Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Selective Aerobic Oxidation of Alcohols to Aldehydes, Carboxylic Acids, and Imines Catalyzed by a Ag-NHC Complex

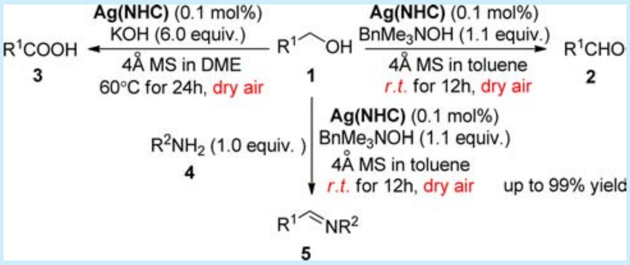
Lei Han,[†] Ping Xing,[†] and Biao Jiang*[,†,‡]

[†]CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai, 200032, China

[‡]Shanghai Advanced Research Institute, Chinese Academy of Sciences, 99 Haike Road, Shanghai 201210, China

*Supporting Information*

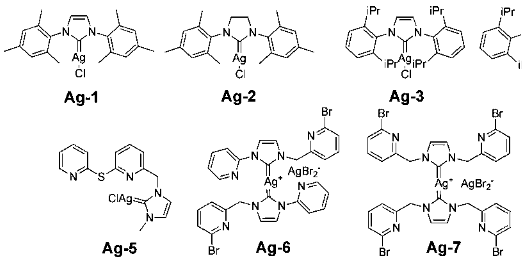
**ABSTRACT:** Silver NHC catalysts have been developed for the selective oxidation of alcohols to aldehydes or carboxylic acids in the presence of $BnMe_3NOH$ or KOH under dry air. The aerobic oxidation conditions are mild, and the yield is excellent. Further tandem catalysis enables the one-pot synthesis of imines in excellent yield. Only 0.1 mol % of the catalyst is required.



Metal N-heterocyclic carbene (NHC) complexes have been widely studied for their intriguing structural properties and numerous applications.[1] Ag-NHC complexes are the most studied metal-NHC complexes due to their facile preparation using $Ag_2O$.[2] Although many Ag-NHC complexes have been reported because of their ease of synthesis, their catalytic properties have scarcely been investigated. Applications have primarily included NHC ligand transmetalation from silver to other late-transition metals.[3] Peris and Fernandez first reported the use of a Ag-NHC catalyst in alkene diboration reactions.[4] A combination of NHC and AgOTf has been successfully utilized for the hydrosilylation of aldehydes.[5] Ag-NHC complexes have also been tested in the ring-opening polymerization of L-lactides.[6] Ag-NHC catalysis has been recently applied to carbometalation,[7] the silylcyanation of imines,[8] and cross-coupling.[9] However, their potential in aerobic oxidation has not been fully elucidated. A number of anaerobic[10] and aerobic[11]catalytic methods have been explored for alcohol oxidation. Noble metal catalysts (Ru,[10a−f] Rh,[10g] Ir,[10h,i] and Pd[11a−c]) were developed in the presence of external or internal oxidants. A Co(PNP) complex,[10j] a cheap metal catalyst, was reported for acceptorless dehydrogenation, whereas the $Cu^I$/TEMPO system[11d−g] was also considered as a promising methodology. Silver oxide is a classic, mild oxidizing agent for the oxidation of aldehydes to carboxylic acids. We envision that Ag-NHC complexes could serve as a catalyst for aerobic oxidation. In this report, we describe the mild selective oxidation of benzylic and allylic alcohols to aldehydes, carboxylic acids, or imines in high yields catalyzed by Ag-NHC complexes.

Ag(I)-NHC (**Ag-1**) was initially tested with different bases and at different reaction temperatures (Scheme 1). It was found that a base is necessary for Ag(I)-NHC catalyzed aerobic oxidation (Table 1). The reaction was carried out with 2 equiv of KOH and 0.1% mol of **Ag-1** to give an almost 1:1 ratio of the corresponding aldehyde and acid, whereas the reaction gave a 65% yield of the aldehyde as the only product with *t*-BuOK (entries 1−2). Using $BnMe_3NOH$ (BTMAH) as a base in the aerobic oxidation afforded a moderate yield of aldehyde (entry 3). Thus, various Ag-NHC complexes were tested for aerobic oxidation using BTMAH as a base (Scheme 1, Table 1).

