Organic LETTERS

Letter

pubs.acs.org/OrgLett

Modular Synthesis of Sulfonyl Benzoheteroles by Silver-Catalyzed Heteroaromatization of Propargylic Alcohols with *p*-Toluenesulfonylmethyl Isocyanide (TosMIC): Dual Roles of TosMIC

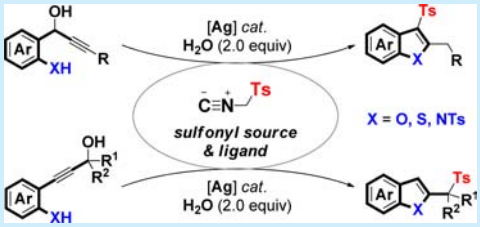
Jianquan Liu,[†] Zhenhua Liu,[†] Peiqiu Liao,[†] and Xihe Bi*[,†,‡]

[†]Department of Chemistry, Northeast Normal University, Changchun 130024, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

ABSTRACT: A new silver-catalyzed heteroaromatization of propargylic alcohols with *p*-toluenesulfonylmethyl isocyanide (TosMIC) has been developed that provides an efficient and modular approach to sulfonyl benzoheteroles. For the first time, TosMIC plays a dual role in one reaction: sulfonyl source and ligand. An unprecedented deoxysulfonylation/hydration/condensation reaction pathway is disclosed.



Benzoheteroles such as benzofurans, indoles, and benzothiophenes not only are 'privileged structures' encountered in numerous natural products and synthetic functional molecules[1] but also function as valuable intermediates in organic synthesis.[2] In the past decade, substantial advances in the transition-metal-catalyzed synthetic methods for these heterocycles have been witnessed.[3] Among these, intra- and intermolecular heteroaromatization using alkynes may be one of the most popular synthetic strategies.[4−6] For intramolecular heteroaromatization reactions, it is well recognized that the activation of the alkynyl π-bond is initiated by the coordination of a π-electrophilic transition-metal (TM) catalyst to the C≡C triple bond, followed by the generation of an (alkenyl)metal intermediate (Figure 1a). Despite the impressive progress, the methods allowing for the modular synthesis of benzoheteroles simply by changing the heteroatom center under the same catalytic conditions are rare.[7] Propargylic alcohols are readily available bifunctional building blocks; recently, the exploration of their synthetic potency has attracted much attention.[8] As part of our continued efforts to develop novel reactions using functionalized alkynes,[9] we herein report a new silver-catalyzed heteroaromatization reaction of propargylic alcohols with *p*-toluenesulfonylmethyl isocyanide (TosMIC), thus providing a conceptually novel and modular approach to pharmaceutically relevant sulfonyl benzoheteroles (Figure 1b).[10] An unprecedented reaction pathway, different from the classical intramolecular heteroaromatization of alkynes, is disclosed. TosMIC plays a dual role as the sulfonyl source and ligand. To the best of our knowledge, this is the first example in which TosMIC plays such a role in one reaction, even though it has been widely used in organic synthesis.[11]

Recently, we and the Lei group realized the first silver-catalyzed [3 + 2] cycloaddition reaction of alkynes with isocyanides.[9c,d] When we tried to expand the substrate scope to propargylic alcohol **1a**, unexpectedly, the reaction catalyzed by

