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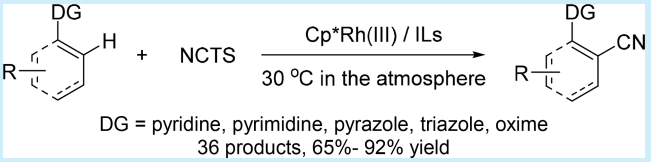
Rhodium-Catalyzed Direct C-H Bond Cyanation in Ionic Liquids

Songyang Lv, Yaling Li, Tian Yao, Xinling Yu, Chen Zhang, Li Hai,* and Yong Wu*

Key Laboratory of Drug-Targeting of Education Ministry and Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. China

Supporting Information

ABSTRACT: A Cp*Rh(III)/IL-based direct C-H bond cyanation system was developed for the first time. The system is a mild, efficient, and recyclable method for the synthesis of aryl nitriles. Many different directing groups can be used in this cyanation, and the reaction tolerates a variety of functional groups.



Aryl nitriles are a class of important compounds that are widely encountered as key structural features in drugs, agrochemicals, and natural products. For example, Neratinib is an anticancer drug and Etravirine is an effective anti-HIV drug (Figure 1).[1] In addition, the cyano functional group as a valuable

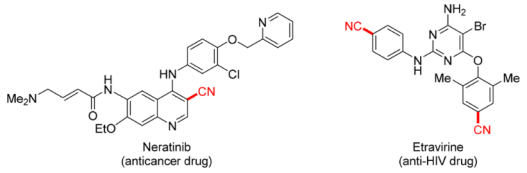
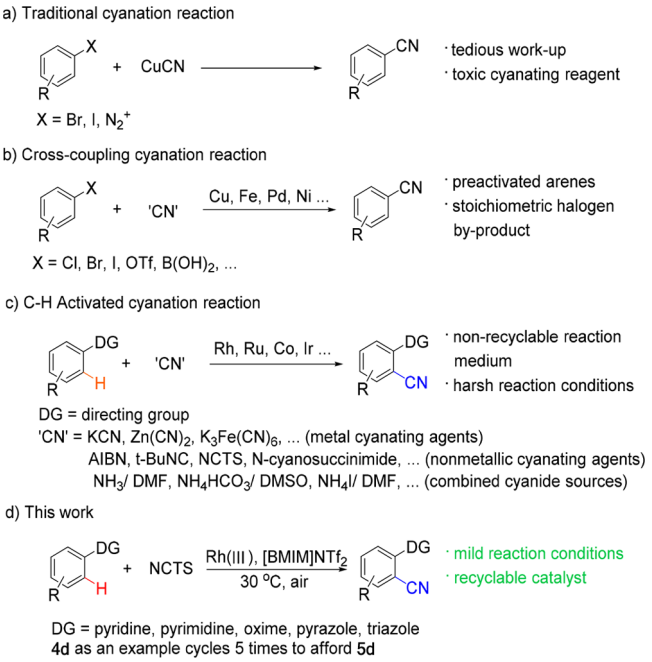


Figure 1. Representative important nitrile-containing molecules.

intermediate can be readily derivatized into various important functional groups such as carboxyl derivatives, aldehydes, amines, and heterocycles.[2] Thus, developing methods for the synthesis of cyano aromatics is of great interest to chemists. Traditionally, cyanations are achieved through the Rosenmund−von Braun reaction or the Sandmeyer reaction (Scheme 1a),[3] which both require tedious workup and stoichiometric amounts of CuCN. Cross-coupling cyanations of aryl (pseudo)halides were developed to solve the problems mentioned above, but those reactions require preactivated arenes or produce halogen byproducts (Scheme 1b).[4] To overcome these issues, transition-metal-catalyzed direct C-H bond cyanation reactions have become an attractive, efficient, and user-friendly alternative for the synthesis of aromatic cyanides, and a range of ecofriendly cyanating agents were successfully developed for these processes (Scheme 1c).[5] Although C-H bond cyanations have already made significant advances, harsh reaction conditions (heating over 100 °C) and the use of nonrecyclable reaction systems limit their practical application. Hence, a mild, efficient, and recyclable strategy is still highly desired to facilitate cyanations in organic synthesis.