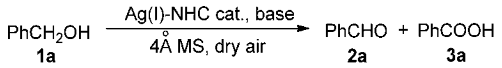
**Scheme 1. Silver NHC Complexes**



The silver NHC catalysts bearing unsaturated NHC ligands (**Ag-1**/**3**, entries 3 and 5) performed better than their analogues bearing a saturated NHC ligand (**Ag-2**/**4**, entries 4 and 6), whereas sterically constrained complexes (**Ag-3**/**4**, entries 5 and 6) gave lower yields than their more flexible counterparts (**Ag-1**/**2**, entries 3 and 4). **Ag-5**, a silver NHC complex containing a sulfur atom, which might poison the reactive metal center, gave a low yield of aldehyde (entry 7). The catalytic activity of Ag(I)-NHC complexes bearing pyridyl groups was also examined, and product specificity was maintained. **Ag-7**, bearing a symmetrically *N*,*N*′-pyridyl NHC ligand, showed excellent catalytic activity and gave an excellent yield of aldehyde (98% yield, entry 9) whereas **Ag-6**, bearing an

**Received:** February 24, 2014
**Published:** June 17, 2014

### Table 1. Optimization of the Ag(I)-NHC Catalyzed Aerobic Oxidation[a]



$$\underset{\textbf{1a}}{PhCH_2OH} \xrightarrow[\text{4Å MS, dry air}]{\text{Ag(I)-NHC cat., base}} \underset{\textbf{2a}}{PhCHO} + \underset{\textbf{3a}}{PhCOOH}$$

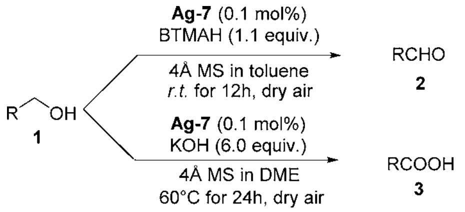
| entry | Ag cat. (mol %) base (equiv) | $T$ (°C) $t$ (h) | **2a**/**3a** yield (%)$^{d}$ |
|---|---|---|---|
| 1$^{b,e}$ | **Ag-1** (0.1), KOH (2.0) | rt, 12 | 48/49 |
| 2$^{b,e}$ | **Ag-1** (0.1), *t*-BuOK (2.0) | rt, 12 | 65/− |
| 3$^{b,c,e}$ | **Ag-1** (0.1), BTMAH (1.1) | rt, 12 | 70/− |
| 4$^{c,e}$ | **Ag-2** (0.1), BTMAH (1.1) | rt, 12 | 57/− |
| 5$^{c,e}$ | **Ag-3** (0.1), BTMAH (1.1) | rt, 12 | 62/− |
| 6$^{c,e}$ | **Ag-4** (0.1), BTMAH (1.1) | rt, 48 | 53/− |
| 7$^{c,e}$ | **Ag-5** (0.1), BTMAH (1.1) | rt, 12 | 18/5 |
| 8$^{c,e}$ | **Ag-6** (0.1), BTMAH (1.1) | rt, 12 | 54/− |
| 9$^{c,e}$ | **Ag-7** (0.1), BTMAH (1.1) | rt, 12 | 98/− |
| 10$^{c,f}$ | **Ag-7** (0.1), KOH (2.0) | rt 12 | 65/34 |
| 11$^{c,f}$ | **Ag-7** (0.1), KOH (6.0) | 60, 24 | −/99 |

[a] The mixture of **1a**, Ag-NHC catalyst, base, and 4 Å MS was stirred under dry air or pure oxygen and monitored by $^1$H NMR. [b] The oxidation reaction was carried out under pure oxygen. [c] The oxidation reaction was carried out under dry air. [d] Isolated yield. [e] In toluene (0.1 M). [f] In DME (2.0 M).