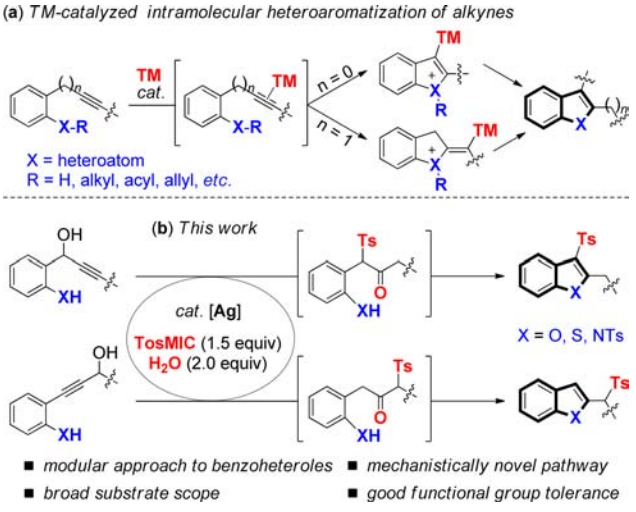


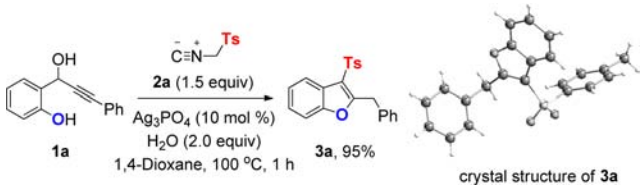
Figure 1. Synthesis of benzoheteroles by transition-metal-catalyzed intramolecular heteroaromatization of alkynes.

Ag_2CO_3 in the presence of 2 equiv of H_2O afforded 3-sulfonylated benzofuran **3a** in 80% yield. The structure of compound **3a** was unambiguously confirmed by X-ray diffraction (XRD) analysis. This reaction represents a new route to access benzofurans. Therefore, we carried out an extensive optimization of the reaction conditions (for the details, see the Supporting Information). Finally, the yield was improved to 95% under the optimal conditions (Ag_3PO_4 (10 mol %), H_2O (2.0 equiv), 1,4-dioxane, 100 °C). Subsequently, two questions related to the reaction mechanism were raised: (1) how the Ts group was transferred to the 3-position of benzofurans; (2) whether the

Received: October 27, 2014
Published: November 17, 2014

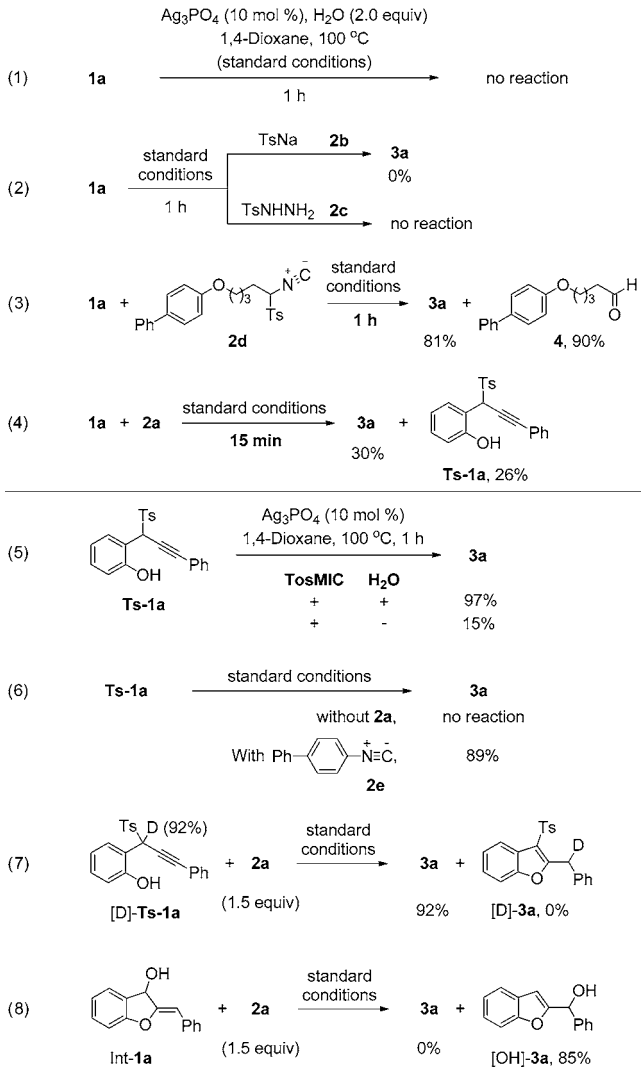
dx.doi.org/10.1021/ol5031316 | *Org. Lett.* 2014, 16, 6204−6207

heteroaromatization followed the classical TM-catalyzed cyclization pathway. To elucidate these mechanistic questions, the following experimental investigations were carried out.