In recent years, ionic liquids (ILs) have been widely used as stable and recyclable reaction media and catalysts in organic synthesis. Compared with traditional organic agents, ILs have unique advantages such as low melting points, negligible vapor pressures, low toxicities, high conductivities, and excellent

Scheme 1. Strategies for the Synthesis of Aryl Nitriles



chemical and thermal stability, and they are also easy to recycle and can readily dissolve many organic and inorganic compounds.[6] To date, ILs have been successfully applied in Suzuki, Heck, Wittig, and Friedel−Crafts reactions, Michael additions, Diels−Alder cycloadditions, and stereoselective halogenations.[7] However, their application in C-H activation cyanations has not been reported. Considering recent developments and our previous work in Rh-catalyzed *ortho*-cyanations of 2-aryl-1,2,3-triazole,[8] we describe a direct C-H bond cyanation strategy using a mild, efficient, and recyclable Cp*Rh(III)/IL system.

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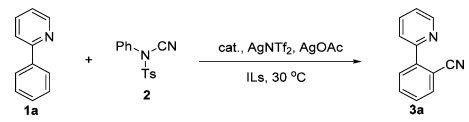
At the start of our investigation, the Rh-catalyzed C-H bond cyanation of 2-phenylpyridine (**1a**) with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS, **2**) was studied as a model reaction. When 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide ([BMIM]NTf_2) was used as the reaction medium, desired *ortho*-cyanide product **3a** was obtained in 58% yield (Table 1, entry 1). To optimize the yield of **3a**, we

Table 1. Optimization of the Reaction Conditions[a]



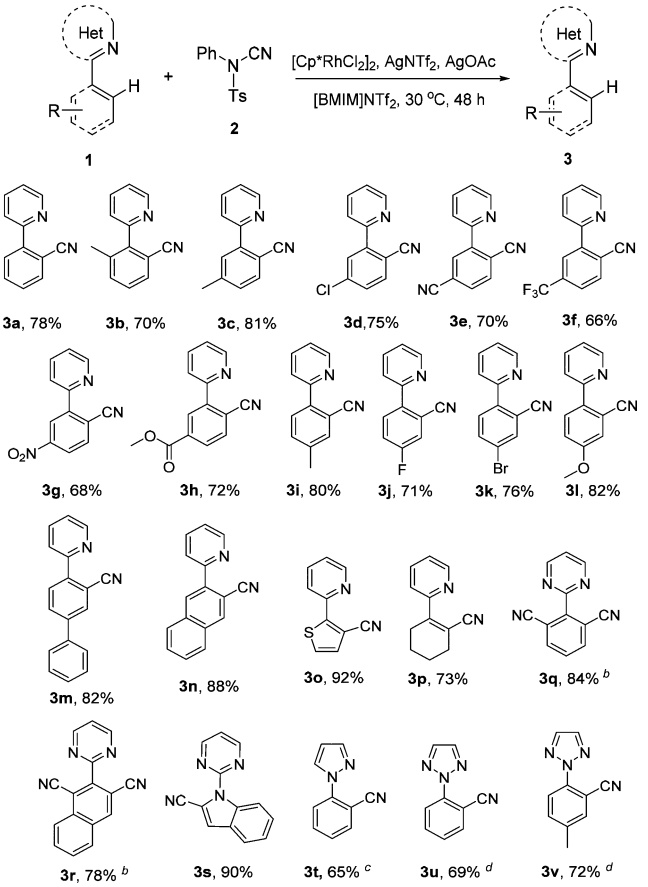
entry	cat. (5 mol %)	ILs	time (h)	yield[b] (%)
1	$[Cp^*RhCl_2]_2$	[BMIM]NTf_2	24	58
2	$Cp^*Rh(OAc)_2$	[BMIM]NTf_2	24	trace
3	$RhCl_3·H_2O$	[BMIM]NTf_2	24	NR
4	$[Cp^*Rh(Me\text{-}CN)_3](SbF_6)_2$	[BMIM]NTf_2	24	52
5	$[Cp^*RhCl_2]_2$	[BMIM]OTf	24	54
6	$[Cp^*RhCl_2]_2$	[BMIM]BF_4	24	49
7	$[Cp^*RhCl_2]_2$	[BDMIM]BF_4	24	45
8	$[Cp^*RhCl_2]_2$	[MTMG]BF_4	24	trace
9	$[Cp^*RhCl_2]_2$	[BTMG]NTf_2	24	trace
10	$[Cp^*RhCl_2]_2$	[BMIM]NTf_2	48	66
11	$[Cp^*RhCl_2]_2$	[BMIM]NTf_2	72	67
12[c]	$[Cp^*RhCl_2]_2$	[BMIM]NTf_2	48	73
13[c,d]	$[Cp^*RhCl_2]_2$	[BMIM]NTf_2	48	78