unsymmetrically N, N′-pyridyl NHC ligand, showed lower performance (54% yield, entry 8). Although performing the oxidation with 2 equiv of KOH could still result in a high conversion but poor specificity with **Ag-7** (entry 10), we attempted direct oxidation of the alcohol to the carboxylic acid by increasing the amount of base. When the reaction was performed with 6 equiv of KOH in dimethoxyethane with heat, **Ag-7** could efficiently catalyze the oxidation of the alcohol into the carboxylic acid in nearly quantitative yield (entry 11). We also performed control experiments to demonstrate that the Ag(I)-NHC catalysts were necessary.[11h]

With the optimized conditions in hand, **Ag-7** was chosen as the universal catalyst and utilized with various alcohol substrates to test the breadth of substrates tolerated in the oxidation (Table 2). In the selective oxidations, *para*-substituted benzyl alcohols **1** listed reacted efficiently and universally to afford the corresponding aldehydes **2** in almost quantitative yields, regardless of whether the substituents were electron-rich or -deficient (entries 1−5). The reaction of *para*-, *meta*-, or *ortho*-methoxybenzyl alcohols **1f**−**1h** under standard conditions showed no obvious effect of steric hindrance on the aldehyde yields (entries 5−7). Active hydrogen substrates such as **1i** and **1j** were also tested and afforded high yields (entries 8−9), whereas the high yield of salicyl aldehyde **2i** indicated that our oxidative method was chemoselective for alcohols over phenols. Similar to benzyl alcohols, heterobenzylic counterparts **1k**−**1m** reacted efficiently to afford moderate to high yields of the heterobenzylic aldehydes **2k**−**2m** (entries 10−12). For some allylic alcohols, a high yield of cinnamyl aldehyde **2n** and cinnamyl acid **3n** were obtained from cinnamyl alcohol **1n** (entry 13). A cis−trans isomeric citral mixture **2o** ($E/Z$ = 1:1) could be afforded in moderate yield from geraniol **1o** (entry 14). In addition, the optimized conditions for cascade catalysis produced carboxylic acids **3** in high yields from most alcohol substrates. Fluoro- and nitro-substrates (**1b**/**c**) were intolerant of the concentrated base, and the furyl structure **1k** was sensitive to heat. We also tried to afford carboxylic acid **3o** under the standard conditions, but the crude reaction solution became complex.

### Table 2. Ag(I)-NHC Catalyzed Aerobic Oxidative Preparation of Aldehydes and Carboxylic Acids



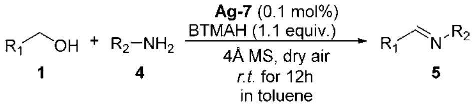
| entry | **1** | **2** yield (%)$^{a}$ | **3** yield (%)$^{a}$ |
|---|---|---|---|
| 1 | $p$-$O_2NC_6H_4CH_2OH$ (**1b**) | 96 (**2b**) | − (**3b**) |
| 2 | $p$-$FC_6H_4CH_2OH$ (**1c**) | 94 (**2c**) | − (**3c**) |
| 3 | $p$-$ClC_6H_4CH_2OH$ (**1d**) | 99 (**2d**) | 98 (**3d**) |
| 4 | $p$-$BrC_6H_4CH_2OH$ (**1e**) | 98 (**2e**) | 98 (**3e**) |
| 5 | $p$-$MeOC_6H_4CH_2OH$ (**1f**) | 99 (**2f**) | 99 (**3f**) |
| 6 | $m$-$MeOC_6H_4CH_2OH$ (**1g**) | 97 (**2g**) | 96 (**3g**) |
| 7 | $o$-$MeOC_6H_4CH_2OH$ (**1h**) | 95 (**2h**) | 93 (**3h**) |
| 8 | $o$-$HOC_6H_4CH_2OH$ (**1i**) | 89 (**2i**) | 88 (**3i**) |
| 9 | $o$-$H_2NC_6H_4CH_2OH$ (**1j**) | 94 (**2j**) | 95 (**3j**) |
| 10 | 2-furanmethanol (**1k**) | 90 (**2k**) | − (**3k**) |
| 11 | 2-pyridinemethanol (**1l**) | 86 (**2l**) | 80 (**3l**) |
| 12 | 2-thiophenemethanol (**1m**) | 92 (**2m**) | 92 (**3m**) |
| 13 | cinnamyl alcohol (**1n**) | 96 (**2n**) | 95 (**3n**) |
| 14 | geraniol (**1o**) | 80 (**2o**) | − |

[a] Reactions were monitored by $^1$H NMR.