As shown in Scheme 1, first, we found that, in the absence of TosMIC, the reaction of **1a** under the optimized reaction conditions failed, thus demonstrating the necessity of TosMIC (eq 1). Furthermore, instead of TosMIC, other reported Ts sources such as TsNa and $TsNHNH_2$ were investigated;[12] however, either no desired product **3a** was obtained or no reaction occurred (eq 2). To capture the side product from TosMIC, a TosMIC derivative **2d** with a large biphenyl tail was designed and prepared. Delightfully, the reaction of **1a** with **2d** smoothly proceeded to afford product **3a** in a slightly decreased yield (81%); importantly, an aldehyde byproduct **4** was isolated in 90% yield (eq 3). This result suggests that TosMIC may decompose to formaldehyde and a Ts group, probably accompanied by the generation of a cyanide ion (CN^-).[13] Furthermore, when quenching the reaction mixture of **1a** and **2a** in 15 min, a key intermediate, **Ts-1a**, was obtained in 26% yield (eq 4). Clearly, a deoxysulfonylation process occurred in the initial stage of the reaction.

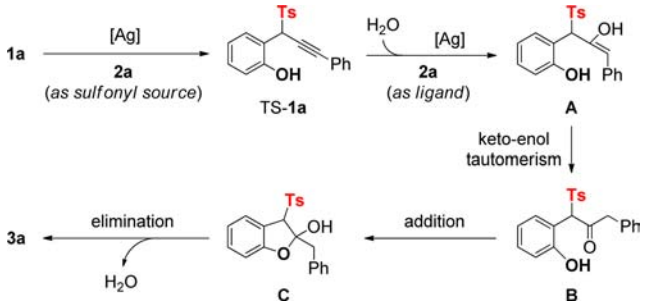
Scheme 1. Mechanistic Investigations



After identifying the first step in the reaction as deoxysulfonylation, we turned our attention to the subsequent heteroaromatization pathway starting from intermediate **Ts-1a**, which was synthesized by a reported method.[14] The critical role of H_2O in the heteroaromatization of **Ts-1a** was established: in the presence of H_2O, **3a** could be obtained in nearly quantitative yield (97%), whereas, in the absence of H_2O, **3a** was obtained in a poor yield (15%) (eq 5). These results demonstrated **Ts-1a** to be the reaction intermediate and also proved the necessity of H_2O as the additive. Interestingly, no reaction occurred in the absence of TosMIC, thus suggesting that TosMIC acted as a ligand in the cyclization of **TS-1a**. This assumption was further confirmed using aryl isocyanide (**2e**) instead of TosMIC, which afforded **3a** in 89% yield (eq 6). Although isocyanide–metal complexes are common in organometallic chemistry,[15] to the best of our knowledge, the use of TosMIC as a ligand in transition-metal-catalyzed reactions has not been reported.[16] The cyclization of **Ts-1a** probably proceeded through an unusual hydration/condensation cascade. Such a hypothesis was confirmed by the reaction of deuterium-labeled compound [D]-**Ts-1a**, which only afforded benzofuran **3a** in 92% yield without deuterium incorporation, while [D]-**3a** that was expected to be formed by the addition of alkynes and isomerization was not found (eq 7).[17] The classical process was further excluded by the reaction of Int-**1a**, which only afforded [OH]-**3a** in 85% yield by a reported 1,3-hydroxyl transfer process, while the **3a** yield was 0% (eq 8).[18]

Based on the above results, a plausible mechanism was proposed (Scheme 2). The domino reaction starts with the reaction of propargylic alcohol **1a** with TosMIC **2a** to yield the intermediate **Ts-1a** by deoxysulfonylation, in which TosMIC acts as the sulfonyl source. Next, the regioselective hydration of **Ts-1a** with H_2O takes place using TosMIC as the ligand, thus affording enol **A**. The regioselectivity of the reaction can be attributed to the directing effect of the Ts group. Following keto–enol tautomerism, α-Ts ketone intermediate **B** is formed. Finally, benzofuran **3a** is formed by a sequential addition/elimination cascade (i.e., condensation reaction).[19]