[a]Reaction conditions: 2-phenylpyridine (**1a**, 0.10 mmol), NCTS (**2** 0.15 mmol), cat. 5 mol % $AgNTf_2$ (0.03 mmol), AgOAc (0.05 mmol), and IL 0.3 mL. [b]Isolated yield by chromatography on silica gel. [c]AgOAc 0.10 mmol. [d]NCTS 0.20 mmol. Cp* = pentamethylcyclopentadienyl; [BMIM] = 1-butyl-3-methylimidazolium; [BDMIM] = 1-butyl-2,3-dimethylimidazolium; [MTMG] = *N*,*N*,*N*′,*N*′,*N*′-pentamethyl-quinone; [BTMG] = *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-butylhydrazine.

screened several parameters, and the results are shown in Table 1. It was found that $[Cp^*RhCl_2]_2$ showed better catalytic activity than other Rh(III) catalysts (entries 1−4). Then, combinations of anions and cations for the ionic liquids were explored (entries 5−9). Notably, only ILs with imidazolium as the cation were effective, and [BMIM]NTf_2 afforded the best result. Extending the reaction time to 48 h increased the yield, but further prolonging the reaction time to 72 h had no effect on the reaction outcome (entries 10−11). In addition, increasing the amount of NCTS and silver salt improved the yield to 78% (entries 12−13). Furthermore, other catalysts and additives were also screened, but no better results were found (Supporting Information (SI), Table S1). Accordingly, the reaction conditions were optimized to the following: 1.0 equiv 2-phenylpyridine, 2.0 equiv NCTS, 5 mol % $[Cp^*RhCl_2]_2$, 0.3 equiv $AgNTf_2$, and 1.0 equiv AgOAc in [BMIM]NTf_2 at 30 °C for 48 h.

With the optimized reaction conditions in hand, the C-H bond cyanation of 2-phenylpyridines was examined. The results are shown in Scheme 2. Unsubstituted 2-phenylpyridine **1a** gave 78% isolated yield of **3a**, and the 4′-Me and 5′-Me derivatives gave slightly increased yields of **3c** and **3i**, i.e., 81% and 80%, respectively. In contrast, the 6′-Me derivative only afforded a 70% isolated yield of **3b**. This result was probably because the steric hindrance from the 6′-Me group interferes with the formation of the product. Both electron-donating and -with-

Scheme 2. Scope of 2-Phenylpyridines[a]



[a](a) Reaction conditions: 2-phenylpyridine **1** (0.30 mmol), NCTS (**2**, 0.60 mmol), 5 mol % $[Cp^*RhCl_2]_2$, $AgNTf_2$ (0.09 mmol), AgOAc (0.30 mmol), and [BMIM]NTf_2 (0.5 mL), 30 °C for 48 h. The product yields were determined following column chromatography. (b) NCTS (**2**, 0.90 mmol). (c) Temp = 50 °C. (d) Temp = 80 °C.

drawing groups can tolerate this reaction, and it was demonstrated by the isolation of 82% of **3l** and 66−70% of **3e**−**g**. Halogen substituents were well tolerated in this process, and there was a positive correlation between conjugation and yield. When the 2-phenyl moiety was replaced with 2-biphenyl, 2-naphthyl, and 2-thienyl groups, the yields of **3m**−**o** were significantly increased compared to that of **3a**. Interestingly, when the 2-aromatic ring was replaced with a 2-aliphatic ring such as 2-cyclohexenyl, the cyanation still proceeded and afforded **3p** in 73% yield. This result showed that this reaction was not limited to direct aromatic functionalizations but can also be applied to aliphatic alkenes. It is worth noting that changing the directing group (DG) to other *N*-heterocycles such as pyrimidine, pyrazole, and triazole can also successfully afford cyanide products through this strategy (**3q**−**v**). Notably, pyrimidine-substituted substrates afforded mixtures of the mono- and biscyanide products, but **1q** and **1r** remained.

Increasing the equivalents of NCTS (**2**) afforded exclusively biscyanide products **3q** and **3r**. In all cases, this strategy showed a wide substrate scope with mild conditions and high efficiency under the optimized conditions.