Imines, also known as Schiff bases, are an important class of nitrogen compounds in chemistry. Due to the high reactivity of their C═N double bonds, they are important nitrogen sources and key intermediates in biological, pharmaceutical, industrial, and natural product synthetic applications. Therefore, developing methods for the preparation of imines is an important challenge.[12] Tandem catalysis that enables a one-pot multistep reaction shows great potential for increasing the efficiency of chemical synthesis. Because mild conditions were used for the selective oxidation of alcohols, a cascade reaction was attempted for the one-pot oxidative tandem synthesis of imines from alcohols and amines (Table 3). We found that benzyl alcohol **1a** could react efficiently with aliphatic, aromatic, and steric amines (**4a**−**d**) to afford the corresponding imines in high yields (entries 1−4). Amines **4a**/**d** likewise reacted with benzyl alcohols **1b**−**j** with electron-donating and -withdrawing substituents (entries 5−13), heterobenzyl alcohols **1k**−**m** (entries 14−16), and allyl alcohols **1n**−**o** (entries 17−18). No obvious electronic effect contributing to the yield of imine **5** (entries 19−23) was found when para-substituted amines **4e**−**i** bearing electron-deficient or -rich groups were used as a substrate. Comparative experiments on *para*-, *meta*-, and *ortho*-methoxyaniline (**4i**/**j**/**k**) identified that steric hindrance more or less influences the yields of the imines (entries 23−25).

In addition, the mechanism of the mild oxidation process was explored.[13] When ethyl sulfide or TEMPO was added, the yield of aldehyde **2a** was dramatically decreased and the catalytic rate was slower, respectively. TEMPO could trap radical intermediates and interrupt the catalytic cycle (Scheme 2, entry 1). The sulfide may coordinate with silver and poison the active metal center (entry 2). Electron paramagnetic resonance (EPR) experiments clearly showed that radicals were present in the reaction solution, indicating a direct molecular oxygen activation process. AgOTf was used as a substitute for **Ag-7** but failed to catalyze the reaction (entry 3), indicating the importance of the NHC ligands. Basic luminol and $K_3$[Fe-

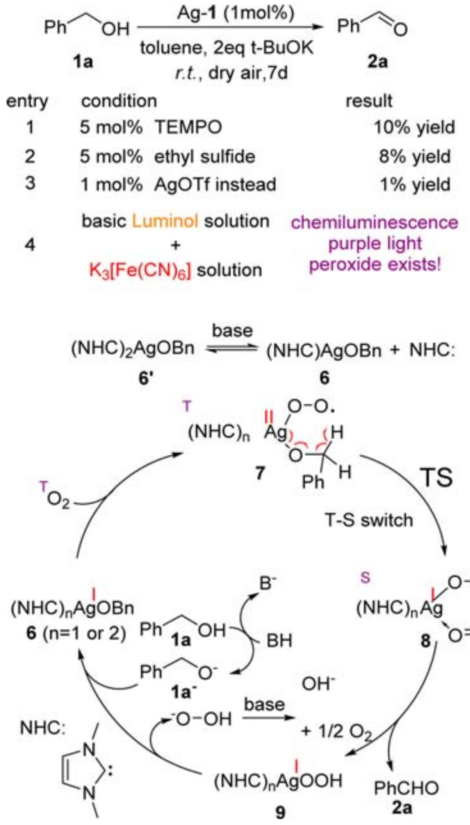
### Table 3. Ag(I)-NHC Catalyzed Aerobic Oxidative Preparation of Imines from Alcohols and Amines



