Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synergistic Acid-Catalyzed Synthesis of *N*-Aryl-Substituted Azacycles from Anilines and Cyclic Ethers

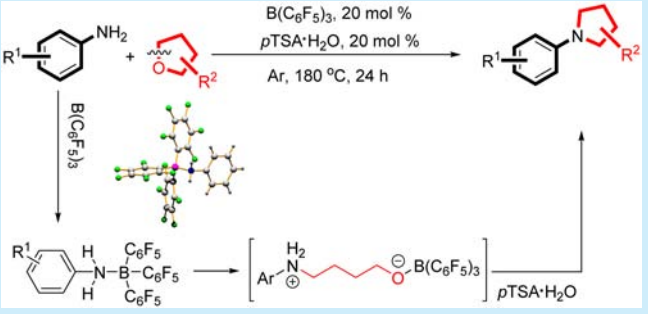
Zhenbei Zhang,[†,‡] Chengxia Miao,[†] Chungu Xia,[†] and Wei Sun*[,†]

[†]State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, P. R. China

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

Supporting Information

ABSTRACT: A metal-free and efficient approach to *N*-aryl-substituted azacycles from arylamines and cyclic ethers is described. In this synthesis, the synergistic effect between Lewis and Brønsted acids is crucial to the ring-opening of cyclic ethers and the subsequent cyclization. The use of $B(C_6F_5)_3$ enabled the formation of frustrated Lewis pairs (FLPs) from the reactants, and the resulting FLPs allowed ready access to the *N*-arylazacycles in moderate to good yields via further cyclization. Water is the sole waste resulting from the reaction, thereby making it an environmentally benign process.



N-Substituted azacycles are important structural motifs that are featured prominently in pharmaceuticals, agrochemicals, and organic materials.[1] For example, the most common *N*-arylpyrrolidines have received much attention because of their diverse useful biological activities (Figure 1).[2] In addition, *N*-arylpyrrolidines also frequently serve as versatile synthetic building blocks for the construction of complex molecules.[3−5] They have attracted broad research interests from different areas, especially in organic synthesis and medicinal synthesis. To date, there are many synthetic methods to form these compounds, for example, using dihalides with primary arylamines or nitrobenzene,[6] using diols with primary arylamines,[7] reductive amination of dicarbonyl compounds,[8] using aryl halides with *N*-unsubstituted azacycles through a cross-coupling reaction,[9] as well as using cyclic ethers with primary arylamines (Scheme 1, a).[10] Among them, the preparation of *N*-arylpyrrolidines from cyclic ethers and primary arylamines represents an appealing approach due to the formation of water as the sole waste product. To our knowledge, there are several systems involved in the construction of *N*-aryl-substituted pyrrolidines using the cyclic ether methods. Minkina and co-workers described the first approach to *N*-phenylpyrrolidine using tetrahydrofuran and aniline over activated alumina at 400 °C.[10a] Subsequently, various metal-based protocols, including aluminum oxide,[10b] aluminum trichloride,[10c] and titanium(IV) oxide,[10d] have been established. Recently, Lee and Korbad developed the synthesis of *N*-aryl-substituted azacycles promoted by $AlMe_3$ via the dimethylaluminum amide pathway, tolerating a wide scope of arylamines and cyclic ethers.[10e]

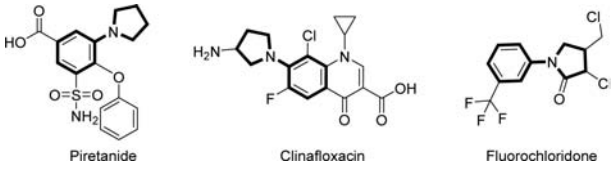
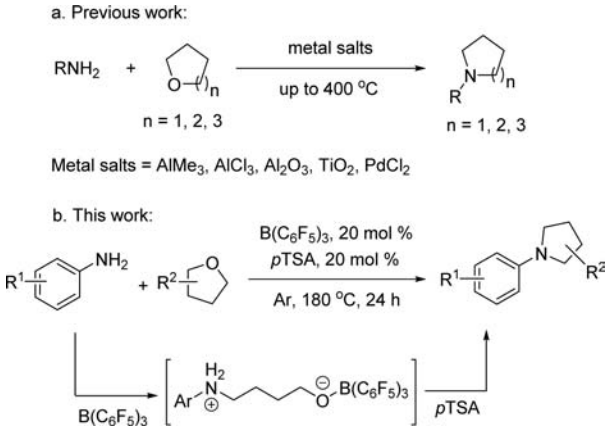


Figure 1. Representative *N*-aryl-substituted pyrrolidines.