Encouraged by these initial findings, we sought to further define the scope of this reaction. The feasibility of using an oxime, a commonly used DG, was also examined in this cyanation (Scheme 3). Fortunately, 1-phenyl-*O*-methyloxime

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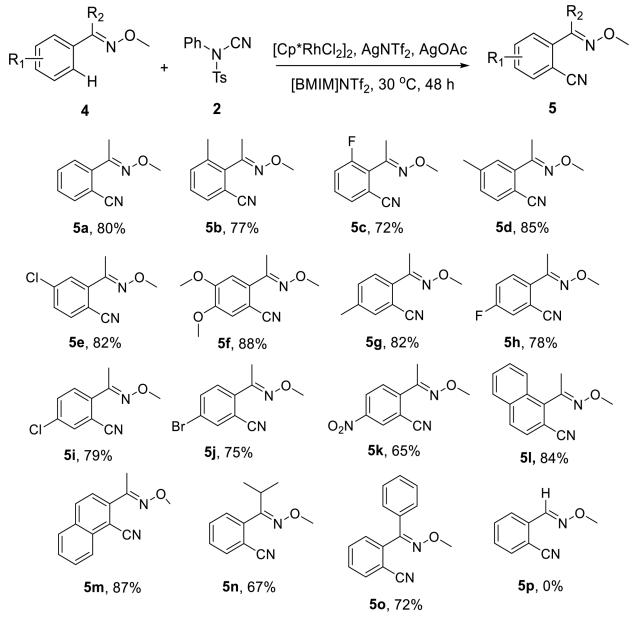
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of Aryl Ketone Oxime Ethers[a]

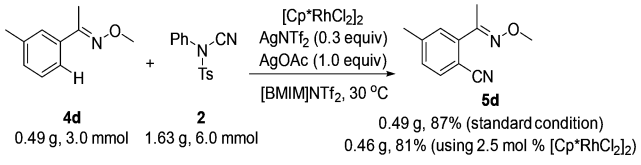


[a]Reaction conditions: aryl ketone oxime **4** (0.30 mmol), NCTS (**2**, 0.60 mmol), 5 mol % $[Cp^*RhCl_2]_2$, $AgNTf_2$ (0.09 mmol), AgOAc (0.30 mmol), and $[BMIM]NTf_2$ (0.5 mL), 30 °C for 48 h. The product yields were determined following column chromatography.

led to 80% isolated yield of **5a**. Various common functional groups, including methyl, methoxy, halogens, and even nitro moieties, were well tolerated and furnished the corresponding products in good to excellent yields (**5b**–**k**). As the amount of conjugation was increased, the cyanation reaction afforded higher yields of the products (**5l**, **5m**). The steric hindrance from the oxime ethers decreased the yields of **5n** and **5o**, and product **5p** was not observed. Our data indicated that *O*-methyl oxime ethers served as viable substrates in this reaction (65–88% yield of **5a**–**o**). Compared with *N*-heterocycles, oxime ethers are useful groups for additional functionalization steps and have more potential applications.[5c,10]

To investigate the efficiency and further practicality of this transformation, a 10-fold scale-up of the reaction using **4d** and **2** was performed. The desired product **5d** was isolated in 87% yield. Pleasingly, when the amount of the catalyst was decreased to 2.5 mmol %, **5d** was also obtained in 81% yield after stirring for only 24 h (Scheme 4). On this basis, we further investigated

Scheme 4. 10-Fold Scale-up Reaction and the Study of the ILs Reaction System Reusability



the reusability of the catalyst and solvent. The yields of product **5d** determined following column chromatography are shown in Figure 2. The reusability of the ionic liquid reaction system (without adding fresh Rh catalyst) was studied for five cycles, and only a marginal decrease in the yield of the desired product was observed. These results strongly suggested that the ILs were indeed an easily recycled reaction medium.

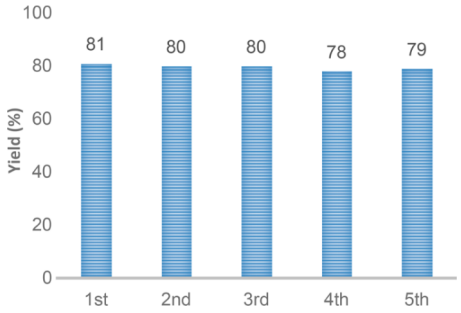
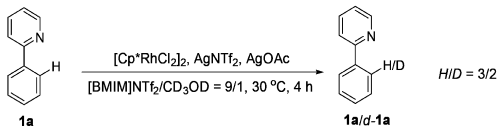


Figure 2. Recycling study results.