| entry | 1 | 4 | 5 yield (%)[a] |
|---|---|---|---|
| 1 | **1a** | $PhNH_2$ (**4a**) | 92 |
| 2 | **1a** | *n*-$C_3H_7NH_2$ (**4b**) | 99 |
| 3 | **1a** | *cyclo*-$C_6H_{11}NH_2$ (**4c**) | 97 |
| 4 | **1a** | $BnNH_2$ (**4d**) | 98 |
| 5 | **1b** | **4a**/**4d** | 95/95 |
| 6 | **1c** | **4a**/**4d** | 94/94 |
| 7 | **1d** | **4a**/**4d** | 98/97 |
| 8 | **1e** | **4a**/**4d** | 98/98 |
| 9 | **1f** | **4a**/**4d** | 99/97 |
| 10 | **1g** | **4a**/**4d** | 96/94 |
| 11 | **1h** | **4a**/**4d** | 94/92 |
| 12 | **1i** | **4a**/**4d** | 88/87 |
| 13 | **1j** | **4d** | 96 |
| 14 | **1k** | **4a**/**4d** | 83/85 |
| 15 | **1l** | **4a**/**4d** | 80/82 |
| 16 | **1m** | **4a**/**4d** | 91/90 |
| 17 | **1n** | **4a**/**4d** | 94/96 |
| 18 | **1o** | **4a**/**4d** | 84/75 |
| 19 | **1a** | *p*-$O_2NC_6H_4NH_2$ (**4e**) | 83 |
| 20 | **1a** | *p*-$FC_6H_4NH_2$ (**4f**) | 85 |
| 21 | **1a** | *p*-$ClC_6H_4NH_2$ (**4g**) | 90 |
| 22 | **1a** | *p*-$BrC_6H_4NH_2$ (**4h**) | 91 |
| 23 | **1a** | *p*-$MeOC_6H_4NH_2$ (**4i**) | 93 |
| 24 | **1a** | *m*-$MeOC_6H_4NH_2$ (**4j**) | 86 |
| 25 | **1a** | *o*-$MeOC_6H_4NH_2$ (**4k**) | 82 |

[a] Reactions were monitored by $^1H$ NMR.

### Scheme 2. Experiments for Proposed Mechanism



$(CN)_6]$ solutions were added to the reaction mixture, and purple chemiluminescence was immediately observed, which suggests that peroxide species were present.

A plausible mechanism of molecular oxygen activation for the selective oxidation was proposed based on previous experiments and *in situ* ESI-MS. Alkoxide-coordinated silver NHC complex **6** activates molecular oxygen to afford a triplet $Ag^{II}$ complex **7** bearing a peroxy radical ($\Delta G = 5.6$ kcal/mol). The peroxy radical then removes a benzyl hydrogen via a six-membered-ring transition state (TS, $\Delta\Delta G^{\ddagger} = 15.9$ kcal/mol) without the assistance of exogenous radicals (e.g., TEMPO), which is followed by a spin flip to singlet complex **8** ($\Delta G = -9.9$ kcal/mol). Complex **8** dissociates into aldehyde **2a** and peroxide **9** ($\Delta G = -20.6$ kcal/mol). Finally, the catalytic cycle is completed by metathesis of the anion to regenerate complex **6**, and peroxide decomposes into oxygen and hydroxide under basic conditions. In addition, theoretical computations of the catalytic cycle were performed for both the mono- and bis-NHC silver complexes. Ligand disassociation of the bis-NHC complex **6′** is facile and nearly thermoneutral ($\Delta G = -1.5$ kcal/mol), but mono-NHC complex **6** activates molecular oxygen more efficiently than does **6′**.

In conclusion, a robust and effective Ag catalyst for the aerobic oxidation of a variety of alcohols has been discovered and studied. Using BTMAH or KOH, the oxidation can be carried out aerobically to selectively afford aldehydes or carboxylic acids in excellent yield. In addition, tandem catalysis was explored for the one-pot synthesis of imines from an amine. This method has great potential for the preparation of imines because it tolerates a wide range of substrates and is high yielding.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Full experimental details, spectroscopic data, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: jiangb@sioc.ac.cn.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Basic Research Program of China (973-2010CB833200 and 973-2010CB833300), the National Natural Science Foundation of China (20832007 and 21102167), the Science and Technology Commission of Shanghai Municipality (12DZ1930902), and the Knowledge Innovation Program of the Chinese Academy of Sciences.

## ■ REFERENCES

(1) Lin, J. C. Y.; Huang, R. T. W.; Lee, C. S.; Bhattacharyya, M.; Hwang, W. S.; Lin, I. J. B. *Chem. Rev.* **2009**, *109*, 3561.