Scheme 1. Synthesis of *N*-Substituted Pyrrolidines

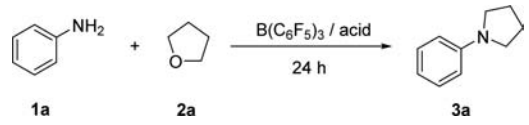


Despite the progress that has been made in this field, the aforementioned methods generally require the use of stoichiometric metal-based promotors. Further, with increasing concerns on the development of green methodology in synthetic chemistry, a metal-free catalytic process toward the synthesis of *N*-arylpyrrolidines is still highly desirable. As such,

Received: January 17, 2016
Published: March 10, 2016

DOI: 10.1021/acs.orglett.6b00157
Org. Lett. 2016, 18, 1522−1525

Table 1. Screening the Reaction Conditions[a]

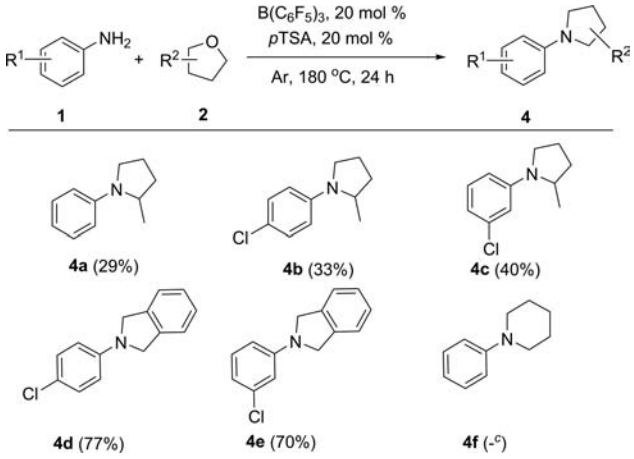


1a 2a 3a

entry	1a/$B(C_6F_5)_3$/acid[b]	acid	temp (°C)	yield[c] (%)
1	10:2:0		180	17
2	10:2:1	MSA	180	60
3	10:2:1	AA	180	45
4	10:2:1	*p*TSA·H_2O	180	80
5	10:0:1	*p*TSA·H_2O	180	10
6	10:2:2	*p*TSA·H_2O	180	84
7	10:1:2	*p*TSA·H_2O	180	73
8[d]	10:2:2	*p*TSA·H_2O	180	81
9	10:2:2	*p*TSA·H_2O	160	65

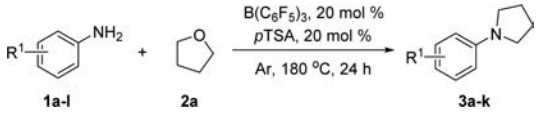
[a]The reactions were carried out with **1a** (0.25 mmol), $B(C_6F_5)_3$ (10 mol % or 20 mol %) and acid (10 mol % or 20 mol %) in 2 mL of THF at specified temperature for 24 h under Ar atmosphere. [b]Molar ratio of components **1a**/$B(C_6F_5)_3$/acid. [c]Isolated yield based on aniline. [d]This reaction was carried out for 20 h. MSA = methanesulfonic acid, AA = acetic acid, *p*TSA = *p*-toluenesulfonic acid.

Scheme 2. Evaluation of Cyclic Ethers[a,b]



[a]The reactions were carried out at 180 °C with aniline **1** (0.25 mmol), $B(C_6F_5)_3$ (20 mol %), and *p*TSA·H_2O (20 mol %) in 2 mL of cyclic ether **2** under argon for 24 h. [b]Isolated yield based on aromatic amines. [c]Not detected.