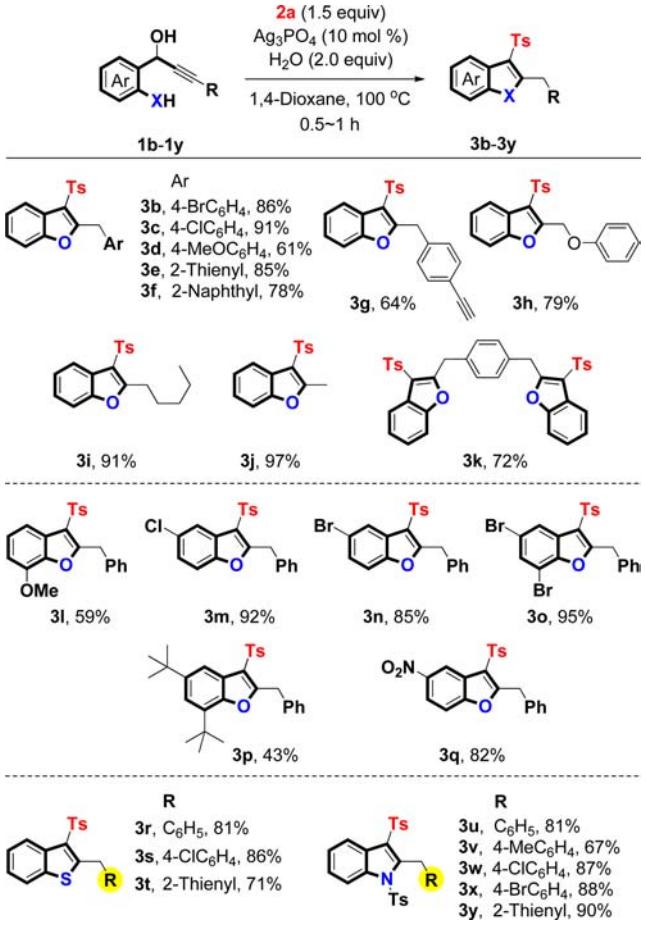
Scheme 2. A Plausible Reaction Mechanism



Next, the substrate scope of propargylic alcohols that could be used in this domino heteroaromatization reaction was investigated (Scheme 3). A range of substrates (**1b–1q**) were converted into the corresponding benzofuran products (**3b–3q**) in synthetically useful yields using the initial optimized reaction conditions. A range of R groups including (hetero)aryl, fused

dx.doi.org/10.1021/ol5031316 | Org. Lett. 2014, 16, 6204–6207

Scheme 3. Synthesis of 3-Sulfonyl Benzofurans, Indoles, and Benzothiophenes[a]

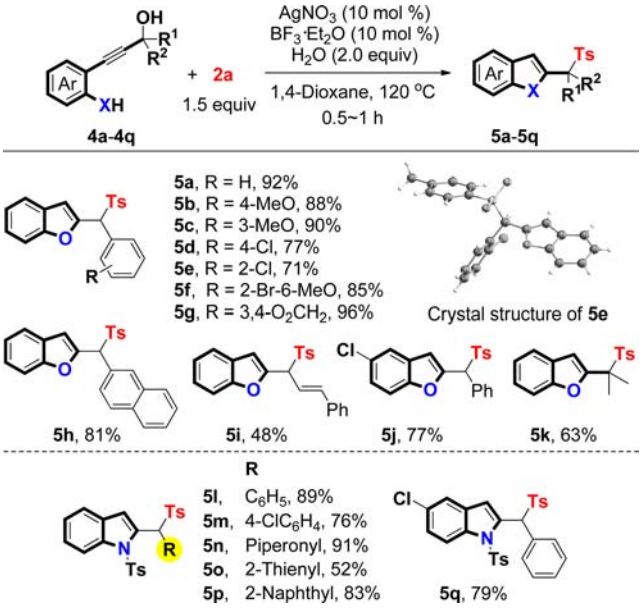


[a]Isolated yields.

