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 13775.

(5) Aviv, I.; Gross, Z. *Chem. - Eur. J.* **2008**, *14*, 3995.

(6) Chen, D.; Zhu, D.-X.; Xu, M.-H. *J. Am. Chem. Soc.* **2016**, *138*, 1498.

(7) (a) Chen, D.; Zhang, X.; Qi, W.-Y.; Xu, B.; Xu, M.-H. *J. Am. Chem. Soc.* **2015**, *137*, 5268. (b) Yang, J.-M.; Li, Z.-Q.; Li, M.-L.; He, Q.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2017**, *139*, 3784.

(8) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270.

(9) Qin, G. P.; Li, L. X.; Li, J. W.; Huang, H. M. *J. Am. Chem. Soc.* **2015**, *137*, 12490.

(10) Miura, T.; Fujimoto, Y.; Funakoshi, Y.; Murakami, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 9967.

(11) Song, Z.; Wu, Y. Z.; Xin, T.; Jin, C.; Wen, X. A.; Sun, H. B.; Xu, Q.-L. *Chem. Commun.* **2016**, *52*, 6079.

(12) (a) Yada, A.; Fujita, S.; Murakami, M. *J. Am. Chem. Soc.* **2014**, *136*, 7217. (b) Xia, Y.; Liu, Z. X.; Liu, Z.; Ge, R.; Ye, F.; Hossain, M.; Zhang, Y.; Wang, J. B. *J. Am. Chem. Soc.* **2014**, *136*, 3013. (c) Feng, S.; Mo, F. Y.; Xia, Y.; Liu, Z. X.; Liu, Z.; Zhang, Y.; Wang, J. B. *Angew. Chem., Int. Ed.* **2016**, *55*, 15401.

(13) Büchner, E.; Curtius, T. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2377.

(14) (a) Galan, B. R.; Gembicky, M.; Dominiak, P. M.; Keister, J. B.; Diver, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 15702. (b) Maestre, L.; Ozkal, E.; Ayats, C.; Beltrán, Á.; Díaz-Requejo, M. M.; Pérez, P. J.; Pericàs, M. A. *Chem. Sci.* **2015**, *6*, 1510.

(15) Liu, Z. X.; Tan, H. C.; Wang, L.; Fu, T. R.; Xia, Y.; Zhang, Y.; Wang, J. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 3056.

(16) (a) Huang, F.; Wu, P.; Wang, L. D.; Chen, J. P.; Sun, C. L.; Yu, Z. K. *J. Org. Chem.* **2014**, *79*, 10553. (b) Huang, F.; Wu, P.; Wang, L. D.; Chen, J. P.; Sun, C. L.; Yu, Z. K. *Chem. Commun.* **2014**, *50*, 12479. (c) Wen, L.-R.; Man, N.-N.; Yuan, W.-K.; Li, M. *J. Org. Chem.* **2016**, *81*, 5942.

(17) Wang, L. D.; He, W.; Yu, Z. K. *Chem. Soc. Rev.* **2013**, *42*, 599.

(18) Mehta, S.; Waldo, J. P.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *ACS Comb. Sci.* **2013**, *15*, 247.

(19) De Sarlo, F.; Renzi, G. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1113.

(20) Pan, F.; Shi, Z.-J. *ACS Catal.* **2014**, *4*, 280.

(21) (a) Xu, S.; Wu, G. J.; Ye, F.; Wang, X.; Li, H.; Zhao, X.; Zhang, Y.; Wang, J. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 4669. (b) Su, N. J.; Theorell, J. A.; Wink, D. J.; Driver, T. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 12942.

DOI: 10.1021/acs.orglett.7b01668
Org. Lett. 2017, 19, 3660−3663