Table 2. Evaluation of Anilines with THF[a]



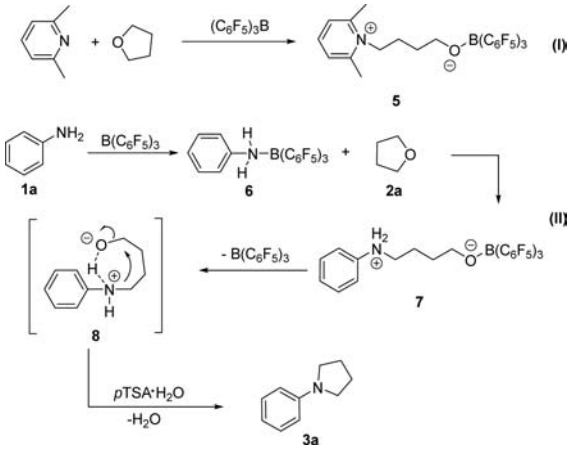
1a-l 2a 3a-k

entry	amine 1	product 3	yield[b] (%)	entry	amine 1	product 3	yield[b] (%)
1	1a	3a	84	8	1h	3h	71
2	1b	3b	76	9	1i	3i	68
3	1c	3c	87	10	1j	3j	33
4	1d	3d	88	11	1k	3k	24
5	1e	3e	82	12	1l	3l	50
6	1f	3f	50	13	1m	3m	61
7	1g	3g	77	14[c]	1n	3a	47

[a]The reactions were carried out at 180 °C with aniline **1** (0.25 mmol), $B(C_6F_5)_3$ (20 mol %), and *p*TSA·H_2O (20 mol %) in 2 mL of THF under argon for 24 h. [b]Isolated yield based on aromatic amine. [c]The product was 1-phenylpyrrolidine (**3a**).

DOI: 10.1021/acs.orglett.6b00157
Org. Lett. 2016, 18, 1522−1525

Scheme 3. Plausible Mechanism for $B(C_6F_5)_3$-Mediated Synthesis of *N*-Aryl-Substituted Azacycles from Arylamines and THF



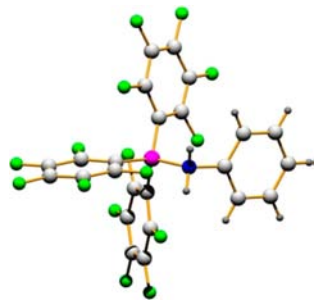


Figure 2. Crystal structure of $[(C_6F_5)_3B(C_6H_7N)]$ **6** (CCDC-1441903). Atom colors: green, F; pink, B; blue, N; light gray, C; dark gray, H.

we describe herein a metal-free and efficient approach to *N*-aryl-substituted azacycles from arylamines and cyclic ethers via $B(C_6F_5)_3$-mediated frustrated Lewis pair (FLP) pathway (Scheme 1, b). Water is the sole waste product from the reaction, thereby making it an environmentally benign process.

Recently, the advent of frustrated Lewis pair chemistry provides an important approach for the metal-free homogeneous catalysis.[11] A variety of small molecules including molecular hydrogen, olefins, as well as THF can be activated by FLP catalysts.[12,13] Ring-opening of THF mediated by $B(C_6F_5)_3$ in combination with either nitrogen- or phosphorus-based Lewis bases to form FLPs has been reported.[14] Accordingly, we envisioned that $B(C_6F_5)_3$ may lead to the ring opening of cyclic ether with arylamine to form FLPs, and the resulting FLPs could further coordinate to provide the desired *N*-arylpyrrolidines (Scheme 1, b). To test our hypothesis, initial reaction development employed THF and aniline **1a** in the presence of $B(C_6F_5)_3$. Initially, *N*-phenylpyrrolidine **3a** was formed in a 17% yield in the presence of 20 mol % of $B(C_6F_5)_3$ at 180 °C for 24 h (Table 1, entry 1). It was found that the addition of various Brønsted acids could improve the reaction outcome (Table 1, entries 2−4). When 10 mol % of *p*TSA·H_2O was employed as an additive, the reaction provided the desired azacycle **3a** in an 80% yield (Table 1, entry 4). The yield was increased to 84% using 20 mol % of *p*TSA·H_2O (Table 1, entry 6). A poor result was observed using *p*TSA·H_2O as the only catalyst in the absence of $B(C_6F_5)_3$ (Table 1, entry 5). Shortening reaction time or lowering reaction temperature led to the decrease in the yield of *N*-phenylpyrrolidine **3a** (Table 1, entries 8 and 9).