aryl, and alkyl were compatible with the cyclization reaction conditions. Substrate **1j** containing a terminal alkyne unit (i.e., R = H) also smoothly participated in the reaction with TosMIC, thus affording the corresponding 2-methyl-3-sulfonyl benzofuran **3j** in 97% yield. Moreover, a benzofuran dimer **3k** was prepared in 72% yield starting from a bispropargylic alcohol substrate. Furthermore, wide variation of the substituents on the benzene ring including electron-donating (e.g., MeO and *t*-Bu) and -withdrawing groups (e.g., Br, Cl, and NO_2) allowed the formation of diverse highly functionalized benzofurans (**3l**−**3q**) in moderate to excellent yields. To our delight, this method was also capable of preparing 3-sulfonyl benzothiophenes (**3r**−**3t**) and indoles (**3u**−**3z**) simply by changing the heteroatoms. Sulfonyl benzoheteroles are pharmaceutically important;[10] however, the reported synthetic methods are mostly limited to the sulfonylation on a benzoheterole skeleton.[19] Herein, we developed a straightforward method for the synthesis of such compounds from acyclic precursors.

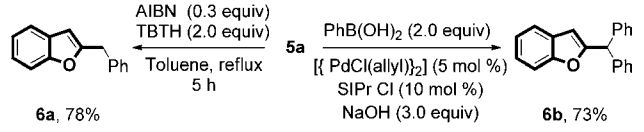
To expand the scope of this methodology, propargylic alcohols (**4**) were synthesized by the Sonogashira coupling of terminal propargylic alcohols with the corresponding *ortho*-halophenols/anilines.[20] Structurally, the positions of the hydroxyl group and C≡C triple bond are interchanged in propargylic alcohols **4** and **1**. As shown in Scheme 4, under slightly modified reaction conditions, to our delight, they were also useful for the heteroaromatization with TosMIC to afford 2-sulfonylmethyl

Scheme 4. Synthesis of 2-Sulfonylmethyl Benzofurans and Indoles[a]

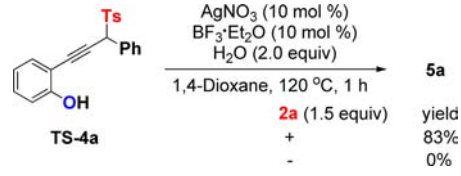


[a]Isolated yields.

benzofurans (**5a**−**5k**) and indoles (**5l**−**5q**) in moderate to high yields (48−92%). The structure of compound **5e** was unambiguously established by XRD analysis. Notably, compounds **5** are newly substituted benzoheteroles.[21] The easy availability of sulfonyl benzoheteroles **5** opens new synthetic opportunities for a suitable functionalization at the 2-position because of the well-known ability of the arenesulfonyl moiety as a good leaving group.[22] Therefore, an alkylation reaction of the benzofuran **5a** was realized under radical conditions by the substitution of the Ts group with a hydrogen atom leading to the 2-alkyl benzofuran derivative **6a**; meanwhile, triarylmethane **6b** was obtained by the palladium-catalyzed coupling reaction with phenylboronic acid.[23]



The preliminary mechanistic studies on the heteroaromatization of propargylic alcohols **4** suggested a similar reaction pathway to that of propargylic alcohols **1**. For example, the deoxysulfonylated intermediate **TS-4a** was smoothly converted into the desired product **5a** in 83% yield in the presence of TosMIC, whereas no reaction occurred without TosMIC.



In conclusion, we have developed a novel silver-catalyzed heteroaromatization reaction of propargylic alcohols and TosMIC, which provides a very convenient and modular approach to a range of functionalized benzoheteroles including benzofurans, indoles, and benzothiophenes. For the first time,

dx.doi.org/10.1021/ol5031316 | Org. Lett. 2014, 16, 6204−6207

the role of TosMIC was found to be twofold, as the sulfonyl source and ligand. A mechanistically novel deoxysulfonylation/hydration/condensation reaction pathway, different from the classical transition-metal-catalyzed intramolecular heteroaromatization of alkynes, was disclosed. Considering the practicality and novelty of this method and the extreme importance of benzoheteroles in medicinal chemistry and material science, the methodology described here undoubtedly will find wide applications in future synthetic endeavors.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectra copies. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bixh507@nenu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (21172029, 21202016, 21372038), the MEPRC (NCET-13-0714), and the Jilin Provincial Research Foundation for Basic Research (20140519008JH).