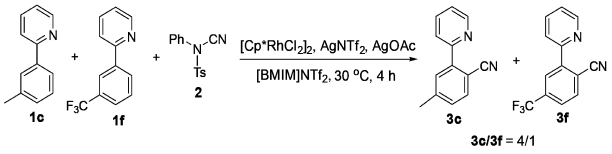
To elucidate the mechanism of this reaction, a series of experiments were conducted.[9,10] The H/D exchange experiment was performed by treating **1a** with CD_3OD in $[BMIM]NTf_2$. The ^1H NMR spectrum showed that 40% of the *ortho*-C-H bond in **1a** was deuterated after 4 h, which suggested that the C-H activation was reversible (Scheme 5a). The intermolecular

Scheme 5. Mechanistic Studies

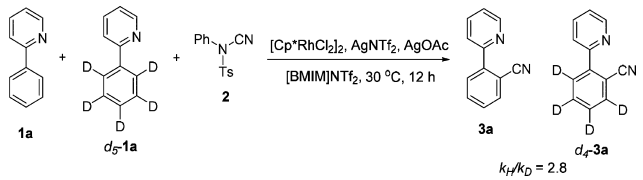
a) H/D exchange study



b) Competitive experiment



c) Independent KIE study



competition experiment between **1c** and **1f** highlighted an obvious preference for electron-rich substrate **1c** in the C-H bond cyanation reaction (Scheme 5b). The kinetic isotope effect was also measured from experiments conducted under identical conditions using **1a** and d_5-**1a** with NCTS (**2**) as the coupling partner. A value of $k_H/k_D = 2.8$ was obtained. This indicates that the C-H bond cleavage occurs during the rate-determining step (Scheme 5c).

On the basis of the above results and previous related studies,[5c,7g,h,8] a possible mechanism for this C-H cyanation is given in Scheme 6. First, treatment of the Rh precursor with AgOAc generates reactive cationic Rh species **A**. This reacts with 2-phenylpyridine **1a** to afford cyclic Rh species **B** with a vacant coordination site. **B** reacts with **2** to form tight transition states **C**. **C** is the key intermediate in this reaction. Subsequently, transition states **C** lead to product **3a** and rhodium complex **D**. Finally, in the presence of protons, active Rh species **A** is obtained and participates in the next catalytic cycle.

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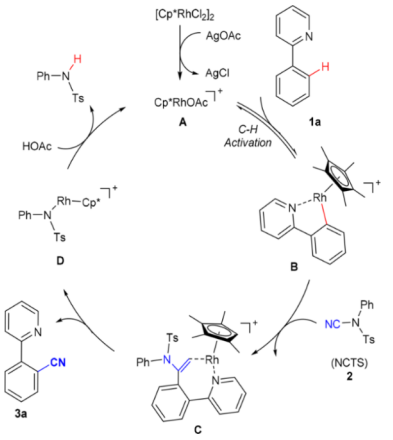
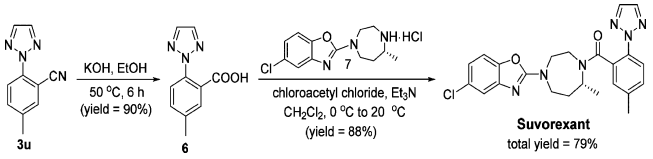
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 6. Proposed Mechanism



Importantly, aromatic cyanides are of great interest as building blocks in drug design. For example, Suvorexant, a listed drug, was recognized as a novel orexin antagonist and has emerged as a new class of therapeutic agents for the treatment of primary insomnia.[2] 5-Methyl-2-(2*H*-1,2,3-triazol-2-yl)-benzonitrile (product **3u**) was used to synthesize Suvorexant in two steps and gave a 79% yield (Scheme 7). Our work may provide new ideas for drug design and synthesis.

Scheme 7. Synthesis of Suvorexant



In summary, we have developed an unprecedented strategy of C-H bond cyanation using an ionic liquid, [BMIM]NTf_2, as a recyclable medium. Although there are some reports about the mild reaction conditions of C-H activation,[11] cyanation has not been described. These transformations extended the chemistry and scope of the poplar Rh-catalyzed C-H functionalization reactions, i.e., the cyanation reactions were realized near room temperature and in a recyclable manner for the first time. In addition, many different directing groups can be used in this method, and a number of aromatic and heteroaromatic nitriles were successfully synthesized. Furthermore, because the cyano group can be readily converted to many other synthetically useful groups, this reaction may provide a practical tool for the rapid derivatization of functional molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01952.