With the optimized reaction conditions in hand, we turned to examine the scope of arylamines and cyclic ethers. First, a variety of arylamines were evaluated (Table 2). The arylamines bearing electron-donating and -withdrawing groups were tolerated well under the reaction conditions, affording the desired *N*-arylpyrrolidines in 50% to 88% yields. However, the *p*-methoxy-substituted aniline resulted in a moderate yield (Table 2, entry 6). The steric hindrance of substituted anilines displayed a noteworthy impact on the reaction outcome; the reaction of *p*-*t*-Bu-substituted aniline (**1l**) only provides a 50% yield, while the *p*-toluidine (**1g**) leads to a 77% yield. As expected, *ortho*-substituted anilines usually afforded lower yields than those of the *para*- and *meta*-substituted anilines (Table 2, entries 3−5 and 7−9). 2,6-Disubstituted anilines **1j** and **1k** could also give the corresponding products **3j** and **3k**, although inferior yields were obtained because of the bulky substituents (Table 2, entries 10 and 11). 1-Naphthylamine also reacted with THF smoothly and gave the corresponding product in a 50% yield (Table 2, entry 13). To our surprise, 1-phenylpyrrolidine (**3a**) was produced as the only product in a 47% yield when *N*-methylaniline (**1n**) was employed under the reaction conditions (Table 2, entry 14). Clearly, a demethylation reaction occurred during the reaction.

Next, the reaction of different cyclic ethers including 2-methyltetrahydrofuran, 1,3-dihydroisobenzofuran, and tetrahydropyran was also investigated. 2-Methyltetrahydrofuran showed less reactivity in comparison with that of THF and gave corresponding products in low yields, probably owing to its steric hindrance (Scheme 2, **4a**−**c**). To our delight, 1,3-dihydroisobenzofuran could serve as a good cyclic ether partner to readily access the *N*-arylpyrrolidines in good yields (Scheme 2, **4d**, **4e**). When a six-membered cyclic ether, tetrahydropyran, was employed, no appreciable reaction occurred at all (Scheme 2, **4f**).

After an exploration of the substrate scope, we turned our attention to elucidating the mechanism. To our knowledge, addition of THF to the reaction mixture of 2,6-lutidine and $B(C_6F_5)_3$ resulted in the ring opening of THF to give compound **5** (Scheme 3, I).[14b] On the basis of this finding, a plausible mechanism for the formation of *N*-aryl-substituted pyrrolidines, via a FLP pathway from aniline (**1a**) and THF (**2a**) in the presence of $B(C_6F_5)_3$, is depicted in Scheme 3 (II). First, $B(C_6F_5)_3$ reacted with aniline **1a** to provide the adduct $[(C_6F_5)_3B(C_6H_7N)]$ **6**, which could be isolated after treatment of aniline with $B(C_6F_5)_3$ and confirmed by crystal X-ray and NMR (Figure 2 and Figure S1, SI).[14b] Next, THF **2a** coordinated with adduct **6**, and the ring opening took place to provide the species **7**, which could be generated in situ under the reaction conditions and then confirmed by NMR (Figure S2, SI).[14b] Afterward, $B(C_6F_5)_3$ was removed **7** to provide the intermediate **8**. Then the dehydration and cyclization of the resulting species **8** occurred to give the desired 1-phenylpyrrolidine **3a** in the presence of *p*TSA·H_2O.[15]

In summary, we describe a metal-free and efficient synthetic method for the preparation of *N*-aryl-substituted azacycles from arylamines and cyclic ether catalyzed by $B(C_6F_5)_3$ and *p*TSA·H_2O via the FLP pathway. The synergistic effect between $B(C_6F_5)_3$ and *p*TSA·H_2O is crucial to this reaction outcome. Notably, water is the sole waste product resulting from the reaction, and a metal-free method is involved, thereby making it an environmentally benign process. Further studies are

DOI: 10.1021/acs.orglett.6b00157
Org. Lett. 2016, 18, 1522−1525

underway to fully acquire the role of $B(C_6F_5)_3$ and to expand the reaction scope.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00157.

Experimental procedures, characterization data, and copies of NMR (PDF)
Crystallographic data for $[(C_6F_5)_3B(C_6H_7N)]$ **6** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wsun@licp.cas.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support of this work from the National Natural Science Foundation of China (Nos. 21473226 and 21133011).