■ REFERENCES

(1) Bronner, S. M.; Im, G. Y. J.; Garg, N. K. *Heterocycles in Natural Product Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: 2011.
(2) (a) Bartoli, G.; Dalpozzo, R.; Nardi, M. *Chem. Soc. Rev.* **2014**, *43*, 4728. (b) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.
(3) For recent reviews, see: (a) Zeng, X. *Chem. Rev.* **2013**, *113*, 6864. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783.
(4) For examples of benzofuran synthesis, see: (a) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (c) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387. (d) Han, Z.; Zhang, L.; Li, Z.; Fan, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 6805 and references cited therein.
(5) For examples of indole synthesis, see: (a) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (b) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546. (c) Liu, B.; Song, C.; Sun, C.; Zhou, S.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 16625 and references cited therein.
(6) For examples of benzothiophene synthesis, see: (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473. (b) Liu, K.; Jia, F.; Xi, H.; Li, Y.; Zheng, X.; Guo, Q.; Shen, B.; Li, Z. *Org. Lett.* **2013**, *15*, 2026 and references cited therein.
(7) (a) Syu, S.; Lee, Y.; Jang, Y.; Lin, W. *Org. Lett.* **2011**, *13*, 2970. (b) Qin, X.; Cong, X.; Zhao, D.; You, J.; Lan, J. *Chem. Commun.* **2011**, *47*, 5611.
(8) For examples, see: (a) Nagashima, Y.; Hirano, K.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2014**, *136*, 8532. (b) Collins, B. S. L.; Suero, M. G.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 5799.
(9) (a) Fang, Z.; Liu, J.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 7209. (b) Liu, Z.; Liu, J.; Zhang, L.; Liao, P.; Song, J.; Bi, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 5305. (c) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953. (d) Gao, M.; He, C.; Chen, H.; Bai, R.; Cheng, B.; Lei, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 6958.
(10) (a) Zhou, N.; Zeller, W.; Krohn, M.; Anderson, H.; Zhang, J.; Onua, E.; Kiselyov, A. S.; Ramirez, J.; Halldorsdottir, G.; Andrésson, T.; Gurney, M. E.; Singh, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 123. (b) Silvestri, R.; De Martino, G.; La Regina, G.; Artico, M.; Massa, S.; Vargiu, L.; Mura, M.; Loi, A. G.; Marceddu, T.; La Colla, P. *J. Med. Chem.* **2003**, *46*, 2482.
(11) Tandon, V. K.; Rai, S. *Sulfur Rep.* **2003**, *24*, 307.
(12) Tang, S.; Wu, Y.; Liao, W.; Bai, R.; Liu, C.; Lei, A. *Chem. Commun.* **2014**, *50*, 4496.
(13) (a) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966. (b) Vishnu, G.; Srivastava, P.; Dhar, L.; Yadav, S. *Tetrahedron Lett.* **2011**, *52*, 4622.
(14) Reddy, M. A.; Reddy, P. S.; Sreedhar, B. *Adv. Synth. Catal.* **2010**, *352*, 1861.
(15) Luzyanin, K. V.; Pombeiro, A. J. L. In *Isocyanide Chemistry: Applications in Synthesis and Material Science*, 1st ed.; Nenajdenko, V., Ed.; Wiley-VCH Verlag GmbH & Co.: 2012; pp 531−550.
(16) For Ito's catalyst using *tert*-alkyl isocyanide as a ligand, see: Ito, Y.; Suginome, M.; Murakami, M. *J. Org. Chem.* **1991**, *56*, 1948.
(17) Wongsa, N.; Sommart, U.; Ritthiwigrom, T.; Yazici, A.; Kanokmedhakul, S.; Kanokmedhakul, K.; Willis, A. C.; Pyne, S. G. *J. Org. Chem.* **2013**, *78*, 1138.
(18) Li, X.; Xue, J.; Chen, R.; Li, Y. *Synlett* **2012**, *23*, 1043.
(19) Xiao, F.; Chen, H.; Xie, H.; Chen, S.; Yang, L.; Deng, G. *Org. Lett.* **2014**, *16*, 50.
(20) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.
(21) Li, Y.; Shi, F.; He, Q.; You, S. *Org. Lett.* **2009**, *11*, 3182.
(22) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.
(23) Nambo, M.; Crudden, C. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 742.