Experimental details and characterization of new compounds (^{1}H, ^{13}C, ^{19}F NMR spectra) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*(Y.W.) E-mail: wyong@scu.edu.cn.
*(L.H.) E-mail: smile@scu.edu.cn.

ORCID

Yong Wu: 0000-0003-0719-4963

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*, 4th ed.; Thieme: Stuttgart, 2001.

(2) Mangion, I. K.; Sherry, B. D.; Yin, J.; Fleitz, F. J. *Org. Lett.* **2012**, *14*, 3458.

(3) (a) Rosenmund, K. W.; Struck, E. *Ber. Dtsch. Chem. Ges. B* **1919**, *52*, 1749. (b) Sandmeyer, T. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2650.

(4) (a) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (b) Yan, G.; Kuang, C.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 1052. (c) Liskey, C. W.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 11389. (d) Ushkov, A. V.; Grushin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 10999.

(5) (a) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966. (b) Gong, T.; Xiao, B.; Cheng, W.; Su, W.; Xu, J.; Liu, Z.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 10630. (c) Cotugno, P.; Monopoli, A.; Ciminale, F.; Milella, A.; Nacci, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 13563. (d) Yu, D.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722. (e) Chaitanya, M.; Yadagiri, D.; Anbarasan, P. *Org. Lett.* **2013**, *15*, 4960. (f) Chaitanya, M.; Anbarasan, P. *Org. Lett.* **2015**, *17*, 3766. (g) Pawar, A. B.; Chang, S. *Org. Lett.* **2015**, *17*, 660. (h) Kou, X.; Zhao, M.; Qiao, X.; Zhu, Y.; Tong, X.; Shen, Z. *Chem. - Eur. J.* **2013**, *19*, 16880. (i) Shu, Z.; Ji, W.; Wang, X.; Zhou, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 2186. (j) Qi, C.; Hu, X.; Jiang, H. *Chem. Commun.* **2017**, *53*, 7994. (k) Kim, J.; Kim, H.; Chang, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11948. (l) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.

(6) (a) Matuszek, K.; Coffie, S.; Chrobok, A.; Swadźba-Kwaśny, M. *Catal. Sci. Technol.* **2017**, *7*, 1045. (b) Vahdat, S. M.; Zolfigol, M. A.; Baghery, S. *Appl. Organomet. Chem.* **2016**, *30*, 311. (c) Tomé, L. C.; Marrucho, I. M. *Chem. Soc. Rev.* **2016**, *45*, 2785. (d) Rad-Moghadam, K.; Taghizadeh Valadi, A.; Alipour, A. *Appl. Organomet. Chem.* **2014**, *28*, 146.

(7) (a) Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Appl. Catal., A* **2017**, *543*, 150. (b) Srivastava, V. *Catal. Lett.* **2017**, *147*, 693. (c) Zong, Y.; Wang, J.; He, Y.; Yue, G.; Wang, X.; Pan, Y. *RSC Adv.* **2016**, *6*, 89621. (d) Vekariya, R. *J. Mol. Liq.* **2017**, *227*, 44. (e) Wasserscheid, P.; Sesing, M.; Korth, W. *Green Chem.* **2002**, *4*, 134. (f) Dell'Anna, M. M.; Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. *Chem. Commun.* **2002**, 434. (g) Chiappe, C.; Malvaldi, M.; Pomelli, C. *Green Chem.* **2010**, *12*, 1330. (h) Chiappe, C.; Capraro, D.; Conte, V.; Pieraccini, D. *Org. Lett.* **2001**, *3*, 1061.

(8) Zhang, H.; Jing, L.; Zheng, Y.; Sang, R.; Zhao, Y.; Wang, Q.; Wu, Y. *Eur. J. Org. Chem.* **2018**, *2018*, 723.

(9) Zhou, X.; Yu, S.; Kong, L.; Li, X. *ACS Catal.* **2016**, *6*, 647.

(10) Gong, W.; Zhou, Z.; Shi, J.; Wu, B.; Huang, B.; Yi, W. *Org. Lett.* **2018**, *20*, 182.

(11) (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.

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