■ REFERENCES

(1) (a) Wu, X.-F.; Beller, M. *Economic Synthesis of Heterocycles: Zinc, Iron, Copper, Cobalt, Manganese and Nickel Catalysts*; RSC Catalysis Series; Royal Society of Chemistry, 2014 (b) Friedrichsen, W. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1996.

(2) (a) Ma, J.; Zheng, R.; Xu, L.; Wang, S. *Ecotoxicol. Environ. Saf.* **2002**, *52*, 57−61. (b) Faris, R.; Flather, M.; Purcell, H.; Henein, M.; Poole-Wilson, P.; Coats, A. *Int. J. Cardiol.* **2002**, *82*, 149−158. (c) Zeuthen, T.; Ramos, M.; Ellory, J. C. *Nature* **1978**, *273*, 678−680. (d) Roberts, C. J. C.; Homeida, M.; Roberts, F.; Bogie, W. *Br. J. Clin. Pharmacol.* **1978**, *6*, 129−133. (e) Jursík, M.; Andr, J.; Holec, J.; Soukup, J. *Plant. Soil Environ.* **2011**, *57*, 532−539. (f) Appelbaum, P. C.; Hunter, P. A. *Int. J. Antimicrob. Agents* **2000**, *16*, 5−15. (g) Friedland, I. R.; Paris, M.; Ehrett, S.; Hickey, S.; Olsen, K.; Mccracken, G. H. *Antimicrob. Agents Chemother.* **1993**, *37*, 1630−1636. (h) Bauernfeind, A. *J. Antimicrob. Chemother.* **1997**, *40*, 639−651. (i) Kamath, K. *Am. J. Trop. Med. Hyg.* **1973**, *22*, 600−605.

(3) (a) Paras, N. A.; MacMillan, W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895. (b) Sarma, M.; Chatterjee, T.; Ghanta, S.; Das, S. K. *J. Org. Chem.* **2012**, *77*, 432−444. (c) Rao, V. P.; Jen, A. K.-Y.; Wong, K. Y.; Drost, K. J. *J. Chem. Soc., Chem. Commun.* **1993**, 1118−1120.

(4) (a) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 5284−5285. (b) Zhang, Y.; Peng, H.; Zhang, M.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2011**, *47*, 2354−2356. (c) Li, Z. L.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672−3673. (d) Xiao, T.; Li, L.; Lin, G.; Mao, Z. W.; Zhou, L. *Org. Lett.* **2014**, *16*, 4232−4235. (e) Zhou, H.; Lu, P.; Gu, X.; Li, P. *Org. Lett.* **2013**, *15*, 5646−5649.

(5) (a) Bonnaud, B.; Bigg, D. C. H. *Synthesis* **1994**, *1994*, 465−467. (b) Adkins, H.; Lundsted, L. G. *J. Am. Chem. Soc.* **1949**, *71*, 2964−2965. (c) *Justus Liebigs Ann. Chem.* **1955**, *596*, 158−224 DOI: 10.1002/jlac.19555960109.

(6) (a) Craig, L. C.; Hixon, R. M. *J. Am. Chem. Soc.* **1930**, *52*, 804−808. (b) Degrand, C.; Compagnon, P. L.; Belot, G.; Jacquin, D. *J. Org. Chem.* **1980**, *45*, 1189−1196. (c) Clark, J. H.; Pile, J. D.; Miller, J. M.; Paone, S.; Tan, S. Y. *Can. J. Chem.* **1982**, *60*, 1815−1820. (d) Romera, J. L.; Cid, J. M.; Trabanco, A. A. *Tetrahedron Lett.* **2004**, *45*, 8797−8800. (e) Ju, Y. H.; Varma, R. S. *Org. Lett.* **2005**, *7*, 2409−2411. (f) Sarma, M.; Chatterjee, T.; Ghanta, S.; Das, S. K. *J. Org. Chem.* **2012**, *77*, 432−444.