(2) (a) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978. (b) Lin, I. J. B.; Vasam, C. S. *Comments Inorg. Chem.* **2004**, *25*, 75. (c) Arnold, P. L. *Heteroat. Chem.* **2002**, *13*, 534.

(3) (a) Clavier, H.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2007**, *103*, 193. (b) Lin, I. J. B.; Vasam, C. S. *Coord. Chem. Rev.* **2007**, *251*, 642.

(4) Corberan, R.; Ramirez, J.; Poyatos, M.; Peris, E.; Fernandez, E. *Tetrahedron: Asymmetry* **2006**, *17*, 1759.

(5) (a) Poyatos, M.; Maisse-Francois, A.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2006**, *25*, 2634. (b) Wile, B. M.; Stradiotto, M. *Chem. Commun.* **2006**, 4104.

(6) Samantaray, M. K.; Katiyar, V.; Roy, D.; Pang, K.; Nanavati, H.; Stephen, R.; Sunoj, R. B.; Ghosh, P. *Eur. J. Inorg. Chem.* **2006**, *15*, 2975.

(7) (a) Fujii, Y.; Terao, J.; Kambe, N. *Chem. Commun.* **2009**, 1115. (b) Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2672.

(8) Wang, D.; Zhang, B.; He, C.; Wu, P.; Duan, C. *Chem. Commun.* **2010**, *46*, 4728.

(9) Li, F.; Bai, S.; Hor, T. S. A. *Organometallics* **2008**, *27*, 672.

(10) Ru catalyst: (a) Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. *Organometallics* **2013**, *32*, 660−664. (b) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643−2649. (c) Manzini, S.; Urbina-Blanco, C. A.; Poater, A.; Slawin, A. M. Z.; Cavallo, L.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 1042−1045. (d) Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Rozenberg, H.; Milstein, D. *Organometallics* **2004**, *23*, 4026−4033. (e) Hamid, M. H. S. A.; Williams, J. M. J. *Chem. Commun.* **2007**, 725−727. (f) Montag, M.; Zhang, J.; Milstein, D. *J. Am. Chem. Soc.* **2012**, *134*, 10325−10328. Rh catalyst: (g) Zweifel, T.; Naubron, J.-V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559−563. Ir catalyst: (h) Prades, A.; Corberán, R.; Poyatos, M.; Peris, E. *Chem.—Eur. J.* **2008**, *14*, 11474−11479. (i) Mena, I.; Casado, M. A.; Polo, V.; García-Orduña, P.; Lahoz, F. J.; Oro, L. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8259−8263. Co catalyst: (j) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650−653.

(11) Pd catalyst: (a) Jiang, L.; Jin, L.; Tian, H.; Yuan, X.; Yu, X.; Xu, Q. *Chem. Commun.* **2011**, *47*, 10833−10835. (b) Sheldon, R. A.; Arends, I. W. C. E.; ten Brink, G.-J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774−781. (c) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221−229. $\mathrm{Cu^I}$/TEMPO catalyst: (d) Mannam, S.; Alamsetti, S. K.; Sekar, G. *Adv. Synth. Catal.* **2007**, *349*, 2253−2258. (e) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901−16910. (f) Hoover, J. M.; Steves, J. E.; Stahl, S. S. *Nat. Protoc.* **2012**, *7*, 1161−1166. (g) Hoover, J. M.; Ryland, B. L.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 2357−2367. Nonmetal: (h) Wang, J.; Liu, C.; Yuan, J.; Lei, A. *New J. Chem.* **2013**, *37*, 1700−1703.

(12) (a) Jiang, L.; Jin, L.; Tian, H.; Yuan, X.; Yu, X.; Xu, Q. *Chem. Commun.* **2011**, *47*, 10833. (b) Liu, P.; Li, C.; Hensen, E. J. M. *Chem.—Eur. J.* **2012**, *18*, 12122. (c) Sun, H.; Su, F.-Z.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4390. (d) Tian, H.; Yu, X.; Li, Q.; Wang, J.; Xu, Q. *Adv. Synth. Catal.* **2012**, *354*, 2671. (e) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650.

(13) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188.