(7) (a) Abbenhuis, R.; Boersma, J.; van Koten, G. *J. Org. Chem.* **1998**, *63*, 4282−4290. (b) Fujita, K. I.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525−3528. (c) Yamaguchi, R.; Fujita, K.; Fujii, T.; Komatsubara, A.; Enoki, Y. *Heterocycles* **2007**, *74*, 673−682. (d) Du, Y.; Oishi, S.; Saito, S. *Chem. - Eur. J.* **2011**, *17*, 12262−12267. (e) Wang, L. D.; He, W.; Wu, K. K.; He, S. B.; Sun, C. L.; Yu, Z. K. *Tetrahedron Lett.* **2011**, *52*, 7103−7107. (f) Cui, X. J.; Dai, X. C.; Deng, Y. Q.; Shi, F. *Chem. - Eur. J.* **2013**, *19*, 3665−3675.

(8) (a) Shim, S. C.; Huh, K. T.; Park, W. H. *Tetrahedron* **1986**, *42*, 259−263. (b) Katritzky, A. R.; Fan, W. *J. Org. Chem.* **1990**, *55*, 3205−3209. (c) Watanabe, Y.; Shim, S. C.; Uchida, H.; Mitsudo, T.; Takegami, Y. *Tetrahedron* **1979**, *35*, 1433−1436. (d) Suwa, T.; Sugiyama, E.; Shibata, I.; Baba, A. *Synthesis* **2000**, *2000*, 789−800.

(9) (a) Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett.* **2007**, *9*, 3397−3399. (b) Guo, D. L.; Huang, H.; Xu, J. Y.; Jiang, H. L.; Liu, H. *Org. Lett.* **2008**, *10*, 4513−4516. (c) Yong, F. F.; Teo, Y. C. *Tetrahedron Lett.* **2010**, *51*, 3910−3912. (d) Cano, R.; Ramon, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654−660. (e) Khatri, P. K.; Jain, S. L. *Tetrahedron Lett.* **2013**, *54*, 2740−2743. (f) Mantel, M. L. H.; Lindhardt, A. T.; Lupp, D.; Skrydstrup, T. *Chem. - Eur. J.* **2010**, *16*, 5437−5442.

(10) (a) Yur'ev, Y. K.; Minkina, G. A. *J. . Gen. Chem. (USSR)* **1937**, *1*, 2945. (b) Bourns, A. N.; Embleton, H. W.; Hansuld, M. K. *Can. J. Chem.* **1952**, *30*, 1−8. (c) Olsen, C. J.; Furst, A. *J. Am. Chem. Soc.* **1953**, *75*, 3026−3026. (d) Hargis, D. C.; Shubkin, R. L. *Tetrahedron Lett.* **1990**, *31*, 2991−2994. (e) Korbad, B. L.; Lee, S.-H. *Chem. Commun.* **2014**, *50*, 8985−8988.

(11) (a) McCahill, J. S. J.; Welch, G. C.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4968−4971. (b) Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023−4078. (c) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46−76. (d) Stephan, D. W. *J. Am. Chem. Soc.* **2015**, *137*, 10018−10032. (e) Stephan, D. W. *Acc. Chem. Res.* **2015**, *48*, 306−316.

(12) (a) Stephan, D. W. *Dalton Trans.* **2009**, 3129−3136. (c) Stephan, D. W. *Org. Biomol. Chem.* **2008**, *6*, 1535−1539. (b) Stephan, D. W. *Org. Biomol. Chem.* **2012**, *10*, 5740−5746. (c) Power, P. P. *Nature* **2010**, *463*, 171−177.

(13) (a) Wei, S.; Du, H. *J. Am. Chem. Soc.* **2014**, *136*, 12261−12264. (b) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 12968−12971. (c) Liu, Y.; Du, H. *J. Am. Chem. Soc.* **2013**, *135*, 6810−6813. (d) Zhang, Z.; Du, H. *Org. Lett.* **2015**, *17*, 2816−2819. (e) Zhu, X.; Du, H. *Org. Lett.* **2015**, *17*, 3106−3109.

(14) (a) Welch, G. C.; Masuda, J. D.; Stephan, D. W. *Inorg. Chem.* **2006**, *45*, 478−480. (b) Geier, S. J.; Stephan, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 3476−3477.

(15) Shi, W.; Bai, C.-M.; Zhu, K.; Cui, D.-M.; Zhang, C. *Tetrahedron* **2014**, *70*, 434−438.

DOI: 10.1021/acs.orglett.6b00157
Org. Lett. 2016, 18, 1522−1525